Evidenzbericht für die S3-Leitlinie: „Empfehlungen zur Therapie von Patienten mit COVID-19“

AWMF-Registernummer: 113 – 001

Aktueller Stand: Februar 2025

Version 11.0

Das dieser Veröffentlichung zugrundliegende Projekt wurde mit Mitteln des Innovationsausschusses beim Gemeinsamen Bundesausschuss unter dem Förderkennzeichen 01VSF2300 gefördert.

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1 Informationen zum Evidenzbericht

1.1 Autor*innen des Evidenzberichts

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- UK Köln: Prof. Dr. Nicole Skoetz, Nina Kreuzberger, Caroline Hirsch, Sonja Mahler

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1.2 Federführende Fachgesellschaft(en) der Leitlinie

- Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN)
- Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)
- Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)
- Deutsche Gesellschaft für Infektiologie (DGI)

1.3 Finanzierung der Leitlinie

Die vorliegende Aktualisierung wird unter dem Projekt „S3Cov19live – Living Guideline: Empfehlungen zur Therapie von Patienten mit COVID-19“ (Förderkennzeichen: 01VSF2300) durch den Gemeinsamen Bundesausschuss (Innofonds) für den Zeitraum 01.08.2023 und 31.07.2026 gefördert.

Die Vorgängerversion dieser Leitlinie wurde durch das Projekt CEOsys, das im Rahmen des Nationalen Forschungsnetzwerks der Universitätsmedizin (NaFoUniMedCovid19) durch das Bundesministerium für Bildung und Forschung (BMBF) gefördert wurde, unterstützt; FKZ: 01KX2021. Die Förderung von CEOsys endete zum 31.12.2021.

1.4 Weitere Dokumente zur Leitlinie

- https://register.awmf.org/de/leitlinien/detail/113-001LG
- https://app.magicapp.org/#/guideline/jxRvyn

1.5 Abkürzungsverzeichnis

Auf eine Übersetzung englischer Abkürzungen wurde verzichtet.

Abkürzung	Erläuterung
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
EtD	Evidence to Decision Framework
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFNC	High flow Sauerstoff über Nasenbrille
IMV	Invasive mechanische Beatmung
JAK	Januskinase (JAK) Inhibitoren

Abkürzung	Erläuterung
MAGICapp	Making GRADE an Irresistable Choice application
NIV	Nicht-invasive Beatmung
RCT	Randomisiert kontrollierte Studie
RoB	Risk of Bias
ROBINS-I	Risk of bias tool to assess non-randomized studies of interventions
SoC	Standard of Care

2 Geltungsbereich und Zweck der Leitlinie

2.1 Zielsetzung und Zielpopulation der Leitlinie

Diese Leitlinie verfolgt das Ziel, Empfehlungen zur zugrundeliegenden Pathophysiologie, Diagnostik und therapeutischen Strategien bei Patienten mit COVID-19 zu vermitteln. Die Leitlinie wendet sich an alle tätigen Ärzte und weitere Berufsgruppen, die Patienten mit COVID-19 betreuen. Zugleich soll sie als Orientierung für Personen und Organisationen dienen, die direkt oder indirekt mit diesem Thema befasst sind.

2.2 Adressaten der Leitlinie

Adressaten der Leitlinie sind mit der Behandlung von COVID-19 Patienten befasste Ärzte, insbesondere Anästhesisten, Infektiologen, Pneumologen, Gastroenterologen, Kardiologen, Internist*innen, Rheumatolog*innen, Kinderärzte, Nephrologen, Neurologen, Gerinnungsspezialisten, Angiologen, Palliativmediziner*innen, und Experten für Mikrobiologie/Hygiene sowie betroffene Patienten. Die Leitlinie dient zur Information für alle weiteren an der Versorgung Beteiligten.

2.3 Gültigkeitsdauer und Aktualisierungsverfahren

- Datum der letzten inhaltlichen Überarbeitung: 02/2025
- Gültigkeitsdauer der Leitlinie: bis Dezember 2025

3 Zusammensetzung der Leitliniengruppe und Beteiligung von Interessengruppen

3.1 Koordination und Redaktion

- Prof. Dr. Stefan Kluge
- Prof. Dr. Nicole Skoetz

3.2 Beteiligte Fachgesellschaften und Betroffene/Patient*innenvertretung

Fachgesellschaft	Kürzel	Bisherige/r Mandatsträger/in
Patient*innenenvertretende		Reiner Haase
Deutsche Gesellschaft für Neurologie e.V.	DGN	Peter Berlit
Deutscher Rat für Wiederbelebung	GRC	Bernd W. Böttiger

Deutsche Gesellschaft für Hygiene und Mikrobiologie e.V.	DGHM	Christian Brandt
Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.	DGKJ	Florian Hoffmann
Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e. V.	DIVI	Uwe Janssens
Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin	DGIIN	Christian Karagiannidis Stefan Kluge
Deutsche Gesellschaft für Kardiologie – Herz und Kreislaufforschung e.V.	DGK	Alexander Kersten
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten	DGVS	Marcin Krawczyk
Gesellschaft für Thrombose und Hämostaseforschung e.V.	GTH	Florian Langer
Deutsche Gesellschaft für Infektiologie e.V.	DGI	Miriam Stegemann Jakob J. Malin Christoph D. Spinner
Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin	DGAI	Gernot Marx Henrik Bracht Gereon Schälte
Deutsche Gesellschaft für Angiologie	DGA	Oliver J. Müller
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin	DGP	Michael Pfeifer Klaus F. Rabe Michael Westhoff
Deutsche Gesellschaft Für Innere Medizin	DGIM	Marcel Schorrlepp Michael Pfeifer
Deutsche Gesellschaft für Rheumatologie e.V.	DGRh	Christof Specker
Deutsche Gesellschaft für Nephrologie	DGfN	Julia Weinmann-Menke
Deutsche Gesellschaft für Palliativmedizin		Wiebke Nehls, Vertretung: Claudia Bausewein

4 Methodisches Vorgehen

4.1 Formulierung der Schlüsselfragen und Priorisierung von Endpunkten

Die Schlüsselfragen wurden im PICO-Format von der Leitliniengruppe zusammengetragen und wichtige therapeutische Fragestellungen nach klinischer Relevanz priorisiert. Die Endpunkte lehnen sich an die Vorgängerversionen der Leitlinie an und wurden von Koordinierenden der Leitlinie noch einmal begutachtet, jedoch nicht formal priorisiert.

4.2 Systematische Recherche, Auswahl der Evidenz

Für die Beantwortung der Schlüsselfrage 10 dieser Leitlinienaktualisierung führte eine erfahrene Informationsspezialistin systematische Recherchen in den Datenbanken MEDLINE und Scopus für den Zeitraum von 1946 bis zum 07.08.2024 durch. Für die Beantwortung der Schlüsselfrage 9, wurde auf den bisherigen Versionen aufgebaut und eine systematische Recherche in den Datenbanken MEDLINE und Embase ab dem letzten Suchdatum am 09.11.2023 bis zum 09.08.2024 durchgeführt.

Die identifizierten Studien wurden jeweils im zweistufigen Verfahren von wissenschaftlich Tätigen in enger Kooperation mit erfahrenen Kliniker*innen gesichtet und ausgewählt. Zunächst wurden per festgelegter Schlüsselfrage gezielt nach randomisiert-kontrollierten Studien recherchiert.

Sofern keine randomisierten-kontrollierten Studien identifiziert werden konnten, wurden nach Möglichkeit aktuelle, qualitativ hochwertige systematische Übersichtsarbeiten herangezogen. Die Qualitätsbewertung der identifizierten systematischen Übersichtsarbeiten erfolgt mit dem Bewertungsinstrument AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews). Bei hoher methodischer Qualität und inhaltlicher Übereinstimmung der definierten Schlüsselfrage, wurden die eingeschlossenen Einzelstudien in Evidenztabellen extrahiert und die Datensynthese, sofern möglich, für die Erstellung eines Evidenzprofils herangezogen. Bei Abwesenheit aktueller systematischer Reviews von hoher Qualität wurden Recherchen nach kontrollierten nicht-randomisierten Interventionsstudien durchgeführt.

Die Ergebnisse der einzelnen Literaturrecherchen, einschließlich Suchdatum, Flow Charts, Evidenztabellen und Bewertungen, sind unter der Überschrift 5 zusammengefasst.

4.3 Datenextraktion und Bewertung des Verzerrungsrisikos

Die identifizierten Studien wurden systematisch in MS Excel Datenextraktionsformulare extrahiert. RCTs wurden mit dem Cochrane Risk of Bias 2 Tool bewertet, nicht-randomisierte Studien wurden mit ROBINS-I oder einer ähnlich geeigneten Checkliste bewertet worden. Meta-analysen wurden mit der Software R erstellt.

4.4 Evidenzklassifikation nach GRADE und Evidence-to-Decision Framework

Die Bewertung der Studien erfolgte endpunktbezogen nach der GRADE (Grading of recommendations assessment, development and evaluation) Methodik. In die GRADE Bewertung gehen das Verzerrungsrisiko der einzelnen Studien (randomisierte Studien bewertet mit dem Cochrane Risk of Bias Tool bzw. nichtrandomisierte Studien mit dem ROBINS I Tool) die Heterogenität der Effektschätzer, die Direktheit der untersuchten Patientenpopulation, Intervention, Vergleich bzw. Endpunkte, die Präzision der Effektschätzer und die Wahrscheinlichkeit eines Publikationsbias ein. Die Bewertung ist aus den Evidenztabellen (Summary of findings tables) im Evidenzbericht ersichtlich. Die Qualität der Evidenz (Vertrauen in die Evidenz) wird nach GRADE eingeteilt in hoch/Moderate/Low/Very low.

Als Basis für die Empfehlungsformulierung wurden definierte Entscheidungskriterien benutzt, basierend auf dem GRADE Evidence to Decision Framework (EtD). Die Bewertung erfolgte in der MAGICapp unter Benutzung der GRADE EtD Ansicht mit den Kriterien: Nutzen/Schaden, Abwägung/Sicherheit der Evidenz, Wertevorstellungen und Präferenzen von Patienten, Ressourcen, Equity (Zugangs- und Versorgungsgerechtigkeit), Akzeptanz und Machbarkeit. Die Kriterien wurden in vorbereitenden Sitzungen gemeinsam von den evidenzaufarbeitenden Kolleg*innen und Vertreter*innen der Leitliniengruppe bearbeitet. Alle Bewertungen für Kriterien, für die keine systematische recherchierte Evidenz vorlag, erfolgten auf Basis von subjektiven Einschätzungen.

5 Resultate nach Schlüsselfrage

Der Evidenzbericht beinhaltet all die Fragen, die bearbeitet wurden, auch wenn nicht alle Fragestellungen in positiven Empfehlungen resultierten.

5.1 Rechercheübersicht

Empfehlung	Recherchedatum V1	Recherchedatum V2	Recherchedatum V3
Schlüsselfrage 1: Paxlovid und SoC vs. SoC alone	18.10.2023	NA	NA
Schlüsselfrage 2: Remdesivir und SoC vs. Remdesivir alone	09.11.2023	NA	NA
Schlüsselfrage 3: Paxlovid oder Remdesivir vs. SoC alone bei SARS-CoV-2 Viruspersistenz	NA	12.04.2024	NA
Schlüsselfrage 4a: Systemische Kortikosteroide	06.10.2023	NA	NA
Schlüsselfrage 4b: Inhalative Kortikosteroide	06.10.2023	NA	NA
Schlüsselfrage 5: Tocilizumab und SoC vs. SoC	13.10.2023	NA	NA
Schlüsselfrage 6: SARS-CoV-2 spezifische monoklonale Antikörper (Literatur nicht verwendet, da Daten aus in Vitro Studien einen Wirkungsverlust bei jetzigen Varianten aufzeigen)	15.10.2023	NA	NA
Schlüsselfrage 7: Anakinra und SoCvs. SoC alone	11.10.2023	NA	NA
Schlüsselfrage 8: Antikoagulation	25.07.2023	NA	NA
Schlüsselfrage 9: Wachbauchlagerung	09.11.2023	NA	09.08.2024
Schlüsselfrage 10: Early vs. late intubation	NA	NA	07.08.2024

5.2 Schlüsselfrage 1: Paxlovid und SoC vs. SoC alone

Autor*innen: Nina Kreuzberger

Es wurde ein systematisches Review zugrunde gelegt, dass jeweils eine Studie zu ambulanten und stationären COVID-19 Patient*innen einschloss.

5.2.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.2.1.1 *Evidenzprofil 1: Outpatients*

Population: Outpatients with confirmed SARS-CoV-2 infection (at high risk of disease progression)

Intervention: Nirmatrelvir / ritonavir plus standard of care

Vergleichsintervention: Placebo plus standard of care

		Absolute effect estimates		Summary

Outcome Timeframe	**Study results and measurements**	placebo + SoC	paxlovid + SoC	**Certainty of the Evidence** (Quality of evidence)	
All-cause mortality, day 28	Relative Risk: 0.04 (CI 95% 0.0 - 0.68) Based on data from 2224 patients in 1 study[1]	**11** per 1000	**0** per 1000	**Low** Due to serious imprecision, Due to serious risk of bias[2]	Paxlovid plus standard of care may decrease all-cause mortality by day 28.
		Difference: **11 less per 1000** (CI 95% 11 less - 4 less)			
All-cause mortality, day 90	Relative risk (CI 95% -)	per 1000	per 1000		No studies were found that looked at all-cause mortality by day 90.
		Difference: **less per 1000**			
Admission to hospital or death, day 28	Relative risk: 0.13 (CI 95% 0.07 - 0.27) Based on data from 2224 patients in 1 studies	**61** per 1000	**8** per 1000	**Low** Due to serious risk of bias, Due to serious indirectness[3]	Paxlovid plus standard of care may decrease admission to hospital or death by day 28.
		Difference: **53 less per 1000** (CI 95% 57 less - 45 less)			
Symptom resolution	Relative risk (CI 95% -)	per 1000	per 1000		No studies were found that looked at symptom resolution.
		Difference: **less per 1000**			
Adverse events, any grade during study period	Relative risk: 0.95 (CI 95% 0.82 - 1.1) Based on data from 2224 patients in 1 studies	**239** per 1000	**227** per 1000	**Moderate** Due to serious risk of bias[4]	Paxlovid plus standard of care perbably has little or no effect on any grade adverse events.
		Difference: **12 less per 1000** (CI 95% 43 less - 24 more)			
Adverse events, grade 3-4[5] during study period	Relative risk: 0.49 (CI 95% 0.34 - 0.69) Based on data from 2224 patients in 1 studies	**83** per 1000	**41** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Paxlovid plus standard of care may decrease the incidence of grade 3 to 4 adverse events.
		Difference: **42 less per 1000** (CI 95% 55 less - 26 less)			
Serious adverse events suring study period	Relative risk: 0.24 (CI 95% 0.15 - 0.41) Based on data from 0 patients in 1 studies	**66** per 1000	**16** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[7]	Paxlovid plus standard of care may decrease the incidence of serious adverse events.
		Difference: **50 less per 1000** (CI 95% 56 less - 39 less)			
Post COVID19 condition	Relative risk (CI 95% -)	per 1000	per 1000		No studies were found that looked at Post Covid19 condition.
		Difference: **less per 1000**			
Quality of life		**Mean**	**Mean**		

				No studies were found that looked at quality of life.

1. Systematic review [40] with included studies: [38] Baseline/comparison intervention Control arm from the reference for intervention arm.
2. Risk of bias: very serious. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Imprecision: very serious. Low number of events;
3. Risk of bias: very serious. Inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Indirectness: very serious. Differences between the outcomes of interest and those reported (COVID-19 related hospitalisation instead of all-cause hospitalisation);
4. Risk of bias: very serious. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status.");
5. undefined
6. Risk of bias: very serious. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Imprecision: very serious. Wide confidence intervals;
7. Risk of bias: very serious. inappropriate analysis („All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status."); Imprecision: very serious. Few SAE other than hospitaliation or death;

5.2.1.2 *Evidenzprofil 2: Inpatients*

Population: Hospitalised patients

Intervention: Paxlovid plus standard of care

Vergleichsintervention: Standard of care alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SoC	Paxlovid + SoC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality, day 28	Relative Risk: 0.63 (CI 95% 0.21 - 1.86) Based on data from 264 patients in 1 study[1] Observation time 28 days	**61** per 1000	**38** per 1000 Difference: **23 less per 1000** (CI 95% 48 less - 52 more)	**Very low** Due to serious indirectness, Due to very serious imprecision[2]	We are uncertain whether paxlovid plus standard of care decreases or increases mortality by day 28.
IMV or death, day 28	Relative risk (CI 95% -)				No studies were found that looked at need for IMV or death by day 28
Discharged alive	Relative risk (CI 95% -)				No studies were found that looked at the number of participants discharged alive.
Serious adverse events	Relative risk (CI 95% -)				

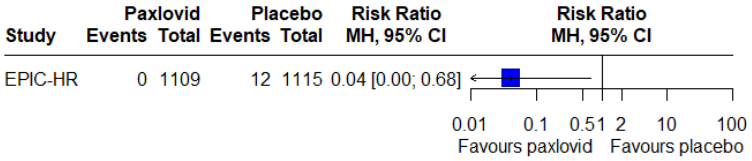
				No studies were found that looked at serious adverse events.
Adverse events	Relative risk (CI 95% -)			No studies were found that looked at adverse events.
Post Covid-19 condition	Relative risk (CI 95% -)			No studies were found that looked at post Covid-19 condition.
Quality of life				No studies were found that looked at quality of life.

1. Systematic review [40] with included studies: [39] Baseline/comparison intervention Control arm from the reference for intervention arm.
2. Indirectness: serious. Differences between the population of interest and those studied: Atypical hospital population, WHO 2-4; Imprecision: very serious. Wide confidence intervals, Low number of patients.

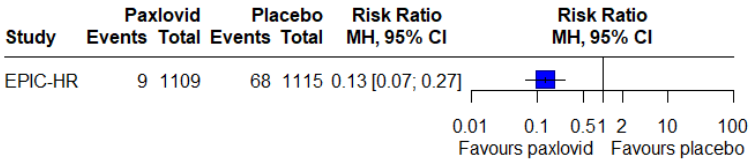
5.2.2 Analysen / Forest Plots

5.2.2.1 *Outpatients*

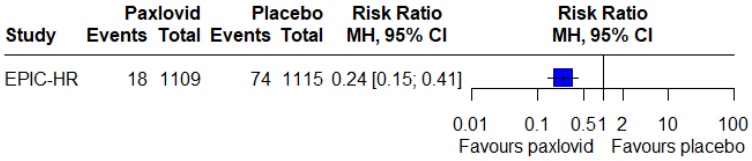
Mortality, day 28



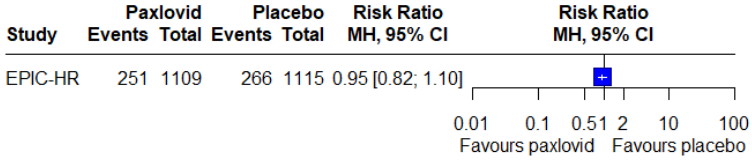
Admission to hospital or death, day 30



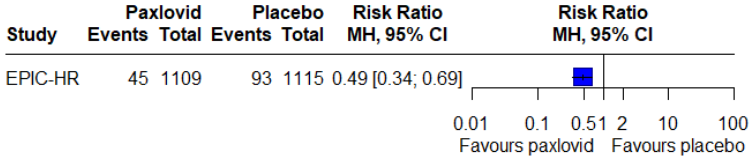
Serious adverse events



Adverse events, any grade

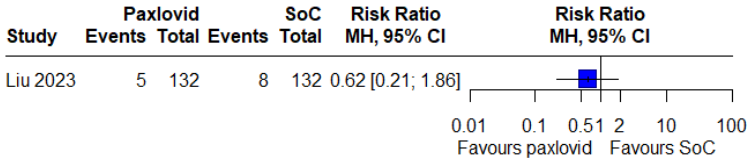


Adverse events, grade 3-4



5.2.2.2 *Inpatients*

Mortality, day 28



5.2.3 Referenzen der eingeschlossenen Studien

5.2.3.1 *RCT-Recherche*

Studien eingeschlossen im Cochrane Review: Reis S, Metzendorf MI, Kuehn R, Popp M, Gagyor I, Kranke P, Meybohm P, Skoetz N, Weibel S. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. Cochrane Database Syst Rev. 2022 Sep 20;9(9):CD015395. doi: 10.1002/14651858.CD015395.pub2. Update in: Cochrane Database Syst Rev. 2023

- Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R, Rusnak JM; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Apr 14;386(15):1397-1408. doi: 10.1056/NEJMoa2118542. Epub 2022 Feb 16. PMID: 35172054; PMCID: PMC8908851.
- Liu J, Pan X, Zhang S, Li M, Ma K, Fan C, Lv Y, Guan X, Yang Y, Ye X, Deng X, Wang Y, Qin L, Xia Z, Ge Z, Zhou Q, Zhang X, Ling Y, Qi T, Wen Z, Huang S, Zhang L, Wang T, Liu Y, Huang Y, Li W, Du H, Chen Y, Xu Y, Zhao Q, Zhao R, Annane D, Qu J, Chen D. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac. 2023 Apr;33:100694. doi: 10.1016/j.lanwpc.2023.100694. Epub 2023 Feb 6. PMID: 36777445; PMCID: PMC9899586.

Keine weiteren RCTs identifiziert.

5.2.3.2 *Kohorten-Recherche*

Nicht weiter verwendet.

5.2.4 Charakteristika der eingeschlossenen Studien

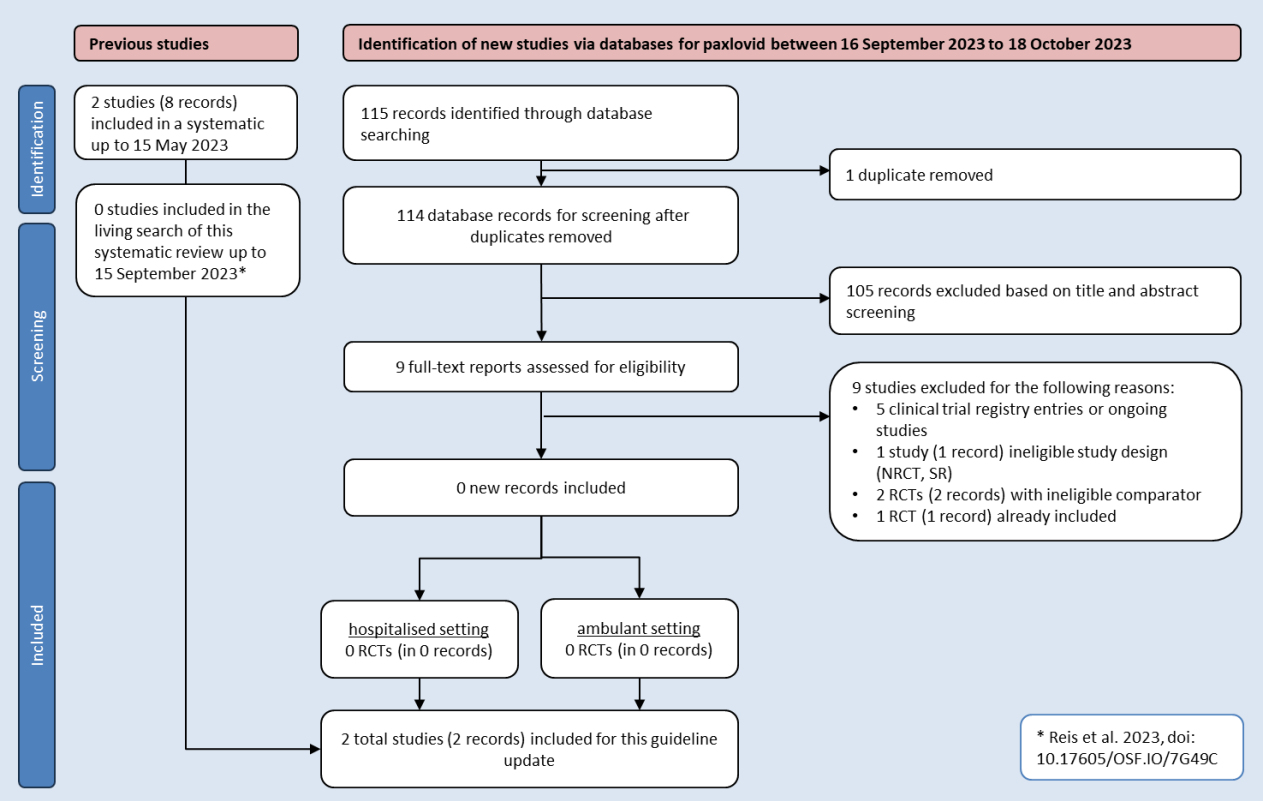
5.2.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodolical Notes	Included publications
Reis 2023 Systematic review with MA	**Study design:** RCTs **Search time frame** From inception to 11 July 2022 **Sources:** · Cochrane COVID-19 Study Register (CCSR) (comprises MEDLINE, Embase, clinicaltrials.gov, ICTRP, medRxiv,	**Intervention A** Nirmatrelvir/ Ritonavir + standard of care **Intervention B** Placebo, standard of care, or any other intervention fro treating COVID-19	2 studies, one inpatient, one outpatient **Outpatient** *N = 2246* *Recruitment:* 16.07.2021 to 09.12.2021 worldwide *Age (median, range, years)* · Exp: 45 (18 to 86) · Plcb: 46.5 (18 to 88) *Sex (% female)* · Exp: 49.5% · Plcb: 48.3% *vaccination status*: 0% *Median time since SO:* · Exp: 3.00 (0.00–7.00) · Plcb: 3.00 (0.00–9.00) *At least one risk factor for severe disease:* All participants **Inpatients** *N = 264* *Recruitment:* 10.04.2022 to 19.05.2022, China	**Comparison 1: outpatients** Number of studies: 1 Number of participants: 2246 **Critical outcomes:** · All-cause mortality (at up tp day 28): HR 0.04 (95% CI 0.00 to 0.68) · All-cause mortality (at up tp day 60): not reported · New need for IMV or death within 28 days: not reported · Admission to hospital or death: HR 0.13 (95% CI 0.07 to 0.27) · Serious adverse events at up to day 28: RR 0.24 (95% CI 0.15 to 0.42) · Adverse events (any grade) at up to day 28: RR 0.95 (95% CI 0.82 to 1.10)	**Methodological quality of included studies assessed using the Risk of bias 2 tool:** *Outpatients:* All outcomes have some concern regarding risk of bias due to an inappropriate per-protocol analysis *Inpatients:* No concerns, only one outcome. **Evidence synthesis:** · ITT, safety population für (serious) adverse events · Random-effects-Model in case of heterogeneity (not applicable, as only one study per comparison)	Hammond 2022 Liu 2023

	CENTRAL) · Scopus · WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** · Confirmed SARS-CoV-2 infection · PEP, PrEP nirmatrelvir/ritonavir · Treatment with nirmatrelvir/ ritonavir · Any dose		*Age (mean, sd years)* · Exp: 71.50 ± 11.61 · Plcb: 69.20 ± 14.43 Sex (% female) · Exp: 45.45% · SoC: 46.97% *vaccination status*: · Exp: 21.21% · SoC: 28.78% *Median time since SO:* · Exp: 3 (1, 5) · SoC: 3 (2, 6) *At least one risk factor for severe disease:* All participants		**GRADE** · Mortality: Low · Admission to hospital or death: low · SAE: Low · AE, any grade, grade 3-4: Moderatee All outcomes downgraded due to serious risk of bias, admission to hospital downgraded due to serious indirectness, SAE for serious imprecsion	

5.2.5 Studienselektion: Flow Chart

5.2.5.1 *Flow chart für die RCT-Recherche*



5.2.6 Literaturrecherche

5.2.6.1 *Literaturrecherche für RCTs*

Date of search for all databases: 18.10.2023			
Database/Register	**Search**	**Update Search**	**Update Search**
CCSR	5 references		
WOS (SCI+ECI) ab 06.10.2023 Scopus	110		
Total	**115**		
Total (after deduplication)	**114**		

Grundlage für diese Fragestellung ist das folgende Living systematische Cochrane Review „Nirmatrelvir combined with ritonavir for preventing and treating COVID-19“ mit regelmäßigen Aktualisierungssuchen (verfügbar unter https://osf.io/7g49c/). Für die vorliegende Version wurde das Dokument vom 27.09.2023 mit Suchdatum bis 15.09.2023 genutzt, die Aktualisierungssuche lief zwischen dem 16.09.2023 und dem 18.10.2023.

Cochrane COVID-19 Study Register (CCSR)

Search string: "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

Results available:

Report results

Study characteristics:

1) "Intervention assignment": “Randomised” OR "Unclear"

2) "Study design": "Parallel/Crossover" OR "Unclear" OR

Scopus (via Elsevier)

TITLE-ABS ("PF-08208;07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*)

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") AND PUBYEAR = 2023

AND (LIMIT-TO (DOCTYPE , "ar"))

5.2.6.2 *Literaturrecherche für Kohortenstudien*

Date of search for all databases: 18.10.2023				
Database/Register	**Search**	**Update Search**	**Update Search**	**Update Search**
CCSR	201 references			
Scopus	138			
WHO COVID-19 DB*	150			
Total	**489**			
Total (after deduplication)	**382 (108 included CT.gov und preprints)**			

*The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.

Cochrane COVID-19 Study Register (CCSR)

Search string**:** "PF-07321332" OR "PF 07321332" OR "PF07321332" or paxlovid* or nirmatrelvir*

Results available:

report results

Study characteristics:

1) "Study design": case series/case control/cohort

Scopus (via Elsevier)

TITLE-ABS ("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND TITLE-ABS ((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*)

AND PUBYEAR = 2022 OR PUBYEAR = 2023

AND (LIMIT-TO (DOCTYPE , "ar"))

("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND ((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*) AND year_cluster:("2022" OR "2023")

5.3 Schlüsselfrage 2: Remdesivir und SoC vs. SoC alone/with Placebo

Autor*innen: Claire Iannizzi

Es wurden insgesamt 12 RCTs identifiziert und eingeschlossen, davon sind 2 RCTs zur milden COVID-19 Erkrankung (ambulante Behandlungssituation) und 10 RCTs zur schweren COVID-19 Erkrankung (stationäre Behandlungssituation). Zudem wurden 18 Kohortenstudien identifiziert, allerdings wurden diese weder bewertet noch die Evidenz aufbereitet.

5.3.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.3.1.1 *PICO 1. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild to Moderatee disease, according to the WHO clinical progression scale (WHO 2 to 3)*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Remdesivir + Standard of Care

Vergleichsintervention: Standard of Care (with or without placebo)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Summary**
		Placebo or Standard of Care alone	Remdesivir + SOC		
Time to symptom alleviation at day 14	Hazard ratio: 1.41 (CI 95% 0.73 - 2.72) Based on data from 126 Patients in 1 study[1]	**250** per 1000	**333** per 1000 Difference: **83 more per 1000** (CI 95% 61 less - 293 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision[2]	We are uncertain whether remdesivir increases or decreases time to symptom alleviation.
All-cause mortality at up to day 28	Relative Risk (CI 95% -) Based on data from 562 patients in 1 study	per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)	**Low** Due to very serious imprecision[3]	There were no events observed, thus it was not possible to determine whether Remdesivir makes a difference in 28-day mortality.
Hospitalization or death by day 28	Relative Risk: 0.28 (CI 95% 0.11 - 0.75) Based on data from 562 patients und 1 study[4]	**64** per 1000	**18** per 1000 Difference: **46 less per 1000** (CI 95% 57 less - 16 less)	**Moderatee** Due to serious imprecision[5]	Remdesivir probably decreases the rate of hospitalisation or death by day 29.

Adverse events (any grade) at up to day 28	Relative Risik: 0.91 (CI 95% 0.76 - 1.1) Based on data from 562 patients in 1 study[6]	**463** per 1000 **421** per 1000 Difference: **42 less per 1000** (CI 95% 111 less - 46 more)	**Moderatee** Due to serious imprecision[7]	Remdesivir probably has little or no difference on the risk of adverse events (any grade) at up to day 28.
Serious adverse events at up to day 28	Relative Risk: 0.29 (CI 95% 0.12 - 0.72) Based on data from 698 patients in 2 studies[8]	**60** per 1000 **17** per 1000 Difference: **43 less per 1000** (CI 95% 53 less - 17 less)	**Low** Due to serious indirectness, Due to serious imprecision[9]	Remdesivir may decrease the risk of serious adverse events at up to day 28.

1. Systematic review [37]. Baseline/comparison intervention Control arm from the reference for intervention arm.
2. Risk of bias: serious. Difference in pre-defined outcome and measurement.; Indirectness: very serious. Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important); Imprecision: very serious. Low number of patients, Wide confidence intervals, Only data from one study;
3. Imprecision: very serious. Only data from one study, Low number of patients;
4. Systematic review [37] with included studies: Gottlieb 2021 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm
5. Imprecision: serious. Wide confidence intervals and optimal information size not met
6. Systematic review [37] with included studies: Gottlieb 2021 Baseline/Vergleichsintervention Kontrollarm aus der Referenz für Interventionsarm
7. Imprecision: serious. Only data from one study, Wide confidence intervals;
8. Systematic review [37] with included studies: [75], Jittamala 2023 (PLATCOV), Gottlieb 2021 Baseline/comparison intervention Control arm from the reference for intervention arm.
9. Indirectness: serious, due to huge overlap with COVID-19 symptoms, already considered in hospitalisation or death; Imprecision: very serious. Low number of patients;

5.3.1.2 *PICO 2. Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Remdesivir + Standard of Care

Vergleichsintervention: Standard of Care (with or without placebo)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** SOC	Remdesivir	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
All-cause mortality at up to day 28	Relative risk: 0.91 (CI 95% 0.83 - 1.01) Based on data from 10171 patients in 5 studies[1]	**138** per 1000	**126** per 1000 Difference: **12 less per 1000** (CI 95% 23 less - 1 more)	**Moderate** Due to serious imprecision[2]	Remdesivir probably makes little or no difference to all-cause mortality at up to day 28.
All-cause mortality at up to day 60	Relative risk: 0.85 (CI 95% 0.69 - 1.05) Based on data from 1281 patients in 1 studies[3]	**235** per 1000	**200** per 1000 Difference: **35 less per 1000** (CI 95% 73 less - 12 more)	**Moderate** Due to serious risk of bias[4]	Remdesivir probably makes little or no difference to all-cause mortality up to 60 days.
	Relative risk: 0.93 (CI 95% 0.84 - 1.03)	**156** per 1000	**145** per 1000	**Moderate** Due to serious risk of bias[6]	Remdesivir probably makes little or no difference to in-

In-hospital mortality at up to day 150	Based on data from 8275 patients in 1 studies[5]	Difference: **11 less per 1000** (CI 95% 25 less - 5 more)		hospital mortality up to 150 days.
Clinical improvement: participants discharged alive at up to day 28	Relative risk: 1.11 (CI 95% 1.06 - 1.17) Based on data from 2514 patients in 4 studies[7]	**617** per 1000 **685** per 1000 Difference: **68 more per 1000** (CI 95% 37 more - 105 more)	**Moderate** Due to serious risk of bias[8]	Remdesivir probably increases the chance of clinical improvement slightly.
Clinical worsening: new need for invasive mechanical ventilation/death at up to day 28	Relative risk: 0.7 (CI 95% 0.52 - 0.94) Based on data from 683 patients in 1 studies[9]	**253** per 1000 **177** per 1000 Difference: **76 less per 1000** (CI 95% 121 less - 15 less)	**Low** Due to serious imprecision, Due to serious risk of bias[10]	Remdesivir may decrease the risk of clinical worsening: new need for invasive mechanical ventilation or death at up to day 28.
Time to hospital discharge	Hazard ratio: 1.06 (CI 95% 0.93 - 1.2) Based on data from 1225 patients in 2 studies[11]	**618** per 1000 **639** per 1000 Difference: **21 more per 1000** (CI 95% 27 less - 67 more)	**Moderate** Due to serious imprecision[12]	Remdesivir probably increases the chance of clinical improvement slightly.
Adverse events (any grade) at day 28	Relative risk: 1.04 (CI 95% 0.92 - 1.18) Based on data from 2498 patients in 4 studies[13]	**579** per 1000 **602** per 1000 Difference: **23 more per 1000** (CI 95% 46 less - 104 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency[14]	We are very uncertain whether remdesivir increases or decreases the risk for adverse events (any grade).
Serious adverse events at day 28	Relative risk: 0.84 (CI 95% 0.65 - 1.07) Based on data from 2498 patients in 4 studies[15]	**273** per 1000 **229** per 1000 Difference: **44 less per 1000** (CI 95% 96 less - 19 more)	**Low** Due to serious risk of bias, Due to serious imprecision[16]	Remdesivir may have little or no effect on the risk of serious adverse events.
Quality of life (EQ-VAS)[17]	Based on data from 208 patients in 1 studies[18]	One study reported the median of the EQ-VAS Quality of life score (patient-reported outcome measure of quality of life on a scale from 0 to 100): Median EQ-VAS was 75.5 (IQR 67.8–85.0) in the remdesivir and 80 (IQR 67.5–86.5) in SoC group (ordered logistic regression OR 0.83, 95% CI 0.49–1.40).	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness[19]	We are very uncertain whether remdesivir has any effect on quality of life.
Long COVID symptoms[20]	Based on data from 208 patients in 1 studies[21]	One study reported that regarding the 21 potential long-COVID symptoms they assessed, there were no statistically significant differences between treatment arms.	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness[22]	We are very uncertain whether remdesivir has any effect on Long COVID symptoms.

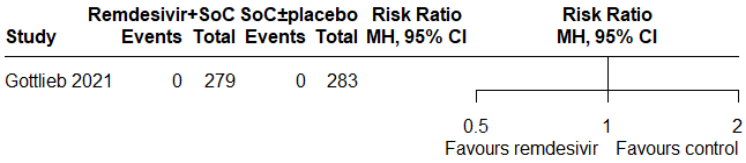
1. Systematic review [36] with included studies: Wang 2020, WHO Solidarity Trial Consortium 2022, Mohiuddin 2022, Spinner 2020, Beigel 2020, [41], [41] Baseline/comparison intervention Control arm from the reference for intervention arm.

2. Risk of bias: none. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; Imprecision: very serious. Because the 95% confidence interval includes both benefits and harms.;
3. Systematic review [36] with included studies: WHO Solidarity Canada 2022 Baseline/comparison intervention Control arm from the reference for intervention arm.
4. Risk of bias: very serious. Incomplete and/or missing outcome data;
5. Systematic review [36] with included studies: WHO Solidarity Trial Consortium 2022 Baseline/comparison intervention Control arm from the reference for intervention arm.
6. Risk of bias: very serious. Selective outcome reporting;
7. Systematic review [36] with included studies: Wang 2020, WHO Solidarity France 2021, Beigel 2020, Spinner 2020 Baseline/comparison intervention Control arm from the reference for intervention arm.
8. Risk of bias: very serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
9. Systematic review [36] with included studies: WHO Solidarity France 2021 Baseline/comparison intervention Control arm from the reference for intervention arm.
10. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Imprecision: very serious. Low number of patients, Only data from one study;
11. Systematic review [36]. Baseline/comparison intervention Control arm from the reference for intervention arm.
12. Imprecision: very serious. Wide confidence intervals;
13. Systematic review [36] with included studies: WHO Solidarity France 2021, Spinner 2020, Wang 2020, Beigel 2020 Baseline/comparison intervention Control arm from the reference for intervention arm.
14. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, one trial stopped earlier than scheduled, resulting in potential for overestimating benefits, due to inappropriate patient population, due to competing risk of death; Inkonsistenz: very serious. The magnitude of statistical heterogeneity was high, with I^2 of 68 %. The direction of the effect is not consistent between the included studies.; Imprecision: very serious. Wide confidence intervals and the 95% confidence interval includes the zero effect line;
15. Systematic review [36] with included studies: WHO Solidarity France 2021, Spinner 2020, Wang 2020, Beigel 2020 Baseline/comparison intervention Control arm from the reference for intervention arm.
16. Risk of bias: very serious. One trial stopped earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to inappropriate patient population, due to competing risk of death, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.; Imprecision: very serious. Wide confidence intervals and the 95% confidence interval includes both benefits and harms.;
17. EQ-VAS: patient-reported outcome measure of quality of life on a scale from 0 to 100
18. Primary study reference [42].
19. Risk of bias: very serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the outcomes of interest and those reported (e.g short-term/surrogate, not patient-important); Imprecision: very serious. Only data from one study;
20. Infection affected quality of life in the last month as: 0 = No symptoms of infection, 1 = Slight harm, 2 = Moderatee harm, 3 = Severe harm
21. Primary study references [42].
22. Risk of bias: very serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the outcomes of interest and those reported (e.g short-term/surrogate, not patient-important); Imprecision: very serious. Only data from one study;

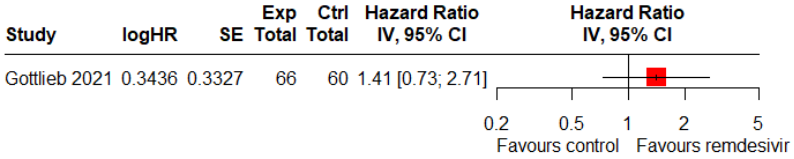
5.3.2 Analysen / Forest Plots

5.3.2.1 *PICO 1. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild to Moderatee disease, according to the WHO clinical progression scale (WHO 2 to 3)*

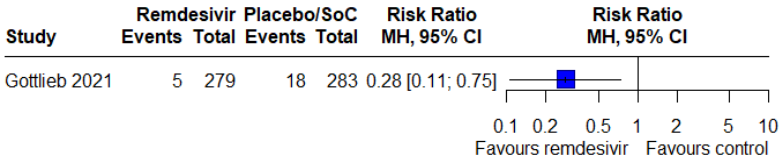
All-cause mortality at up to day 28



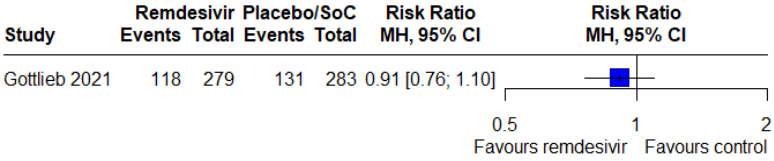
Time to symptom alleviation at day 14



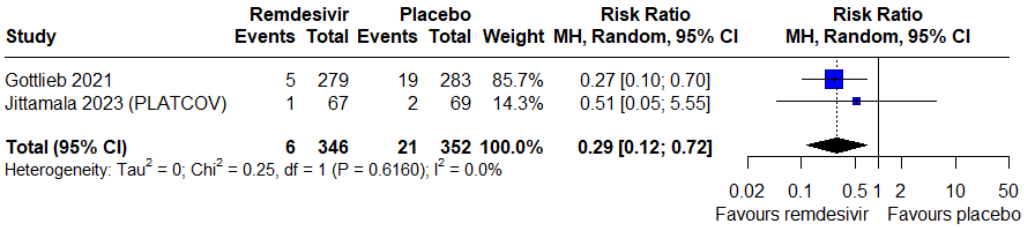
Hospitalization or death by day 28



Adverse events (any grade) at up to day 28

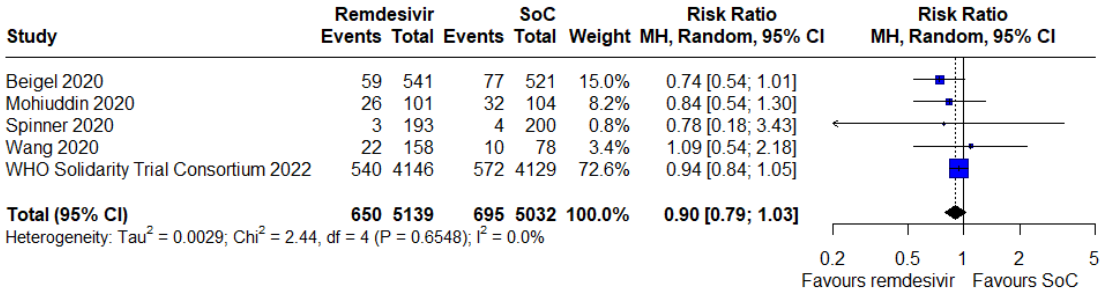


Serious adverse events at up to day 28

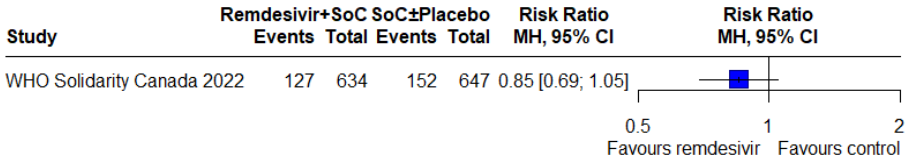


5.3.2.2 *PICO 2. Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)*

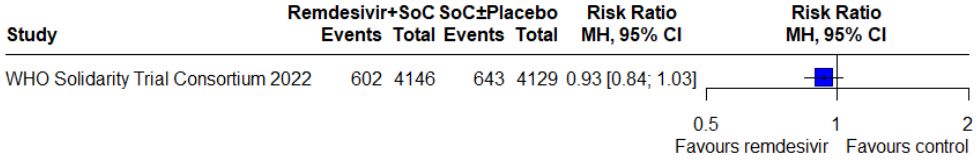
All-cause mortality at up to day 28



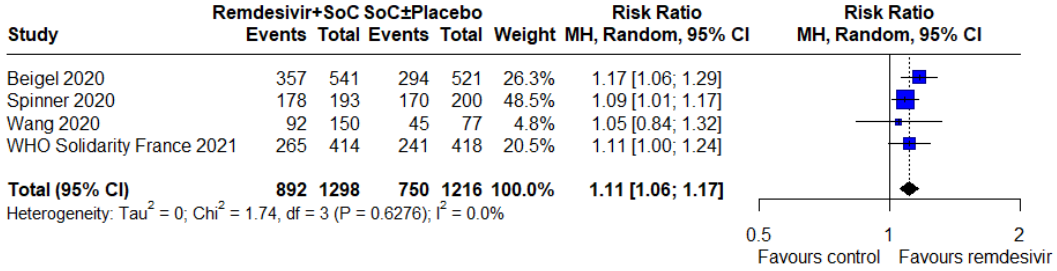
All-cause mortality at up to day 60



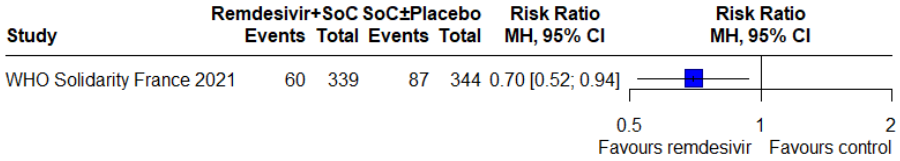
In-hospital mortality at up to day 150



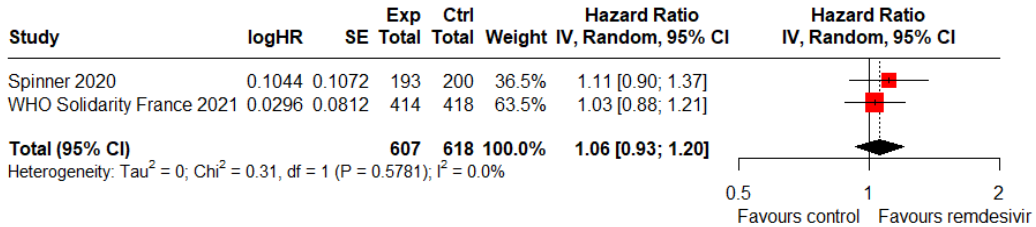
Clinical improvement: participants discharged alive at up to day 28



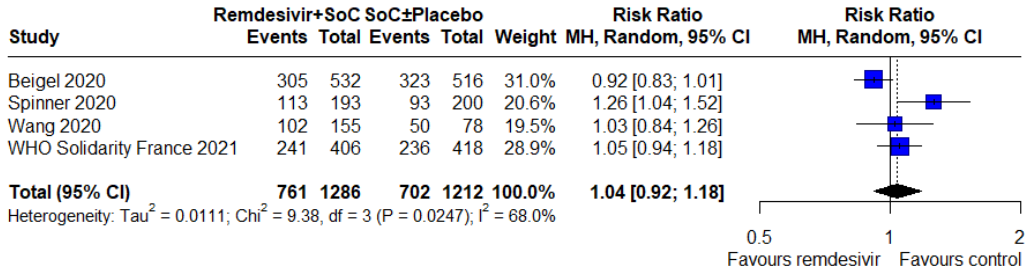
Clinical worsening: new need for invasive mechanical ventilation/death at up to day 28



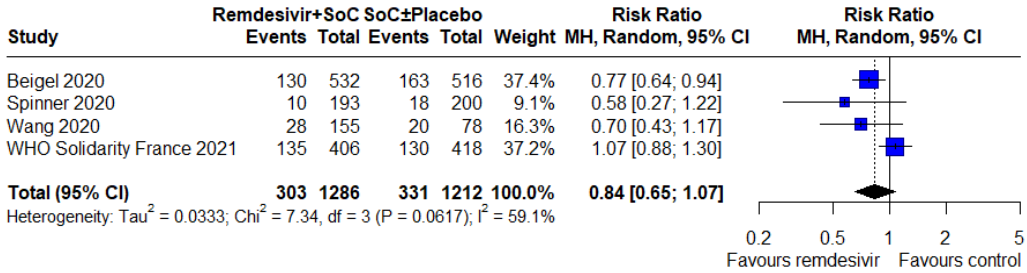
Time to hospital discharge



Adverse events (any grade) at day 28



Serious adverse events at day 28



5.3.3 Referenzen der eingeschlossenen Studien

- Grundeis F, Ansems K, Dahms K, Thieme V, Metzendorf M-I, Skoetz N, et al. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev 2023;1(1):CD014962.
- Jittamala P, Schilling WHK, Watson JA, Luvira V, Siripoon T, Ngamprasertchai T, et al. Clinical Antiviral Efficacy of Remdesivir in Coronavirus Disease 2019: An Open-Label, Randomized Controlled Adaptive Platform Trial (PLATCOV). The Journal of infectious diseases 2023;228(10):1318-1325.
- Mohiuddin Chowdhury ATM, Kamal A, Abbas KU, Talukder S, Karim MR, Ali MA, et al. Efficacy and Outcome of Remdesivir and Tocilizumab Combination Against Dexamethasone for the Treatment of Severe COVID-19: A Randomized Controlled Trial. Frontiers in pharmacology 2022;13:690726.
- Nevalainen OPO, Horstia S, Laakkonen S, Rutanen J, Mustonen JMJ, Kalliala IEJ, et al. Effect of remdesivir post hospitalization for COVID-19 infection from the randomized SOLIDARITY Finland trial. Nature communications 2022;13(1):6152.

5.3.4 Charakteristika der eingeschlossenen Studien

5.3.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

5.3.4.2 *PICO 1. Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild to Moderatee disease, according to the WHO clinical progression scale (WHO 2 to 3)*

Reference / Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodischical Notes	Included publications
Grundeis, 2023a Systematic review with MA	**Study design** Living systematic review **Search time frame** Inception of each database to 31.05.2022 **Sources:** · Cochrane COVID-19 Study Register (CCSR) (PubMed, Embase, ClinicalTrials, WHO ICTRP, medRxiv, CENTRAL) · Web of Science Clarivate (Science Citation Index Expanded, Emerging Sources Citation Index) · WHO COVID-19 Global literature on coronavirus disease	**Intervention A** · Remdesivir and standard care for the treatment of SARS-CoV-2 infection **Intervention B** · Standard care (plus/minus placebo).	1 study on 562 patients **Descriptive statistics:** Setting: outpatient Age: mean age 50 years, included adolescents younger than 18 Gender: 52.10% male Severity of illness at beginning: mild	**<u>Comparison X:</u>** Number of studies: 1 Number of participants: 562 **Critical outcomes:** · All-cause mortality (at up to day 28): no events observed, therefore not estimable N=562 in 1 RCT) · Clinical improvement: symptom alleviation at up to day 14: 250 per 1000 in comparison group, Difference: 61 fewer to 289 more (HR 1.41, CI 95% 0.73 to 2.71, N=126 in 1 RCT, very low certainty) · Clinical worsening: admission to hospital or death at up to day 28: 64 per 1000 in comparison group, Difference: 57 fewer to 16 fewer (RR 0.28, CI 95% 0.11 to 0.75, N=562	**Methodological quality of included studies assessed using GRADE tool:** **Evidence synthesis:** · ITT, safety population für (serious) adverse events · Random-effects-Modell due to heterogeinity of population **GRADE** · All-cause mortality at up to day 28: /no events · Clinical improvement: symptom alleviation at up to day 14: **low** due to high risk	Gottlieb 2021

	Eligibility criteria **Study type:** randomized controlled trials · **Participants:** adults with a confirmed diagnosis of COVID-19 (as described in the study) without exclusion of any studies based on gender, ethnicity, disease severity, or setting. · The review excluded studies evaluating remdesivir against other coronavirus diseases such as SARS or MERS, or other viral diseases, such as ebola. · If studies enrolled populations with or exposed to mixed viral diseases, the review authors had planned to only include these if study authors provided subgroup data for SARS-CoV-2 infection.	· Standard care in both arms should be similar.		in 1 RCT, Moderatee certainty) · Quality of life: nicht berichtet · Serious adverse events at up to day 28: 67 per 1000 in comparison group, Difference: 60 fewer to 20 fewer (RR 0.27, CI 95% 0.10 to 0.70, N=562 in 1 RCT, low certainty) · Adverse events (any grade) at up to day 28: 463 per 1000 in comparison group, Difference: 111 fewer to 46 more (RR 0.91, CI 95% 0.76 to 1.10, N=562 in 1 RCT, Moderatee certainty) **Additional outcomes:** · Severity: Non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19	of bias and imprecision (wide CIs) · Clinical worsening: admission to hospital or death at up to day 28: Moderatee due to imprecision (wide CIs) · Serious adverse events: low due to imprecision (wide CIs) and indirectness · Adverse events (any grade): Moderatee due to imprecision (wide CIs)	

5.3.4.2.1 PICO 2. Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodischical Notes	Included publications
Grundeis, 2023b Systematic review with MA	**Study design** Living systematic review **Search time frame** Inception of each database to 31.05.2022 **Sources:** · Cochrane COVID-19 Study Register (CCSR) (PubMed, Embase, ClinicalTrials, WHO ICTRP, medRxiv, CENTRAL) · Web of Science Clarivate (Science	**Intervention A** · Remdesivir and standard care for the treatment of SARS-CoV-2 infection **Intervention B** · Standard care (plus/ minus	8 studies on 10656 patients **Descriptive statistics:** Setting: hospitalized Age: mean age 60.9 years Gender: 65.0% male Severity of illness at beginning: Moderatee – high/critical	**<u>Comparison X:</u>** · **NUMBER OF STUDIES: 8** · **NUMBER OF PARTICIPANTS: 10656** **Critical outcomes:** · All-cause mortality (at up to day 28): 108 per 1000 in comparison group, Difference: 8 fewer per 1000 (RR 0.93, CI 95% 0.81 to 1.06, N=7142 in 4 RCTs, I^2 = 0%, Moderatee certainty) · All-cause mortality (at up to day 60): 235 per 1000 in comparison group, Difference: 35 fewer per 1000 (RR 0.85, CI 95% 0.69 to 1.05, N=1281 in 1 RCT, Moderatee certainty) · In-hospital mortality (at up to day 150): 156 per 1000 in comparison group, Difference: 11 fewer per	**Methodological quality of included studies assessed using GRADE tool:** **Evidence synthesis:** · ITT, safety population für (serious) adverse events · Random-effects-Modell due to heterogeinity of population **GRADE** · All-cause mortality at up to day 28: Moderatee due to imprecision (wide CIs) · All-cause mortality at up to day 60: Moderatee due to	Beigel 2020 Mahajan 2021 Spinner 2020 Wang 2020 WHO Solidarity Canada 2022 WHO Solidarity France 2021 WHO Solidarity Norway 2021 WHO Solidarity Trial Consortium 2022

	Citation Index Expanded, Emerging Sources Citation Index) · WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** **Study type:** randomized controlled trials **Participants:** · adults with a confirmed diagnosis of COVID-19 (as described in the study) without exclusion of any studies based on gender, ethnicity, disease severity, or setting. · The review excluded	placebo). · Standard care in both arms should be similar.		1000 (RR 0.93, CI 95% 0.84 to 1.03, N=8275 in 1 RCT, Moderatee certainty) · Clinical improvement participants discharges alive (at up to day 28): 617 per 1000 in comparison group, Difference: 68 more per 1000 (RR 1.11, CI 95% 1.06 to 1.17, N=2514 in 4 RCTs, I^2 = 0%, Moderatee certainty) · Clinical worsening: new need for IMV or death within 28 days: 544 per 1000 in comparison group, Difference: 135 fewer per 1000 (HR 0.67, CI 95% 0.54 to 0.82, N=1734 in 2 RCTs, I^2 = 0%, Moderatee certainty) · Adverse events (any grade) at up to day 28: 579 per 1000 in comparison group, Difference: 23 more per 1000 (RR 1.04, CI 95% 0.92 to 1.18, N=2498 in 4 RCTs, I^2 = 68%, low certainty) · Serious adverse events at up to day 28: 273 per 1000 in comparison group, Difference: 44 fewer per 1000 (RR 0.84, CI 95% 0.65 to 1.07, N=2498 in 4 RCT, I^2 = 59%, low certainty) **Additional outcomes:**	imprecision (optimal information size not reached) · In-hospital mortality: Moderatee due to high risk of bias (selective reporting) · Clinical improvement participants discharges alive: Moderatee due to high risk of bias (no blinding) · Clinical worsening: new need for IMV or death: Moderatee due to high risk of bias (no blinding) · Serious adverse events: low die to imprecision (wide CIs) and high risk of bias (no blinding) · Adverse events (any grade): low due to imprecision (wide CIs) and high risk of bias (no blinding)	

	studies evaluating remdesivir against other coronavirus diseases such as SARS or MERS, or other viral diseases, such as ebola · If studies enrolled populations with or exposed to mixed viral diseases, the review authors had planned to only include these if study authors provided subgroup data for SARS-CoV-2 infection.			· All-cause mortality, time to event: HR 0.88, 95% CI 0.67 to 1.16, N=6513 in 2 RCTs, I^2 = 57%) · Quality of life: not reported · Adverse events grade 3 to 4, at up to day 28: 39 fewer per 1000 (RR 0.92, 95% CI 0.84 to 1.01, N=2498 in 4 RCTs, I^2 = 0%) · Ventilator-free days: mean difference 1.90, 95% CI 0.61 to 3.19; P value = 0.004; N=1281 in 1 RCT		

5.3.4.3 *Charakteristika der zusätzlich eingeschlossenen Studien*

5.3.4.3.1 Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Jittamala 2023 (PLATCOV) RCT Platform trial	**Sample size:** N = 131 pts. (337 pts. Planned: 136 Remdesivir or SOC alone and 201 for other interventions) **Enrolment period:** 30.09.2021 to 10.06.2022 (remdesivir enrollment was stopped as the prespecified success margin had been reached) **Inclusion criteria:** · Previously healthy adults aged between 18 and 50 years if they had had early symptomatic COVID-19 (i.e., reported symptoms for ≤4 days), oxygen saturation ≥96%, were unimpeded in activities of daily living, and gave fully informed consent. · SARS-CoV-2 positivity was defined either as a nasal lateral flow antigen test that became positive within 2 minutes	**Experimental:** · intravenous remdesivir plus optimized standard of care (SOC) · Dose: over 60 minutes (reconstituted & added to 250 mL 0.9% saline) in an initial adult dose of 200 mg, followed by 100 mg once daily for 4 days to complete a 5-day course · N = 67 **Control:** · optimized standard of care (SOC) alone · N = 64	Viral clearance: expressed as a slope coefficient and estimated under a Bayesian hierarchical linear model fitted to the daily log10 viral load measurements between days 0 and 7 (18 measurements per patient), using weakly informative priors and treating non-detectable viral loads (cycle threshold value ≥40) as left censored	Relative to the control arm, clearance of oropharyngeal virus in patients randomized to remdesivir was 42% faster (95% CrI, 18%–73%; probability of >12.5% acceleration: 0.99). The median estimated viral clearance half-lives under the linear model were 12.8 (range, 4.8–50.0) hours in the remdesivir arm and 18.0 (range, 3.6–46.7) hours in the contemporaneous control arm	**For all outcomes:** 1) Randomisation and allocation concealment: (**low risk of bias**) 2) Deviations from the indented interventions, Blinding: **(low)** 3) Missing data outcome, Attrition bias: (**low**) **Outcome-specific:** 4) Outcome measurement: open label **(some concerns)** 5) Selective reporting: No protocol available (**some concerns**) --- 6) Overall: **some concerns**
			All cause hospitalization for clinical deterioration (day 28)	Not reported	
			Adverse events >/= grade 3	Exp: 1/67 Ctrl: 3/69	
			Serious adverse events	Exp: 1/67 Ctrl: 3/69 Two patients in the control arm and 1 in the remdesivir arm had asymptomatic raised creatinine phosphokinase levels (>10 times upper limit of normal) attributed to COVID-19–related skeletal muscle	

	(STANDARD Q COVID-19 Ag Test, SD Biosensor, Suwon-si, Korea) or a positive polymerase chain reaction (PCR) test within the previous 24 hours with a cycle threshold value <25 (all viral gene targets), both suggesting high viral loads. **Days since symptom onset (mean, SD):** · Exp: 2.4 (0.8) · Ctrl: 2.2 (0.7) **<u>Characteristics</u>** **Age (mean, SD)** · Exp: 30.1 (8.2) · Ctrl: 30.1 (6.5) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR			damage. There were no treatment-related SAEs.	

5.3.4.3.2 Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Nevalainen 2022 (Solidarity Finland) RCT, NCT04978259	**Sample size:** N baseline = 208 pts. (208 pts. planned) N after 1 years = 181 **Enrolment period:** · 23 July 2020 to 27 January 2021 **Inclusion criteria:** · Adult patients, 18 years and older · Laboratory-confirmed SARS-CoV-2 infection · Admitted to the hospital ward or the intensive care unit (ICU) · Patient provides written informed consent prior to initiation of the study OR close relative/legal representative provides written informed consent prior to initiation of the study according to the presumed will of the patient when patient is unable to give consent. · No anticipated transfer within 72 hours to a non-study hospital **<u>Characteristics baseline</u>** **Age (mean, SD)**	**Experimental:** · intravenous remdesivir plus optimized standard of care (SOC) · Dose: 200 mg on 1st day and 100 mg per day until discharge or for a maximum duration of 10 days · N = 114 **Control:** · optimized standard of care (SOC) alone · N = 94	All-cause mortality (at up to 1 year follow-p)	RR 0.82 (0.25 – 2.76) Exp : 5/98 (4.4%) Ctrl :5/83 (5.3%);	**For all outcomes:** 1) Randomisation and allocation concealment: (**low risk of bias**) 2) Deviations from the indented interventions, Blinding: **(low)** 3) Missing data outcome, Attrition bias: (**low**) **Outcome-specific:** 4) Outcome measurement: **Mortality or registry outcomes → low** **Self-reported outcomes → some concerns** 5) Selective reporting: (**low**) ----------
			Recovering from COVID-19 infection	RR 0.94 (0.47–1.90) Exp : 85% Ctrl : 86%	
			Clinical worsening: new need if IMV or death	Not reported	
			Admission to ICU or death	Not reported	
			Adverse events: Fatique	No or slight fatigue (1–2): Exp: 74 (75.5) Ctrl: 60 (72.2) Moderatee or severe fatigue (3–4): RR 0.88 (0.54 – 1.44) Exp: 24 (24.5) Ctrl: 23 (27.7)	
			Excertional dyspnea	RR 0.61 (0.20 – 1.85) Exp : 5% Ctrl : 8%	
			Long COVID symptoms	Narrative: Regarding the 21 potential long-COVID symptoms, there were no statistically significant differences between treatment arms	
			QoL (median EQ-VAS)	OR 0.83 (0.49 – 1.40) Exp:75.5 (IQR 67.8–85.0) Ctrl: 80 (IQR 67.5–86.5) in SoC group	

	· Exp: 57.2 (13.5) · Ctrl: 59.7 (13.2) **Severity** · Rdv: 26% WHO 4, 74% >/=WHO 5 (any oxygen), 10.5% >/=WHO6 (ICU) · Ctrl: 21% WHO4, 79% >/=WHO 5 (any oxygen), 11.7% >/=WHO6 (ICU) **Received dexamethasone** · Exp: 79 (69.3)	N mortality analysis = 191 (Exp. 103, Ctrl. 88) included in mortality analysis N 1 year follow-up analyses = 181 (Exp. 98, Ctrl. 83) (mind. eine Dosis und ausgewertet)	QoL (EQ-5D-5L)	Mobility, walking: RR 1.03, 95% CI 0.54–1.96 Self-care, washing or dressing oneself: RR 0.51, 95% CI 0.13–2.08 Usual activities, e.g., work, study, housework, family or leisure activities: RR 0.71, 95% CI0.32–1.55 Pain or discomfort: RR 0.85 (0.44 – 1.63) Anxiety or depression: RR 1.27 (0.47 – 3.42)	6) Overall: **Low/some concerns**

	• Ctrl: 72 (76.6) **<u>Characteristics after 1 years</u>** **Age (mean, SD)** Exp: 57.7 (12.9) • Ctrl: 59.4 (13.0) **Severity** • Exp: 25.5% WHO 4, 74.5% <WHO 5 (any oxygen), 10.2% <WHO6 (in ICU) • Crtl: 18.1% WHO4, 81.9% <WHO 5 (any oxygen), 12% <WHO6 (in ICU) **Received dexamethasone** • Exp: 69 (70.4) • Ctrl: 61 (73.5) ***<u>Comorbidities (</u>*<u>baseline pop)</u> **Any** • Exp: NR • Ctrl: NR **Diabetes n (%):** • Exp: 20 (17.5) • Ctrl: 16 (17.0) **BMI (mean, SD)** • Exp: 31.5 (6.35)				

	• Ctrl: 29.6 (6.0) **Hypertension** • Exp: NR • Ctrl: NR **Cardiovascular disease** • Exp: NR • Ctrl: NR **Lung diseases** • Exp: NR • Ctrl: NR **Immunosuppressed** • Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: NR • Ctrl: NR ***Comorbidities (*after 1 year pop)** **Diabetes n (%):** • Exp: 25 (25.5) • Ctrl: 15 (18.1) **BMI (mean, SD)** • Exp: 31.7 (6.09) • Ctrl: 29.9 (6.01)				

Mohiuddin 2022 RCT, NCT04678739	**Sample size:** N = 208 pts. randomized (291 pts. planned) **Enrolment period:** NR Bangladesh **Inclusion criteria:** · Severe COVID-19 patients require hospitalization under HDU/ICU. The SARS-CoV-2 infection will be confirmed by RT PCR / CT Chest in every case. 16 Years to 80 Years (Child, Adult, Older Adult) **Exclusion Criteria:** · Participants with uncontrolled clinical status who were hospitalized from the before. · Contraindication / possible drug interaction. · Participants who have any severe and/or uncontrolled medical conditions like, Severe ischemic heart disease, epilepsy, malignancy, Pulmonary/renal/hepatic disease, AIDS, Pulmonary TB,	**Experimental:** · Remdesivir 100 IV Infusion as a lyophilized powder · Dose: 5 mg/kg (<40 kg) or 200 mg (>40 kg) on day 1 and then 2.5 mg/kg (<40 kg) or 100 mg (>40 kg) daily] + tocilizumab [8 mg/kg up to 800 mg highest 12 h apart · N = 104/101 (3 withdraw themselves from the study)	All-cause mortality (day 30)	Exp: 26/101 (25.74%) Ctrl: 32/104 (30.76%)	**For all outcomes:** 1) Randomisation and allocation concealment: Allocation concealment method not described. (**some concerns**) 2) Deviations from the indented interventions, Blinding: **(low)** 3) Missing data outcome, Attrition bias: (**low**) **Outcome-specific:** 4) Outcome measurement: Open Label, but some outcomes are objective **Mortality or other "objectively" measured outcomes (hospital stay, clinical failure) → low** 5) Selective reporting: not enough information, as no protocol published
			Time to Clinical Improvement (TTCI):	Exp: 9.41 ± 5.38; 3–32 days Ctrl: 14.21 ± 5.694; 6–28 days	
			Duration of ICU Stay (mean, SD)	Exp : 7.68 ± 5.45; 1–27 days Ctrl : 10.59 ± 5.453; 2–42 day	
			Time to Recovery	Exp: 9.41 ± 5.38; 3–32 days Ctrl : 14.21 ± 5.694; 6–28 days	
			Hospital stay/duration of hospitalisation	Exp : 10.02 ± 6.277; 1–35 days Ctrl : 14.48 ± 8.882; 3–42 days	
			Rate of daily Supplemental Oxygen Use	Not reported	
			Time to Clinical Failure	Exp: 6.88 ± 6.139; 1–27 days Ctrl: 10.38 ± 12.27; 3–42 days	

	pregnancy, Corpulmonale, and etc. **Time since symptom onset (median, range):** · NR **<u>Characteristics</u>** **Age (mean, SD)** · Exp: 56.24 ± 15 · Ctrl: 57.04 ± 15.15 **Severity**: ICU patients ***<u>Comorbidities</u>*** **Any** · Exp: 61 (58.7%) · Ctrl: 46 (44.2%) **Diabetes:** · Exp: NR · Ctrl: NR **BMI (mean, SD)** · Exp: 23.6± 5.6 · Ctrl: 22.9 ± 5.8 **Hypertension (MAP(Mean arterial pressure in mm of Hg))** · Exp: 86.16 ± 13.55 · Ctrl: 86.26±12.19	**Control:** · dexamethasone 6 mg/day · N = 101 N 205= (mind. eine Dosis und ausgewertet)	Adverse events	Not reported	(**some concerns**) --- 6) Overall: **some concerns**
			QoL	Not reported	

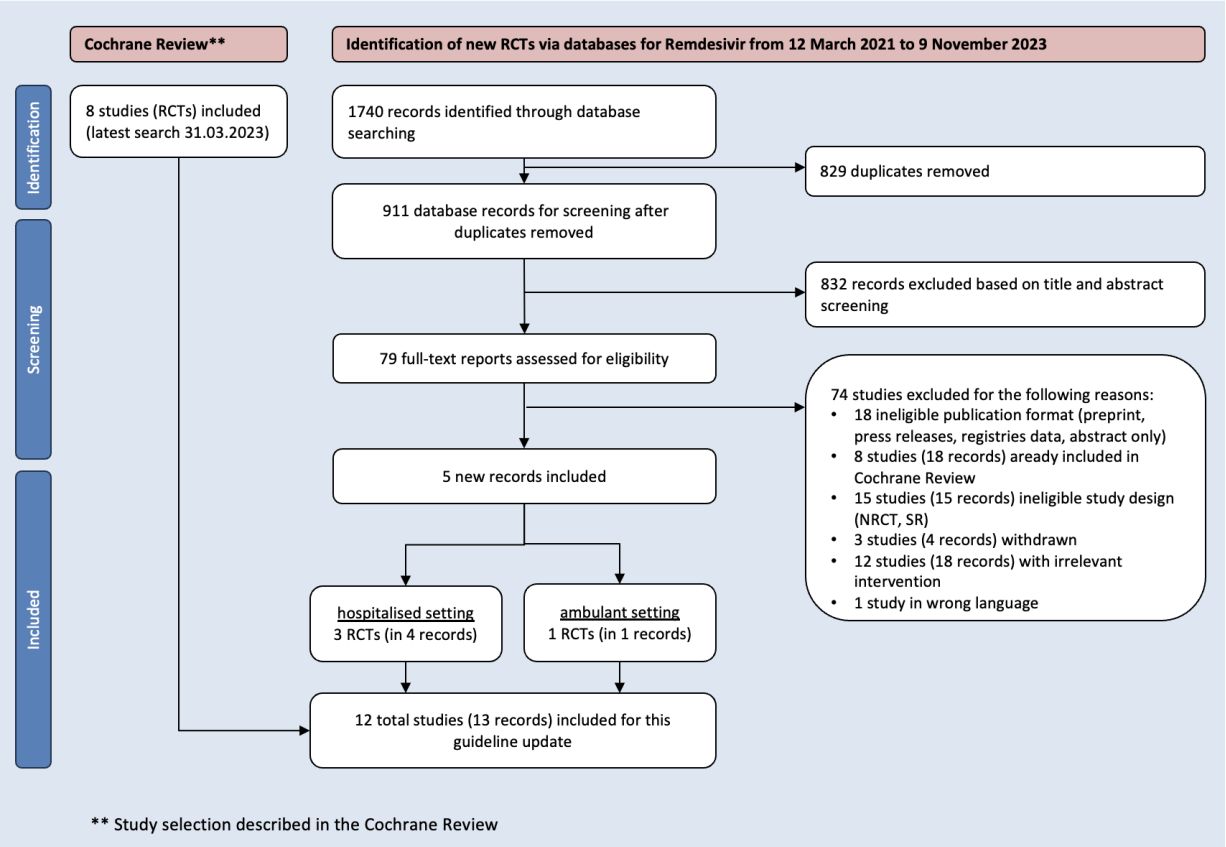
	Cardiovascular disease · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease** · Exp: NR · Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Sarham, 2022 RCT	**Sample size:** N = 108 pts. (108 pts. planned) **Enrolment period:** 01.10.2020 to 10.03.2021 Egypt **Inclusion criteria:** · Patients included in the study who admitted to intensive care unit with confirmed COVID-19 infection through polymerase chain reaction (PCR); after one week of home isolation or after 7 days of inpatient isolation with significant clinical manifestation of systematic hyper inflammation defined as rapid deterioration in oxygen saturation (SaO2) for less than 92% at ambient air or respiratory rate (RR) for more than 30, or PaO2/FiO2 ratio for less than 250; or in radiological findings of CT chest according to CO-RADS classification defined as worsening of lung involvement as an increase in the number and /or expansion of pulmonary areas of consolidation, need for increased FiO2 to maintain stable O2 saturation or worsening O2 saturation of >3% with steady FiO2, as	**Experimental (TCZ-RMV):** · intravenous remdesivir + Tocilizumab (400 mg–800 mg every 24 h for only two doses) · Dose: 200 mg on day 1 followed by 100 mg per day infused over 60 min for 5 days · N = 52 **Control (TCZ-HCQ):** · IV Tocilizumab 400 mg–800 mg every 24 h for only two doses and hydroxychloroquine 400 mg twice daily at day 1 then 200 mg twice daily for 5 days · N = 56	All-cause mortality (no time indication)	Exp: 15 (28.8%) Ctrl: 12 (21.4%), p= 0.06	**For all outcomes:** 1) Randomisation and allocation concealment: Randomization and concealment allocation unclear "Simple randomization was made by allocating patients using a table of random numbers." The study is described as "prospective randomized cohort study". (**come concerns**) 2) Deviations from the indented interventions, Blinding: **(low)** 3) Missing data outcome, Attrition bias: (**low**) **Outcome-specific:** 4) Outcome measurement: Open Label, but some outcomes are objective
			Clinical improvement: discharged alive (day 30)	Not reported	
			Patient discharge after improvememt (no time indication)	Exp: 37 (71.2%) Ctrl: 44 (78.6%), p= 0.4	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Therapeutic failure	Exp: 16 (30.8%) Ctrl: 15 (26.8%)	
			Length of hospitalization (days)	Exp: 8 (5–12) Ctrl: 10 (6–16), p= 0.4	
			Adverse events	Not reported	
			QoL	Not reported	

	well as elevation on inflammatory marker C-reactive protein (CRP, ≥100 mg/L) or ferritin (≥900 ng/mL) and lactate dehydrogenase (LDH, >220 U/L) **Time since symptom onset (median, range): NR** **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 61(52−70) · Ctrl: 53(46−68) **Severity** · Exp: 9(17.3%): Supplemental oxygen at entry = WHO 5-6 · Crl: 49(87.5%): Supplemental oxygen at entry = WHO 5-6 · Exp: 43(82.7%): Mechanical ventilation need = WHO 7 · Crl: 25(44.6%): Mechanical ventilation need = WHO 7 · Crl: 44(78.6%): ICU admission >WHO 5 · Exp: 50(96.2%): ICU admission >WHO 5 ***<u>Comorbidities</u>*** **Any** *(2 or more comorbidities)* · Exp: 26(50%) · Ctrl: 30(53.6%) **Diabetes:** · Exp: 25(48.1%) · Ctrl: 26(46.4%) **Obesity (BMI ≥30 kg/m²)** · Exp:	N = 108 (mind. eine Dosis und ausgewertet)			**Mortality or other "objectively" measured outcomes → low** 5) Selective reporting: not enough information, as no protocol published and in the clinical trial registry, outcomes were not pre-defined (**some concerns**) --- 6) Overall: **some concerns**

	• Ctrl: **Hypertension** • Exp: 29(55.8%) • Ctrl: 37(66.1%) **Cardiovascular disease** *Ischemic heart disease* • Exp: 7(13.5%) • Ctrl: 16(28.6%) *Heart failure* • Exp: 1(1.9%) • Ctrl: 3(5.4%) **Lung diseases** *Asthma* • Exp: 4(7.7%) • Ctrl: 10(17.9%) **Immunosuppressed** • Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: 3(5.8%) • Ctrl: 2(3.6%)				

5.3.5 Studienselektion: Flow Chart



5.3.6 Literaturrecherche

Für Cochrane Review und LL COVID

Database/Register	Search 12.03.2021	Update Search 09.10.2023
CCSR	**156 references** (109 studies)	**583 references (295 studies)**
Scopus	**329**	**871**
WHO COVID-19 DB*	**323**	**340**
Total	**808**	***1740***
Total (after deduplication)	**724**	***911 (zusätzlich noch 115 preprints, 148 trial registry entries***

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Für Ceosys nur in CCSR bis 12.03.2021

Für COVID LL bis 09.10.2023

Suchstrategien:

Cochrane COVID-19 Study Register

Search string:

remdesivir* OR GS5734 OR "GS 5734" OR veklury*

Study characteristics:

1) "Intervention assignment": "Randomised" OR "Unclear"
2) "Study design": "Parallel/Crossover" OR "Unclear" OR "Other"

Scopus Seit 09.10.2023 anstatt von Web of Science

TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS (remdesivir* OR gs5734 OR "GS 5734" OR veklury*)

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

AND PUBYEAR > 2019 AND PUBYEAR < 2024 AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(remdesivir* OR GS5734 OR "GS 5734" OR veklury) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

5.3.6.1 *Literaturrecherche für Kohortenstudien*

Database	Search 31.08.2022, update search 12.10.2023	
CCSR	246	785 references of 759 studies
WOS (SCI+ECI) ab 12.10.23 Scopus	204	443
WHO COVID-19 DB*	219	249
Total	669	1447
Total (after deduplication)	513	825

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued*

Cochrane COVID-19 Study Register

Search strings:

remdesivir* or GS5734 or "GS 5734" or "GS-5734" or veklury

results available: report results

study design: case series/case control/cohort; created: 1 Jan '22 - 12 Oct '23

Web of Science (Core Collection) – Science Citation Index und Emerging Sources Citation Index

Search strings:

#1 TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#2 (TI=((remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*))) OR AB=((remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*))

#3 (TI=((control AND (group* OR study)))) OR AB=((control AND (group* OR study)))

#4 (TI=(((time AND factors) OR program OR survey* OR ci OR cohort OR comparative stud* OR evaluation studies OR follow-up*))) OR AB=(((time AND factors) OR program OR survey* OR ci OR cohort OR comparative stud* OR evaluation studies OR follow-up*))

#5 #1 AND #2 AND (#3 OR #4) and 2022 (Publication Years)

Scopus (via Elsevier) ab 12.10.2023

TITLE-ABS (remdesivir* OR gs5734 OR "GS 5734" OR "GS-5734" OR veklury) AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") AND TITLE-ABS ((control AND study) OR group* OR (time AND factors) OR program OR survey* OR ci OR cohort OR comparative AND stud* OR evaluation AND studies OR follow-up*) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023)) AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

Search I:

(remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*)

AND

(control AND study) OR group OR groups)

Search II:

(remdesivir* OR GS5734 OR "GS 5734" OR "GS-5734" OR veklury*)

AND

((time AND factors) OR program OR survey* OR cohort OR comparative stud* OR evaluation studies OR follow-up*)

In search field: Title, abstract, subject and limit to year 2022 and 2023

5.4 Schlüsselfrage 3: Remdesivir oder Paxlovid bei SARS-CoV-2 Viruspersistenz, jegliche Vergleiche und Kombinationen

Autor*innen: Caroline Hirsch, Nina Kreuzberger

Es gab 11 Fallserien oder Kohorten mit Fällen, die im Detail berichtet wurden.

5.4.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Immunocompromised with persistent SARS-CoV-2 infection

Intervention: Combination therapy

Vergleichsintervention: No therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No therapy Combination therapy	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Viral clearance	Based on data from 118 patients in 11 studies	We identified 11 case series or cohort studies during the omicron era that provided a description of the course of individual cases of persistent SARS-CoV-2 infections within their cohort that provided at minimum nirmatrelvir/ritonavir or remdesivir. Cases typically presented with more than 21 days of viral shedding, sometimes substantially longer (i.e., between 1 and 6 months, up to a maximum of 901 days post infection-onset). Cases of hematological malignancies were included most frequently. In addition, there were 4 cases with solid organ transplantation, 4 cases with autoimmune diseases (rheumatoid arthritis and multiple sclerosis), 4 cases with HIV/AIDS and 1 case with other immunodeficiency. The majority of cases received anti-CD20 monoclonal antibodies as immunosuppressivet treatment. Other immunosuppressive treatments included stem cell transplantation, CAR-T cell therapy, cyclosporine, and tacrolimus. Most cases were treated with a combination of an antiviral substance such as nirmatrelvir/ritonavir or remdesivir together with an at that time effective monoclonal antibody or other antibodies (convalescent plasma, hyperimmune plasma), sometimes after a variety of previous treatment attempts and multiple recurrences. From observation start, the majority of cases cleared the virus 93 out of 118 cases without further persistence, relapse, recurrence, or need for treatment; this means 19 cases needed one or more additional courses of treatment to clear the virus completely	**Very low** Due to very serious risk of bias, Due to extremely serious imprecision[1]	Although conclusions are based on case series only, combination therapy with an antiviral substance and an effective monoclonal antibody or hyperimmune plasma may lead to viral clearance in immunocompromised patients with persistent SARS-CoV-2 infection.
Death	Based on data from 118 patients in 11 studies	Of the identified immunosuppressed cases with persistent SARS-CoV-2 infection, 6 out of 118 died. All 6 died due to SARS-CoV-2 or while SARS-CoV-2 positive	**Very low** Due to very serious risk of bias, Due to extremely serious imprecision[2]	We are uncertain whether combination therapy with antiviral substances and effective monoclonal antibodies or hyperimmune plasma has

				an effect on mortality in immunocompromised patients with persistent SARS-CoV-2 infection.
Viral mutations	Based on data from 5 patients in 1 study	One case series examined the viral mutations of 5 cases with persistent SARS-CoV-2 infections. 4 of those 5 received remdesivir, one case received bebtelovimab, and one sotrovimab. In the patients receiving mAb, mAb-resistent mutations emerged, while no known remdesivir-resistant mutations were detected	**Very low** Due to very serious risk of bias, Due to extremely serious imprecision[3]	
Adverse events	Based on data from 54 patients and 4 studies	In four case series, adverse events were reported. Three out of 54 participants experienced severe adverse events: one participant receiving two antivirals + mAbs had a myocardial infarction, one participant had asymptomatic sinus bradycardia, and one participant treated with remdesivir and nirmatrelvir/ritonavir experienced severe adverse events attributed to suspected hepatotoxicity	**Very low** Due to very serious risk of bias, Due to extremely serious imprecision[4]	We are uncertain whether combination therapy with antiviral substances and effective monoclonal antibodies or hyperimmune plasma has an effect on adverse events in immunocompromised patients with persistent SARS-CoV-2 infection.

1. **Risk of bias: very serious.** The included studies were case series only. Although we did not formally assess risk of bias, no final conclusions can be drawn based on this non-comparative study design.; **Imprecision: extremely serious.** The included studies were case series only. We could not pool the results, and could not undertake a comparison between different treatment options, as many of the included cases received different options sequentially.
2. **Risiko für Bias: very serious.** The included studies were case series only. Although we did not formally assess risk of bias, no final conclusions can be drawn based on this non-comparative study design.; **Imprecision: extremely serious.** The included studies were case series only. We could not pool the results, and could not undertake a comparison between different treatment options, as many of the included cases received different options sequentially.
3. **Risiko für Bias: very serious.** The included study was a case series only. Although we did not formally assess risk of bias, no final conclusions can be drawn based on this non-comparative study design.; **Imprecision: extremely serious.** The included studies were case series only. Extremely small sample size.;
4. **Risiko für Bias: very serious.** The included studies were case series only. Although we did not formally assess risk of bias, no final conclusions can be drawn based on this non-comparative study design.; **Imprecision: extremely serious.** The included studies were case series only. We could not pool the results, and could not undertake a comparison between different treatment options, as many of the included cases received different options sequentially.
5.

5.4.2 Analysen / Forest Plots

Nicht zutreffend. Die Daten aus den identifizierten Fallserien erlauben keine direkten Vergleiche oder Meta-Analysen.

5.4.3 Referenzen der eingeschlossenen Studien

5.4.3.1 *Behandlung von SARS-CoV-2 Viruspersistenz*

- Aiello TF, Peyrony O, Chumbita M, Monzo P, Lopera C, Puerta-Alcalde P, et al. Real-Life Comparison of Antivirals for SARS-CoV-2 Omicron Infection in Patients With Hematologic Malignancies. Influenza other respi. 2024;18(3):e13264.
- Brosh-Nissimov T, Ma'aravi N, Leshin-Carmel D, Edel Y, Ben Barouch S, Segman Y, et al. Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab. J Microbiol Immunol Infect. 2024;57(1):189-94.

- Gentile I, Foggia M, Silvitelli M, Sardanelli A, Cattaneo L, Viceconte G. Optimizing COVID-19 treatment in immunocompromised patients: early combination therapy with remdesivir, nirmatrelvir/ritonavir and sotrovimab. Virol J. 2023;20(1):301.
- Huang L, Tong X, Cui J, Du X, Liao Y, Tan X, et al. Recurrent and persistent fever after SARS-CoV-2 infection in patients with follicular lymphoma: A case series. 2024;141:106973.
- Huygens S, Gharbharan A, Serroukh Y, Snoek B, Franken B, Oude Munnink BB, et al. High-titer convalescent plasma plus nirmatrelvir/ritonavir treatment for non-resolving COVID-19 in six immunocompromised patients. 2023;78(7):1644-8.
- Longo BM, Venuti F, Gaviraghi A, Lupia T, Ranzani FA, Pepe A, et al. Sequential or Combination Treatments as Rescue Therapies in Immunocompromised Patients with Persistent SARS-CoV-2 Infection in the Omicron Era: A Case Series. Antibiotics (Basel). 2023;12(9):19.
- Marques AD, Graham-Wooten J, Fitzgerald AS, Sobel Leonard A, Cook EJ, Everett JK, et al. SARS-CoV-2 evolution during prolonged infection in immunocompromised patients. mBio. 2024;15(3):e0011024.
- Meijer SE, Halutz O, Adler A, Levytskyi K, Tau L, Dekel M, et al. Dual anti-viral treatment for persistent COVID-19 in immunocompromised hemato-oncological patients is associated with a favorable prognosis and minor side effects. J Infect Chemother. 2024;30(3):271-5.
- Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, et al. Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients. Clin Infect Dis. 2023;77(2):280-6.
- Pasquini Z, Toschi A, Casadei B, Pellegrini C, D'Abramo A, Vita S, et al. Dual combined antiviral treatment with remdesivir and nirmatrelvir/ritonavir in patients with impaired humoral immunity and persistent SARS-CoV-2 infection. Hematol Oncol. 2023;41(5):904-11.
- Sanchez E, Krantz EM, Yoke L, Gallaher M, Bhattacharyya P, So L, et al. Clinical outcomes and frequency of persistent infection among immunosuppressed patients treated with bebtelovimab for COVID-19 infection at an ambulatory cancer center. Transpl Infect Dis. 2024;26(1).
- Upasani V, Townsend K, Wu MY, Carr EJ, Hobbs A, Dowgier G, et al. Commercial Immunoglobulin Products Contain Neutralizing Antibodies Against Severe Acute Respiratory Syndrome Coronavirus 2 Spike Protein. Clin Infect Dis. 2023;77(7):950-60.

5.4.3.2 *Inzidenz und Risikofaktoren für Viruspersistenz unter Remdesivir oder Paxlovid*

- Aiello TF, Peyrony O, Chumbita M, Monzo P, Lopera C, Puerta-Alcalde P, et al. Real-Life Comparison of Antivirals for SARS-CoV-2 Omicron Infection in Patients With Hematologic Malignancies. Influenza other respi. 2024;18(3):e13264.
- Chan GCK, Lui GCY, Wong CNS, Yip SST, Li TCM, Cheung CSK, et al. Safety Profile and Clinical and Virological Outcomes of Nirmatrelvir-Ritonavir Treatment in Patients With Advanced Chronic Kidney Disease and Coronavirus Disease 2019. 2023;77(10):1406-12.
- Chan M, Linn MMN, O'Hagan T, Guerra-Assunção JA, Lackenby A, Workman S, et al. Persistent SARS-CoV-2 PCR Positivity Despite Anti-viral Treatment in Immunodeficient Patients. Journal of clinical immunology. 2023;43(6):1083-92.
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- Edelstein GE, Boucau J, Uddin R, Marino C, Liew MY, Barry M, et al. SARS-CoV-2 Virologic Rebound With Nirmatrelvir-Ritonavir Therapy: An Observational Study. Ann Intern Med. 2023;176(12):1577-85.
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- Pinana JL, Heras I, Aiello TF, Garcia-Cadenas I, Vazquez L, Lopez-Jimenez J, et al. Remdesivir or Nirmatrelvir/Ritonavir Therapy for Omicron SARS-CoV-2 Infection in Hematological Patients and Cell Therapy Recipients. Viruses. 2023;15(10):08.
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- Vicente-Valor J, Rodriguez-Gonzalez C, Ferris-Villanueva M, Chamorro-de-Vega E, Romero-Jimenez R, Gomez-Costas D, et al. Remdesivir and SARS-CoV-2 monoclonal antibodies to prevent COVID-19 progression in hematological patients: an observational study. Pharmacol Rep. 2023;75(5):1254-64.
- Yan PD, Markovic D, Hixson RY, Shover CM, Buhr RG, Salehi-Rad R, et al. Eosinophil recovery in hospitalized COVID-19 patients is associated with lower rates of ICU admission and in-hospital mortality: An observational cohort analysis. Respir. 2023;84:101031.

5.4.4 Charakteristika der eingeschlossenen Studien

5.4.4.1 *Behandlung von SARS-CoV-2 Viruspersistenz*

Study ID	Population	N	Timing of presentation	Treatment to treat viral persistence	Narrative outcome	Cleared	recurrence/ relapse	death	death of SARS-CoV-2/ while positive	AE
Aiello 2023	those with persistence AND hospitalised from immunocompromised patients from a cohort of consecutive patients	3	day 14, day 20 and day 33 after infection	2/3 remdesivir (5 days) + hyperimmune plasma 1/3 remdesivir (5 days), hyperimmune plasma + sotrovimab	# 3/3 patients treated with RMD + hyperimmune plasma achieved negativization at discharge # 0/3 patients experienced severe adverse events	3	0	0	0	0
Brosh-Nissimov 2024	severely immunocompromised patients with persistent COVID-19 - 2 kidney transplant - 11 B-cell lymphoprofiferative disease (7 NHL, 4 CLL) receiving BCDT - 1 rheumatoid arthritis treated with BCDT	14	median time from disease onset to presentation: 20 days (IQR 15,39)	**14/14 remdesivir (5-day course)** **11/14 nirmatrelir/Ritonavir (5-day course)** **1/14 molnupiravir (duration not reported)** intramuscular tixegavimab/cilgavimab: 100% dexamethasone 6mg for 5-10 days: 12	# 14/14 patients had a subjective symptomatic improvement # 11/14 patients had a complete response between 4-16 days from treatment onset # 3/14 patients were readmitted due to clinical relapse - of these 3, one died - and 2 received prolonged antiviral treatment with eventual complete remission	11	3	1	1	NR
Huang 2024	immunocompromised individuals with recurrent fever caused by SARS-CoV-2 persistent negative upper respiratory tract test, positive lower respiratory tract test - 6 follicular lymphpma	6	time between positive test and presentation with recurrent fever but negative test at this hospital between 1 and 6 months	**6/6 Nirmatrelvir/ritonavir (immediately)** p1: 5 day nirmatrelvir/ritonavir, again nirmatrelvir/ritonavir 1day 2x (2 months after) p2: 5 day nirmatrel/ritonavir, moxifloxacin; again 5 day nirmatrelvir/ritonavir, methylprednisolone p3: 5 day nirmatrelvir/ritonavir, 5 day molnupiravir, methylprednisolone, prednisolone p4: 5 day nirmatrelvir/ritonavir, 11 day azvudine, methylprednisolone; again nirmatrelvir/ritonavir p5: 5 day nirmatrelvir/ritonavir, 5 day methylprednisolone	# 6/6 rapid resolution of fever & discharge # 3/6 recurrence of fever after discharge with negative SARS-CoV-2 pharyngeal swabs, reception of additional nirmatrelvir/ritonavir treatment; symptoms resolved.	3	3	0	0	NR

				p6: 5 day nirmatrelvir/ritonavir, ceftriaxone 3day, prednisone						
Huygens 2023	immunocompromised individuals with a prolonged SARS-CoV-2 infection (positive PCR with Ct values <30 for ≥20 days) - 4 B-cell malignancy - 1 T-cell malignancy - 1 common varialbe immune deficiency	6	median time between first positive SARS-CoV-2 test and start of nirmatrelvir/ritonavir was 70 days (range 20–231 days)	**6/6 nirmatrevir/ritonavir (5 day course)** + 2 units of 300 mL of high-titer CP with a BA.5 neutralizing titer of 1/640	# 4/6 SARS-CoV-2 genome undetectable within 7 days # 1/6 no viral genome after 32 days after treatment initiation # 1/6 not treated succesfully, cleared spontaneously 257 days after initial testing / 128 days after treatment with N/R + CP and 58 days after additional N/R	5	1	0	0	NR
Longo 2023	immunocompromised patients with persistent SARS-CoV-2 - 11 onco-hematological disease (8 NHL, 1 HL, 1 CLL, 1 Hypogammaglobulinemia) - 4 HIV/Aids	15	median time from the first positive swab to the rescue therapy for persistent SARS-CoV-2 infection was 28 days (IQR 24.5–44.5)	6/15 one antiviral: remdesivir (3-5 days), nirmatrelvir/ritonavor (5-10 days), or molnupiravir 4/15 one antiviral + one mAb, depending on course 2/15 three therapy courses 3/15 four courses (combination therapy)	# 14/15 achieved negativization within 16 days from completion of treatment # 1 patient died due to causes unrelated to SARS-CoV-2 # median time to negativization since the last treatment was 2.5 days (IQR 0.25–4.75) # 1/15 patient treated with remdesivir and nirmatrelvir/r experienced severe adverse events due to suspected hepatotoxicity	14	0	1	1	1
Meijer 2024	immunocompromised haemato-oncological patients - 4/15 CLL - 4/15 MM - 7/15 Malignant lymphoma - 12/15 Hypogammaglobulinemia	15	median symptom duration at initiation of therapy: 32 (IQR 29 to 47)	15/15 combination of nirmatrelvir/ritonavir 300/100 mg PO and remdesivir 200 mg IV on day 1, followed by 100 mg/day for a total of five days + 8/15 corticosteroids + 3/15 tocilizumab + 6/15 tixagevimab/cilgavimab	# 15/15 clinical response at end of treatment # median time to fever resolution: 3 (IQR 1-3) days # 11/15 negative PCR after completion of treatment # 9/15 in full remission after 3 months - 4 relapse/re-infection - 2 indeterminate	9	4	0	0	NR

Mikulska 2023	immunocompromised patients with prolonged/relapsed COVID-19 - 15 NHL - 3 AML - 1 CLL - 2 renal transplant - 1 severe hypogammaglobulinemia	22	median time from SARS-CoV-2 diagnosis to the first combination therapy was 42 days (IQR 29 to 100)	18/22 triple combination therapy: 2 antivirals + mAbs - 3 sotrovimab - 15 tixagevimab/cilgavimab 4/22 combination therapy with 2 antivirals only - 20/22 remdesivir (10-days) and nirmatrelvir/ritonavir (5 days) - 2/22 remdesivir (10 days) and molnupiravir (5 days)	# 15/20 had virological response on day 14 (median time to first negative swab 5 days, IQR 4-7 days) # 16/22 had a response rate at day 30 (alive & negative PCR) # 4/22 received a second combination treatment in a median of 36 days (IQR, 29–78 days) after the first combination course due to persistent positivity and symptoms in 3 and virological relapse in 1 - remdesivir 10 days plus nirmatrelvir/r 10 days plus tixagevimab/cilgavimab 300 mg + 300 mg in 1 (virological response) - remdesivir 10 days plus nirmatrelvir/r 5 days in 2 (failure in 1, virological response and death soon after due to septic shock in 1) - remdesivir 10 days plus molnupiravir 5 days in 1 (failure) # 2/22 experienced severe adverse events - 1/22 myocardial infarction on day 12 after initiation of triple combination therapy - 1/22 asymptomatic sinus bradycardia # end of follow-up 62 days (IQR 47 to 104): - 18/22 alive & negative - 3/22 died while positive - 1/22 persistent antigen and PCR positivity	16	6	3	3	2
Pasquini 2023	Patients with impaired adaptive humoral immunity and SARS-CoV-2 persistent	14	median time between diagnosis of SARS-CoV-2	14/14 combination antiviral therapy with remdesivir (200 mg first day, then 100 mg daily) and nirmatrelvir/ritonavir (300/100 mg	# 14/14 resolution of COVID-19 (median time 6 days (IQR 4.2 to 10.7) # 14/14 viral clearance (median	14	0	0	0	0

	infection - 12 B-cell lymphoma - 1 CLL - 1 MS treated with ocrelizumab		infection and initiation of combination therapy: 42.0 days (IQR 35.0–45.7)	bid, or 150/100 mg in case of mild kidney impairment with estimated glomerular filtration rate (eGFR) <60 mL/min) - 10/14 patients received a 10 day treatment cycle - 3/14 patients had longer courses of 13, 22, and 12 days (due to persistence of PCR test positivity - 1/14 discontinued treatment after 5 days because viral clearance was confirmed after 3 days of treatment	time 9 days (IQR 5.2 to 10.7) # no early rebound during follow-up observed (Follow-up median 26 days, IQR 17.2 to 67.0) # no major adverse events recorded					
Gentile 2023	4 immunocompromised patients - 2 NHL - 1 MM - 1 other immunodeficiency	4	median of 79 (IQR 48–112) days	4/4 combination antiviral treatment with 10 days remdesivir + 5 days N/R	# 0/4 cleared within 14 days # 2/4 cleared within 30 days # 3/4 cleared within 50 days # 1/4 died 57 days after treatment completion (of SARS-CoV-2 infection)	3	1	1	1	NR
Sanchez 2024	10 patients with persistent COVID-19 - 3 B-ALL - 1 myeloid sarcoma - 1 lymphoma - 3 AML - 1 CLL - 1 MM	10	>30 days	Those positive after day 60 received treatment: 3/10 remdesivir 1/10 nirmatrelvir/ritonavir 6/10 no further treatment	# 10/10 patients tested negative at the end of FU # median duration of COVID-19 test positivity was 47 days (range 33–155 days) # 4/10 remained positive after day 60 and received treatment # 0/10 had further complications	10	0	0	0	NR
Marques 2024	immunocompromised patients with persistent COVID-19 (>21 days viral shedding) - 4 lymphoma - 1 transplant	5	> 21 days	4/5 remdesivir; one received 4 courses (earlier variant), and three only 1 course (no duration) 1 bebtelovimab 1 sotrovimab 3 received dexamethasone	# The mAb patients developed specific mutations # while no known remdesivir-resistant mutations were detected					
Upasani 2023	9 immunosuppressed patients with chronic/persistent polymerase chain reaction (PCR)–positive SARS-CoV-2 infection who received immunoglobulin therapy during their treatment	9	between 23 and 901 days post-infection onset	All participants received IVIG as experimental strategy. Previous number of courses of Remdesivir (duration of a course not reported): 1 course: 6 2 courses: 2 3 courses: 1	# 6 patients had 1, 2 patients had 2, and 1 patient had 3 unsuccessful courses of Remdesivir previously # median time from IVIG initiation to the first of consecutively negative tests was 20 days # One patient had a reappearance of positive PCR tests following 3	5	1	0	0	NR

	for COVID-19 - 5 FL - 1 CLL - 2 rheumatoid arthritis - 1 MALT lymphoma				negative tests and, although asymptomatic, was treated with additional nirmatrelvir/ritonavir before achieving sustained negative tests					

5.4.4.2 *Inzidenz und Risikofaktoren für Viruspersistenz unter Remdesivir oder Paxlovid*

Study ID	Patient cohort description	Treatment description / additional concurrent treatments	Outcome	intervention number of events	intervention arm number of patients analysed	Control arm number of events	Control arm number of patients analysed	Narrative summary	Comments
Risk factor treatment for long shedding									
Outcome 1: persistence / prolonged viral shedding				**remdesivir**		**nirmatrelvir /ritonavir**			
Aiello 2024	Haematologic malignancy 43/83 lymphoma 10/83 acute leukemia 15/83 multiple myeloma 5/83 CLL 6/83 high risk myelodysplastic syndrome 4/83 other Treatment overall cohort: 32.5% AHSC 12% CAR T-cell therapy 42.2% prior corticosteroids (3 months) 75.9% prior chemotherapy (3 months) 34.9% prior rituximab use (12 months"	42/83 remdesivir (5-day course) - 23/42 hyperimmune plasma - 11/42 antibiotics - 9/42 sotrovimab - 9/42 glucocorticoids 41/83 nirmatrelvir/ritonavir (5-day course) - 3/41 remdesivir - 1/41 glucocortocoids - 4/41 hyperimmune plasma - 4/41 antiiotics - 1/41 otrovimab seronegative patients with either a Ct < 26 or positive sgRNA also received convalescent plasma and/or sotrovimab; in patients who received nirmatrelvir/ritonavir and had a persistent Ct < 26 at the end of the 5 day treatment, an additional course of remdesivir—with or	SARS-CoV-2positive test longer than 28 days since diagnosis	9	42	4	41		*outcome reported for initial therapy

		without plasma and/or sotrovimab depending on serology							
Pinana 2023	Remdesivir: -AML 41/243 -ALL 9/243 -MDS 21/243 -chronic myeloproliferative disease 8/243 -B-NHL 78/243 -T NHL 7/243 -CLL 20/243 -Plasmatic cell disorder 38/243 -Hodgkin lymphoma 38/243 -AA or others 6/243 Nirmatrelvir -AML 26/223 -ALL 6/223 -MDS 13/233 -chronic myeloproliferative disease 7/223 -B-NHL 88/223 -T NHL 2/223 -CLL 12/223 -Plasmatic cell disorder 57/223 -Hodgkin lymphoma 11/223 -AA or others 1/223	243 Remdesivir (duration not reported) -43 Sotrovimab -4 tixagevimab/cilgavimab -30 CP -79 Corticosteroids 223 Niratrelvir/ritonavor (duration not reported) -7 Sotrovimab -0 tixagevimab/cilgavimab -6 CP -6 Corticosteroids"	SARS-CoV-2 PCR positivity after 25 days from the first detection	80	128	49	122	80/128 (63%) in the remdesivir cohort 49/122 (40%) in the nirmatrelvir cohort	
Aiello 2024	Haematologic malignancy 43/83 lymphoma 10/83 acute leukemia 15/83 multiple myeloma 5/83 CLL 6/83 high risk myelodysplastic syndrome 4/83 other Treatment overall cohort: 32.5% AHSC 12% CAR T-cell therapy 42.2% prior corticosteroids (3	42/83 remdesivir (5-day course) - 23/42 hyperimmune plasma - 11/42 antibiotics - 9/42 sotrovimab - 9/42 glucocorticoids 41/83 nirmatrelvir/ritonavir (5-day course) - 3/41 remdesivir - 1/41 glucocortocoids - 4/41 hyperimmune plasma - 4/41 antiiotics - 1/41 otrovimab	SARS-CoV-2positive test longer than 45 days since diagnosis	4	42	0	41		

	months) 75.9% prior chemotherapy (3 months) 34.9% prior rituximab use (12 months"	seronegative patients with either a Ct < 26 or positive sgRNA also received convalescent plasma and/or sotrovimab; in patients who received nirmatrelvir/ritonavir and had a persistent Ct < 26 at the end of the 5 day treatment, an additional course of remdesivir—with or without plasma and/or sotrovimab depending on serology							
Outcome 1: persistence / prolonged viral shedding				**remdesivir**		**untreated/mixed/ molnupiravir**			
De Vito 2023	Individuals who acquired SARS-CoV-2 infection while being hospitalized for other reasons - 43/175 oncological diseases - 13/175 hematolohical diseases - 51/175 neurodevelopmental diseases	37/175 Molnupiravir (duration not reported 12/172 Nirmatrelvir/ritonavir (duration not reported) 65/175 Remdesivir (3 day course) 8/175 Casirivimab/imdevimab 36/175 Sotrovimab 14/175 untreated	SARS-CoV-2 positive test after 28 days	3	65	7	110	6/10 untreated 3/10 remdesivir 1/10 Molnupiravir **0/10 N/R**	
Outcome 2: viral rebound				**Nirmatarelvir/ ritonavir**		**untreated/mixed/ molnupiravir**			
Edelstein 2023	immuncosuppression, no further information	23/28 nirmatrelvir/ritonavir (5-day course) 5/28 no treatment	viral rebound (only immunosuppressed	2	23	1	5	VR more frequent in immunosuppressed participants treated with N/R compared to untreated immunosuppressed participants	
Qian 2023	704 patients with systemic rheumatic diseases - 347 (49%) rheumatoid arthritis - 113 (16%) prosiatic arthritis - 87 (12%) systemic lupuserythematosus	307 received nirmatrelvir/ritonavir (duration not reported) 105 received mAbs 5 molnupiravir (duration not reported) 3 remdesivir (duration not reported	rebound	24 N/R	311 N/R	0 1	278 7	untreated molnupiravir	

	Immunomodulatory medications - 67% any conventional synthetic DMARDS (MTX, hydroxychloroquine, etc) - 42% any biologic DMARDS (TFN inhibitor, CD20 inhibitor, etc.) - 3% targeted synthetic DMARD (JAK inhibitor)	6 combination therapies 278 no treatment							
Outcome 3: time to viral clearance				**remdesivir**		**Nirmatrelvir/ ritonavir**			
Aiello 2024	Haematologic malignancy 43/83 lymphoma 10/83 acute leukemia 15/83 multiple myeloma 5/83 CLL 6/83 high risk myelodysplastic syndrome 4/83 other Treatment overall cohort: 32.5% AHSC 12% CAR T-cell therapy 42.2% prior corticosteroids (3 months) 75.9% prior chemotherapy (3 months) 34.9% prior rituximab use (12 months"	42/83 remdesivir (5-day course) - 23/42 hyperimmune plasma - 11/42 antibiotics - 9/42 sotrovimab - 9/42 glucocorticoids 41/83 nirmatrelvir/ritonavir (5-day course) - 3/41 remdesivir - 1/41 glucocortocoids - 4/41 hyperimmune plasma - 4/41 antiiotics - 1/41 otrovimab seronegative patients with either a Ct < 26 or positive sgRNA also received convalescent plasma and/or sotrovimab; in patients who received nirmatrelvir/ritonavir and had a persistent Ct < 26 at the end of the 5 day treatment, an additional course of remdesivir—with or without plasma and/or sotrovimab depending on serology	duration of SARS-CoV-2 positivity	18 days (IQR 13 to 23)	42	11 days (IQR 8 to 21)	41		*outcome reported for initial therapy
De Vito 2023	Individuals who acquired SARS-CoV-2 infection while being hospitalized for other reasons	37/175 Molnupiravir (duration not reported 12/172 Nirmatrelvir/ritonavir	time to SARS-CoV-2 negativity	9 days (IQR 7 to 12)	65	10.5 days	12		

	- 43/175 oncological diseases - 13/175 hematolohical diseases - 51/175 neurodevelopmental diseases	(duration not reported) 65/175 Remdesivir (3 day course) 8/175 Casirivimab/imdevimab 36/175 Sotrovimab 14/175 untreated				(IQR 7 to 14)			
Pinana 2024	Remdesivir: -AML 41/243 -ALL 9/243 -MDS 21/243 -chronic myeloproliferative disease 8/243 -B-NHL 78/243 -T NHL 7/243 -CLL 20/243 -Plasmatic cell disorder 38/243 -Hodgkin lymphoma 38/243 -AA or others 6/243 Nirmatrelvir -AML 26/223 -ALL 6/223 -MDS 13/233 -chronic myeloproliferative disease 7/223 -B-NHL 88/223 -T NHL 2/223 -CLL 12/223 -Plasmatic cell disorder 57/223 -Hodgkin lymphoma 11/223 -AA or others 1/223	243 Remdesivir (duration not reported) -43 Sotrovimab -4 tixagevimab/cilgavimab -30 CP -79 Corticosteroids 223 Niratrelvir/ritonavor (duration not reported) -7 Sotrovimab -0 tixagevimab/cilgavimab -6 CP -6 Corticosteroids"	median time to SARS-CoV-2 detection	28.5 days (range 1-208)	128	20 days (range 3-220)	122		
Orth 2023	85.4% with immunodeficiency: - solid organ transplantation with drug immunosuppression: 52.8% - HM: 28.5% - allogenic bone marrow transplant with drug immunosupression: 6.9% - chronic variable immunodeficiency: 1.4% - HIV infection with CD4+ cell	64 Remdesivir + mAb (3, 5, or 10 days) 19 Nirmatrlvir + mAb (5 days) 13 Molnupiravir + mAb (5 days) 23 Remdesivir+molnupiravir 5 Remdesivir+nirmatrelvir 1 molnupiravir+ nirmatrelvir 16 Remdesivir + molnupiravir + mAb	time to viral load copies <10^6 copies	14.1 days	64	16.7 days	19		

	count <200 /microL - rheumatological disease: 3.5% - solid cancer: 9.0%	2 Remdesivir+nirmatrelvir+mAb 1 Molnupiravir+nirmatrelvir+mAb							
Outcome 3: time to viral clearance				**remdesivir**		**untreated/ molnupiravir**			
De Vito 2023	Individuals who acquired SARS-CoV-2 infection while being hospitalized for other reasons - 43/175 oncological diseases - 13/175 hematolohical diseases - 51/175 neurodevelopmental diseases	37/175 Molnupiravir (duration not reported) 12/172 Nirmatrelvir/ritonavir (duration not reported) 65/175 Remdesivir (3 day course) 8/175 Casirivimab/imdevimab 36/175 Sotrovimab 14/175 untreated	time to SARS-CoV-2 negativity	9 days (IQR 7 to 12)	65	untreated: 14 days (IQR 9 to 17) molnupiravir: 10 (IQR 7 to 14)	61 37		
Colaneri 2023			duration of viral load	21 days (range 8-31)		untreated: 15 days (range 8-87) molnupiravir: 17 (8-27)			
Orth 2023	85.4% with immunodeficiency: - solid organ transplantation with drug immunosuppression: 52.8% - HM: 28.5% - allogenic bone marrow transplant with drug immunosupression: 6.9% - chronic variable immunodeficiency: 1.4% - HIV infection with CD4+ cell	64 Remdesivir + mAb (3, 5, or 10 days) 19 Nirmatrlvir + mAb (5 days) 13 Molnupiravir + mAb (5 days) 23 Remdesivir+molnupiravir 5 Remdesivir+nirmatrelvir 1 molnupiravir+ nirmatrelvir 16 Remdesivir + molnupiravir + mAb	time to viral load copies <10^6 copies	8.9 days	remdesivir+molnupiravir	21.8 days	remdesivir+nirmatrelvir/ritonavir	Comined with an effective mAb, there was no difference between antiviral agents.	Note: probably biased by having SOTs not receiving paxlovid, but SOTs in general had shorter viral shedding.

	count <200 /microL - rheumatological disease: 3.5% - solid cancer: 9.0%	2 Remdesivir+nirmatrelvir+mAb 1 Molnupiravir+nirmatrelvir+mAb							
Outcome 3: time to viral clearance				**nirmatrelvir**		**untreated/ molnupiravir**			
De Vito 2023	Individuals who acquired SARS-CoV-2 infection while being hospitalized for other reasons - 43/175 oncological diseases - 13/175 hematolohical diseases - 51/175 neurodevelopmental diseases	37/175 Molnupiravir (duration not reported 12/172 Nirmatrelvir/ritonavir (duration not reported) 65/175 Remdesivir (3 day course) 8/175 Casirivimab/imdevimab 36/175 Sotrovimab 14/175 untreated	time to SARS-CoV-2 negativity	10.5 days (IQR 7 to 14)		untreated: 14 days (IQR 9 to 17) molnupiravir: 10 (IQR 7 to 14)			
Yan 2023			duration of viral shedding	5 days (3-10)	73	13 days (10-17)	122 no treatment group	Viral shedding was significantly shorter in the nirmatrelvir/ritonavir group than the control group (adjusted model 2: HR 3.7, 95% CI 2.6 to 5.28).	
Other outcomes									
Pinana 2023	Remdesivir: -AML 41/243 -ALL 9/243 -MDS 21/243 -chronic myeloproliferative disease 8/243 -B-NHL 78/243 -T NHL 7/243 -CLL 20/243 -Plasmatic cell disorder 38/243 -Hodgkin lymphoma 38/243 -AA or others 6/243 Nirmatrelvir -AML 26/223 -ALL 6/223 -MDS 13/233 -chronic myeloproliferative	243 Remdesivir (duration not reported) -43 Sotrovimab -4 tixagevimab/cilgavimab -30 CP -79 Corticosteroids 223 Niratrelvir/ritonavor (duration not reported) -7 Sotrovimab -0 tixagevimab/cilgavimab -6 CP -6 Corticosteroids"	PCR negativity at last follow-up	132	243	125	223	132/243 (63%) in the remdesivir cohort 125/223 (69%) in the nirmatrelvir cohort	

	disease 7/223 -B-NHL 88/223 -T NHL 2/223 -CLL 12/223 -Plasmatic cell disorder 57/223 -Hodgkin lymphoma 11/223 -AA or others 1/223								
Pinana 2023	Remdesivir: -AML 41/243 -ALL 9/243 -MDS 21/243 -chronic myeloproliferative disease 8/243 -B-NHL 78/243 -T NHL 7/243 -CLL 20/243 -Plasmatic cell disorder 38/243 -Hodgkin lymphoma 38/243 -AA or others 6/243 Nirmatrelvir -AML 26/223 -ALL 6/223 -MDS 13/233 -chronic myeloproliferative disease 7/223 -B-NHL 88/223 -T NHL 2/223 -CLL 12/223 -Plasmatic cell disorder 57/223 -Hodgkin lymphoma 11/223 -AA or others 1/223	243 Remdesivir (duration not reported) -43 Sotrovimab -4 tixagevimab/cilgavimab -30 CP -79 Corticosteroids 223 Niratrelvir/ritonavor (duration not reported) -7 Sotrovimab -0 tixagevimab/cilgavimab -6 CP -6 Corticosteroids"	Need of second course of antivirals due to persistence	12	234	11	223		
Gliga 2023	43/57 imunodeficient -23/43 SOT -7/43 HSCT -6/43 leukemia -2/43 lymphoma -1/43 other malignancy	57/57 sotrovimab Adjunctive therapy 24/57 none 30 /57 Remdesivir (26 3-day course, 4 5-day course) 7/57 Second Remdesivir administration (10-day course) 6/57 Casirivimab/imdevimab	resistance mutations to sotrovimab	14	43				*most of the immunodeficient patients with resistant mutation had prolonged viral shedding

		2/57 Molnupiravir (5 day course) 4/57 N/R (5 or 10 day course) 2/57 tixagevimab/cilgavimab							
Overall incidence under any treatment/no treatment									
Aiello 2024	Haematologic malignancy 43/83 lymphoma 10/83 acute leukemia 15/83 multiple myeloma 5/83 CLL 6/83 high risk myelodysplastic syndrome 4/83 other Treatment overall cohort: 32.5% AHSC 12% CAR T-cell therapy 42.2% prior corticosteroids (3 months) 75.9% prior chemotherapy (3 months) 34.9% prior rituximab use (12 months"	42/83 remdesivir (5-day course) - 23/42 hyperimmune plasma - 11/42 antibiotics - 9/42 sotrovimab - 9/42 glucocorticoids 41/83 nirmatrelvir/ritonavir (5-day course) - 3/41 remdesivir - 1/41 glucocortocoids - 4/41 hyperimmune plasma - 4/41 antiiotics - 1/41 otrovimab seronegative patients with either a Ct < 26 or positive sgRNA also received convalescent plasma and/or sotrovimab; in patients who received nirmatrelvir/ritonavir and had a persistent Ct < 26 at the end of the 5 day treatment, an additional course of remdesivir—with or without plasma and/or sotrovimab depending on serology	SARS-CoV-2positive test longer than 21 days since diagnosis	21	83				
Chan 2023	immunocompromised patients with COVID-19 - 55/75 primary immunodeficiency (CVID: 28, XLA: 4, Other: 23) - 15/75 haematological malignancy	Casirivimab/imdevimab: 28 - 21 remdesivir - 11 dexamethasone - 5 tocilizumab - 4 sarilumab - 13 antibiotics Other treatment group: 75	sustained viral clearance (at least 3 consecutive negative samples)	60	75			Participants with persistence by day 28 were equally likely to receive no treatment or nirmatrelvir/ritonavor, more likely to have received	* 11/28 in the Ronapreve cohort and 60/75 in the other treatment cohort

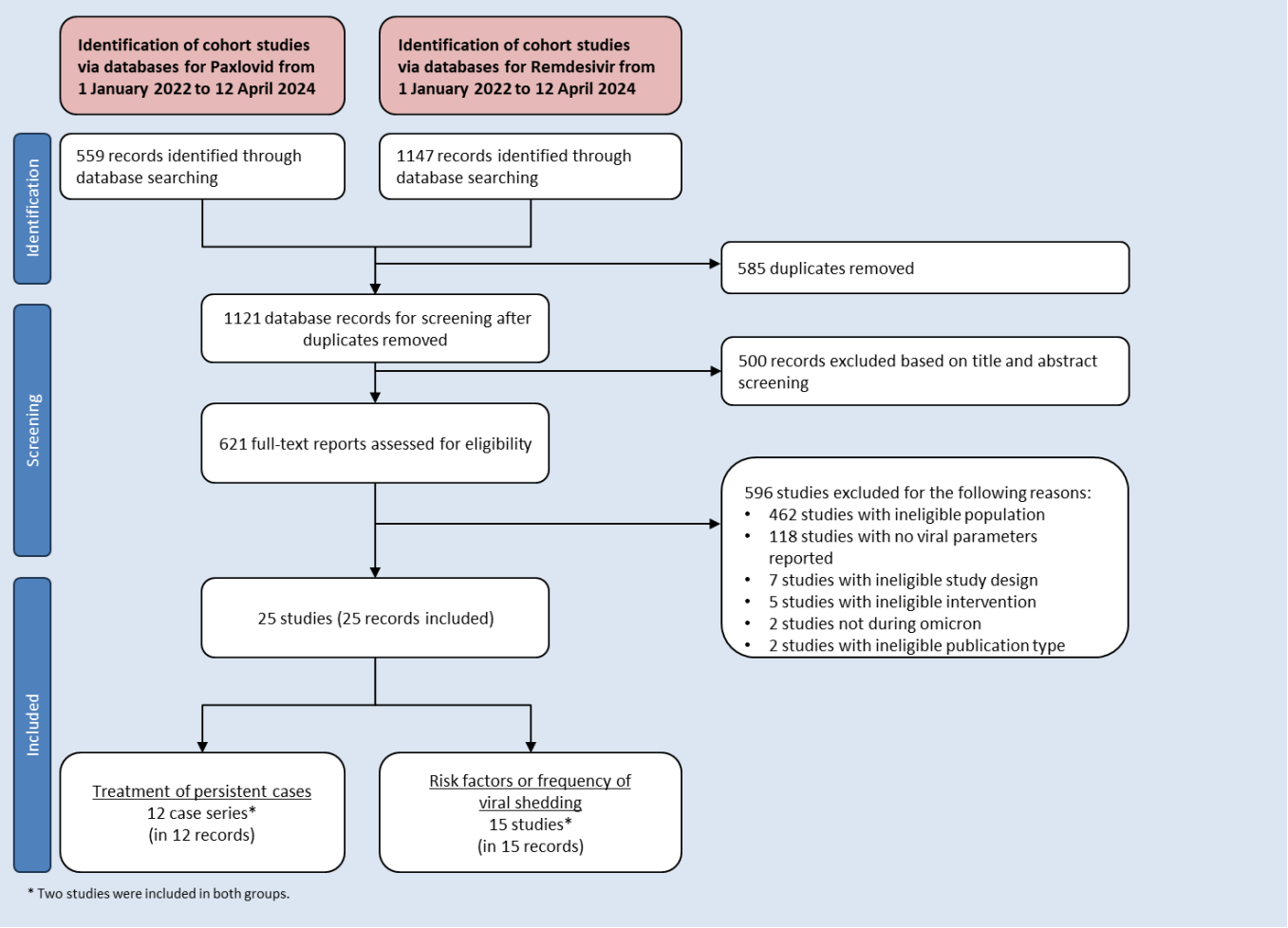
	- 4/75 othe secondary - 1/75 post-transplant	- Molnupiravir: 3 - Nirmatrelvir/ritonavir: 8 - sotrovimab: 31 - remdesivir: 1 - casirivimab + remdesivir: 1 - unclear: 9 - NiL: 22 Durations not reported						molnupiravor, and less likely to have received sotrovimab	
Minoia 2023			recurrence/reinfection at 90 days	13	72			Factors that were associated in univariable analysis with prolonged viral shedding were increased age, having CLL/NHL, and nirmatrelvir/ritonavir as compared to molnupiravir.	
Orth 2023	85.4% with immunodeficiency: - solid organ transplantation with drug immunosuppression: 52.8% - HM: 28.5% - allogenic bone marrow transplant with drug immunosupression: 6.9% - chronic variable immunodeficiency: 1.4% - HIV infection with CD4+ cell count <200 /microL - rheumatological disease: 3.5% - solid cancer: 9.0%	64 Remdesivir + mAb (3, 5, or 10 days) 19 Nirmatrlvir + mAb (5 days) 13 Molnupiravir + mAb (5 days) 23 Remdesivir+molnupiravir 5 Remdesivir+nirmatrelvir 1 molnupiravir+ nirmatrelvir 16 Remdesivir + molnupiravir + mAb 2 Remdesivir+nirmatrelvir+mAb 1 Molnupiravir+nirmatrelvir+mAb	prolonged viral shedding (viral load >10^6 copies/ml after more than 21 days	21	144			Risk factors for prolonged viral shedding were immunosuppression, late treatment initiation, HM, and immunosupressive treatment after allogenic stem cell transplantation. Treatment strategies did not make a difference.	
Sanchez 2024		all had received bebtelovimab 2 received nirmatrelvir/ritonavir ("extended duration") 2 received remdesivir (duration not reported)	persistent COVID-19 infection (beyond day 30)	10	93			From 93 patients with hematological malignancies or solid tumors treated early with bebteloimab, 10 showed persistent	

								infection with a median duration of 47 days (range 33 to 155 days). 5 showed persistent symptoms. Four received additional therapy with remdesivir or nirmatrelvir/ritonavir. None of the patients developed complications	
Gliga 2023	43/57 imunodeficient -23/43 SOT -7/43 HSCT -6/43 leukemia -2/43 lymphoma -1/43 other malignancy	57/57 sotrovimab Adjunctive therapy 24/57 none 30 /57 Remdesivir (26 3-day course, 4 5-day course) 7/57 Second Remdesivir administration (10-day course) 6/57 Casirivimab/imdevimab 2/57 Molnupiravir (5 day course) 4/57 N/R (5 or 10 day course) 2/57 tixagevimab/cilgavimab	prolonged viral shedding at day 21	12	43				* the only immunocompetent patient with prolonged shedding was lost-to-follow up and therefore considered as positive
Vicente-Valor 2023	55 Haematological malignancy - AML: 11 - ALL: 4 - myeloproliferative neoplasms: 3 - CLL: 4 - HL: 2 - NHL: 16 - MM: 11 - Myelodysplastic syndromes: 4	44 remdesivir (3 day course) 11 mAbs	prolonged viral shedding (> day 28)	14	41			This study compared remdesivir to mAbs in immunosuppresed HM patients. Viral load at day 28 and beyond is reported for the overall group only.	
Pinana 2023	Remdesivir: -AML 41/243 -ALL 9/243 -MDS 21/243 -chronic myeloproliferative	243 Remdesivir (duration not reported) -43 Sotrovimab -4 tixagevimab/cilgavimab -30 CP	SARS-CoV-2 PCR positivity after 25 days from the first detection	129	250			80/128 (63%) in the remdesivir cohort 49/122 (40%) in the nirmatrelvir cohort	

	disease 8/243 -B-NHL 78/243 -T NHL 7/243 -CLL 20/243 -Plasmatic cell disorder 38/243 -Hodgkin lymphoma 38/243 -AA or others 6/243 Nirmatrelvir -AML 26/223 -ALL 6/223 -MDS 13/233 -chronic myeloproliferative disease 7/223 -B-NHL 88/223 -T NHL 2/223 -CLL 12/223 -Plasmatic cell disorder 57/223 -Hodgkin lymphoma 11/223 -AA or others 1/223	-79 Corticosteroids 223 Niratrelvir/ritonavor (duration not reported) -7 Sotrovimab -0 tixagevimab/cilgavimab -6 CP -6 Corticosteroids"							
Edelstein 2023	immuncosuppression, no further information	23/28 nirmatrelvir/ritonavir (5-day course) 5/28 no treatment	viral rebound (only immunosuppressed	3	28			VR more frequent in immunosuppressed participants treated with N/R compared to untreated immunosuppressed participants	
Qian 2023	704 patients with systemic rheumatic diseases - 347 (49%) rheumatoid arthritis - 113 (16%) prosiatic arthritis - 87 (12%) systemic lupuserythematosus Immunomodulatory medications - 67% any conventional synthetic DMARDS (MTX, hydroxychloroquine, etc)	307 received nirmatrelvir/ritonavir (duration not reported) 105 received mAbs 5 molnupiravir (duration not reported) 3 remdesivir (duration not reported 6 combination therapies 278 no treatment	rebound	25	596			N/R untreated molnupiravir	

	- 42% any biologic DMARDS (TFN inhibitor, CD20 inhibitor, etc.) - 3% targeted synthetic DMARD (JAK inhibitor)								
Overall incidence under nirmatrelvir / ritonavir only									
Chan 2023_CKD	85 patients low GFR group (dialysis + eGFR<30): 65 high GFR group (eGFR 30-60ml + eGFR >60): 20	10/85 eGFR > 60: nirmatrelvir 300mg & ritonavir 100mg twice per day (day 1 to 5) 10/85 eGFR 30-60: nirmatrelvir 300mg & ritonavir 100mg twice per day (day 1 to 5) 6/85 eGFR <30: nirmatrelvir 300mg & ritonavir 100mg once (day 1); nirmatrelvir 150mg & ritonavir 100mg once per day (day 2 to 5) 59/85 dialysis: - body weight > 40kg: nirmatrelvir 300mg & ritonavir 100mg once (day 1); nirmatrelvir 150mg & ritonavir 100mg once per day (day 2 to 5) - body weight < 40kg: nirmatrelvir 150mg & ritonavir 100mg once (day 1); nirmatrelvir 100mg & ritonavir 100mg every 48 hours (day 2 to 5)	virological rebound (by PCR)	4	80				

5.4.5 Studienselektion: Flow Chart



5.4.6 Literaturrecherche Paxlovid, Studiendesign Kohorten

Search limit from 2022 to present

Exclude case reports

Database	search 12.04.2024
MEDLINE ALL	**342**
Scopus	**217**
Total	**559**
Total (after deduplication)	**369**

5.4.6.1 *Ovid MEDLINE(R) ALL*

1946 to April 11, 2024

#	Searches
1	SARS-CoV-2/ or COVID-19/

2 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab.

3 or/1-2

4 ("PF-07321332" or "PF 07321332" or "PF07321332" or paxlovid* or nirmatrelvir*).ti,ab,kf.

5 3 and 4

6 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/

7 ((control and study) or group* or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp.

8 or/6-7

9 (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/

10 hi.fs. or case report.mp. or case report.pt.

11 or/9-10

12 8 not 11

13 5 and 12

14 limit 13 to yr="2022 -Current"

15 remove duplicates from 14

5.4.6.2 *Scopus (via Elsevier)*

TITLE-ABS ("PF-07321332" OR "PF 07321332" OR "PF07321332" OR paxlovid* OR nirmatrelvir*) AND TITLE-ABS (((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*)) AND PUBYEAR > 2021 AND PUBYEAR < 2025 AND NOT TITLE-ABS ("case report") AND (LIMIT-TO (DOCTYPE , "ar"))

5.4.7 Literaturrecherche Remdesivir, Studiendesign Kohorten

Search limit from 2022 to present

Exclude case reports

Database	search 12.04.2024
MEDLINE ALL	**639**
Scopus	**508**
Total	**1147**
Total (after deduplication)	**752**

5.4.7.1 *Ovid MEDLINE(R) ALL*

1946 to April 11, 2024

Searches

1 SARS-CoV-2/ or COVID-19/

2 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab.

3 or/1-2

4 (remdesivir* or GS5734 or "GS 5734" or "GS-5734" or veklury).ti,ab,kf.

5 3 and 4

6 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/

7 ((control and study) or group* or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp.

8 or/6-7

9 (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/

10 hi.fs. or case report.mp. or case reports.pt.

11 or/9-10

12 8 not 11

13 5 and 12

14 limit 13 to yr="2022 -Current"

15 remove duplicates from 14

5.4.7.2 *Scopus (via Elsevier)*

Advanced search

TITLE-ABS (remdesivir* OR gs5734 OR "GS 5734" OR "GS-5734" OR veklury)
AND
TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2" OR omicron* OR omikron*)
AND
TITLE-ABS (((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*))
AND PUBYEAR > 2021 AND PUBYEAR < 2025
AND NOT TITLE-ABS ("case report")

5.5 Schlüsselfrage 4a.1) systemische Kortikosteroide und SoC vs. SoC

Autor*innen: Caroline Hirsch

Es gab 11 RCTs mit 8252 Teilnehmenden.

5.5.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Systemic corticosteroids + Standard of care

Vergleichsintervention: Standard of Care (plus/minus Placebo)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of Care (plus/minus Placebo)	**Absolute effect estimates** Systemic corticosteroids + Standard of care	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality up to 30 days	Relative risk: 0.9 (CI 95% 0.84 - 0.97) Based on data from 7898 patients in 9 studies[1]	**273** per 1000	**246** per 1000 Difference: **27 less per 1000** (CI 95% 44 less - 8 less)	**Moderate** Due to serious risk of bias[2]	Systemic corticosteroids likely reduce the all-cause mortality up to 30 days.
All-cause mortality up to 120 days	Relative risk: 0.74 (CI 95% 0.23 - 2.34) Based on data from 485 patients in 3 studies[3]	**402** per 1000	**297** per 1000 Difference: **105 less per 1000** (CI 95% 310 less - 539 more)	**Low** Due to serious inconsistency, Due to serious risk of bias[4]	Systemic corticosteroids may reduce all-cause mortality up to 120 days.
Clinical improvement: Discharged alive	Relative risk: 1.36 (CI 95% 0.95 - 1.96) Based on data from 6786 patients in 3 studies[5]	**620** per 1000	**843** per 1000 Difference: **223 more per 1000** (CI 95% 31 less - 595 more)	**Low** Due to serious inconsistency, Due to serious risk of bias[6]	Systemic corticosteroids may increase the outcome discharged alive.
Clinical worsening: New need for IMV or death	Relative risk: 0.92 (CI 95% 0.84 - 1.01) Based on data from 5586 patients in 2 studies[7]	**282** per 1000	**259** per 1000 Difference: **23 less per 1000** (CI 95% 45 less - 3 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[8]	Systemic corticosteroids may decrease the outcome new need for IMV or death.
Ventilator-free days	Gemessen mit: Mean difference Skala: - Höher ist besser Based on data from 299 patients in 1 studies[9]	**4** daysMittelwert	**6.6** daysMittelwert Difference: **MD 2.6 more** (CI 95% 0.67 more - 4.53 more)	**Low** Due to serious imprecision and due to serious risk of bias[10]	Systemic corticosteroids may increase ventilator-free days.
Serious adverse events during treatment	Based on data from 678 patients in 2 studies[11]	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. Therefore, we only present descriptive statistics with effects below 1 in favour of corticosteroids: Angus 2020 shock-		**Very low** Due to very serious risk of bias, serious imprecision.[12]	We are uncertain whether systemic corticosteroids increase or reduce the number of serious adverse events.

		dependent hydrocortisone: RR 4.11 (95% CI 0.23, 72.98); Angus 2020 fixed-dose hydrocortisone: RR 1.43 (95% CI 0.16, 12.49); Tomazini 2020: RR 0.54 (95% CI 0.19, 1.59).		
Adverse events during treatment	Based on data from 660 patients in 5 studies[13]	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. We only present descriptive statistics with effects below 1 in favour of corticosteroids: Corral-Gudino 2021: RR 11.60 (95% CI 1.62, 83.03); Dequin 2020: RR 0.77 (95% CI 0.59, 1.00); Edalatifard 2020: RR 0.82 (95% CI 0.12, 5.48); Tang 2021: RR 0.63 (95% CI 0.22, 1.76); Tomazini 2020: RR 0.69 (95% CI 0.50, 0.96).	**Very low** Due to very serious risk of bias, serious imprecision[14]	We are uncertain whether systemic corticosteroids increase or reduce the number of adverse events.
Hospital-acquired infections during treatment	Based on data from 660 patients in 5 studies[15]	We did not perform meta-analyses because of high risk of bias, heterogeneous definitions, and underreporting. We present descriptive statistics only: Corral-Gudino 2021: RR 4.14 (95% CI 0.51, 33.49); Dequin 2020: RR 0.77 (95% CI 0.59, 1.00); Edalatifard 2020: RR 2.49 (95% CI 0.11, 58.74); Tang 2021: RR 2.00 (95% CI 0.19, 21.24); Tomazini 2020: RR 0.75 (95% CI 0.52, 1.09).	**Very low** Due to very serious risk of bias, serious imprecision[16]	We are uncertain whether systemic corticosteroids increase or reduce the number of hospital-acquired infections.

1. Systematic review . Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [5].
2. Risk of bias: very serious. We downgraded for risk of bias for deviation from intended interventions (Angus 2020; Horby 2021; Jeronimo 2020; Tomazini 2020), for selective reporting (Corral-Gudino 2021; Dequin 2020; Jamaati 2021), for missing information about the allocation concealment (Corral-Gudino 2021), for baseline differences (Jamaati 2021).;
3. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [5].
4. Risk of bias: very serious. Edalatifard 2020: no information about the allocation concealment, deviation from the intended intervention (17%), no SAP and protocol available; Jeronimo 2020: deviations from the intended intervention and selective reporting; Inkonsistenz: very serious. I^2 = 79%;
5. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [5].
6. Risk of bias: very serious. No information about the allocation concealment (Edalatifard 2020), protocol deviations (Edalatifard 2020, Horby 2021, Tomazini 2020), selective reporting (Edalatifard 2020); Inkonsistenz: very serious. I^2 = 81%;
7. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [5].
8. Risk of bias: very serious. Protocol deviations (Angus 2020, Horby 2021); Inkonsistenz: very serious. I^2 = 72%;
9. Primary study. Baseline/Comparison Systematic review. Reference[5].
10. Risk of bias: very serious. We downgraded because of risk of bias through deviation from intended interventions (Tomazini 2020; 1 point).; Imprecision: very serious. imprecision (broad confidence interval, low number of evaluated participants, 1 point).;
11. Primary study references [5].
12. Risk of bias: very serious. We downgraded for risk of bias for deviations from intended interventions (Angus 2020; Tomazini 2020), missing adjustment for competing risk (Angus 2020; Tomazini 2020; 2 points), selective

outcome reporting: 2 out 10 studies including the largest, Horby 2021, did not report this major safety outcome (downgrade 1 point).; Imprecision: very serious. Imprecision (fewer than 500 events, downgrade 1 point);

13. Primary study references [5].

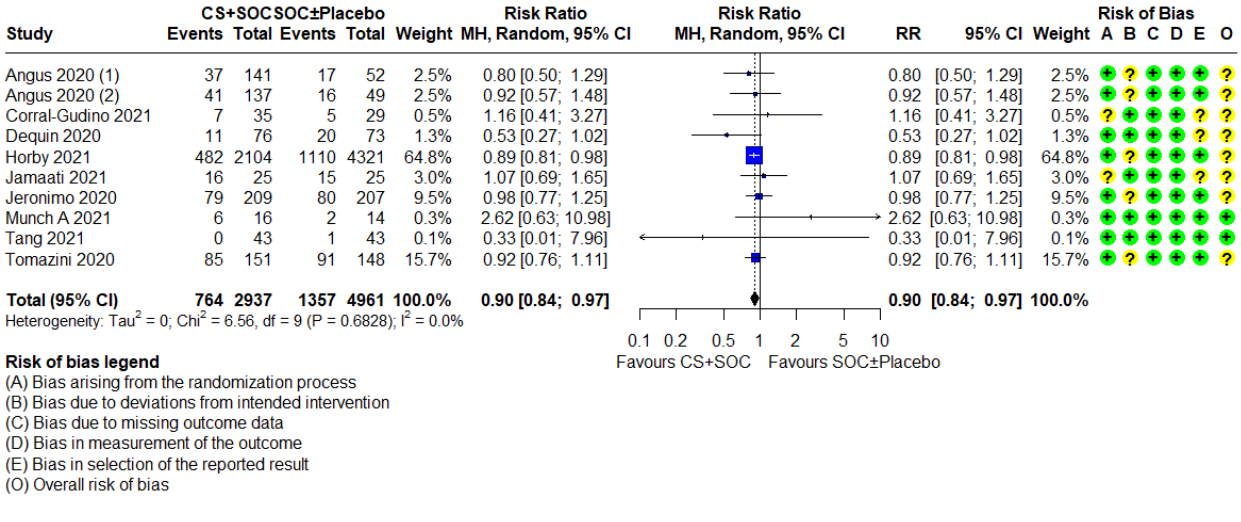
14. Risk of bias: very serious. We downgraded because of risk of bias mainly through deviation from intended intervention (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020) and selection of adverse events usually associated with steroids (Corral-Gudino 2021; Edalatifard 2020; Tang 2021, 2 points). selective outcome reporting (only 5 out of 10 reported this established safety outcome, 1 point); Imprecision: very serious. Imprecision (fewer than 500 events, 1 point),;

15. Primary study references [5].

16. Risk of bias: very serious. We downgraded because of risk of bias mainly from deviation from intended interventions (Edalatifard 2020; Tomazini 2020), missing adjustment for competing risk (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021; Tomazini 2020), missing information about the allocation concealment (Corral-Gudino 2021; Edalatifard 2020), missing pre-specification of its definition (Corral-Gudino 2021; Dequin 2020; Edalatifard 2020; Tang 2021, 2 points). selective outcome reporting (only 5 out of 10 reported this established safety outcome, 1 point); Imprecision: very serious. Imprecision (fewer than 500 events, 1 point).;

5.5.2 Analysen / Forest Plots

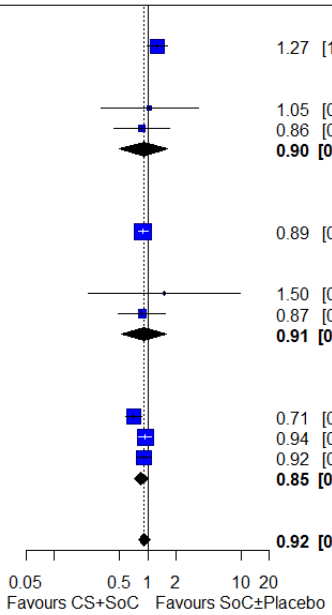
Mortality, day 30



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Subgruppenanalyse: Respiratory support, Mortality day 30

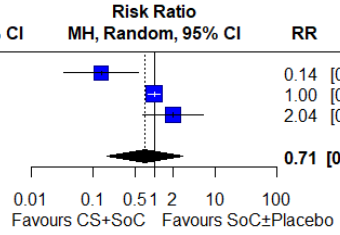
Study or Subgroup	CS+SoC Events	CS+SoC Total	SoC±Placebo Events	SoC±Placebo Total	Weight	Risk Ratio MH, Random, 95% CI	RR	95% CI	Weight	Risk of Bias A	B	C	D	E	O
Subgroup = No oxygen															
Horby 2021	89	501	145	1034	14.5%	1.27 [1.00; 1.61]	1.27	[1.00; 1.61]	14.5%	+	?	+	+	+	?
Subgroup = Low-flow oxygen only															
Corral-Gudino 2021	5	31	4	26	1.3%	1.05 [0.31; 3.51]	1.05	[0.31; 3.51]	1.3%	?	+	+	+	?	?
Jeronimo 2020	8	16	7	12	3.6%	0.86 [0.43; 1.70]	0.86	[0.43; 1.70]	3.6%	+	?	+	+	+	?
Total (95% CI)	**13**	**47**	**11**	**38**	**4.9%**	**0.90 [0.50; 1.63]**	**0.90**	**[0.50; 1.63]**	**4.9%**						
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.08$, df = 1 (P = 0.7761); $I^2 = 0\%$															
Subgroup = NIV, high-flow, and low-flow oxygen combined															
Horby 2021	298	1279	682	2604	21.4%	0.89 [0.79; 1.00]	0.89	[0.79; 1.00]	21.4%	+	?	+	+	+	?
Subgroup = NIV or high-flow oxygen only															
Corral-Gudino 2021	2	4	1	3	0.5%	1.50 [0.23; 9.80]	1.50	[0.23; 9.80]	0.5%	?	+	+	+	?	?
Jeronimo 2020	18	98	19	90	4.8%	0.87 [0.49; 1.55]	0.87	[0.49; 1.55]	4.8%	+	?	+	+	+	?
Total (95% CI)	**20**	**102**	**20**	**93**	**5.3%**	**0.91 [0.53; 1.58]**	**0.91**	**[0.53; 1.58]**	**5.3%**						
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.3$, df = 1 (P = 0.5866); $I^2 = 0\%$															
Subgroup = Invasive ventilation															
Horby 2021	95	324	283	683	17.2%	0.71 [0.58; 0.86]	0.71	[0.58; 0.86]	17.2%	+	?	+	+	+	?
Jeronimo 2020	53	66	57	67	19.3%	0.94 [0.81; 1.10]	0.94	[0.81; 1.10]	19.3%	+	?	+	+	+	?
Tomazini 2020	85	151	91	148	17.3%	0.92 [0.76; 1.11]	0.92	[0.76; 1.11]	17.3%	+	?	+	+	+	?
Total (95% CI)	**233**	**541**	**431**	**898**	**53.8%**	**0.85 [0.72; 1.02]**	**0.85**	**[0.72; 1.02]**	**53.8%**						
Heterogeneity: $Tau^2 = 0.0160$; $Chi^2 = 5.78$, df = 2 (P = 0.0555); $I^2 = 65.4\%$															
Total (95% CI)	**653**	**2470**	**1289**	**4667**	**100.0%**	**0.92 [0.80; 1.06]**	**0.92**	**[0.80; 1.06]**	**100.0%**						
Heterogeneity: $Tau^2 = 0.0204$; $Chi^2 = 14.57$, df = 8 (P = 0.0680); $I^2 = 45.1\%$															
Test for subgroup differences: $Chi^2 = 7.76$, df = 4 (P = 0.1009)															



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Mortality, day 120

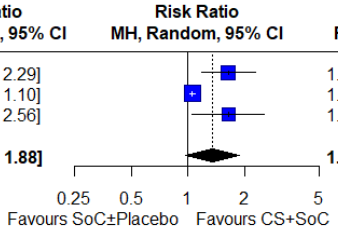
Study	CS+SoC Events	CS+SoC Total	SoC±Placebo Events	SoC±Placebo Total	Weight	Risk Ratio MH, Random, 95% CI	RR	95% CI	Weight	Risk of Bias A	B	C	D	E	O
Edalatifard 2020	2	34	12	28	28.8%	0.14 [0.03; 0.56]	0.14	[0.03; 0.56]	28.8%	?	?	+	+	?	?
Jeronimo 2020	80	194	82	199	39.4%	1.00 [0.79; 1.27]	1.00	[0.79; 1.27]	39.4%	+	?	+	+	?	?
Munch A 2021	7	16	3	14	31.8%	2.04 [0.65; 6.43]	2.04	[0.65; 6.43]	31.8%	+	+	+	+	+	+
Total (95% CI)	**89**	**244**	**97**	**241**	**100.0%**	**0.71 [0.17; 2.98]**	**0.71**	**[0.17; 2.98]**	**100.0%**						
Heterogeneity: $Tau^2 = 1.3481$; $Chi^2 = 9.06$, df = 2 (P = 0.0108); $I^2 = 77.9\%$															



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

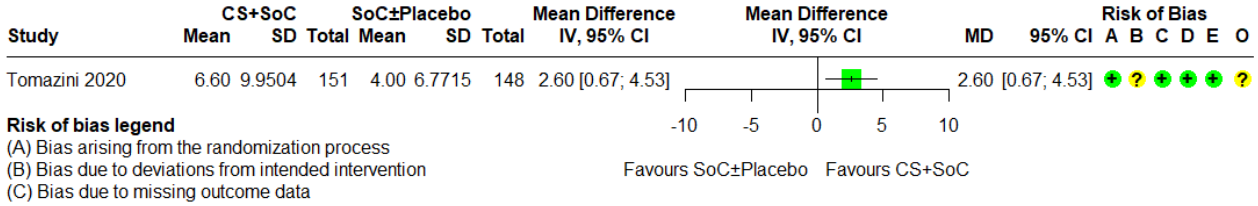
Clinical improvement: discharged alive

Study	CS+SoC Events	CS+SoC Total	SoC±Placebo Events	SoC±Placebo Total	Weight	Risk Ratio MH, Random, 95% CI	RR	95% CI	Weight	Risk of Bias A	B	C	D	E	O
Edalatifard 2020	32	34	16	28	30.7%	1.65 [1.18; 2.29]	1.65	[1.18; 2.29]	30.7%	?	?	+	?	?	?
Horby 2021	1416	2104	2748	4321	44.6%	1.06 [1.02; 1.10]	1.06	[1.02; 1.10]	44.6%	+	?	+	?	+	?
Tomazini 2020	42	151	25	148	24.7%	1.65 [1.06; 2.56]	1.65	[1.06; 2.56]	24.7%	+	?	+	?	+	?
Total (95% CI)	**1490**	**2289**	**2789**	**4497**	**100.0%**	**1.35 [0.98; 1.88]**	**1.35**	**[0.98; 1.88]**	**100.0%**						
Heterogeneity: $Tau^2 = 0.0621$; $Chi^2 = 10.50$, df = 2 (P = 0.0052); $I^2 = 81.0\%$															



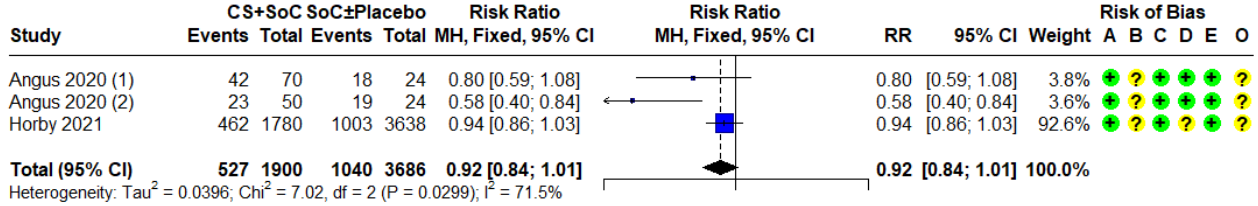
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Ventilator-free days



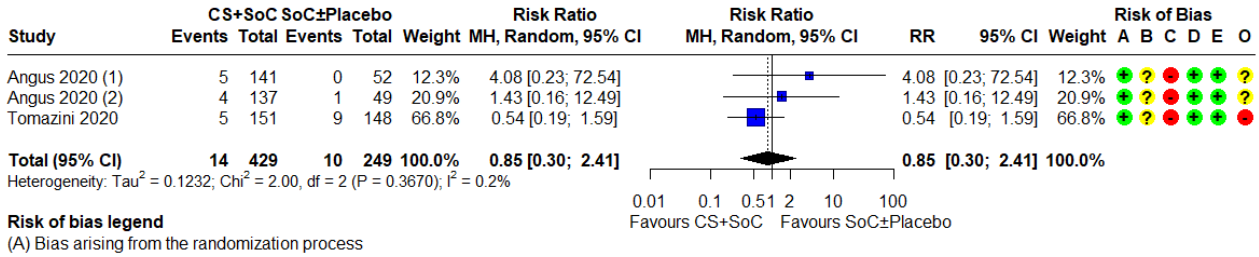
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Clinical worsening: new need for IMV or death



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Serious adverse events



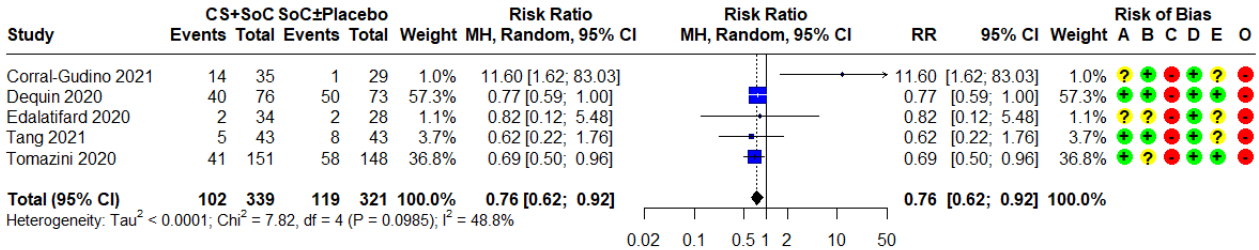
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Footnotes

(1) Angus 2020 intervention arm: shock-dependent hydrocortisone

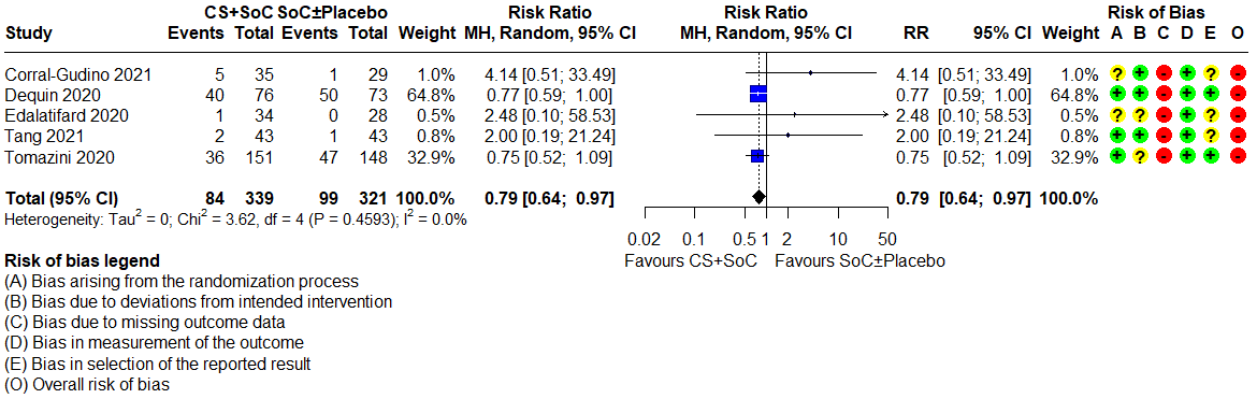
(2) Angus 2020 intervention arm: fixed-dose hydrocortisone

Adverse events



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Hospital-acquired infections



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

5.5.3 Referenzen der eingeschlossenen Studien

- Wagner C, Griesel M, Mikolajewska A, Metzendorf MI, Fischer AL, Stegemann M, et al. (2022). Systemic corticosteroids for the treatment of COVID-19: Equity-related analyses and update on evidence. Cochrane Database of Systematic Reviews(11). doi:10.1002/14651858.CD014963.pub2

5.5.4 Charakteristika der eingeschlossenen Studien

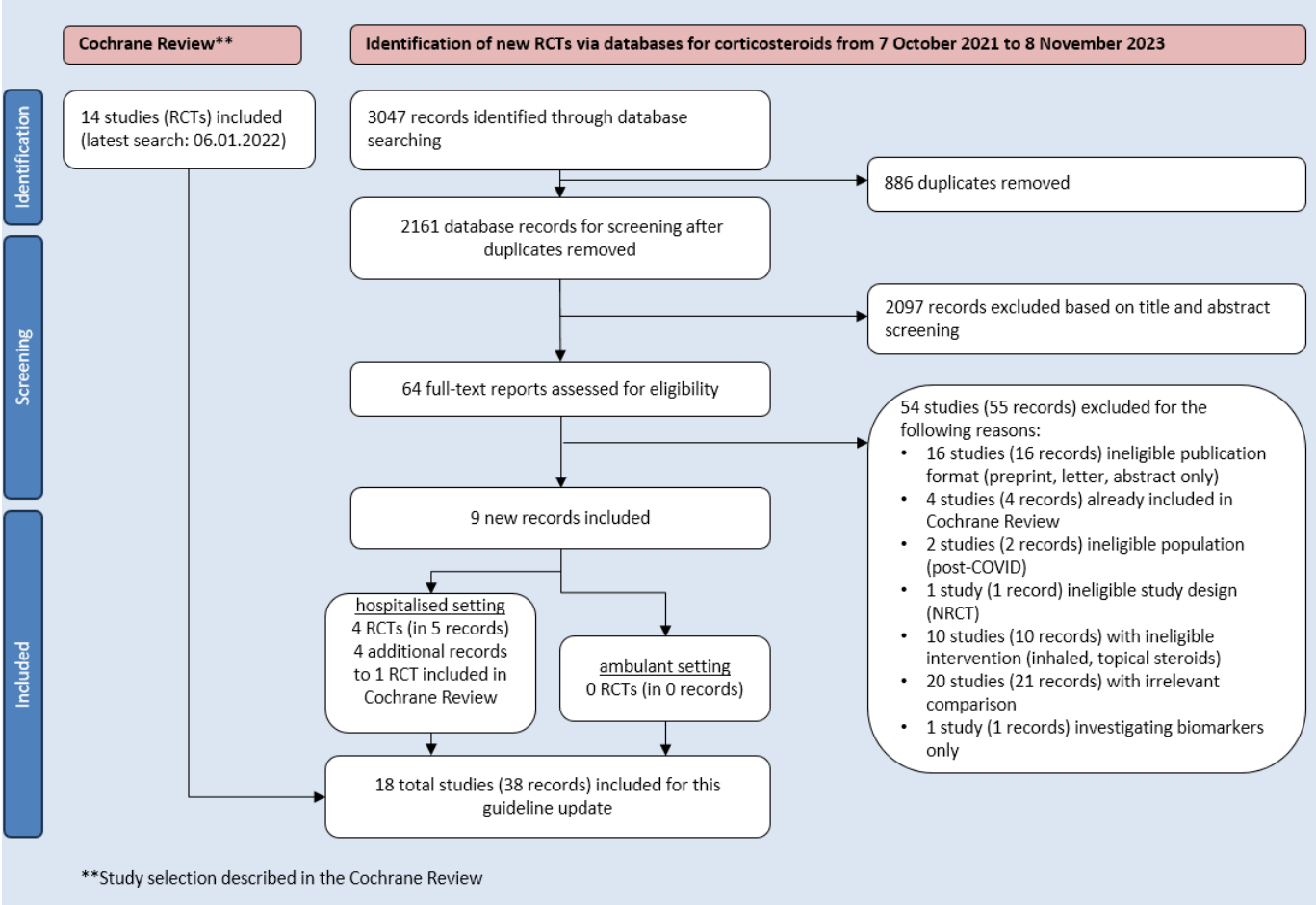
5.5.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodological Notes	Included publications
Wagner 2022 Systematic review with MA	**Study design** **Search time frame** Inception of each database to 6 January 2022 **Sources:** Cochrane COVID-19 Study Register (CCSR) comprising: - MEDLINE (PubMed) - Embase.com - ClinicalTrials.gov - WHO International Clinical Trials Registry Platform (ICTRP) - medRxiv - Cochrane Central Register of Controlled Trials (CENTRAL) Web of Science Core Collection (Clarivate)	**Intervention A** Systemic corticosteroids **Intervention B** Standard of care + / - placebo	11 studies on 8019 patients **Descriptive statistics:** NR	**<u>Comparison systemic corticosteroids vs. standard of care (+ / - placebo)</u>** Number of studies: 11 Number of participants: 8019 **Critical outcomes:** · All-cause mortality (at up to day 30): 274 per 1000 in SoC group, Difference 28 per 1000 (RR 0.90, CI 95% 0.84 to 0.97, N = 7898 in 9 RCTs, I^2 = 0%) · All-cause mortality (at up to day 60): NR · All-cause mortality at up to longest follow-up (day 120): 402 per 1000 in SoC group, Difference 104 per 1000 (RR 0.74, CI 95% 0.23 to 2.34, N = 485 in 3 RCTs, I^2 = 0%) · Clinical improvement participants discharged alive at up to day 28: 620 per 1000 in SoC group, Difference 44 per 1000 (RR 1.07, CI 95% 1.03 to 1.11, N = 6786 in 3 RCTs) Clinical worsening: new need for IMV or death within 28 days: 282 per 1000 in SoC group, Difference 22 per 1000 (RR 0.92, CI 95% 0.84 to 1.01, N = 5586 in 2 RCTs)	**Methodological quality of included studies assessed using RoB 2 tool:** Some concerns to high risk of bias **Evidence synthesis:** · ITT · Random-effects model and in rare cases fixed-effects model that very small studies did not receive extraordinary weight **GRADE** · Mortality, day 30: Moderatee · Mortality, day 120: very low · Clinical improvement: discharged alive: low · Serious adverse events: very low	Angus 2020 Corral-Gudino 2021 Dequin 2020 Edalatifard 2020 Farhani 2021 Horby 2021 Jamaati 2021 Jeronimo 2020 Munch 2021a Tang 2021 Tomazini 2020

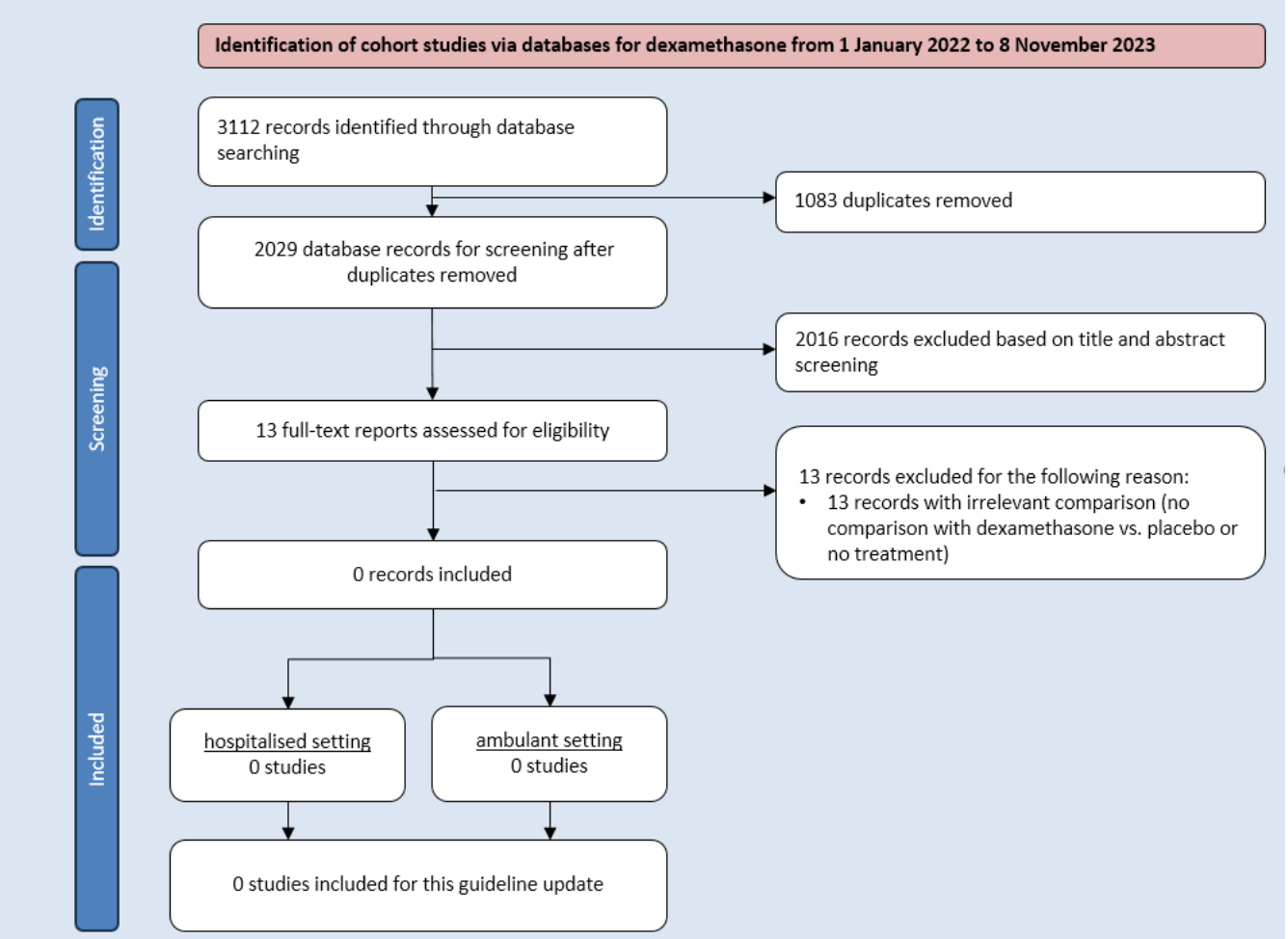
	- Science Citation Index Expanded (1945 to present) - Emerging Sources Citation Index (2015 to present) WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** - hospitalised individuals with unknown vaccination status and a confirmed diagnosis of symptomatic COVID-19; any age, sex, or ethnicity **Study type:** RCTs			· Admission to ICU or death: NR · Serious adverse events at up to day 28: Angus 2020 shock-dependent hydrocortisone: RR 4.11 (95% CI 0.23 to 72.98); Angus 2020 fixed-dose hydrocortisone: RR 1.43 (95% CI 0.16 to 12.49); Tomazini 2020: RR 0.54 (95% CI 0.19 to 1.59), N = 678 in 2 RCTs · Adverse events (any grade) at up to day 28: Edalatifard 2020: RR 0.82 (95% CI 0.12 to 5.48); Tang 2021: RR 0.63 (95% CI 0.22 to 1.76); Tomazini 2020: RR 0.99 (95% CI 0.89 to 1.10), N = 447 in 3 RCTs · Hospital-acquired infections: Corral-Gudino 2021: RR 4.14 (95% CI 0.51 to 33.49); Dequin 2020: RR 0.90 (95% CI 0.60 to 1.34); Tang 2021: RR 2.00 (95% CI 0.19 to 21.24); Tomazini 2020: RR 0.75 (95% CI 0.50 to 1.15), N = 598 in 4 RCTs · Quality of life: NR **Additional outcomes:** Invasive fungal infections: Corral-Gudino 2021: RR 2.50 (95% CI 0.11 to 59.15), N = 64 in 1 RCT	· Adverse events: very low · Hospital-acquired infections: very low	

5.5.5 Studienselektion: Flow chart 4a

5.5.5.1 *Flow Chart 4a für die RCT-Recherche*



5.5.5.2 *Flow Chart 3a für die Kohorten-Recherche*



5.5.6 Literaturrecherche 4a

5.5.6.1 *Litraturrecherche für RCTs*

Date of search for all databases: 03.03.2021, update 07.10.2021, update 06.10.2023			
Database/Register	Search	Update Search	Update Search
CCSR	250 references (169 studies)	357 references (233 studies)	1065 references (562 studies)
WOS (SCI+ECI) ab 06.10.2023 Scopus	305	390	1441
WHO COVID-19 DB*	573	650	541
Total	1128	*1397*	*3047*
Total (after deduplication)	1029	*1029+398=1427*	*2164 (include 487 Preprint, clinical trial records)*

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023.*

Since June 2023, manual updates to the database have been discontinued.

Cochrane COVID-19 Study Register

Search string:

corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosон* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR Emmetipi OR esameton* OR firmacort OR medlon* OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone Or precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR Komed OR Nutracort OR Proctocort OR Rectoid OR Hydrocort OR locoid OR Solu-Glyc

Study characteristics:

1) "Intervention assignment": "Randomised"; "Quasi-Randomised" OR "Unclear"
2) "Study design": "Parallel/Crossover" OR "Unclear"

Scopus Seit 06.10.2023 anstatt von Web of Science

TITLE-ABS (corticosteroid* OR corticoid* OR prednison* OR dehydrocortison* OR deltason* OR decortin* OR orasone* OR deltra* OR meticorten* OR cortancyl* OR deltacorten* OR dacortin* OR adasone* OR "delta-cortison" OR panasol* OR decorton* OR metacortandracin* OR paracort* OR predicor* OR decortisyl* OR delta-1-cortison* OR "delta-dome" OR deltadehydrocortison* OR ofisolon* OR panafcort* OR predicorten* OR predni* OR econonson* OR promifen* OR servison* OR deltison* OR lisacort* OR meprosон* OR rayos OR sterapred* OR "liquid pred" OR cortan* OR rectodelt* OR predeltin* OR prednisolon* OR methylprednisolon* OR medrol OR "pred forte" OR medrone OR urbason OR wyacort OR "Delta-F" OR duralon* OR medrate OR omnipred OR adlone OR caberdelta OR depmedalon* OR "Depo Moderin" OR "Depo-Nisolone" OR emmetipi OR esameton* OR firmacort OR medlon*

OR "Mega-Star" OR meprolon* OR metilbetason* OR metrocort OR metypresol OR metysolon* OR orapred OR "Predni-M-Tablinen" OR radilem OR sieropresol OR solpredon* OR "A-MethaPred" OR prelone OR medrone OR aprednislon OR pediapred OR hostacortin OR "Di-Adreson-F" OR adnisolon* OR capsoid OR cortalon* OR cortisolon* OR deltacortril OR estilsona OR panafcortelone OR sterane OR "Delta-Cortef" OR econopred OR dacortin OR decaprednil OR "Delta-Diona" OR "Delta-Phoricol" OR deltahydrocortison* OR deltasolon* OR deltidrosol OR dhasolone OR fisopred OR frisolona OR gupison* OR hydeltra OR hydeltrasol OR klismacort OR kuhlprednon OR lenisolon* OR "Lepi-Cortinolo" OR "Linola-H" OR longiprednil OR metacortandralon* OR "Meti Derm" OR meticortelon* OR opredsone OR precortisyl OR "Pred-Clysma" OR predeltilon* OR prenilone OR hydrocortancyl OR "Solu Moderin" OR predonin* OR metypred OR prednisol OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR maxidex OR dextenza OR dexasone OR dexpak OR hydrocortison* OR cortisol OR cortef OR hydrocorton* OR cetacort OR barseb OR aeroseb OR "Cort-Dome" OR cortenema OR cortril OR cortifan OR cortispray OR dermacort OR domolene OR eldecort OR hautosone OR "Heb-Cort" OR hytone OR komed OR nutracort OR proctocort OR rectoid OR hydrocort OR locoid OR solu-glyc)
AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")
AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023))

WHO COVID-19 Global literature on coronavirus disease

(corticosteroid* OR corticoid* OR prednis* OR hydrocorti* OR methylpredni* OR deltahydrocorti* OR dehydrocorti* OR dexameth* OR desameth*) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

5.5.6.2 *Literaturrecherche für Kohortenstudien*

Intervention Dexamethason

Zeitraum ab 01.01.2022

Date of search for all databases: 08.11.2023		
Database/Register	Search	Update Search
CCSR	2151 (1881 studies)	
Scopus	789	
WHO COVID-19 DB*	172	

Total	3112	
Total (after deduplication)	2029	

Cochrane COVID-19 Study Register

Search string:

corticosteroid* OR corticoid* OR dexamethason* OR "BB 1101" OR decadron OR hexadrol OR fortecortin OR dexameth OR dexone OR hexadecadrol OR desamethason* OR ozurdex OR deronil OR baycuten OR aacidexam OR spersadex OR dexacortal OR gammacorten OR visumetazon* OR adexone OR "Alba-Dex" OR cortidexason OR decacort OR decadrol OR dectancyl OR desameton OR loverine OR millicorten OR orgadrone OR alin OR auxiloson OR cortisumman OR decalix OR decameth OR decasone OR dekacort OR deltafluorene OR "Dexa-Mamallet" OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR fluorodelta OR lokalison OR methylfluorprednisolon* OR mymethason* OR "Dexa-Rhinosan" OR "Dexa-Scheroson" OR "Dexa-sine" OR dexacortin OR dexafarma OR dinormon OR baycadron OR "Aeroseb-Dex" OR Maxidex OR Dextenza OR dexasone OR dexpak

5.6 Schlüsselfrage 4a.2) hohe Dosis Dexamethason (12 mg oder höher) vs. Lowe Dosis Dexamethason (6 bis 8 mg)

Autor*innen: Caroline Hirsch

Es gab 7 RCTs mit 3784 Teilnehmenden.

5.6.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: High-dose dexamethasone (12 mg or higher)

Vergleichsintervention: Low-dose dexamethasone (6-8 mg)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Low-dose dexamethasone (6-8 mg)	**Absolute effect estimates** High-dose dexamethasone (12 mg or higher)	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality up to 30 days	Relative risk: 1.18 (CI 95% 0.81 - 1.72) Based on data from 2648 patients in 5 studies[1] Observation time up to 30 days	**200** per 1000	**236** per 1000 Difference: **36 more per 1000** (CI 95% 38 less - 144 more)	**Very low** Due to very serious inconsistency, Due to serious imprecision, Due to serious risk of bias[2]	We are uncertain whether high-dose dexamethasone (12mg or higher) increases or decreases all-cause mortality up to 30 days compared to low-dose dexamethasone
All-cause mortality up to 60 days	Relative risk: 1.19 (CI 95% 0.71 - 2.01) Based on data from 863 patients in 3 studies[3] Observation time up to 60 days	**217** per 1000	**258** per 1000 Difference: **41 more per 1000** (CI 95% 63 less - 219 more)	**Very low** Due to serious inconsistency, Due to serious imprecision, Due to serious risk of bias[4]	We are uncertain whether high-dose dexamethasone (12mg or higher) increases or decreases all-cause mortality up to 60 days compared to low-dose dexamethasone

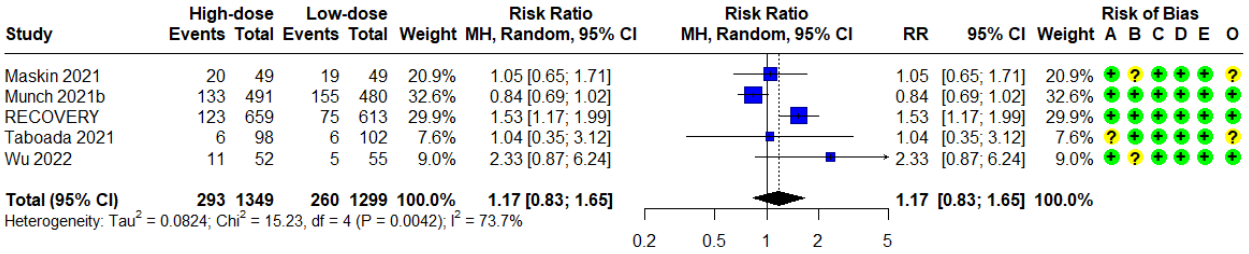
All-cause mortality up to longest follow-up	Relative risk: 0.87 (CI 95% 0.74 - 1.04) Based on data from 963 patients in 1 studies[5] Observation time up to 180 days	**386** per 1000 **336** per 1000 Difference: **50 less per 1000** (CI 95% 100 less - 15 more)	**Moderate** Due to serious imprecision[6]	High-dose dexamethasone (12mg or higher) probably decreases all-cause mortality up to 180 days compared to low-dose dexamethasone
Clinical improvement: discharged alive up to 30 days	Relative risk: 0.97 (CI 95% 0.93 - 1.02) Based on data from 1472 patients in 2 studies[7] Observation time up to 30 days	**831** per 1000 **806** per 1000 Difference: **25 less per 1000** (CI 95% 58 less - 17 more)	**Moderate** Due to serious risk of bias[8]	High-dose dexamethasone (12mg or higher) probably has little or no difference on the number of participants discharged alive up to 30 days compared to low-dose dexamethasone
Clinical worsening: new need for IMV or death up to 30 days	Relative risk: 1.52 (CI 95% 1.18 - 1.97) Based on data from 1272 patients in 1 studies[9] Observation time up to 30 days	**131** per 1000 **199** per 1000 Difference: **68 more per 1000** (CI 95% 24 more - 127 more)	**Moderate** Due to serious imprecision[10]	High-dose dexamethasone (12mg or higher) probably increases the number of participants with new need for IMV or death up to 30 days compared to low-dose dexamethasone
Admission to ICU or death up to 30 days	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at admission to ICU or death up to 30 days
Post COVID-19 condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post COVID-19 condition
Serious adverse events[11] during treatment	Based on data from 1080 patients in 2 studies[12] Observation time during treatment	We did not perform meta-analyses because of high risk of bias arising from the missing adjustment for competing risk of death. We present descriptive data only: Munch 2021b: RR 0.80 (95% CI 0.60 to 1.07); Maskin 2021: RR 1.05 (95% CI 0.88 to 1.25).	**Very low** Due to serious risk of bias, Due to very serious imprecision[13]	We are uncertain whether high-dose dexamethasone (12mg or higher) increases or decreases serious adverse events during treatment compared to low-dose dexamethasone
Adverse events any grade[14] during treatment	Based on data from 644 patients in 2 studies[15] Observation time during treatment	We did not perform meta-analyses because of high risk of bias arising from the missing adjustment for competing risk of death. We present descriptive data only: Bouadma 2022: RR 0.99 (95% CI 0.90 to 1.09); Maskin 2021: RR 1.02 (95% CI 0.96 to 1.08).	**Low** Due to serious risk of bias, Due to serious imprecision[16]	High-dose dexamethasone (12 mg or higher) may have little or no difference on adverse events any grade during treatment compared to low-dose dexamethasone
Hospital acquired infections during treatment	Based on data from 1626 patients in 3 studies[17] Observation time during treatment	We did not perform meta-analyses because of high risk of bias arising from the missing adjustment for competing risk of death. We present descriptive data only: Bouadma 2022: RR 1.10 (95% CI 0.82 to 1.44); Maskin 2021: RR 0.89 (95% CI 0.70 to 1.14);	**Low** Due to serious risk of bias, Due to serious imprecision[18]	High-dose dexamethasone (12mg or higher) may have little or no difference on hospital acquired infections during

		Munch 2021b: RR 0.80 (95% CI 0.56 to 1.14).		treatment compared to low-dose dexamethasone
Quality of life	Based on data from 963 patients in 1 studies[19] Observation time at 180 days	We did not perform meta-analysis because data were reported as median (IQR) and adjusted mean differences. We present descriptive data only. Granholm 2022: EQ-5D-5L* value index 0.80 (0 to 0.97) vs. 0.68 (0 to 0.92), adjusted mean difference 0.06 (99% CI -0.01 to 0.12); EQ VAS* 65 (0 to 90) vs. 55 (0 to 55) adjusted mean difference 4 (99% CI -3 to 4) *higher values indicate better quality of life; adjusted for stratification variables (being trial site, age below 70 years and the use of invasive mechanical ventilation at baseline)	**Low** Due to serious imprecision, Due to serious risk of bias[20]	High-dose dexamethasone (12mg or higher) may have little or no difference on quality of life at 180 days compared to low-dose dexamethasone

1. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [4]. [6]. [5].
2. Risk of bias: very serious. no information about allocation concealment (Taboada 2021), protocol deviations (Maskin 2021); Inkonsistenz: very serious. The magnitude of statistical heterogeneity was high, with I^2: 74%., The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies, Point estimates vary widely; Imprecision: very serious. Wide confidence intervals;
3. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [5]. [1].
4. Risk of bias: very serious. no information about allocation concealment (Taboada 2021); Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was Moderatee, with I^2: 55%.; Imprecision: very serious. Wide confidence intervals;
5. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [2].
6. Imprecision: very serious. Only data from one study;
7. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [5]. [4].
8. Risk of bias: very serious. no information about allocation concealment (Taboada 2021);
9. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [4].
10. Imprecision: very serious. Only data from one study;
11. undefined
12. Systematic review Referenzen [5].
13. Risk of bias: very serious. due to missing adjustment for competing risk of death; Imprecision: very serious. due to very low number of events/participants;
14. undefined
15. Primary study references [1]. [5].
16. Risk of bias: very serious. due to missing adjustment for competing risk of death; Imprecision: very serious. Wide confidence intervals;
17. Primary study references [1]. [5].
18. Risk of bias: very serious. missing adjustment for competing risk of death, protocol deviations, measurement of the outcome, no information about the allocation concealment; Indirectness: very serious.
19. Primary study references [2].
20. Risk of bias: very serious. missing data multiply imputed; Imprecision: very serious. Only data from one study;

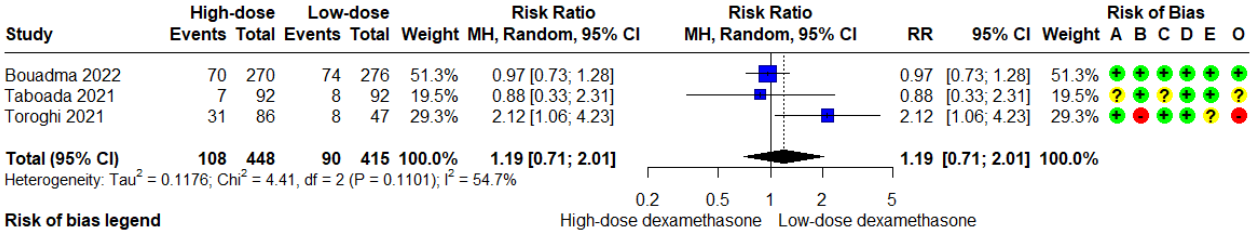
5.6.2 Analysen / Forest Plots

Mortality, day 30



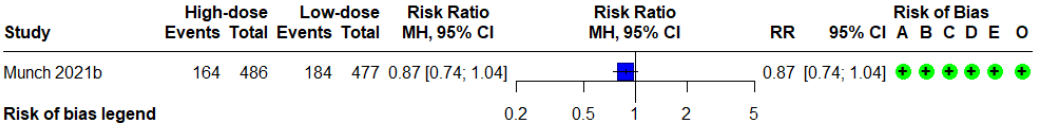
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Mortality, day 60



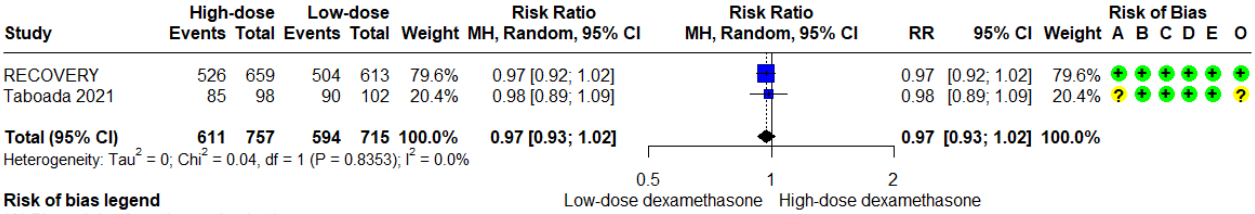
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Mortality, day 180



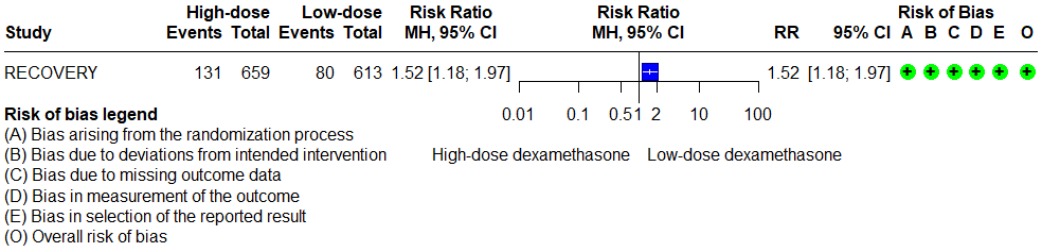
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

Clinical improvement: discharged alive, day 30

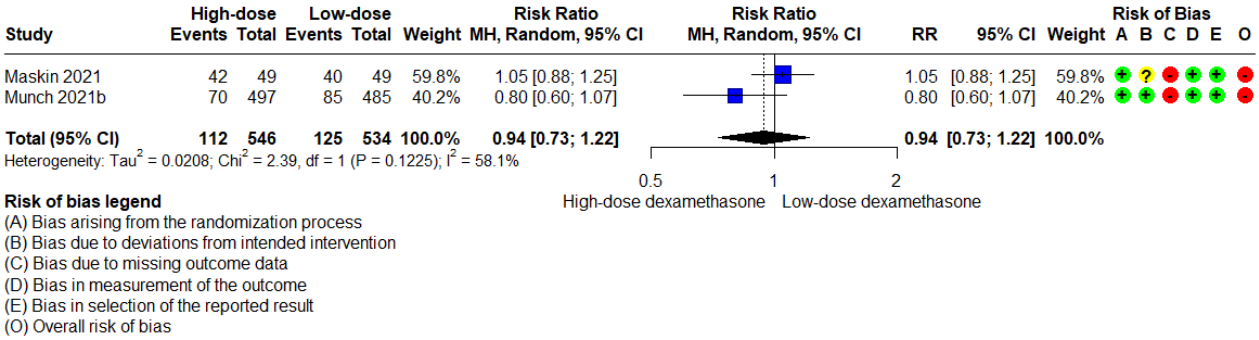


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(O) Overall risk of bias

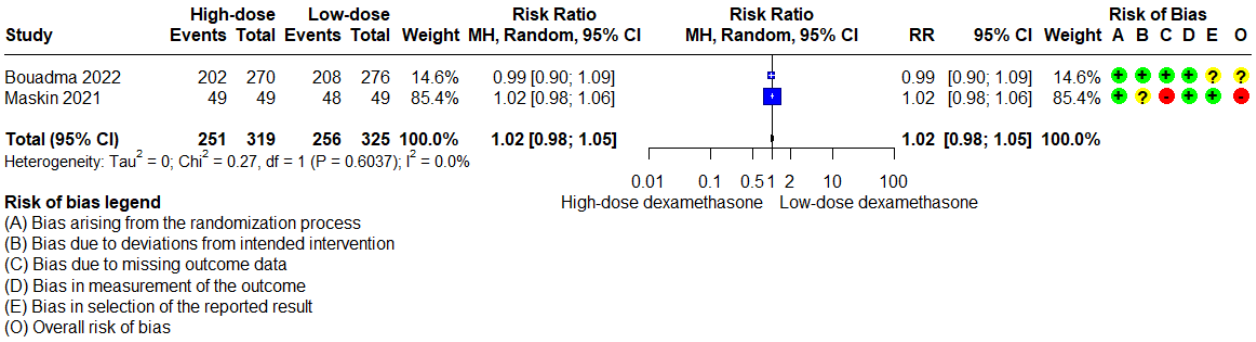
Clinical worsening: new need for IMV or death, day 30



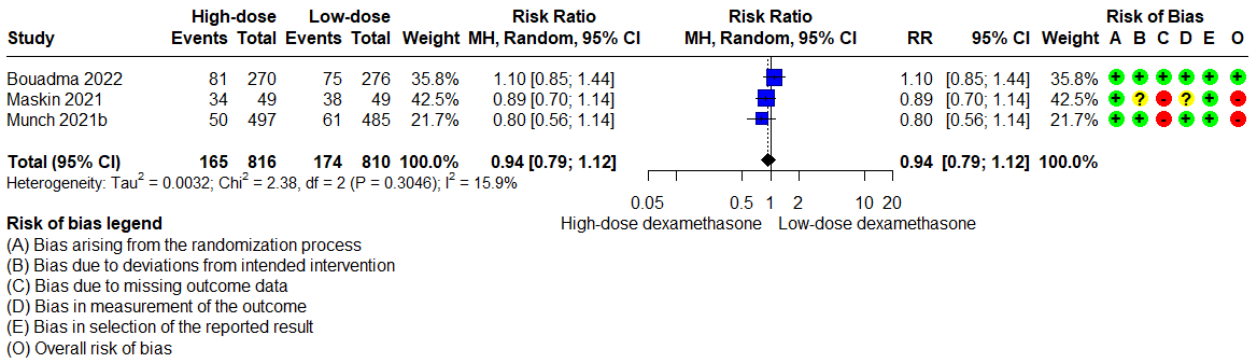
Serious adverse events



Adverse events



Hospital-acquired infections



5.6.3 Referenzen der eingeschlossenen Studien

- Bouadma L, Mekontso-Dessap A, Burdet C, Merdji H, Poissy J, Dupuis C, Guitton C, et al. (2022). High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute

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5.6.4 Charakteristika der eingeschlossenen Studien

5.6.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodological Notes	Included publications
Wagner 2022 Systematic review with MA	**Study design** **Search time frame** Inception of each database to 6 January 2022 **Sources:** Cochrane COVID-19 Study Register (CCSR) comprising: - MEDLINE (PubMed) - Embase.com - ClinicalTrials.gov - WHO International Clinical Trials Registry Platform (ICTRP) - medRxiv - Cochrane Central Register of Controlled Trials (CENTRAL) Web of Science Core Collection (Clarivate) - Science Citation Index Expanded (1945 to present)	**Intervention A** high-dose dexamethasone (12 mg or higher) **Intervention B** low-dose dexamethasone (6 mg to 8 mg)	4 studies on 1383 patients **Descriptive statistics:** NR	**<u>Comparison high-dose dexamethasone (12 mg or higher) vs. low-dose dexamethasone (6 mg to 8 mg):</u>** Number of studies: 4 Number of participants: 1383 **Critical outcomes:** · All-cause mortality (at up to day 30): 285 per 1000 in low-dose group, Difference 37 per 1000 (RR 0.87, CI 95% 0.73 to 1.04, N = 1269 in 3 RCTs, I^2 = 0%) · All-cause mortality (at up to day 60): NR · All-cause mortality at up to longest follow-up (day 120): 329 per 1000 in low-dose group, Difference 23 per 1000 (RR 0.93, CI 95% 0.79 to 1.08, N = 1383 in 4 RCTs, I^2 = 0%) · Clinical improvement participants discharged alive at up to day 28: 882 per 1000 in low-dose group, Difference 17 per 1000 (RR 0.98, CI 95% 0.89 to 1.09, N = 200 in 1 RCT) · Clinical worsening: new need for IMV or death within 28 days: NR	**Methodological quality of included studies assessed using RoB 2 tool:** Some concerns to high risk of bias **Evidence synthesis:** · ITT · Random-effects model and in rare cases fixed-effects model that very small studies did not receive extraordinary weight **GRADE** · Mortality, day 30: low · Mortality, day 120: very low · Clinical improvement: discharged alive: low · Serious adverse events: very low	Maskin 2021 Munch 2021b Taboada 2021 Toroghi 2021

	- Emerging Sources Citation Index (2015 to present) WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** - hospitalised individuals with unknown vaccination status and a confirmed diagnosis of symptomatic COVID-19; any age, sex, or ethnicity **Study type:** RCTs			· Admission to ICU or death: NR · Serious adverse events at up to day 28: Munch 2021b: RR 0.80 · (95% CI 0.60 to 1.07); Maskin 2021: RR 1.05 (95% CI 0.88 to 1.25: RR 1.02 (95% CI 0.96 to 1.08), N = 1080 in 2 RCTs · Adverse events (any grade) at up to day 28: Maskin 2021: RR 1.02 (95% CI 0.96 to 1.08), N = 98 in 1 RCT · Hospital-acquired infections: Maskin 2021: RR 0.89 (95% CI 0.70 to 1.14); Munch 2021b: RR 0.80 (95% CI 0.56 to 1.14), N = 1080 in 2 RCTs · Quality of life: NR **Additional outcomes:** · Invasive fungal infections: Munch 2021b: RR 0.70 (95% CI 0.36 to 1.34); Maskin 2021: RR 1.00 (95% CI 0.21 to 4.71), N = 1080 in 2 RCTs	· Adverse events: very low · Hospital-acquired infections: very low	

5.6.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Bouadma 2022 COVIDICUS Triple-blinded RCT	**Sample size:** N = 550 (1:1) randomised to standard of care dexamethasone or high-dose dexamethasone · 6 mg standard of care dexamethasone + an additional dose of 14 mg from day 1 to 5, then 4 mg from day 6 to day 10: N = 270 · 6 mg daily + placebo: N = 276 **Enrolment period:** 10.04.2020 to 17.09.2020 France **Inclusion criteria:** · adults aged at least 18 years admitted to an ICU within the last 48 hours for confirmed or highly suspected COVID-19 · with AHRF (defined as arterial partial pressure of oxygen,	**Experimental:** · intravenous dexamethasone · 6 mg standard of care dexamethasone + an additional dose of 14 mg from day 1 to 5, then 4 mg from day 6 to day 10 · N = 270 **Control:** · Intravenous dexamethasone · Dose: 6 mg + placebo · N = 276 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	Not reported	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: No concerns: "Blinding was maintained throughout the study" 3) Attrition bias **Outcome-specific:** No concerns, for all outcomes data available for all participants randomised 4) Outcome measurement: No concerns 5) Selective reporting: Outcomes measured and analysed in accordance to protocol; except for adverse events ----------
			All-cause mortality (day 60)	RR: 0.97 (0.73 to 1.28) High-dose dexa: 70/270 Low-dose dexa: 74/276	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	RR: 0.99 (0.90 to 1.09) High-dose dexa: 202/270 Low-dose dexa: 208/276	
			Hospital-acquired infections	RR: 1.10 (0.85 to 1.44) High-dose dexa: 81/270 Low-dose dexa: 75/276	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	[PaO2] < 70 mm Hg, transcutaneous oxygen saturation as measured by pulse oximetry [SpO2] < 90% on room air, tachypnea with > 30 breaths/min, labored breathing, respiratory distress, or need for O2 flow ≥ 6 L/min) · who could receive any available treatment targeting COVID-19 · those with ongoing IMV at inclusion or with anatomical factors precluding the use of nasal cannula, hypercapnia indicating noninvasive ventilation (PaCO2 ≥50 mm Hg), or intolerance at admission to any of the oxygenation strategies, ie, the IMV population were R11only eligible to the				6) Overall: low concerns for risk of bias

	dexamethasone randomization **Time since symptom onset (median, range):** · Exp: 9 (7-11) · Ctrl: 9 (6-11) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 68.1 (IQR 60.1 to 72.9) · Ctrl: 66.3 (IQR 58.9 to 73.8) ***<u>Comorbidities</u>*** **Any** · Exp: 79,3% · Ctrl: 82,2% **Diabetes** · Exp: 34,8% · Ctrl: 39,1% **Obesity (BMI ≥30 kg/m²)** · Exp: 40,7% · Ctrl: 58% **Hypertension** · Exp: 53% · Ctrl: 58% **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed**				

	• <u>Cancer</u> • Exp: 12.2% • Ctrl: 10.1% • <u>SOT</u> • Exp: 1.1% • Ctrl: 2.9% **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: NR • Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
RECOVERY Open-label RCT	**Sample size:** N = 1272 (1:1) randomised to usual care plus higher dose Corticosteroids or usual care alone · oral or intravenous dexamethasone 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days: N = 659 · 6 mg daily: N = 613 **Enrolment period:** 25.05.2021 to 13.05.2022 Africa, Asia, UK **Inclusion criteria:** · aged at least 18 years · clinically suspected or laboratory-confirmed SARS-CoV-2 infection, · clinical evidence of hypoxia (ie,	**Experimental:** · oral or intravenous dexamethasone · Dose: 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days · N = 659 **Control:** · oral or intravenous dexamethasone · Dose: 6 mg · N = 613 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.53 (1.17 to 1.99) High-dose dexa: 123/659 Low-dose dexa: 75/613	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label 3) Attrition bias **Outcome-specific:** data available for all outcomes for all participants randomised ("Recruitment of patients receiving ventilatory support is ongoing") 4) Outcome measurement: No concerns 5) Selective reporting: All outcomes measured and analysed in accordance to protocol ----------
		All-cause mortality (day 60)	Not reported	
		All-cause mortality (longest follow-up)	Not reported	
		Clinical improvement: discharged alive (day 30)	RR: 0.97 (0.92 to 1.02) High-dose dexa: 526/659 Low-dose dexa: 504/613	
		Clinical worsening: new need for IMV or death (day 30)	RR: 1.52 (1.18 to 1.97) High-dose dexa: 131/659 Low-dose dexa: 80/613	
		Admission to ICU or death	Not reported	
		Serious adverse events	Not reported	
		Adverse events, any grade	Not reported	
		Hospital-acquired infections	Not reported	
		Quality of life	Not reported	
		Post COVID-19 condition	Not reported	

	receiving oxygen with or without other forms of respiratory support, or with oxygen saturations <92% on room air) · no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial **Time since symptom onset (median, range):** · Exp: 7 (4-10) · Ctrl: 7 (4-10) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 60.2 · Ctrl: 62.1 ***<u>Comorbidities</u>*** **Any** · Exp: 51% · Ctrl: 50% **Diabetes** · Exp: 20% · Ctrl: 19% **Obesity (BMI ≥30 kg/m²)**				6) Overall: low concerns for risk of bias

	• Exp: NR • Ctrl: NR **Hypertension** • Exp: NR • Ctrl: NR **Cardiovascular disease** • Exp: 28% • Ctrl: 27% **Lung diseases** • Exp: 20% • Ctrl: 22% **Immunosuppressed** <u>HIV</u> • Exp: < 1% • Ctrl: < 1% **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: 3% • Ctrl: 3%				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Wu 2022 Open-label RCT	**Sample size:** N = 107 (1:1) randomised to treatment with dexamethasone 20 mg daily compared with dexamethasone 6 mg daily · dexamethasone 20 mg daily: N = 52 · 6 mg daily: N = 55 **Enrolment period:** 21.01.2021 to 04.03.2022 US **Inclusion criteria:** · aged at least 18 years · PCR-confirmed COVID-19 infection on admission · needing supplemental oxygen	**Experimental:** · Dose: 20 mg daily for five days, followed by 10 mg daily for five days · N = 52 **Control:** · Dose: 6 mg · N = 55 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 2.33 (0.87 to 6.24) High-dose dexa: 11/52 Low-dose dexa: 5/55	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label; some concerns because more participants in the low-dose group received immune Moderateor therapy (tocilizumab or baricitinib) than did participants in the high-dose group (40% vs. 21%; p = 0.035) 3) Attrition bias **Outcome-specific:** no concerns (3 exclusions in the intervention group) 4) Outcome measurement: No concerns 5) Selective reporting:
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	Not reported	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	administered via nasal cannula, face mask, high-flow nasal cannula, or positive pressure ventilation (noninvasive or invasive) **Time since symptom onset (median, range):** · Exp: NR · Ctrl: NR **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 56.1 · Ctrl: 57.9 ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes** · Exp: 25% · Ctrl: 32.7% **Obesity (BMI ≥30 kg/m²)** · Exp: 38.5% · Ctrl: 32.7%				Outcomes measured and analysed according to study registry --- 6) Overall: some concerns for risk of bias

	Hypertension · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 19.2% · Ctrl: 36.4% **Lung diseases** · Exp: 15.4% · Ctrl: 16.4% **Immunosuppressed** <u>Cancer</u> · Exp: 9.6% · Ctrl: 3.6% **Malignancy** · Exp: 9.6 · Ctrl: 3.6 **Kidney disease** · Exp: 7.7% · Ctrl: 14.6%				

5.6.5 **Studienselektion:** siehe 5.5.5

5.6.6 **Literaturrecherche:** siehe 5.5.6

5.7 Schlüsselfrage 4a.3) gewichtsbasierte Dosis Dexamethason vs. Lowe Dosis Dexamethason

Autor*innen: Caroline Hirsch

Es gab 1 RCT mit 142 Teilnehmenden.

5.7.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Weight-based dexamethasone (0.2 mg/kg)

Vergleichsintervention: Low-dose dexamethasone (6-8 mg)

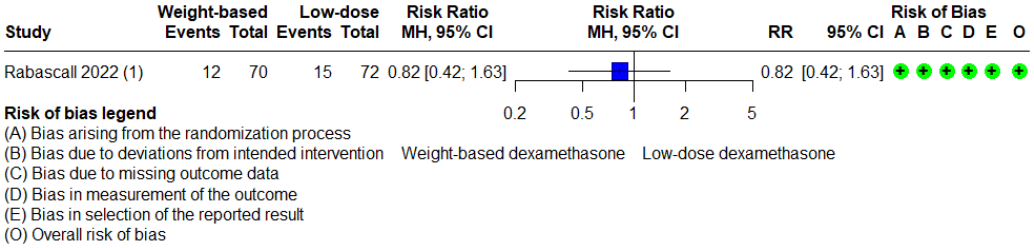
Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Low-dose dexamethasone (6-8 mg)	 Weight-based dexamethasone	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality up to 30 days	Relative risk: 0.82 (CI 95% 0.42 - 1.63) Based on data from 142 patients in 1 studies[1] Observation time up to 30 days	**208** per 1000	**171** per 1000 Difference: **37 less per 1000** (CI 95% 121 less - 131 more)	**Low** Due to very serious imprecision[2]	Weight-based dexamethasone may decrease all-cause mortality up to 30 days compared to low-dose dexamethasone
All-cause mortality up to 60 days	Relative risk (CI 95% -)	per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)		No studies were found that looked at all-cause mortality up to 60 days
All-cause mortality up to longest follow-up	Relative risk (CI 95% -)	per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)		No studies were found that looked at all-cause mortality up to longest follow-up
Clinical worsening: new need for IMV or death up to 30 days	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **less per 1000**		No studies were found that looked at new need for IMV or death up to 30 days
Clinical improvement: discharged alive up to 30 days	Relative risk: 1.08 (CI 95% 0.92 - 1.28) Based on data from 142 patients in 1 studies[3] Observation time up to 30 days	**764** per 1000	**825** per 1000 Difference: **61 more per 1000** (CI 95% 61 less - 214 more)	**Moderate** Due to serious imprecision[4]	Weight-based dexamethasone probably increases the number of participants discharged alive up to day 30 compared to low-dose dexamethasone

Admission to ICU or death[5]	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at admission to ICU or death up to 30 days
Serious adverse events during treatment	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at serious adverse events up to 30 days
Adverse events any grade during treatment	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at adverse events any grade up to 30 days
Hospital acquired infections during treatment	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at hospital acquired infections up to 30 days
Post COVID-19 condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post COVID-19 condition
Quality of life	Gemessen mit: Skala: -			No studies were found that looked at quality of life

1. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [3].
2. Imprecision: very serious. Wide confidence intervals, Only data from one study;
3. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [3].
4. Imprecision: very serious. Only data from one study;
5. up to 30 days

5.7.2 Analysen / Forest Plots

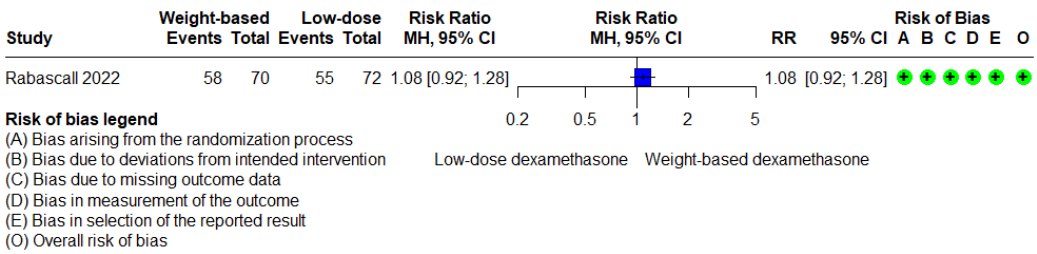
Mortality, day 30



Footnotes

(1) 0.2 mg/kg with a maximum dose of 20 mg

Clinical improvement: discharged alive, day 30



5.7.3 Referenzen der eingeschlossenen Studien

- Rabascall C, Lou BX, Dhar S, Hasan Z, Fryman C, Izard S, et al. (2022). Randomized Open Investigation Determining Steroid Dose in Severe COVID-19: the ROIDS-Dose Clinical Trial. Cureus, 14(11), e31086. doi:10.7759/cureus.31086

5.7.4 Charakteristika der eingeschlossenen Studien

5.7.4.1 *Charakteristika der eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Rabascall 2022 Open-label RCT	**Sample size:** N = 142 (1:1) randomised to dexamethasone 0.2 mg/kg intravenously daily, 6 mg daily · 0.2 mg/kg intravenously daily: N = 70 · 6 mg daily: N = 72 **Enrolment period:** 19.03.2021 to 28.12.2021 USA **Inclusion criteria:** · adults ≥18 years of age · positive SARS-CoV-2 polymerase chain reaction test · required oxygen supplementation or had a documented oxygen saturation of less than 94% **Time since symptom onset (median, range):** · NR ("data were not collected regarding the timing of initiation of corticosteroid	**Experimental:** · intravenous dexamethasone · Dose: 0.2 mg/kg with a maximum dose of 20 mg · N = 70 **Control:** · Intravenous dexamethasone · Dose: 6mg · N = 72 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.82 (0.42 to 1.63) Weight-based dexa: 12/70 Low-dose dexa: 15/72	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: open-label 3) Attrition bias: data available for all participants randomised **Outcome-specific:** 4) Outcome measurement: low for all outcomes 5) Selective reporting: low concern for all outcomes, according to trial registry specified outcomes and time-points analysed --- 6) Overall: low concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	RR: 1.08 (0.92 to 1.28) Weight-based dexa: 58/70 Low-dose dexa: 55/72	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	Not reported	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	therapy in relation to symptom onset") **<u>Characteristics</u>** **Age (median, IQR)** · Exp:55.46 (SD 15.11) · Ctrl: 57.22 (SD 15.18) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes** · Exp: NR · Ctrl: NR **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease**				

	• Exp: NR • Ctrl: NR				

5.7.5 **Studienselektion:** siehe 5.5.5

5.7.6 **Literaturrecherche:** siehe 5.5.6

5.8 Schlüsselfrage 4b) inhalative Steroide und SoC vs. SoC

Autor*innen: Marius Goldkuhle

Die verfügbare Evidenz umfasst 6 RCTs mit insgesamt 3824 eingeschlossenen Teilnehmern.

5.8.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: All adult patients (with or without risk factors for COVID-19) with positive PCR test for SARS-CoV-2

Intervention: inhaled corticosteroid

Vergleichsintervention: placebo and/or standard of care

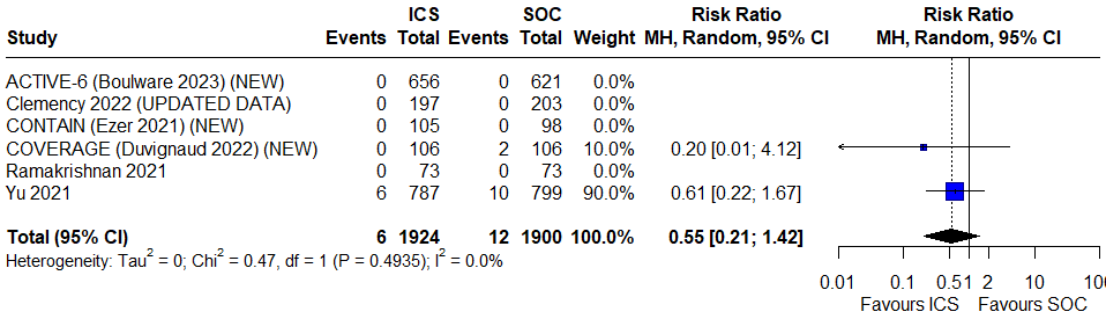
Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** placebo and/or standard of care	**Absolute effect estimates** inhaled corticosteroid	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality Up to 30 days	Relative risk: 0.55 (CI 95% 0.21 - 1.42) Based on data from 3824 patients in 6 studies	**6** per 1000	**3** per 1000 Difference: **3 less per 1000** (CI 95% 5 less - 3 more)	**Very low** Due to serious indirectness, Due to very serious imprecision[1]	We are uncertain whether inhaled corticosteroids reduce all-cause mortality up to 30 days.
Admission to hospital or death Up to 30 days	Relative risk: 0.77 (CI 95% 0.57 - 1.02) Based on data from 3717 patients in 5 studies	**55** per 1000	**42** per 1000 Difference: **13 less per 1000** (CI 95% 24 less - 1 more)	**Low** Due to serious indirectness, Due to serious imprecision[2]	Inhaled corticosteroids may reduce the risk of admission to hospital or death up to day 30.
Symptom resolution Up to 14 days	Relative risk: 1.01 (CI 95% 0.82 - 1.25) Based on data from 2401 patients in 4 studies	**481** per 1000	**486** per 1000 Difference: **5 more per 1000** (CI 95% 87 less - 120 more)	**Low** Due to serious risk of bias, Due to serious indirectness[3]	Inhaled corticosteroids probably improve symptom resolution up to day 14 slightly.
Serious adverse events	Relative risk: 0.54 (CI 95% 0.18 - 1.61) Based on data from 2863 patients in 2 studies	**6** per 1000	**3** per 1000 Difference: **3 less per 1000** (CI 95% 5 less - 4 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[4]	We are uncertain whether inhaled corticosteroids increase serious adverse events.
Adverse events	Relative risk: 0.72 (CI 95% 0.51 - 1.01) Based on data from 1880 patients in 3 studies	**73** per 1000	**53** per 1000 Difference: **20 less per 1000** (CI 95% 36 less - 1 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision[5]	We are uncertain whether inhaled corticosteroids increase adverse events.
Time to symptom resolution	Gemessen mit: Skala: - Lower ist besser	**12.1** DaysMittelwert	**9.97** DaysMittelwert	**Very low**	We are uncertain whether inhaled corticosteroids

	Based on data from 353 patients in 2 studies	Difference: **MD 2.13 less** (CI 95% 3.90 less - 0.35 less)	Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision[6]	decrease the time to symptom resolution.
Quality of life At day 28	Gemessen mit: WHO-5 Well-Being Questionnaire Skala: 0 - 100 Höher ist besser Based on data from 1434 patients in 2 studies	**52** PercentMittelwert **54.6** PercentMittelwert Difference: **MD 2.60 more** (CI 95% 0.02 more - 5.18 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias[7]	We are uncertain whether inhaled corticosteroids increase quality of life at day 28.

1. Risk of bias: none. Trials stopped earlier than scheduled, resulting in potential for overestimating benefits; Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials); Imprecision: very serious. Wide confidence intervals;
2. Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials); Imprecision: very serious. Wide confidence intervals;
3. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials);
4. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).; Imprecision: very serious. Wide confidence intervals;
5. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).; Imprecision: very serious. Wide confidence intervals;
6. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high; Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).
7. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the population of interest and those studied (Only minor proportion of vaccinated individuals in included trials).; Imprecision: very serious. Only data from one study, Wide confidence intervals;

5.8.2 Analysen / Forest Plots

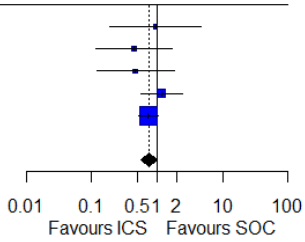
All-cause mortality



Admission to hospital or death

Study	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio MH, Random, 95% CI
ACTIVE-6 (Boulware 2023) (NEW)	3	656	3	621	3.3%	0.95 [0.19; 4.67]
Clemency 2022 (UPDATED DATA)	3	197	7	203	4.6%	0.44 [0.12; 1.68]
CONTAIN (Ezer 2021) (NEW)	3	105	6	98	4.5%	0.47 [0.12; 1.82]
COVERAGE (Duvignaud 2022) (NEW)	14	106	12	106	15.9%	1.17 [0.57; 2.40]
Yu 2021	52	787	75	838	71.7%	0.74 [0.53; 1.04]
Total (95% CI)	**75**	**1851**	**103**	**1866**	**100.0%**	**0.77 [0.57; 1.02]**

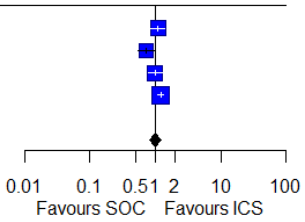
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.58$, df = 4 (P = 0.6309); $I^2 = 0.0\%$



Symptom resolution

Study	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio MH, Random, 95% CI
Clemency 2022 (UPDATED DATA)	81	197	76	203	23.5%	1.10 [0.86; 1.40]
CONTAIN (Ezer 2021) (NEW)	44	105	57	98	21.3%	0.72 [0.54; 0.95]
COVERAGE (Duvignaud 2022) (NEW)	57	106	57	106	23.2%	1.00 [0.78; 1.28]
Yu 2021	462	787	390	799	32.0%	1.20 [1.10; 1.32]
Total (95% CI)	**644**	**1195**	**580**	**1206**	**100.0%**	**1.01 [0.82; 1.25]**

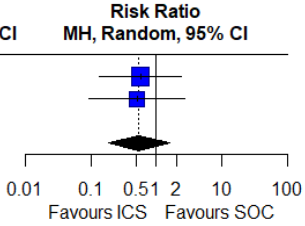
Heterogeneity: $Tau^2 = 0.0343$; $Chi^2 = 12.58$, df = 3 (P = 0.0056); $I^2 = 76.2\%$



Serious adverse events

Study	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio MH, Random, 95% CI
ACTIVE-6 (Boulware 2023) (NEW)	3	656	5	621	58.5%	0.57 [0.14; 2.37]
Yu 2021	2	787	4	799	41.5%	0.51 [0.09; 2.76]
Total (95% CI)	**5**	**1443**	**9**	**1420**	**100.0%**	**0.54 [0.18; 1.61]**

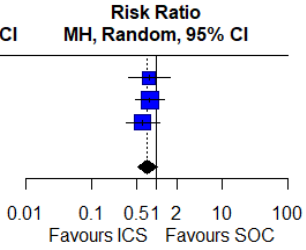
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.01$, df = 1 (P = 0.9208); $I^2 = 0.0\%$



Adverse events

Study	ICS Events	ICS Total	SOC Events	SOC Total	Weight	Risk Ratio MH, Random, 95% CI
ACTIVE-6 (Boulware 2023) (NEW)	13	656	16	621	22.4%	0.77 [0.37; 1.59]
Clemency 2022 (UPDATED DATA)	22	197	29	203	43.7%	0.78 [0.47; 1.31]
CONTAIN (Ezer 2021) (NEW)	15	105	23	98	33.8%	0.61 [0.34; 1.10]
Total (95% CI)	**50**	**958**	**68**	**922**	**100.0%**	**0.72 [0.51; 1.01]**

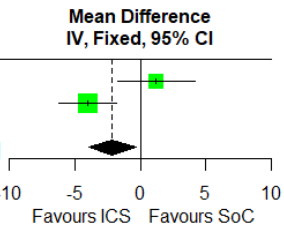
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.44$, df = 2 (P = 0.8027); $I^2 = 0.0\%$



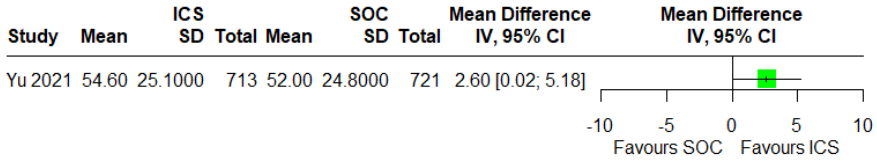
Time to symptom resolution

Study	ICS Mean	ICS SD	ICS Total	SOC Mean	SOC SD	SOC Total	Weight	Mean Difference IV, Fixed, 95% CI
COVERAGE (Duvignaud 2022) (NEW)	13.30	11.0000	106	12.10	11.0000	106	36.0%	1.20 [-1.76; 4.16]
Ramakrishnan 2021	8.00	5.0000	70	12.00	8.0000	69	64.0%	-4.00 [-6.22; -1.78]
Total (95% CI)			**176**			**175**	**100.0%**	**-2.13 [-3.90; -0.35]**

Heterogeneity: $Tau^2 = 11.7362$; $Chi^2 = 7.58$, df = 1 (P = 0.0059); $I^2 = 86.8\%$



Quality of life



5.8.3 Referenzen der eingeschlossenen Studien

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- Yu, L. M., Bafadhel, M., Dorward, J., Hayward, G., Saville, B. R., Gbinigie, O., Van Hecke, O., Ogburn, E., Evans, P. H., Thomas, N. P. B., Patel, M. G., Richards, D., Berry, N., Detry, M. A., Saunders, C., Fitzgerald, M., Harris, V., Shanyinde, M., de Lusignan, S., Andersson, M. I., … PRINCIPLE Trial Collaborative Group (2021). Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet, 398(10303), 843–855. https://doi.org/10.1016/S0140-6736(21)01744-X

5.8.4 Charakteristika der eingeschlossenen Studien

5.8.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodischical Notes	Included publications
Griesel, 2022 Systematic review with MA	**Study design** **Search time frame** Inception of each database to 07.10.2021 **Sources:** · Cochrane COVID-19 Study Register (CENTRAL, MEDLINE; EMBASE; ClinicalTrials.gov,), WHO International Clinical Trials Registry Platform, medRxiv) · • Web of Science Core Collection (Clarivate), from 1 January 2020	**Intervention A** Inhaled corticosteroids plus standard care **Intervention B** Standard care (with or without placebo)	3 studies on 3607 patients included in quantitative synthesis **Descriptive statistics:** · Age: in two studies all participants were adults, in one study the participants had to be at least 12 years old (mean age: 43.3 (SD 16.89)) · Sex: NR · Comorbidities: the most common morbiditie s in the	**<u>Comparison X:</u>** Number of studies: 3 Number of participants: 3607 **Critical outcomes:** · All-cause mortality (at up tp day 30): risk of corticosteroids 6 per 1000 vs. risk of standard care 9 per 1000; RR 0.61 (0.22 – 1.67) (3 studies, n = 2132) · All-cause mortality (at up tp day 60): NR · In-hospital mortality at up to longest follow-up: · Clinical worsening: new need for IMV or death within 28 days: · Clinical improvement participants discharges alive at up to day 28: · Serious adverse events during study period: risk of corticosteroids 3 per 1000 vs. risk of standard care 5 per 1000; RR 0.51 (0.09 – 2.76) (1 study, n = 1586) · Adverse events (any grade) at up to day 30: risk of corticosteroids 30 per 1000 vs. risk of standard care 34 per	**Methodological quality of included studies assessed using GRADE tool:** **Evidence synthesis:** · Random-effects-Modell **GRADE** · All-cause mortality: low (downgraded 2 levels) due to very serious imprecision (very low numbers of events, wide CI) · In-hospital mortality: · Clinical worsening: · Clinical improvement: · Serious adverse events: very low (Downgraded three levels) due to very serious imprecision (very low number of events, wide CI) and serious risk of bias	Ramakrishan et al. 2021 Clemency et al. 2021 Yu et al. 2021

	· Onwards (Science Citation Index Expanded · Emerging Sources Citation Index, · WHO COVID-19 Global literature on coronavirus disease **Eligibility criteria** **Study type:** RCTs as full-text publications or preprint articles, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes **Participants:** people with a confirmed diagnosis of COVID-19 and Moderatee-to-severe disease and		studies were asthma or arterial hypertension	1000; RR 0.88 (0.30 – 2.58) (1 study, n = 400) **Additional outcomes:** · Symptom resolution at day 14: risk of corticosteroids 553 per 1000 vs. risk of standard care 465 per 1000; RR 1.19 (1.09 – 1.30) (2 studies, n = 1986) · Admission to hospital or death at up to day 30: risk of corticosteroids 57 per 1000 vs. risk of standard care 79 per 1000; RR 0.72 (0.51 – 0.99) (2 studies, n = 2025) · Infections during study period: risk of corticosteroids 30 per 1000 vs. risk of standard care 34 per 1000; RR 0.88 (0.30. – 2.58) (1 study, n = 400)	· Adverse events: low (downgraded two levels) due to serious risk of bias and serious imprecision · Symptom resolution: · admission to hospital or death: Moderatee (Downgraded one level) due to serious imprecision (low number of participants/events and optimal information size would be 3764 participants) · Infections: low (downgraded two levels) due to very serious imprecision	

	people with a confirmed diagnosis of asymptomatic SARS-CoV-2 infection or mild COVID-19					

5.8.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Clemency, 2021 RCT	**Sample size:** N = 400 pts. (1:1) randomized to MDI or placebo (400 pts. planned) **Enrolment period:** 11.06.2020 to 03.11.2020 **Inclusion criteria:** · ≥ 12 years · Positive SARS-CoV-2 molecular antigen diagnostic sample obtained during the previous 72h · not hospitalized or under consideration for hospitalization · oxygen · saturation level ≥ 93% on room air · able to demonstrate successful use of an MDI at least 1 of the following symptomsofCOVID-19: fever, cough, or dyspnea. **Time since symptom onset (median, range):** · **NR**	**Experimental:** · ciclesonide MDI plus standard supportive care · Dose: 160 µg per actuation, for a total of 2 actuations (AM and PM) twice a day (total daily dose, 640 µg) for 30 days · N = 197 **Control:** · Placebo MDI twice a day plus standard supportive care (for 30 days) · N = 203	All-cause mortality (29 days)	Exp: 0/197 Ctrl: 0/203	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: mITT; blinded participants and personell; SOC similar (**low**) 3) Attrition bias: substantial, but equal between groups 19 vs. 22; similar reasons (**unclear)** **Outcome-specific:** 4) Outcome measurement: self assessed, but tripple blind (**low**) 5) Selective reporting: non objective outcomes; some outcomes participant reported (**high**)

	<u>Characteristics</u> **Age (mean, IQR)** • Exp: 43.7 (SD: 17.53; IQR: 13 – 87) • Ctrl: 42.9 (SD: 16.28; IQR: 14 – 83) **Vaccination status** • NR **Country** • US		Admission to hospital or death (30 days)	OR 0.45 (0.11-1.84) **Exp: 3/197** **Ctrl: 7/203**	----------
			Symptom resolution: all initial symptoms resolved (day 14)	OR 1.19 (0.78-1.81) Exp: 81/197 Ctrl: 76/203 At 30 days: 139 vs. 129 (OR 1.28 (0.84-1.97))	
			Adverse events	Exp: 22/197 Ctrl: 203	

	Comorbidities **Any** · Exp: NR · Ctrl: NR **Diabetes (Type 2):** · Exp: 22/197 (11.2%) · Ctrl: 8/203 (3.9%) **Obesity (BMI ≥30 kg/m²)** · Exp: mean BMI under obesity · Ctrl: mean BMI 30.0 (SD: 6.87) **Hypertension** · Exp: 47/197 (23.9%) · Ctrl: 42/203 (20.7%) **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases (Asthma)** · Exp: 18/197 (9.1%) · Ctrl: 8/203 (3.9%) **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease** · Exp: NR · Ctrl: NR			87/344 (25%)

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Boulware, 2023 (ACTIVE-6) RCT	**Sample size:** N = 1407 pts. Randomized to fluticasone furoate or placebo (planned number of pts. NR) **Enrolment period:** 06.08.2021 to 09.02.2022 **Inclusion criteria:** · Age ≥ 30 years old · Confirmed SARS-CoV-2 infection by any authorized or approved PCR or antigen test collected within 10 days of screening · Two or more current symptoms of acute infection for ≤7 days.	**Experimental:** · Inhaled fluticasone furoate · Dose: 200 µg (packaged as 1 blister) once daily for 14 days · N = 715 (656 included in analysis) **Control:** · matched placebo inhaler or contributing placebo (matched placebo for a	All-cause mortality (28 days)	Exp: 0/656 Ctrl: 0/621	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: no blinding (**high**) 3) Attrition bias: mITT, 59 vs. 71, low number of outcome events for nearly all outcomes (**unclear**) **Outcome-specific:**
			Admission to hospital or death (28 days)	HR 1.9 (0.8 to 3.5) **Exp: 3/656** **Ctrl: 3/621**	
			Serious adverse events (28 days)	Exp: 3/656 Ctrl: 5/621	
			Adverse events (28 days)	Exp: 13/656 Ctrl: 16/621	
			Time to symptom resolution	HR 1.01 (0.89 to 1.14)	

	• Symptoms include the following: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell **Time since symptom onset (median, range):** • NR **<u>Characteristics</u>** **Age (median, IQR)** • Exp: 45 (37-55) • Ctrl: 46 (38 – 56) **Vaccination status** <u>Not vaccinated</u> • Exp: 220 (33.5%) • Ctrl: 211 (34.0%) <u>Vaccinated – 1 dose</u> • Exp: 8 (1.2%) • Ctrl: 11 (1.8%) <u>Vaccinated – 2+ doses</u> • Exp: 428 (65.2%) • Ctrl: 399 (64.3%) **Country** • US ***<u>Comorbidities</u>*** **Any** • Exp: NR	different active study drug, with data from those groups "contributing" to the pooled analyses) • Dose: matched placebo once daily for 14 days or ivermectin-matched placebo for 3 days or fluvoxamine-matched placebo for 14 days • N = 692 (621 included in analysis)		4) Outcome measurement: no blinding; non objective outcomes; some participant reported (**high**) 87/344 (25%) 5) Selective reporting: low concerns (**low**) ----------

	• Ctrl: NR **Diabetes** • Exp: 56/640 (3.9%) • Ctrl: 65/606 (10.7%) **Obesity (BMI ≥30 kg/m²)** • Exp: 260/656 (39.6%) • Ctrl: 239/620 (38.5%) **Hypertension** • Exp: 156/640 (24.4%) • Ctrl: 169/606 (27.9%) **Cardiovascular disease (Heart disease)** • Exp: 25/640 (3.9%) • Ctrl: 33/606 (5.4%) **Lung diseases** COPD • Exp: 7/640 (1.1%) • Ctrl: 11/606 (1.8%) Asthma • Exp: 76/640 (11.9%) • Ctrl: 86/606 (14.2%) **Immunosuppressed** Cancer • Exp: 20/640 (3.0%) • Ctrl: 23/606 (3.7%) **Malignancy** • Exp: 20/640 (3.0%) • Ctrl: 23/606 (3.7%) **Kidney disease** • Exp: 6/640 (0.9%) • Ctrl: 4/606 (0.7%)			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Duvignaud, 2022 (COVERAGE) RCT	**Sample size:** N = 217 pts. (1:1) Randomized to ciclesonid or Azinc Vitality (planned number of pts. NR) **Enrolment period:** 29.12.2020 to 23.06.2021 **Inclusion criteria:** · Clinical picture suggestive of COVID-19 ≤ 7 days old · Positive test for acute SARS-CoV-2 · No criteria for hospitalization or acute oxygen therapy · Age ≥ 60 years or between 50 and 59 years of age plus presence of at least one of the following risk factors: HTA under treatment, Obesity, Diabetes, Ischemic heart disease, Heart failure, History of stroke, COPD, Stage 3 chronic kidney disease, Solid tumours or haematological malignancies (within the last 5 years), · Immunodeficiency, **Time since symptom onset (median, range):** · Exp: 4 days (3 – 5) · Ctrl: 4 days (3 – 6)	**Experimental:** · Inhaled ciclesonide (Alvesco) · Dose: 160 mg, two puffs twice a day using an inhalation chamber (640 mg of ciclesonide per day) for 10 days · N = 110 **Control:** · Azinc Vitality (a combination of vitamins and trace elements) · Dose: 2 pills per	All-cause mortality (28 days)	Exp: 0/106 Ctrl: 2/106	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: mITT; blinded participants and personell (**low**) 3) Attrition bias: few drop-outs; similar reasons (**low**) **Outcome-specific:** 4) Outcome measurement: self assessed, but tripple blind (**low**) 5) Selective reporting: (**?**) Other bias: Stopped early for futility ----------
			Admission to hospital or death (28 days)	Exp: 14/106 Ctrl: 12/106	
			Symptom resolution: all initial symptoms resolved (14 days)	Exp: 57/106 Ctrl: 57/106	
			Time to symptom resolution	Exp: 79/106 (mean 13.3, SD 11.0) Ctrl: 78/106 (mean 12.1, SD 11.0)	

	<u>Characteristics</u> **Age (median, IQR)** · Exp: 62 (58 – 67) · Ctrl: 63 (59 – 70) **Vaccination status** <u>Not vaccinated</u> · Exp: NR · Ctrl: NR <u>Vaccinated – 1 dose</u> · Exp: 13 · Ctrl: 15 <u>Vaccinated – 2+ doses</u> · Exp: 1 · Ctrl: 1 **Country** · France ***<u>Comorbidities</u>*** **Any** · Exp: 84/110 (76.4%) · Ctrl: 73/107 (68.2%) **Diabetes** · Exp: 17/110 (15.5%) · Ctrl: 16/107 (15.0%) **Obesity (BMI ≥30 kg/m²)** · Exp: 33/110 (30.0%) · Ctrl: 31/107 (29.0%) **Hypertension** · Exp: 51/110 (46.4%) · Ctrl: 38/107 (35.5%) **Cardiovascular disease** <u>ischemic heart disease</u> · Exp: 4/110 (3.6%)	day for 10 days · N = 107			

	• Ctrl: 7/107 (6.5%) <u>Cardiac insufficiency</u> • Exp: 2/110 (1.8%) • Ctrl: 3/107 (2.8%) **Lung diseases (COPD)** • Exp: 3/110 (2.7%) • Ctrl: 4/107 (3.7%) **Immunosuppressed** <u>HIV</u> • Exp: 0/110 (0.0%) • Ctrl: 1/107 (0.95) **Malignancy (solid tumour or heamatlogical malignancy <5y)** • Exp: 7/110 (6.4%) • Ctrl: 6/107 (5.6%) **Kidney disease** • Exp: NR • Ctrl: NR				

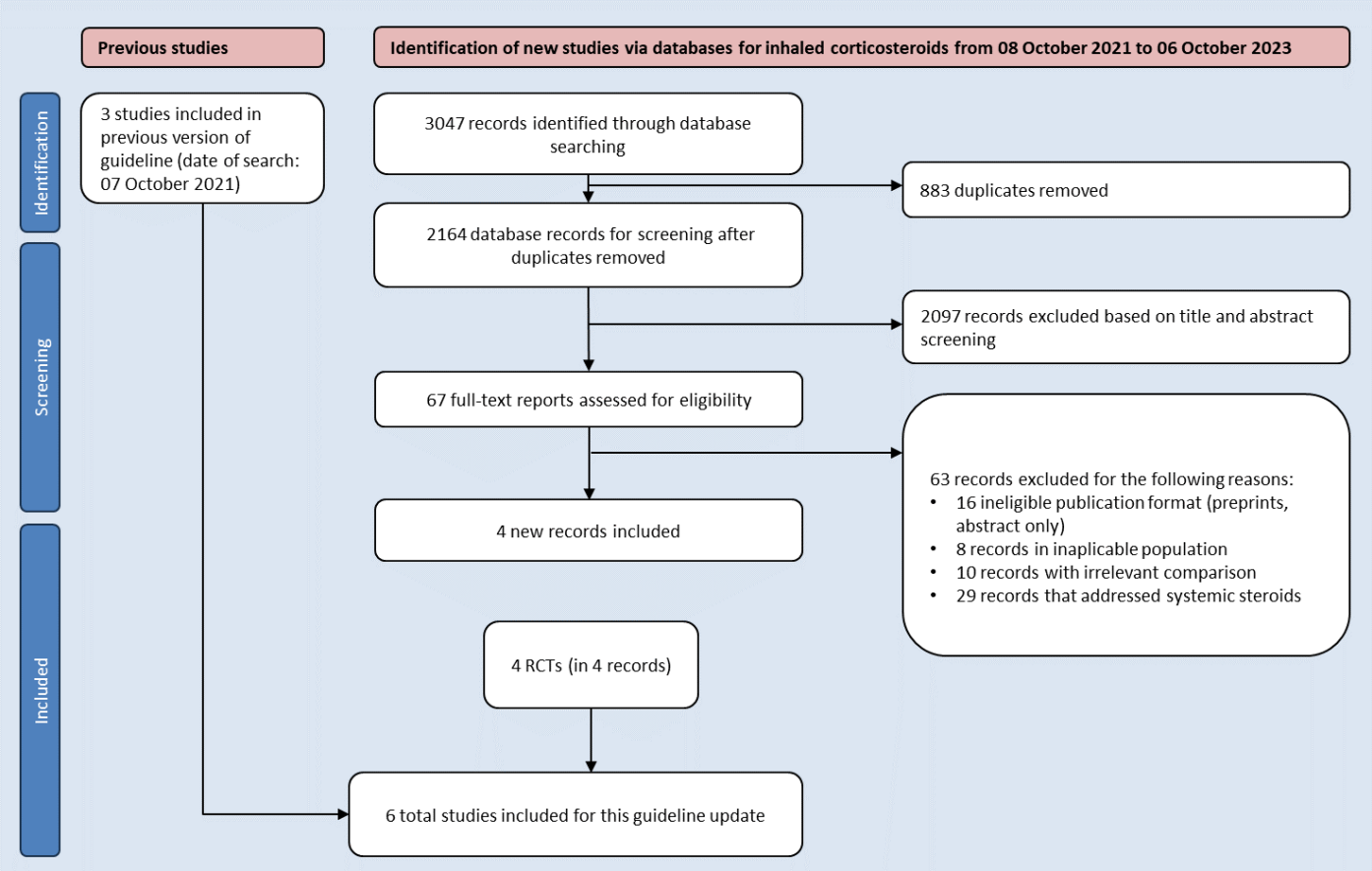
Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ezer, 2021 (CONTAIN) RCT	**Sample size:** N = 2015 pts. (1:1) Randomized to ciclesonide or placebo (XX pts. planned) **Enrolment period:** Quebec: 15.09.2020 to 08.06.2021 Ontario: 09.02.2021 to 08.06.2021 British Columbia: 22.03.2021 to 08.06.2021 **Inclusion criteria:** · ≥ 18 years of age · Symptomatic COVID-19 disease (fever, cough, OR shortness of breath) AND confirmed diagnosis with PCR+ SARS-CoV-2 within <= 5 days of enrolment* · At least one of the following symptoms: o Fever >38C by self-report o "dry cough" or "wet cough" by self-report o Shortness of breath	**Experimental:** · Inhaled and intranasal ciclesonide · Dose: 1200 µg (divided twice daily) along with 200 µg/day of intranasal ciclesonide for 14 days · N = 108 **Control:** · Inhaled and intranasal placebo · Dose: Same dosing schedule as the Experimental · N = 107	All-cause mortality (29 days	Exp: 0 Ctrl: 0	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: blinded participants and personell; ITT (**low**) 3) Attrition bias: minor few dropouts; similar reasons (**low**) **Outcome-specific:** 4) Outcome measurement: self-assessed, but double-blinded (**low**) 5) Selective reporting: (**?**) Other bias: Stopped early for futility ----------
			Admission to hospital or death (14 days)	**adjusted RD 2.3 (−3.0 to 7.6)** **Exp: 3/105** **Ctrl: 7/98**	
			Symptom resolution: all initial symptoms resolved (14 days)	adjusted RD 9.1 (−4.6 to 22.8) Exp: 44/105 Ctrl: 57/98	
			Adverse events	"Side effects" (e.g., headache, nausea, throad irritation) Exp: 15/105 Ctrl: 23/98	

	Time since symptom onset (median, range): • NR **<u>Characteristics</u>** **Age (median, IQR)** • Exp: 35 (27 -47) • Ctrl: 35 (27 – 45) **Vaccination status** • Exp: no vaccination (exclusion criteria) • Ctrl: no vaccination (exclusion criteria) **Country** • Canada ***<u>Comorbidities</u>*** **Any** • Exp: NR • Ctrl: NR **Diabetes** • Exp: 1/105 (1.0%) • Ctrl: 4/98 (4.0%) **Obesity (BMI ≥30 kg/m²)** • Exp: NR • Ctrl: NR **Hypertension** • Exp: 7/105 (7.0%) • Ctrl: 5/98 (5.0%) **Cardiovascular disease (ischaemic heart disease)** • Exp: 0/105 (0.0%) • Ctrl: 1/98 (1.0%)				

	Lung diseases (Asthma) · Exp: 4/105 (4.0%) · Ctrl: 6/98 (6.0%) **Immunosuppressed** <u>Active cancer</u> · Exp: 1/105 (1.0%) · Ctrl: 1/98 (1.0%) **Malignancy (Active cancer)** · Exp: 1/105 (1.0%) · Ctrl: 1/98 (1.0%) **Kidney disease** · Exp: NR · Ctrl: NR				

5.8.5 Studienselektion: Flow Chart 4b

5.8.5.1 *Flow Chart 3b*



5.8.6 **Literaturrecherche:** siehe 5.5.6

5.9 Schlüsselfrage 5a: Tocilizumab und SoC vs. SoC alone

Autor*innen: Caroline Hirsch

Es gab 14 RCTs mit 7597 Teilnehmenden.

5.9.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Tocilizumab + Standard of Care

Vergleichsintervention: Standard of Care (plus/minus Placebo)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Summary**
		Standard of Care (plus/minus Placebo)	Tocilizumab + Standard of Care		

All-cause mortality up to 30 days	Relative risk: 0.88 (CI 95% 0.81 - 0.96) Based on data from 6482 patients in 9 studies[1] Observation time up to 30 days	**302** per 1000 **266** per 1000 Difference: **36 less per 1000** (CI 95% 57 less - 12 less)	**Low** Due to serious inconsistency, Due to serious imprecision[2]	Tocilizumab + standard of care may decrease all-cause mortality up to 30 days compared to standard of care alone
All-cause mortality up to 60 days	Relative risk: 0.92 (CI 95% 0.71 - 1.21) Based on data from 1265 patients in 3 studies[3] Observation time up to 60 days	**149** per 1000 **137** per 1000 Difference: **12 less per 1000** (CI 95% 43 less - 31 more)	**Moderate** Due to serious imprecision[4]	Tocilizumab + standard of care probably has little or no difference on all-cause mortality up to 60 days compared to standard of care alone
All-cause mortality up to 180 days	Relative risk: 0.9 (CI 95% 0.77 - 1.05) Based on data from 1181 patients in 1 studies[5] Observation time up to 180 days	**400** per 1000 **360** per 1000 Difference: **40 less per 1000** (CI 95% 92 less - 20 more)	**Low** Due to very serious imprecision[6]	Tocilizumab + standard of care may decrease all-cause mortality up to 180 days compared to standard of care alone
Clinical improvement: time to discharged alive	Hazard ratio: 1.22 (CI 95% 1.13 - 1.32) Based on data from 4566 patients in 2 studies[7]	**458** per 1000 **526** per 1000 Difference: **68 more per 1000** (CI 95% 41 more - 96 more)	**Low** Due to serious imprecision, Due to serious risk of bias[8]	Tocilizumab + standard of care may improve time to discharged alive compared to standard of care alone (baseline risk from Rosas 2021)
Clinical improvement: discharged alive[9] up to 30 days	Relative risk: 1.17 (CI 95% 0.95 - 1.43) Based on data from 438 patients in 1 studies[10] Observation time up to 30 days	**458** per 1000 **536** per 1000 Difference: **78 more per 1000** (CI 95% 23 less - 197 more)	**Low** Due to very serious imprecision[11]	Tocilizumab + standard of care may increase the number of participants discharged alive up to 30 days compared to standard of care alone
Clinical worsening: new need for IMV or death up to 30 days	Relative risk: 0.82 (CI 95% 0.76 - 0.89) Based on data from 4865 patients in 5 studies[12] Observation time up to 30 days	**368** per 1000 **302** per 1000 Difference: **66 less per 1000** (CI 95% 88 less - 40 less)	**Low** Due to serious imprecision, Due to serious risk of bias[13]	Tocilizumab + standard of care may decrease the number of participants with new need for IMV or death up to 30 days compared to standard of care alone
Admission to ICU or death up to 30 days	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at admission to ICU or death
Serious adverse events up to 30 days	Relative risk: 0.9 (CI 95% 0.76 - 1.07) Based on data from 1758 patients in 8 studies[14] Observation time up to 30 days	**231** per 1000 **208** per 1000 Difference: **23 less per 1000** (CI 95% 55 less - 16 more)	**Very low** Due to serious inconsistency, Due to serious imprecision, Due to serious risk of bias[15]	We are uncertain whether tocilizumab + standard of care increases or decreases the number of participants with serious adverse events up to 30 days compared to standard of care alone

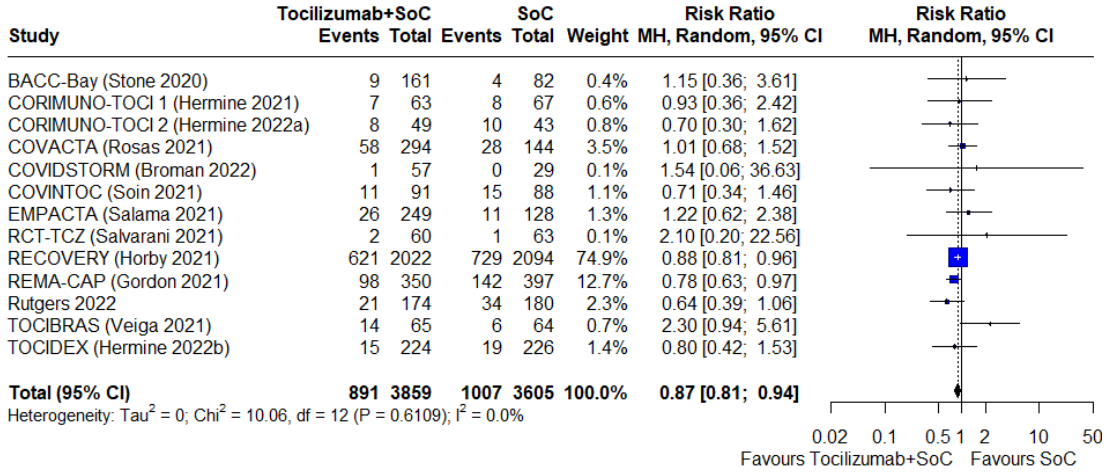
Serious adverse events[16] 60 to 90 days	Relative risk: 0.9 (CI 95% 0.76 - 1.07) Based on data from 1662 patients in 4 studies[17] Observation time 60 to 90 days	**178** per 1000 **160** per 1000 Difference: **18 less per 1000** (CI 95% 43 less - 12 more)	**Low** Due to serious imprecision, Due to serious risk of bias[18]	Tocilizumab + standard of care may have little or no difference on serious adverse events 60 to 90 days compared to standard of care alone
Adverse events up to 30 days	Relative risk: 1.1 (CI 95% 0.91 - 1.33) Based on data from 1758 patients in 8 studies[19] Observation time up to 30 days	**471** per 1000 **518** per 1000 Difference: **47 more per 1000** (CI 95% 42 less - 155 more)	**Very low** Due to serious imprecision, Due to serious inconsistency, Due to serious risk of bias[20]	We are uncertain whether tocilizumab + standard of care increases or decreases the number of participants with adverse events up to 30 days compared to standard of care alone
Adverse events 60 to 90 days	Relative risk: 0.98 (CI 95% 0.9 - 1.06) Based on data from 907 patients in 3 studies[21] Observation time 60 to 90 days	**687** per 1000 **673** per 1000 Difference: **14 less per 1000** (CI 95% 69 less - 41 more)	**Low** Due to serious imprecision, Due to serious risk of bias[22]	Tocilizumab + standard of care may have little or no difference on adverse events 60 to 90 days compared to standard of care alone
Hospital-acquired infections up to 60 days	Relative risk: 0.82 (CI 95% 0.59 - 1.13) Based on data from 438 patients in 1 studies[23] Observation time up to 60 days	**497** per 1000 **408** per 1000 Difference: **89 less per 1000** (CI 95% 204 less - 65 more)	**Low** Due to very serious imprecision[24]	Tocilizumab + standard of care may decrease hospital-acquired infections up to 60 days compared to standard of care alone
Post COVID-19 condition[25]	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post COVID-19 condition
Quality of life	Measured with: EQ VAS Scale: 0 - 100 higher is better Based on data from 332 patients in 1 studies[26] Observation time at 180 days	**68.5** Mean **69.1** Mean Difference: **MD 0.60 Higher** (CI 95% 4.43 lower - 5.63 higher)	**Low** Due to serious risk of bias, Due to serious imprecision[27]	Tocilizumab + standard of care may have little or no difference on quality of life at 180 days compared to standard of care alone

1. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [8]. [7]. [30]. [13]. [29]. [28]. [16]. [32]. [31].
2. Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies; Imprecision: very serious. Wide confidence intervals;
3. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [12]. [14]. [30].
4. Imprecision: very serious. Wide confidence intervals;
5. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [9].
6. Imprecision: very serious. Only data from one study, Wide confidence intervals;
7. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [10]. [16]. [13].

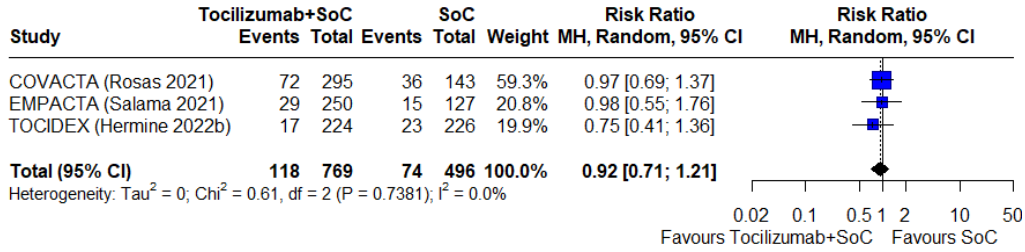
8. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals;
9. undefined
10. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [13].
11. Imprecision: very serious. Wide confidence intervals, Only data from one study;
12. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [30]. [12]. [16]. [15]. [7].
13. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals;
14. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [32]. [31]. [13]. [29]. [35]. [7]. [28].
15. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies; Imprecision: very serious. Wide confidence intervals;
16. undefined
17. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [30]. [8]. [13]. [10].
18. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals;
19. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [32]. [7]. [35]. [31]. [13]. [29]. [12]. [28].
20. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies, The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.; Imprecision: very serious. Wide confidence intervals;
21. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [10]. [30]. [13].
22. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals;
23. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [13].
24. Imprecision: very serious. Only data from one study, Wide confidence intervals;
25. undefined
26. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [9].
27. Risk of bias: very serious. Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Imprecision: very serious. Only data from one study;

5.9.2 Analysen / Forest Plots

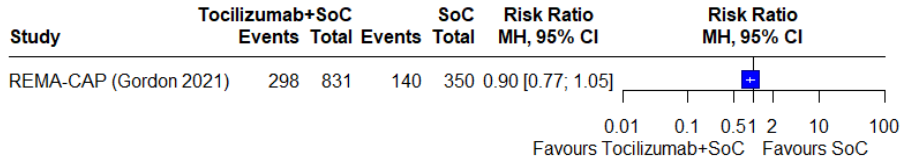
Mortality, day 30



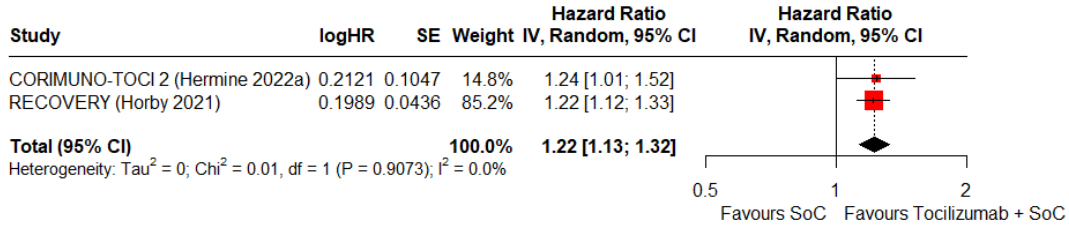
Mortality, day 60



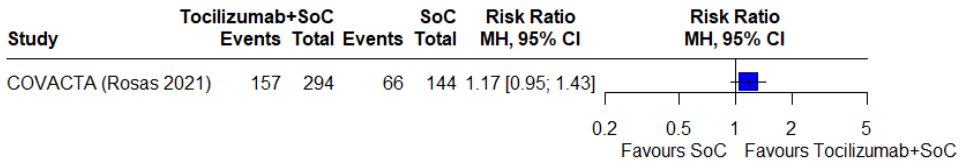
Mortality, day 180



Clinial improvement: time to discharged alive, day 30



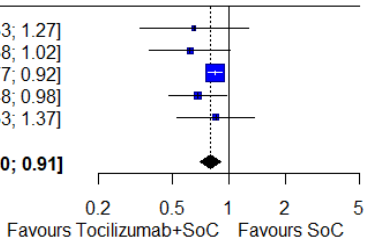
Clinial improvement: discharged alive, day 30



Clinial worsening: new need for IMV or death, day 30

Study	Tocilizumab+SoC Events	Total	SoC Events	Total	Weight	Risk Ratio MH, Random, 95% CI
CORIMUNO-TOCI 1 (Hermine 2021)	11	63	18	67	3.7%	0.65 [0.33; 1.27]
EMPACTA (Salama 2021)	29	249	24	128	6.5%	0.62 [0.38; 1.02]
RECOVERY (Horby 2021)	619	1754	754	1800	70.9%	0.84 [0.77; 0.92]
Rutgers 2022	37	174	56	180	11.8%	0.68 [0.48; 0.98]
TOCIDEX (Hermine 2022b)	27	224	32	226	7.0%	0.85 [0.53; 1.37]
Total (95% CI)	**723**	**2464**	**884**	**2401**	**100.0%**	**0.80 [0.70; 0.91]**

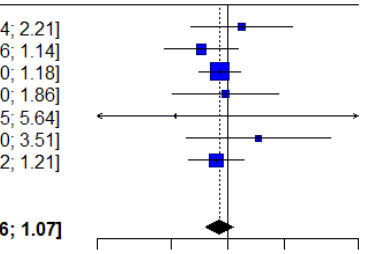
Heterogeneity: $Tau^2 = 0.0045$; $Chi^2 = 3.06$, df = 4 (P = 0.5483); $I^2 = 0.0\%$



Serious adverse events, day 30

Study	Tocilizumab+SoC Events	Total	SoC Events	Total	Weight	Risk Ratio MH, Random, 95% CI
BACC-Bay (Stone 2020)	28	161	12	82	7.4%	1.19 [0.64; 2.21]
CORIMUNO-TOCI 1 (Hermine 2021)	20	64	29	67	13.9%	0.72 [0.46; 1.14]
COVACTA (Rosas 2021)	103	295	55	143	42.7%	0.91 [0.70; 1.18]
COVINTOC (Soin 2021)	15	91	15	88	6.7%	0.97 [0.50; 1.86]
RCT-TCZ (Salvarani 2021)	1	60	2	63	0.5%	0.52 [0.05; 5.64]
TOCIBRAS (Veiga 2021)	11	67	7	62	3.7%	1.45 [0.60; 3.51]
TOCIDEX (Hermine 2022b)	48	224	56	226	25.1%	0.86 [0.62; 1.21]
Wang 2020	0	34	0	31	0.0%	
Total (95% CI)	**226**	**996**	**176**	**762**	**100.0%**	**0.90 [0.76; 1.07]**

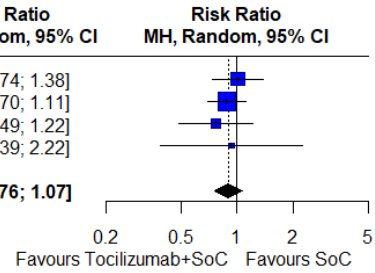
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.10$, df = 6 (P = 0.7956); $I^2 = 0.0\%$



Serious adverse events, 60 to 90 days

Study	Tocilizumab+SoC Events	Total	SoC Events	Total	Weight	Risk Ratio MH, Random, 95% CI
CORIMUNO-TOCI 2 (Hermine 2022a)	31	49	27	43	29.0%	1.01 [0.74; 1.38]
COVACTA (Rosas 2021)	116	295	64	143	53.6%	0.88 [0.70; 1.11]
EMPACTA (Salama 2021)	38	250	25	127	13.6%	0.77 [0.49; 1.22]
REMA-CAP (Gordon 2021)	9	353	11	402	3.8%	0.93 [0.39; 2.22]
Total (95% CI)	**194**	**947**	**127**	**715**	**100.0%**	**0.90 [0.76; 1.07]**

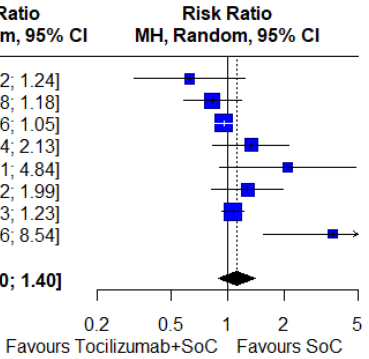
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.98$, df = 3 (P = 0.8070); $I^2 = 0.0\%$



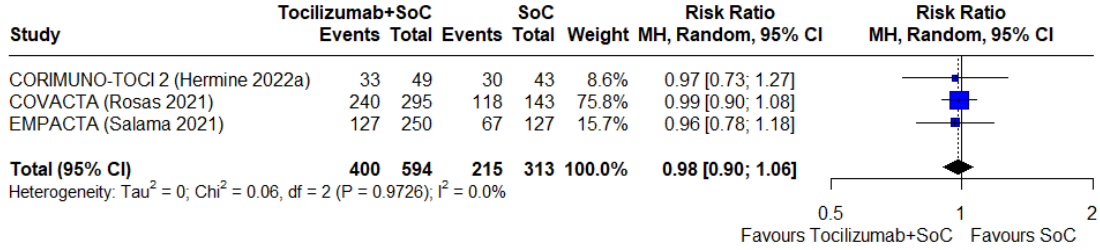
Adverse events, day 30

Study	Tocilizumab+SoC Events	Total	SoC Events	Total	Weight	Risk Ratio MH, Random, 95% CI
BACC-Bay (Stone 2020)	16	161	13	82	7.4%	0.63 [0.32; 1.24]
CORIMUNO-TOCI 1 (Hermine 2021)	28	63	36	67	14.7%	0.83 [0.58; 1.18]
COVACTA (Rosas 2021)	228	295	116	143	22.2%	0.95 [0.86; 1.05]
COVINTOC (Soin 2021)	30	91	22	89	11.6%	1.33 [0.84; 2.13]
RCT-TCZ (Salavarani 2021)	14	60	7	63	5.5%	2.10 [0.91; 4.84]
TOCIBRAS (Veiga 2021)	29	67	21	62	12.2%	1.28 [0.82; 1.99]
TOCIDEX (Hermine 2022b)	147	224	139	226	21.3%	1.07 [0.93; 1.23]
Wang 2020	20	34	5	31	5.3%	3.65 [1.56; 8.54]
Total (95% CI)	**512**	**995**	**359**	**763**	**100.0%**	**1.12 [0.90; 1.40]**

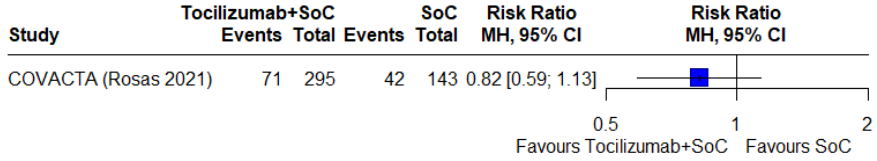
Heterogeneity: $Tau^2 = 0.0562$; $Chi^2 = 19.14$, df = 7 (P = 0.0078); $I^2 = 63.4\%$



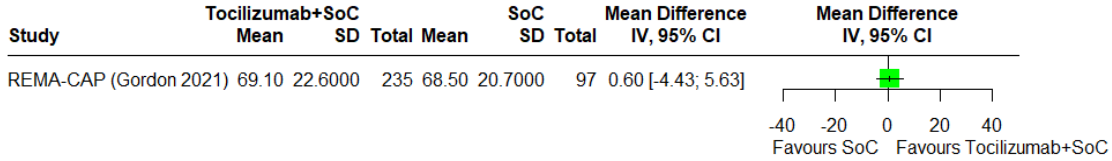
Adverse events, 60 to 90 days



Hospital-acquired infections, day 60



Quality of life, day 180 (EQ VAS)



5.9.3 Referenzen der eingeschlossenen Studien

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5.9.4 Charakteristika der eingeschlossenen Studien

5.9.4.1 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Broman, 2022 COVIDSTORM RCT, NCT04577534	**Sample size:** N = 88 pts. (90 pts. planned) **Enrolment period:** 12.08.2020 to 16.06.2021 Finland **Inclusion criteria:** · Written consent obtained · Hospitalized with COVID-19 · Age >18 y · SARS-CoV-2 PCR positive · Peripheral oxygen saturation < 93% on ambient airor respiratory rate >30/min · At least 2 of 4: Interleukin-6 >11.8 ng/L(2 xULN); Ferritin >300 mg/L in women or >800 mg/L in men(2 x ULN); D-dimer >1.5 mg/L; C-reactive protein >40 mg/L **Time since symptom onset (median, range):** · Exp: 10 (4 to 18) · Ctrl: 10 (4 to 18) **<u>Characteristics</u>** **Age (median, IQR)**	**Experimental:** · Intravenous tocilizumab plus standard of care · Dose: single infusion dependent on body weight (400 mg for <60 kg, 600 mg for 60 to 90 kg, and 800 mg for > 90 kg) · N = 59 **Control:** · Standard of Care (subcutaneous low-molecular weight heparin and glucocorticoids) · N = 29 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.55 (0.07 to 36.95) Tocilizumab: 1/57 SoC: 0/29	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label 3) Attrition bias Low, data available for nearly all participants randomised (2 exclusions post-randomisation) **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns, according to trial registry the outcome was pre-specified --- 6) Overall: No concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	Not reported	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	· Exp: 63.2 (59.4 to 70.9) · Ctrl: 65.4 (57.6 to 70.5) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 26.3% · Ctrl: 20.7% **Obesity (BMI ≥30 kg/m²)** · Exp: 60.7% · Ctrl: 69% **Hypertension** · Exp: 38.6% · Ctrl: 20.7% **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** Asthma · Exp: 15.8% · Ctrl: 10.3% COPD · Exp: 3.5% · Ctrl: 3.5% **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: 10.5% · Ctrl: 13.8% **Kidney disease** · Exp: NR				

	· Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Gordon, 2021 REMAP-CAP RCT, NCT02735707	**Sample size:** N = 826 pts. Randomized (including N = 48 Sarilumab) (pts. Planned: not reported) **Enrolment period:** 09.03.2020 to 19.11.2020 United Kingdom **Inclusion criteria:** · Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (Covid-19) infection · Severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an ICU · Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur **Time since symptom onset (median, range):** · NR **<u>Characteristics</u>**	**Experimental:** · Intravenous tocilizumab · Dose: (8 mg/kg infusion, maximum 800 mg), a 2nd infusion could be administered 12 to 24 hours after the 1st at the discretion of the treating clinician. 29% received a 2nd dose. Treatment initiated within 24 hours after starting organ support in the ICU · Cointervention: Steroid use at baseline or any time during the study in > 80% of participants. Remdesivir use was recorded in 33% (265/807) of patients · N = 366	All-cause mortality (day 30)	RR: 0.78 (0.63 to 0.97) Tocilizumab: 98/350 SoC: 142/397	**For all outcomes:** 1) Randomisation and allocation concealment: Group-specific data on the distribution of co-interventions (remdesivir and steroids) are missing 2) Blinding: Open-label 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	RR: 0.90 (0.77 to 1.05) Tocilizumab: 298/831 SoC: 140/350	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	Not reported	
			Hospital-acquired infections	Not reported	
			Quality of life	Mean difference 0.60 (-4.43 to 5.63)	

	Age (mean, IQR) · Exp: 61.4 – 63.4 · Ctrl: 61.1 ***<u>Comorbidities</u>*** **Any** · Exp**:** NR · Ctrl: NR **Diabetes:** · Exp**:** NR · Ctrl: NR **Obesity (BMI ≥30 kg/m²)** · Exp: median BMI 30.5 (29.2 in Sarilumab): 337/353 (39/48 in Sarilumab) · Ctrl: median BMI 30.9: 377/402 **Hypertension** · Exp**:** NR · Ctrl: NR **Cardiovascular disease** · Exp**:** NR · Ctrl: NR **Lung diseases** · Exp**:** NR · Ctrl: NR **Immunosuppressed** · Exp**:** NR · Ctrl: NR **Malignancy** · Exp**:** NR · Ctrl: NR **Kidney disease** · Exp**:** NR · Ctrl: NR	**Control:** · standard of care · N = 412		Tocilizumab: mean 69.1 (SD 22.6) SoC: mean 68.5 (SD 20.7)	
			Post COVID-19 condition	Not reported	

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Hermine, 2021 CORIMUNO-TOCI 1 RCT, NCT04331808; EudraCT: 2020-001246-18	**Sample size:** N = 131 pts. Randomized (pts. Planned: not reported) **Enrolment period:** 31.03.2020 to 18.04.2020 France **Inclusion criteria:** · Confirmed SARS-CoV-2 infection (positive on rRT-PCR and/or typical chest CT scan); · requiring more than 3L/min of oxygen; · WHO progression scale = 5 · no NIV or High flow **Time since symptom onset (median, range):** · Exp: 10 days (7-13) · Ctrl: 10 days (8-13) **<u>Characteristics</u>** **Age (median, IQR)** Exp: 64.0 (75.1-74.3) · Ctrl: 63.3 (75.1-72.3)	**Experimental:** · Tocilizumab · Dose: (8 mg/kg infusion) on day 1, an additional fixed dose of 400 mg IV on day 3 at physician discretion. · N = 64 **Control:** · standard of care alone (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants; provided at the discretion of the clinicians) · N = 67 **Cointervention:** · Steroids at baseline or any time during the study: Tocilizumab: 21	All-cause mortality (day 30)	RR: 0.93 (0.36 to 3.61) Tocilizumab: 7/63 SoC: 8/67	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, co-intervention steroid unevenly distributed (absolute difference >10%) 2) Blinding: Open-label, 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.65 (0.33 to 1.27) Tocilizumab: 11/63 SoC: 18/67	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 0.72 (0.46 to 1.14) Tocilizumab: 20/64 SoC: 29/67	
			Adverse events, any grade (day 30)	RR: 0.83 (0.58 to 1.18) Tocilizumab: 28/63 SoC: 36/67	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	Comorbidities **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 20/61 (33%) · Ctrl: 20/67 (30%) **Obesity (BMI ≥30 kg/m²)** · Exp: median BMI under obesity · Ctrl: median BMI under obesity **Hypertension** · Exp: NR · Ctrl:NR **Cardiovascular disease (chronic cardiac disease)** · Exp: 20/61 (33%) · Ctrl: 20/67 (34%) **Lung diseases** chronic pulmonary disease (not asthma) · Exp: 3/61 (5%) · Ctrl: 3/67 (5%) Asthma · Exp: 5/61 (8%) · Ctrl: 3/67 (5%) **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy (Active malignant neoplasm)** · Exp: 4/61 (7%) · Ctrl: 5/67 (8%)	(33%), Standard care: 41 (61%) N = (mind. eine Dosis und ausgewertet)			

	Kidney disease (chronic stage 1-3 or dialysis) • Exp: 5/61 (8%) • Ctrl: 13/67 (19%)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Hermine, 2022a CORIMUNO-TOCI 2 RCT, NCT04324047	**Sample size:** N = 97 pts. (120 pts. planned) **Enrolment period:** 31.03.2020 to 18.04.2020 France **Inclusion criteria:** · confirmed SARS-CoV-2 infection (positive on reverse transcriptase-PCR and/or typical chest computed tomography scan) · Moderatee, severe or critical pneumonia (O2 >3 L·min−1, WHO-CPS score ⩾5 **Time since symptom onset (median, range):** · Exp: 11 (9 to 15) · Ctrl: 11 (9 to 14) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 63.2 (59.4 to 70.9) · Ctrl: 65.4 (57.6 to 70.5)	**Experimental:** · Intravenous tocilizumab plus standard of care · Dose: 8 mg/kg on day 1; additional administration of 400 mg on day 3 at discretion of the treating physician · N = 51 **Control:** · Standard of care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants provided at the discretion of clinicians) · N = 46 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.70 (0.30 to 1.62) Tocilizumab: 8/49 SoC: 10/43	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label 3) Attrition bias No concerns, data available for nearly all participants randomised (5 withdrawals) **Outcome-specific:** 4) Outcome measurement: Some concerns for safety outcomes due to awareness of the intervention received 5) Selective reporting: No concerns --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: time-to-discharged alive (day 30)	HR: 1.24 (1.01 to 1.52)	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 90)	RR: 1.01 (0.74 to 1.38) Tocilizumab: 31/49 SoC: 27/43	
			Adverse events, any grade (day 90)	RR: 0.97 (0.73 to 1.27) Tocilizumab: 33/49 SoC: 30/43	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	<u>Comorbidities</u> **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 41% · Ctrl: 29% **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 29% · Ctrl: 32% **Lung diseases** Asthma · Exp: 6% · Ctrl: 5% COPD · Exp: 6% · Ctrl: 10% **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: 2% · Ctrl: 2% **Kidney disease** · Exp: 6% · Ctrl: 7%				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Hermine, 2022b TOCIDEX RCT, NCT04476979	**Sample size:** N = 453 pts. (660 pts. planned) **Enrolment period:** 24.06.2020 to 18.05.2021 France **Inclusion criteria:** · Patients with confirmed SARS CoV-2 infection (positive PCR and/or typical chest CT-scan) · with Moderatee and severe pneumopathy requiring oxygen (>3 L/min) but without ventilation support (NIV), high flow or MV, WHO class 5 according to the WHO 10 points- Clinical Progression Scale (CPS) for COVID-19 pneumopathy **Time since symptom onset (median, range):** · Exp: 9 (7 to 11) · Ctrl: 9 (7 to 11) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 63.6 (53 to 73) · Ctrl: median 63.2 (54 to 73)	**Experimental:** · intravenous tocilizumab plus dexamethasone · Dose: single dose 8mg/kg · N = 226 **Control:** · Intravenous dexamethasone · N = 227	All-cause mortality (day 30)	RR: 0.80 (0.42 to 1.53) Tocilizumab: 15/224 SoC: 19/226	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label 3) Attrition bias No concerns, data available for nearly all participants randomised (3 withdrawals) **Outcome-specific:** 4) Outcome measurement: Some concerns for safety outcomes due to awareness of the intervention received 5) Selective reporting: No concerns, outcomes reported as pre-specified. --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	RR: 0.75 (0.41 to 1.36) Tocilizumab: 17/224 SoC: 23/226	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.85 (0.53 to 1.37) Tocilizumab: 27/224 SoC: 32/226	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 0.86 (0.62 to 1.21) Tocilizumab: 48/224 SoC: 56/226	
			Adverse events, any grade (day 30)	RR: 1.07 (0.93 to 1.23) Tocilizumab: 147/224 SoC: 139/226	
			Hospital-acquired infections	Not reported	

	Comorbidities **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 25% · Ctrl: 22% **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 36% · Ctrl: 38% **Cardiovascular disease** · Exp: 14% · Ctrl: 17% **Lung diseases** Asthma · Exp: 11% · Ctrl: 6% Chronic pulmonary disease · Exp: 6% · Ctrl: 8% **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: 4% · Ctrl: 5% **Kidney disease** · Exp: 9% · Ctrl: 5%	N = (mind. eine Dosis und ausgewertet)	Quality of life Post COVID-19 condition	Not reported Not reported	

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Horby, 2021 RECOVERY RCT, NCT04381936	**Sample size:** N = 4116 pts. randomized (pts. Planned: not reported) **Enrolment period:** 23.04.2020 – 42.01.2021 UK **Inclusion criteria:** · Hospitalised adults (including pregnant women) with clinically suspected or laboratory-confirmed SARS-CoV-2 infection · Hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy); evidence of systemic inflammation (C reactive protein (CRP) ≥ 75 mg/L) · No medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial **Time since symptom onset (median, range):** · NR **<u>Characteristics</u>** **Age (mean, IQR)**	**Experimental:** · Tocilizumab · Dose: 800 mg if weight > 90 kg; 600 mg if weight > 65 and ≤ 90 kg; 400 mg if weight > 40 and ≤ 65 kg; 8 mg/kg if weight ≤ 40 kg); a 2nd infusion could be administered 12 to 24 hours after the 1st · N = 2022 **Control:** · standard of care · N = 2091 **Cointerventions:** · Steroid use at baseline or any time during the study: Tocilizumab: 1664 (82%); Standard care: 1721 (82%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.88 (0.81 to 0.96) Tocilizumab: 621/2022 SoC: 729/2094	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, many crossovers: 18.5% did not receive tocilizumab despite randomisation and 3.7% of the control group received tocilizumab 2) Blinding: Open-label 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: 5) Selective reporting: Some concerns, some outcomes not reported in accordance with statistical analysis plan ----------
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: time-to-discharged alive (day 30)	HR: 1.22 (1.12 to 1.33)	
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.84 (0.77 to 0.92) Tocilizumab: 619/1754 SoC: 754/1800	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	Not reported	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	• 63.3 ***<u>Comorbidities</u>*** **Any** • Exp: NR • Ctrl: NR **Diabetes:** • Exp: NR • Ctrl: NR **Obesity (BMI ≥30 kg/m²)** • Exp: NR • Ctrl: NR **Hypertension** • Exp: NR • Ctrl: NR **Cardiovascular disease** • Exp: NR • Ctrl: NR **Lung diseases** • Exp: NR • Ctrl: NR **Immunosuppressed** • Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: NR • Ctrl: NR				6) Overall: Some concerns for risk of bias

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Rosas, 2021 COVACTA RCT, NCT04320615	**Sample size:** N = 452 pts. randomized (pts. Planned: not reported) **Enrolment period:** 03.04.2020 to 28.05.2020 Europe and North America (Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, the United Kingdom, and the United States) **Inclusion criteria:** · Patients 18 years or older · severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or CT were enrolled · blood oxygen saturation ≤ 93% or partial pressure of oxygen/fraction of inspired oxygen < 300 mm/Hg · Patients were excluded if the treating physician determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or	**Experimental:** · Tocilizumab · Dose: 8 mg/kg infusion, maximum 800 mg), a second infusion could be administered 8 to 24 hours after the first · N = 301 **Control:** · placebo · N = 151 **Cointerventions:** · Steroid use at baseline or any time during the study: Tocilizumab: 57 (19%), Placebo: 41 (28%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.01 (0.68 to 1.52) Tocilizumab: 58/294 SoC: 28/144	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: No concerns 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns --- 6) Overall: No concerns for risk of bias
			All-cause mortality (day 60)	RR: 0.97 (0.69 to 1.37) Tocilizumab: 72/295 SoC: 36/143	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	RR: 1.17 (0.95 to 1.43) Tocilizumab: 157/294 SoC: 66/144	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 0.91 (0.70 to 1.18) Tocilizumab: 103/295 SoC: 55/143	
			Serious adverse events (day 60)	RR: 0.88 (0.70 to 1.11) Tocilizumab: 116/295 SoC: 64/143	
			Adverse events, any grade (day 30)	RR: 0.95 (0.86 to 1.05) Tocilizumab: 228/295 SoC: 116/143	
			Adverse events, any grade (day 60)	RR: 0.99 (0.90 to 1.08) Tocilizumab: 240/295 SoC: 118/143	

	bacterial, fungal, or viral infection other than SARS-CoV-2. **Time since symptom onset (median, range):** · Exp: 11.0 (1.0 – 49.0) · Ctrl: 10.0 (2.0-50.0) **<u>Characteristics</u>** **Age (mean, IQR)** · Exp: 60.9 · Ctrl: 60.6 ***<u>Comorbidities</u>*** **Any** · Exp: 231/294 (78.6%) · Ctrl: 124/144 (86.1%) **Diabetes:** · Exp: 105/294 (35.7%) · Ctrl: 62/144 (43.1%) **Obesity (BMI ≥30 kg/m²)** · Exp: 63/294 (21.4%) · Ctrl: 27/144 (18.8%) **Hypertension** · Exp: 178/294 (60.5%) · Ctrl: 94/144 (65.3%) **Cardiovascular disease** · Exp: 88/294 (29.9%) · Ctrl: 94/144 (65.3%) **Lung diseases (chronic)** · Exp: 49/294 (16.7%) · Ctrl: 22/144 (15.3%) **Immunosuppressed**		Hospital-acquired infections (day 60)	RR: 0.82 (0.59 to 1.13) Tocilizumab: 71/295 SoC: 42/143	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	• Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: NR • Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Rutgers, 2022 RCT, trialregister.nl/trial/8504	**Sample size:** N = 354. (pts. planned: NR) **Enrolment period:** 06.04.2020 to 12.01.2021 Netherlands **Inclusion criteria:** · 18 years or older, capable of providing informed consent and had SARS-CoV-2 infection confirmed by nasopharyngeal swab polymerase chain reaction · Patients were required to be admitted to a ward · have at least one of the following signs compatible with hyperinflammatio: 1) need for supplemental oxygen (inspired by the ASTCT consensus grade 2 for CRS, generally matching a saturation < 94%) [10] and/or 2) ferritin >2000ug/l or a doubling of serum ferritin in 20–48 hrs **Time since symptom onset (median, range):** · Exp: NR · Ctrl: NR	**Experimental:** · intravenous tocilizumab plus standard of care · Dose: single dose 8mg/kg · N = 174 **Control:** · Standard of care · N = 180 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.64 (0.39 to 1.06) Tocilizumab: 21/174 SoC: 34/180	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label 3) Attrition bias No concerns, all randomised participants analysed **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: Some concerns, protocol and SAP not available and no access to study registry --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.68 (0.48 to 0.98) Tocilizumab: 37/174 SoC: 56/180	
			Admission to ICU or death	Not reported	
			Serious adverse events	Not reported	
			Adverse events, any grade	Not reported	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	<u>Characteristics</u> **Age (median, IQR)** · Exp: 67 (60 to 74) · Ctrl: 66 (56 to 74) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: NR · Ctrl: NR **Obesity (BMI ≥30 kg/m²)** · Exp: 31% · Ctrl: 32% **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease** · Exp: NR · Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Salama, 2021 EMPACTA RCT, NCT04372186	**Sample size:** N = 388 pts. Randomized (pts. Planned: not reported) **Enrolment period:** Not reported US, Mexico, Kenya, South Africa, Peru, or Brazil **Inclusion criteria:** · Patients ≥18 years of age · Hospitalized with Covid-19 pneumonia confirmed by a positive polymerase chain reaction test and radiographic imaging · Blood oxygen saturation <94% on ambient air **Time since symptom onset (median, range):** · NR **<u>Characteristics</u>** **Age (mean, IQR)** · Exp: 56.0 · Ctrl: 55.6 ***<u>Comorbidities</u>*** **Any**	**Experimental:** · Tocilizumab · Dose: 8mg/kg up to 800 mg max infusion · N = 259 **Control:** · Placebo · N = 129 **Cointervention:** · Steroids at baseline or any time during the study: Tocilizumab: 200 (77%) Placebo: 112 (87%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.22 (0.62 to 2.38) Tocilizumab: 26/249 SoC: 11/128	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: No concerns 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: Some concers, as not all pre-defined outcomes reported --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	RR: 0.98 (0.55 to 1.76) Tocilizumab: 29/250 SoC: 15/127	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	RR: 0.62 (0.38 to 1.02) Tocilizumab: 29/249 SoC: 24/128	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 60)	RR: 0.77 (0.49 to 1.22) Tocilizumab: 38/250 SoC: 25/127	
			Adverse events, any grade (day 60)	RR: 0.96 (0.78 to 1.18) Tocilizumab: 127/250 SoC: 67/127	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	• Exp: NR • Ctrl: NR **Diabetes:** • Exp: NR • Ctrl: NR **Obesity (BMI ≥30 kg/m²)** • Exp: mean BMI 32.0 • Ctrl: mean BMI 33.1 **Hypertension** • Exp: NR • Ctrl: NR **Cardiovascular disease** • Exp: NR • Ctrl: NR **Lung diseases** • Exp: NR • Ctrl: NR **Immunosuppressed** • Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: NR • Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Salvarani, 2021 RCT-TCZ RCT, NCT04346355; EudraCT: 2020-001386-37	**Sample size:** N = 126 pts. randomized (pts. Planned: not reported) **Enrolment period:** 31.03.2020 to 11.06.2020 Italy **Inclusion criteria:** · Patients 18 years and older · instrumental diagnosis of COVID-19 pneumonia confirmed by a positive reverse-transcriptase polymerase chain reaction assay for SARS-CoV-2 in a respiratory tract specimen · presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) ratio between 200 and 300 mm/Hg · inflammatory phenotype defined by a temperature greater than 38 ‘C during the last 2 days, and/or serum CRP levels of 10mg/dL or greater and/or CRP level increased to at least twice the admission measurement **Time since symptom onset (mean, range):** · Exp: 7.0 days (4.0-11.0) · Ctrl: 8.0 days (6.0-11.0)	**Experimental:** · Tocilizumab · Dose: 8 mg/kg; on day 1 up to a maximum of 800 mg, followed by a second dose after 12 hours · N = 60 **Control:** · standard of care · N = 66 **Cointervention:** · Steroids at baseline or any time during the study: Tocilizumab: 6 (10%), Standard care: 7 (11%) · Heparin and LMWH 81 Tocilizumab 41 (68.3) , SC 40 (60.6) · Antiretrovirals Tocilizumab 21	All-cause mortality (day 30)	RR: 2.10 (0.20 to 22.56) Tocilizumab: 2/60 SoC: 1/63	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, more men in the intervention group (absolute difference 10%) but fewer obese people, shorter time since symptom onset 2) Blinding: Open-label 3) Attrition bias Some concerns, crossovers allowed in study protocol (20% of the control group were treated with TCM **Outcome-specific:** 4) Outcome measurement: Some concerns, only 14 days observation period planned; but reported for 28 days 5) Selective reporting: No concerns
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 0.53 (0.05 to 5.64) Tocilizumab: 1/60 SoC: 2/63	
			Adverse events, any grade (day 30)	RR: 2.10 (0.91 to 4.84) Tocilizumab: 14/60 SoC: 7/63	
			Hospital-acquired infections	Not reported	

	<u>Characteristics</u> **Age (median, IQR)** · Exp: 61.5 (51.5-73.5) · Ctrl: 60.0 (54.0-69.0) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 10/60 (16.7%) · Ctrl: 9/66 (13.6%) **Obesity (BMI ≥30 kg/m²)** · Exp: 16/60 (28.1%) · Ctrl: 22/66 (36.1%) **Hypertension** · Exp: 27/60 (45.0%) · Ctrl: 29/66 (43.9%) **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases (COPD)** · Exp: 2/60 (3.3%) · Ctrl: 2/66 (3.0%) **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease** · Exp: NR · Ctrl: NR	(35.0) , SC 31 (47.0) · Azithromycin Tocilizumab 10 (16.7), SC 16 (24.2) · Hydroxychloroquine Tocilizumab 53 (88.3), SC 62 (93.9) N = (mind. eine Dosis und ausgewertet)	Quality of life Post COVID-19 condition	Not reported Not reported	---------- 6) Overall: Some concerns for risk of bias

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Soin, 2021 COVINTOC RCT, CTRI/2020/05/025369	**Sample size:** N = 180 pts. (pts. Planned: not reported) **Enrolment period:** 30.03.2020 to 31.08.2020 India **Inclusion criteria:** · Patients aged 18 years or older · admitted to hospital with SARS-CoV-2 infection confirmed by WHO criteria (positive PCR test on any specimen) and Moderatee to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-19 (Moderatee defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO2] 90–94%; and severe defined as respiratory rate ≥30 per min or SpO2 <90% in ambient air, or ARDS or septic shock. **Time since symptom onset (median, range):** · NR **<u>Characteristics</u>**	**Experimental:** · Tocilizumab · Dose: single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. An additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days after administration of the first dose. · N = 91 **Control:** · Cointerventions balanced (91 vs 91% Corticoids, 43 vs 41 % Remdesivir)	All-cause mortality (day 30)	RR: 0.71 (0.34 to 1.46) Tocilizumab: 11/91 SoC: 15/88	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, baseline differences: intervention group more male, older, more diabetics; control group sicker at ordinal scale level 2) Blinding: No concerns 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 0.97 (0.50 to 1.86) Tocilizumab: 15/91 SoC: 15/88	
			Adverse events, any grade (day 30)	RR: 1.33 (0.84 to 2.13) Tocilizumab: 30/91 SoC: 22/89	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	

	Age (median, IQR) · Exp: 56 (47-63) · Ctrl: 54 (43-63) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 31/91 (34%) · Ctrl: 43/88 (49%) **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 36/91 (40%) · Ctrl: 34/88 (39%) **Cardiovascular disease** · Exp: 15/91 (16%) · Ctrl: 12/88 (14%) **Lung diseases (COPD)** · Exp: 1/91 (1%) · Ctrl:3/88 (3%) **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease (renal and urinary disorders)** · Exp: 4/91 (4%) · Ctrl: 4/88 (5%)	· N = 88 N = (mind. eine Dosis und ausgewertet)	Post COVID-19 condition	Not reported	

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Stone, 2020 BACC-Bay RCT, NCT04320615	**Sample size:** N = 243 pts. randomized (pts. Planned: not reported) **Enrolment period:** 20.04.2020 to 15.06.2020 USA **Inclusion criteria:** · 19 to 85 years of age · SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay · at least two of the following signs: fever (body temperature >38°C) within 72 h before enrollment, pulmonary infiltrates, or a need for supplemental oxygen to maintain an oxygen saturation >92% · At least one of the following laboratory criteria: C-reactive protein level >50 mg/l, ferritin level >500 ng/ml, d-dimer level >1000 ng/ml, or lactate dehydrogenase level >250 U/l · Exclusion if >10l/min of Oxygen, hence no HFNC, no NIV, no IMV at inclusion **Time since symptom onset (median, range):** · Exp: 9.0 (6.0-13.0) · Ctrl: 10.0 (7.0-13.0) **<u>Characteristics</u>**	**Experimental:** · Tocilizumab · Dose: 8mg/kg infusion up to 800 mg max) single dose · N = 161 **Control:** · placebo · N = 82 **Cointervention**: · Steroids at baseline or any time during the study Tocilizumab: 18 (11%) Placebo: 5 (6%) N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 1.15 (0.36 to 3.61) Tocilizumab: 9/161 SoC: 4/82	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, baseline differences: intervention group more men, older (absolute difference 10% in the stratum of over 65 year olds); control group at ordinal scale level sicker, more diabetics 2) Blinding: No concerns 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 1.19 (0.64 to 2.21) Tocilizumab: 28/161 SoC: 12/82	
			Adverse events, any grade (day 30)	RR: 0.63 (0.32 to 1.24) Tocilizumab: 16/161 SoC: 13/82	
			Hospital-acquired infections	Not reported	

	Age (median, IQR) · Exp: 61.6 (46.4-69.7) · Ctrl: 56.5 (44.7-67.8) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 45/161 (28%) · Ctrl: 30/82 (37%) **Obesity (BMI ≥30 kg/m²)** · Exp: 80/161 (50%) · Ctrl: 42/82 (51%) **Hypertension** · Exp: 80/161 (50%) · Ctrl: 38/82 (46%) **Cardiovascular disease** Heart failure · Exp: 17/161 (11%) · Ctrl: 7/82 (9%) History of myocardial infarction · Exp: 15/161 (9%) · Ctrl: 6/161 (7%) **Lung diseases** COPD · Exp: 15/161 (9%) · Ctrl: 7/82 (9%) Asthma · Exp: 15/161 (9%) · Ctrl: 7/82 (9%) **Immunosuppressed** · Exp: NR · Ctrl: NR		Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	Malignancy history of cancer · Exp: 22/161 (14%) · Ctrl: 8/82 (19%) **Kidney disease** · Exp: 29/161 (18%) · Ctrl: 13/82 (16%)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Veiga, 2021 TOCIBRAS RCT, NCT04403685	**Sample size:** N = 129 pts. Randomized (pts. Planned: not reported) **Enrolment period:** 08.05.2020 to 17.06.2020 Brazil **Inclusion criteria:** · Confirmed diagnosis of SARS-CoV-2 infection · Computed tomography (or chest X-ray) of the chest consistent with COVID-19 · More than three days of symptoms related to COVID-19 · 18 years or older; · Need for oxygen supplementation to maintain SpO2 > 93% OR need for mechanical ventilation less than 24 hours before the randomization · Two or more of the following inflammatory tests: i. D-dimer > 1,000 ng/mL; ii. C reactive protein > 5 mg/dL; iii. Ferritin > 300 mg/dL; iv. Lactate dehydrogenase > upper limit of normal **Time since symptom onset (mean, SD):** · Exp: 10.0 (3.1) · Ctrl: 9.5 (3.0) **<u>Characteristics</u>** **Age (mean, SD)**	**Experimental:** · Tocilizumab · Dose: 8 mg/kg, IV) on day 1 up to a max of 800 mg · N = 65 **Control:** · standard of care · N = 64 **Cointervention:** · Steroids at baseline or any time during the study Tocilizumab: 56 (86%) Standard care: 55 (86%)	All-cause mortality (day 30)	RR: 2.30 (0.94 to 5.61) Tocilizumab: 14/65 SoC: 6/64	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, unequal distribution of Moderatee and severe COVID at baseline between intervention and control group; early termination of the study after an interim analysis revealed significantly more deaths in the intervention group. 2) Blinding: Open-label 3) Attrition bias No concerns **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: 1.45 (0.60 to 3.51) Tocilizumab: 11/67 SoC: 7/62	
			Adverse events, any grade (day 30)	RR: 1.28 (0.82 to 1.99) Tocilizumab: 29/67	

	· Exp: 57.4 · Ctrl: 57.5 (13.5) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: 22/65 (34%) · Ctrl: 20/64 (31%) **Obesity (BMI ≥30 kg/m²)** · Exp: 15/65 (23%) · Ctrl: 16/64 (25%) **Hypertension** · Exp: 30/65 (64%) · Ctrl: 34/64 (53%) **Cardiovascular disease** Heart failure · Exp: 4/65 (6%) · Ctrl: 3/64 (5%) Myocardial infarction · Exp: 4/65 (6%) · Ctrl: 3/64 (5%) **Lung diseases** COPD · Exp: 2/65 (3%) · Ctrl: 2/64 (3%) Asthma · Exp: 4/65 (6%) · Ctrl: 1/64 (2%) **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy**	N = (mind. eine Dosis und ausgewertet)		SoC: 21/62	---------- - 6) Overall: Some concerns for risk of bias
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	Solid malignancy · Exp: 4/65 (6%) · Ctrl: 5/64 (8%) Heamatological malignancy · Exp: 1/65 (1%) · Ctrl: 0/64 (0%) **Kidney disease** · Exp: 5/65 (8%) · Ctrl: 1/64 (2%)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Wang, 2020 RCT	**Sample size:** N = 65 pts. Randomized (pts. Planned: not reported) **Enrolment period:** 13.02.2020 to 13.03.2020 China **Inclusion criteria:** · 18 to 85 years old · Plasma IL-6 levels elevated · Moderatee (with bilateral pulmonary lesions) or severe in disease degree **Time since symptom onset (median, IQR):** · Exp: 20 (9-29) · Ctrl: 24 (19-33) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 63.5 (58-71) · Ctrl: 63 (54-69) ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR	**Experimental:** · Tocilizumab · Dose: 400 mg infusion; Patients received a 2nd dose only if their condition did not improve or worsened. The number of patients received 2nd dose is not reported. · N = 33 **Control:** · standard of care · N = 32 **Cointerventions** · Steroid use at baseline or any time during the study: Tocilizumab: 15%, Standard care: &5	All-cause mortality (day 30)	Not reported	**For all outcomes:** 1) Randomisation and allocation concealment: Some concerns, cointervention unevenly distributed, symptom onset until randomisation (median (IQR)) TCM 20 (9-29) vs. SOC 24 (19-33) days 2) Blinding: Open-label 3) Attrition bias **Outcome-specific:** 4) Outcome measurement: No concerns 5) Selective reporting: No concerns --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (day 180)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events (day 30)	RR: Not estimable Tocilizumab: 0/34 SoC: 0/31	
			Adverse events, any grade (day 30)	RR: 3.65 (1.56 to 8.54) Tocilizumab: 20/34 SoC: 5/31	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	

	Diabetes: · Exp: 4/34 (11.76%) · Ctrl: 6/31 (19.35%) **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 10/34 (29.41%) · Ctrl: 10/31 (32.26%) **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease** · Exp: NR · Ctrl: NR	N = (mind. eine Dosis und ausgewertet)	Post COVID-19 condition	Not reported	

5.10 Schlüsselfrage 5b: hohe Dosis Tocilizumab (8 mg/kg) vs. Lowe Dosis Tocilizumab (4 mg/kg)

Autor*innen: Caroline Hirsch

Es gab 1 RCT mit 100 Teilnehmenden.

5.10.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: High-dose tocilizumab (8 mg/kg)

Vergleichsintervention: Low-dose tocilizumab (4 mg/kg)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Low-dose tocilizumab	High-dose tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality up to 30 days	Relative risk: 0.73 (CI 95% 0.25 - 2.14) Based on data from 97 patients in 1 studies[1] Observation time up to 30 days	**143** per 1000	**104** per 1000 Difference: **39 less per 1000** (CI 95% 107 less - 163 more)	**Low** Due to very serious imprecision[2]	High-dose tocilizumab may decrease all-cause mortality up to 30 days compared to low-dose tocilizumab
All-cause mortality up to 60 days	Relative risk: 0.77 (CI 95% 0.29 - 2.04) Based on data from 97 patients in 1 studies[3] Observation time up to 60 days	**163** per 1000	**126** per 1000 Difference: **37 less per 1000** (CI 95% 116 less - 170 more)	**Low** Due to very serious imprecision[4]	High-dose tocilizumab may decrease all-cause mortality up to 60 days compared to low-dose tocilizumab
All-cause mortality up to longest follow-up	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **less per 1000**		No studies were found that looked at all-cause mortality up to longest follow-up
Clinical improvement: discharged alive up to 30 days	Relative risk: 0.99 (CI 95% 0.81 - 1.22) Based on data from 97 patients in 1 studies[5] Observation time up to 30 days	**796** per 1000	**788** per 1000 Difference: **8 less per 1000** (CI 95% 151 less - 175 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[6]	We are uncertain whether high-dose tocilizumab increases or decreases the number of participants discharged alive up to 30 days compared to low-dose tocilizumab
Clinical worsening: new need for IMV or death up to 30 days	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **less per 1000**		No studies were found that looked at new need for IMV or death up to 30 days
Admission to ICU or death up to 30 days	Relative risk (CI 95% -)	per 1000	per 1000 Difference: **less per 1000**		No studies were found that looked at admission to ICU or death up to 30 days

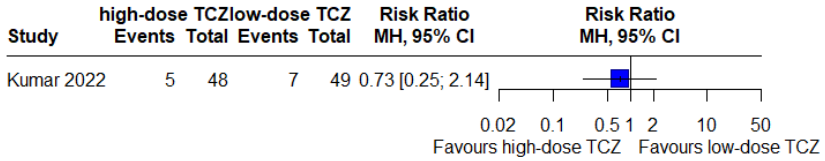
Serious adverse events up to 60 days	Relative risk: 0.82 (CI 95% 0.43 - 1.56) Based on data from 97 patients in 1 studies[7] Observation time up to 60 days	**306** per 1000 **251** per 1000 Difference: **55 less per 1000** (CI 95% 174 less - 171 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[8]	We are uncertain whether high-dose tocilizumab increases or decreases the number of participants with serious adverse events up to 60 days compared to low-dose tocilizumab
Adverse events up to 60 days	Relative risk: 0.8 (CI 95% 0.54 - 1.19) Based on data from 97 patients in 1 studies[9] Observation time up to 60 days	**571** per 1000 **457** per 1000 Difference: **114 less per 1000** (CI 95% 263 less - 108 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[10]	We are uncertain whether high-dose tocilizumab increases or decreases the number of participants with adverse events up to 60 days compared to low-dose tocilizumab
Hospital-acquired infections up to 60 days	Relative risk: 1.02 (CI 95% 0.27 - 3.85) Based on data from 97 patients in 1 studies[11] Observation time up to 60 days	**82** per 1000 **84** per 1000 Difference: **2 more per 1000** (CI 95% 60 less - 234 more)	**Low** Due to very serious imprecision[12]	High-dose tocilizumab may have little or no difference on hospital-acquired infections up to 60 days compared to low-dose tocilizumab
Post COVID-19 condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post COVID-19 condition
Quality of life	Gemessen mit: Skala: -	Mittelwert Mittelwert Difference: **MD null kleiner**		No studies were found that looked at quality of life

1. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [26].
2. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study;
3. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [26].
4. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study;
5. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [26].
6. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study;
7. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [26].
8. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study;
9. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [26].
10. Risk of bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study;

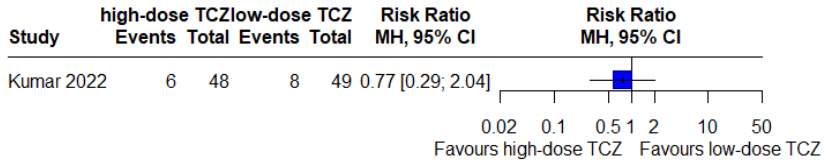
11. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm. Referenzen [26].
12. Imprecision: very serious. Wide confidence intervals, Low number of patients, Only data from one study;

5.10.2 Analysen / Forest Plots

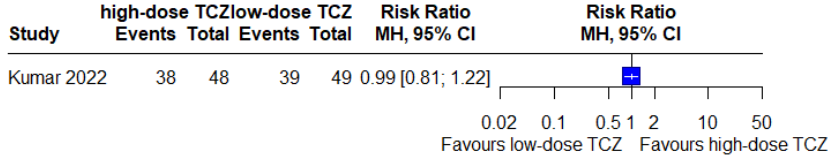
Mortality, day 30



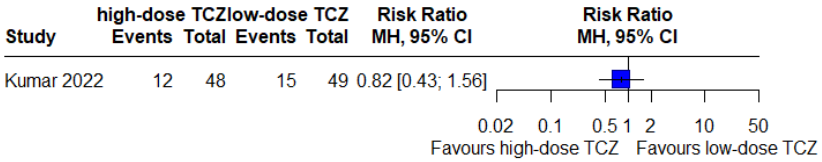
Mortality, day 60



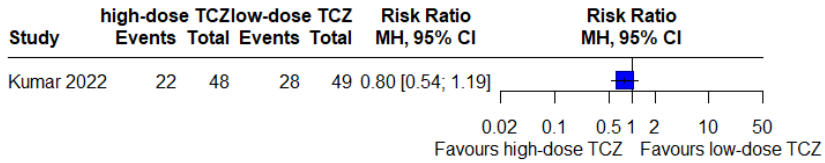
Clinical improvement: discharged alive, day 30



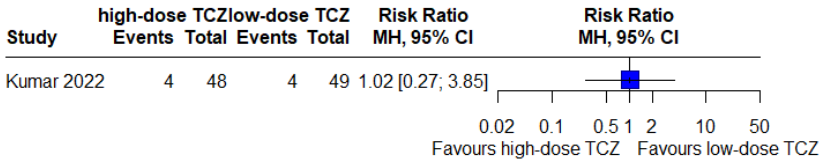
Serious adverse events, day 60



Adverse events, day 60



Hospital-acquired infections, day 60



5.10.3 Referenzen der eingeschlossenen Studien

- Kumar P, Hernandez-Sanchez J, Nagel S, Feng Y, Cai F, Rabin J, et al. Safety and Efficacy of Tocilizumab 4 or 8 mg/kg in Hospitalized Patients with Moderatee to Severe Coronavirus Disease 2019 Pneumonia: a Randomized Clinical Trial. Open forum infectious diseases, 2022. 9(1):ofab608. doi: 10.1093/ofid/ofab608.

5.10.4 Charakteristika der eingeschlossenen Studien

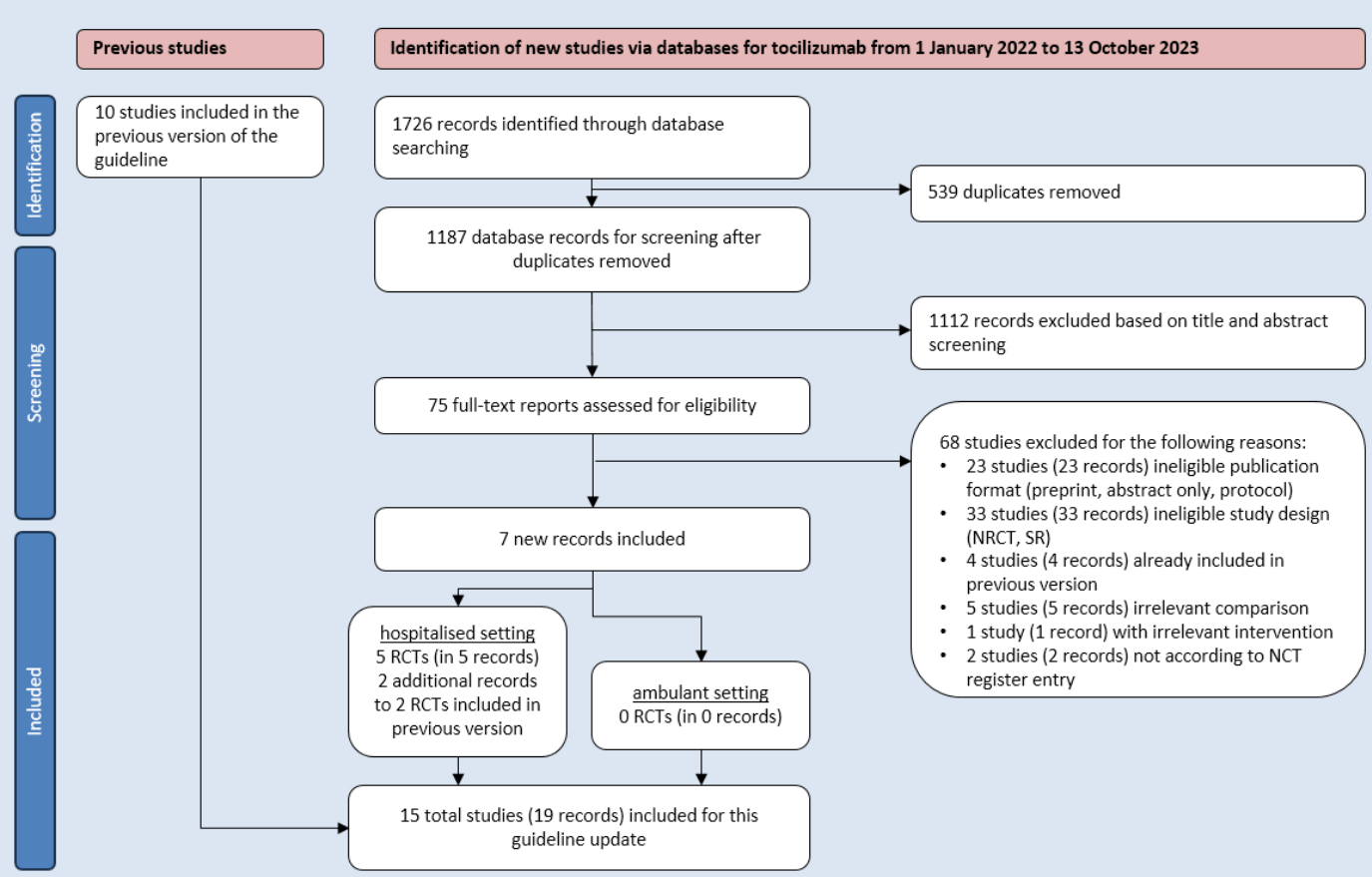
5.10.4.1 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Kumar, 2022 Open-label RCT, NCT04363736	**Sample size:** N = 97 pts. (100 pts. planned) **Enrolment period:** 05.05.2020 to 12.08.2020 USA **Inclusion criteria:** · patients ≥18 years · hospitalized for Moderatee to severe COVID-19 pneumonia detected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive reverse-transcription polymerase chain reaction (RT-PCR) (within 7 days before randomization) · confirmed by chest radiography or computed tomography scan · severe COVID-19 pneumonia was defined as patients having blood oxygen saturation of ≤93% or partial pressure of oxygen to fraction of inspired oxygen ratio of <300 mm Hg	**Experimental:** · Intravenous tocilizumab · Dose: 8 mg/kg (max. 800 mg) · N = 48 **Control:** · Intravenous tocilizumab · Dose: 4 mg/kg · N = 49 N = (mind. eine Dosis und ausgewertet)	All-cause mortality (day 30)	RR: 0.73 (0.25 to 2.14) High-dose tocilizumab: 5/48 Low-dose tocilizumab: 7/49	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: Open-label 3) Attrition bias Low, data available for nearly all participants randomised (3 exclusions due to not receiving tocilizumab) **Outcome-specific:** 4) Outcome measurement: Some concerns for safety outcomes, otherwise low 5) Selective reporting: Some concerns for adverse events, other outcomes reported according to trial registry --- 6) Overall: Some concerns for risk of bias
			All-cause mortality (day 60)	RR: 0.77 (0.29 to 2.04) High-dose tocilizumab: 6/48 Low-dose tocilizumab: 8/49	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	RR: 0.99 (0.81 to 1.22) High-dose tocilizumab: 38/48 Low-dose tocilizumab: 39/49	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse	RR: 0.82 (0.43 to 1.56) High-dose tocilizumab: 12/48	

	Time since symptom onset (median, range): · **<u>Characteristics</u>** **Age (mean, SD)** · Exp: 59.8 (14.6) · Ctrl: 56.8 (14.3) ***<u>Comorbidities</u>*** **Any** · Exp: 59.8 · Ctrl: 56.8 **Diabetes:** · Exp: NR · Ctrl: NR **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR		events (day 60)	Low-dose tocilizumab: 15/49	
			Adverse events, any grade (day 60)	RR: 0.80 (0.54 to 1.19) High-dose tocilizumab: 22/48 Low-dose tocilizumab: 28/49	
			Hospital-acquired infections (day 60)	RR: 1.02 (0.27 to 3.85) High-dose tocilizumab: 4/48 Low-dose tocilizumab: 4/49	
			Quality of life	Not reported	
			Post COVID-19 condition	Not reported	

	Kidney disease • Exp: NR • Ctrl: NR				

5.10.5 Studienselektion: Flow Chart 5a & 5b



5.10.6 Literaturrecherche 5a & 5b

LL COVID **Tocilizumab**

Suchzeitraum ab 01.01.2022

Studiendesign: RCTs

Date of search for all databases: search 13.10.2023			
Database/Register	Search	Update Search	Update Search
CCSR	550 references, 190 studies		
Scopus	965		
WHO COVID-19 DB*	211		
Total	1726		
Total (after deduplication and RCT classified Scopus refernces)	1188		

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023.*

Since June 2023, manual updates to the database have been discontinued.

Search string:

Tocilizumab* OR TCZ* OR atlizumab* OR actemra* OR roactemra* OR lusinex* OR r 1569 OR r1569 OR IL 6 OR interleukin 6 OR anti-interleukine 6 OR anti-interleukin drugs OR receptor OR inter leukin drugs OR IL-6 OR IL-6 blockade OR IL 6 receptor OR IL 6 inhibition OR IL 6

Suchstrategien

Cochrane COVID-19 Study Register

Search string:

tocilizumab* or TCZ* or atlizumab* or actemra* or roactemra* or lusinex* or "r 1569" or r1569 or "IL 6" or "interleukin 6" or "interleukine 6" or "anti-interleukin drugs"

Results available: report results

Study characteristics:

1) "Intervention assignment": "Randomised"; "Quasi-Randomised" OR "Unclear"
2) "Study design": "Parallel/Crossover" OR "Unclear"

Zeitraum: 01.0.2022 – 13.10.2023

Scopus (via Elsevier)

TITLE-ABS (tocilizumab* or TCZ* or atlizumab* or actemra* or roactemra* or lusinex* or "r 1569" or r1569 or "IL 6" or "interleukin 6" or "interleukine 6" or "anti-interleukin drugs")

AND TITLE-ABS(covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") AND AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023)) AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(tocilizumab* or TCZ* or atlizumab* or actemra* or roactemra* or lusinex* or "r 1569" or r1569 or "IL 6" or "interleukin 6" or "interleukine 6" or "anti-interleukin drugs")
AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")
Limit 2022, 2023

5.11 Schlüsselfrage 6a: Tixagevimab/Cilgavimab und SoC vs. SoC alone

Autor*innen: Nina Kreuzberger

5.11.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.11.1.1 *Evidenzprofil 1: Outpatients*

Population: Outpatients with confirmed COVID-19 diagnosis

Intervention: Evushield plus standard of care

Vergleichsintervention: Placebo plus standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo + SOC	Evushield + SOC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
ICU admission or death day 29	Relative risk: 0.28 (CI 95% 0.08 - 0.99) Based on data from 833 patients in 1 studies	**26** per 1000	**7** per 1000 Difference: **19 less per 1000** (CI 95% 24 less - 0 less)	**Very low** Due to very serious risk of bias, Due to very serious indirectness[1]	We are uncertain whether evushield plus standard of care increases or decreases the incidence of ICU admission.
Mortality, day 28	(CI 95% -) Based on data from 337 patients in 2 studies	per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)		There were no events in two comparisons on 337 participants.
Mortality, day 90	Relative risk: 1.0 (CI 95% 0.32 - 3.07) Based on data from 903 patients in 1 studies[2]	**13** per 1000	**13** per 1000 Difference: **0 less per 1000** (CI 95% 9 less - 27 more)	**Moderate** Due to serious imprecision[3]	Evushield plus standard of care probably has little or no difference on mortality through day 90.
Hospital admission or death	Relative risk: 0.44 (CI 95% 0.27 - 0.73) Based on data from 1171 patients in 3 studies[4]	**86** per 1000	**38** per 1000 Difference: **48 less per 1000** (CI 95% 63 less - 23 less)	**Very low** Due to serious risk of bias, Due to very serious indirectness[5]	We are uncertain whether evushield plus standard of care improves or worsen hospital admission or death.
Symptom resolution by day 28	Relative risk: 0.95 (CI 95% 0.82 - 1.2) Based on data from 337 patients in 2 studies	**694** per 1000	**659** per 1000 Difference: **35 less per 1000** (CI 95% 125 less - 139 more)	**Moderate** Due to serious imprecision[6]	Evushield plus standard of care probably has little or no difference on symptom resolution by day 28.
Infusion-related reactions	Relative risk: 1.01 (CI 95% 0.52 - 1.95) Based on data from 1240 patients in 3 studies	**27** per 1000	**27** per 1000 Difference: **0 less per 1000** (CI 95% 13 less - 26 more)	**Moderate** Due to serious imprecision[7]	Evushield plus standard of care has probably little or no effect on infusion-related reactions.
Adverse events, grade 3-4	Relative risk: 0.83 (CI 95% 0.25 - 2.76) Based on data from 337 patients in 1 studies	**80** per 1000	**66** per 1000 Difference: **14 less per 1000** (CI 95% 60 less - 141 more)	**Very low** Due to very serious indirectness, Due to serious imprecision[8]	We are uncertain whether evushield plus standard of care increases or decreases grade 3-4 adverse events.

Serious adverse events	Relative risk: 0.59 (CI 95% 0.4 - 0.87) Based on data from 1240 patients in 3 studies	**104** per 1000 **61** per 1000 Difference: **43 less per 1000** (CI 95% 62 less - 14 less)	**Low** Due to very serious indirectness[9]	Evushield plus standard of care may decrease the incidence of serious adverse events.
Post Covid19-Condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post covid19-condition.
Adverse events, any grade	Relative risk: 0.81 (CI 95% 0.67 - 0.98) Based on data from 903 patients in 1 studies	**361** per 1000 **292** per 1000 Difference: **69 less per 1000** (CI 95% 119 less - 7 less)	**Low** Due to very serious indirectness[10]	Evushield plus standard of care may decrease the number of participants with any grade adverse events.
Quality of life	Measured with: Scale: - Higher is better	Mean **Mean** Difference: **MD**		No studies were found that looked at quality of life.

1. Risk of bias: very serious. Competing events not accounted for.; Indirectness: very serious.
2. Primary study [33] Baseline/comparison intervention Control arm from the reference for intervention arm.
3. Imprecision: very serious. Wide confidence intervals, Low number of events;
4. Systematic review. Baseline/comparison intervention Control arm from the reference for intervention arm [33], [34]
5. Risk of bias: very serious. For TACKLE, the larhest contributing study, competing events "deaths" were not taken into account.; Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC. Participants were not yet immunised.;
6. Imprecision: very serious. Wide confidence intervals, Low number of patients;
7. Imprecision: very serious. Wide confidence intervals;
8. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC.; Imprecision: very serious. Wide confidence intervals;
9. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC. Participants were not yet immunised.;
10. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC. Participants were not yet immunised.

5.11.1.2 *Evidenzprofil 2: Inpatients*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Evushield plus standard of care

Vergleichsintervention: Placebo plus standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo + SOC	 Evushield + SOC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality, day 28 28 days	Hazard ratio: 0.62 (CI 95% 0.42 - 0.92)	**92** per 1000	**58** per 1000	**Very low**	We are uncertain whether Evushield plus standard of care improves or worsens

	Based on data from 1417 patients in 1 studies[1]	Difference: **34 less per 1000** (CI 95% 52 less - 7 less)	Due to serious imprecision, Due to very serious indirectness[2]	mortality by day 28, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Mortality, day 90 90 days	Hazard ratio: 0.7 (CI 95% 0.5 - 0.97) Based on data from 1417 patients in 1 studies[3]	**122** per 1000 **74** per 1000 Difference: **1 more per 1000** (CI 95% 37 less - 79 more)	**Very low** Due to very serious imprecision, Due to very serious indirectness[4]	We are uncertain whether Evushield plus standard of care improves or worsens mortality by day 90, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Time to sustained recovery through day 90 90 days	Hazard ratio: 1.08 (CI 95% 0.97 - 1.2) Based on data from 1417 patients in 1 studies[5]	**842** per 1000 **864** per 1000 Difference: **22 more per 1000** (CI 95% 9 less - 49 more)	**Very low** Due to serious imprecision, Due to very serious indirectness[6]	We are uncertain whether Evushield plus standard of care shortens or increases time to sustained recovery, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Time to hospital discharge absolute effect calculated for day 10	Hazard ratio (CI 95% -)	**0** per 1000 **0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)		No studies were found that looked at time to hospital discharge.
Adverse events, grade 3-4	Relative risk: 0.95 (CI 95% 0.8 - 1.14) Based on data from 1417 patients in 1 studies	**260** per 1000 **247** per 1000 Difference: **13 less per 1000** (CI 95% 52 less - 36 more)	**Moderate** Due to serious imprecision[7]	Evushield plus standard of care probably has little or no difference on grade 3-4 adverse events.
Need for IMV or death, day 28 28 days	Relative risk: 0.8 (CI 95% 0.6 - 1.06) Based on data from 1384 patients in 1 studies	**137** per 1000 **110** per 1000 Difference: **27 less per 1000** (CI 95% 55 less - 8 more)	**Very low** Due to serious imprecision, Due to very serious indirectness[8]	We are uncertain whether Evushield plus standard of care improves or worsens IMV or death by day 28, as participants were recruited before the omicron VOC and only around 15% of participants were vaccinated.
Adverse events, any grade 28 days	Relative risk: 1.09 (CI 95% 0.9 - 1.32) Based on data from 1417 patients in 1 studies	**222** per 1000 **242** per 1000 Difference: **20 more per 1000** (CI 95% 22 less - 71 more)	**Moderate** Due to serious imprecision[9]	Evushield plus standard of care probably has little or no difference on any adverse events.
Serious adverse events or death	Relative risk: 0.76 (CI 95% 0.58 - 0.98)	**158** per 1000 **120** per 1000	**Low**	Evushield plus standard of care may decrease serious

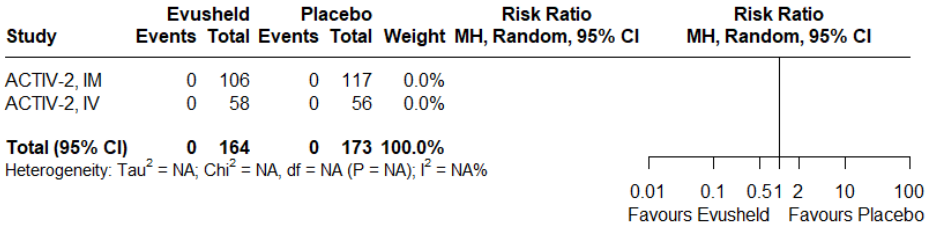
90 days	Based on data from 1417 patients in 1 studies	Difference: **38 less per 1000** (CI 95% 66 less - 3 less)	Due to very serious indirectness[10]	adverse events or death by day 90.
Post-Covid19 condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post-covid19 condition.
Quality of life	Measured with: Scale: - Higher is better	Mean **Mean** Difference: **MD**		No studies were found that looked at quality of life.

1. Primary study [27] Baseline/comparison intervention Control arm from the reference for intervention arm.
2. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals, Low number of events.;
3. Primary study [27] Baseline/comparison intervention Control arm from the reference for intervention arm.
4. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals, Low number of patients and events.;
5. Primary study [27] Baseline/comparison intervention Control arm from the reference for intervention arm.
6. Indirectness: very serious. Differences between the population of interest and those studied; Imprecision: very serious. Wide confidence intervals;
7. Imprecision: very serious. Wide confidence intervals;
8. Indirectness: very serious. Differences between the population of interest and those studied; Imprecision: very serious. Wide confidence intervals;
9. Indirectness: Differences between the population of interest and those studied; Imprecision: very serious. Wie confidence intervals including the line of no effect.
10. Indirectness: very serious. Differences between the population of interest and those studied;

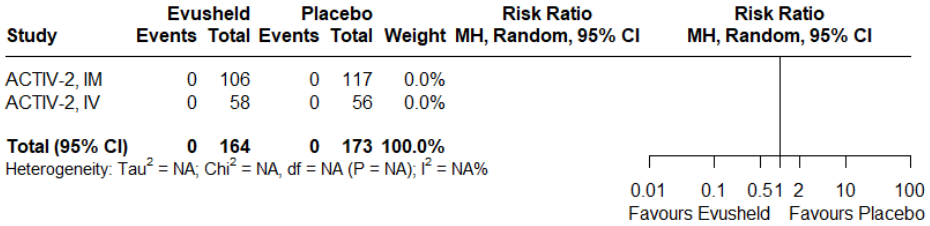
5.11.2 Analysen / Forest Plots der RCTs

5.11.2.1 *Outpatients*

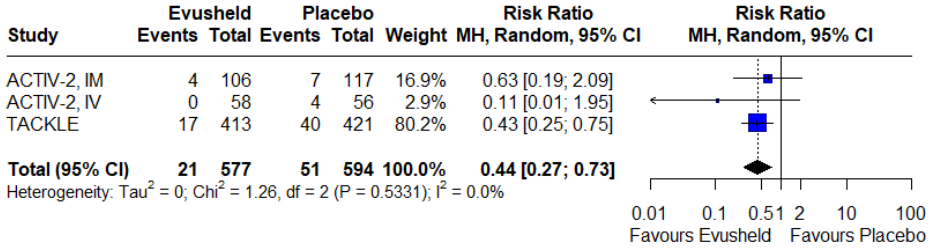
Mortality, day 28



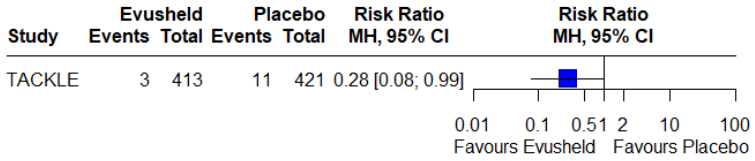
Mortality, day 84



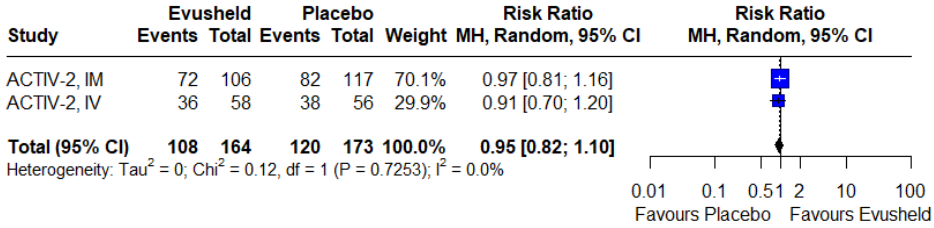
Hospital admission or death



Admission to ICU, day 29

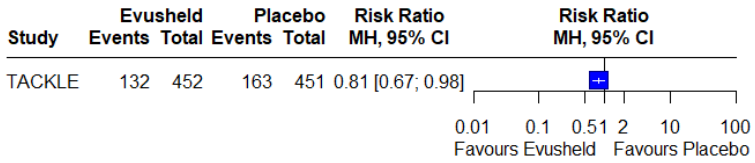


Symptom resolution by day 28

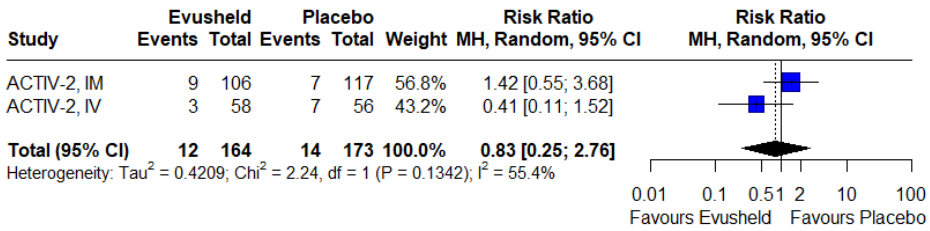


* symptom resolution by day 29 was reported for TACKLE in Hobbs 2023, however, incomplete reporting, data could not be used (unclear unit).

Adverse events, any grade

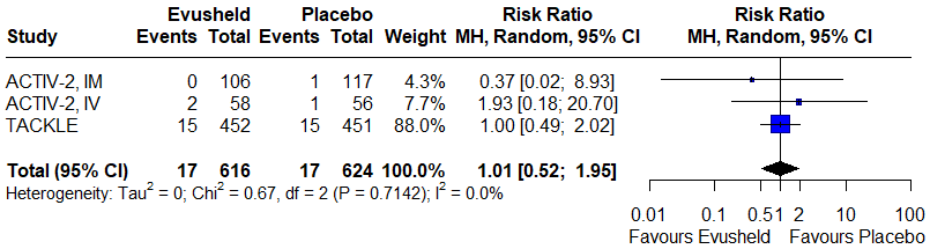


Adverse events, grade 3-4

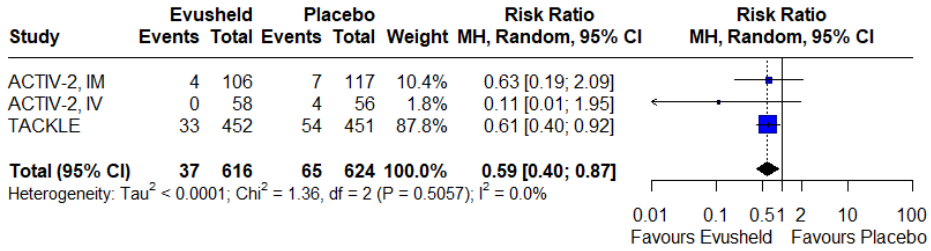


* Adverse events were reported in TACKLE as mild, Moderatee, severe; for short term and 170 day follow-up.

Infusion-related events

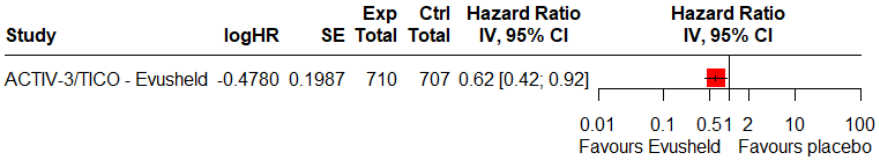


Serious adverse events / death by day 28/29

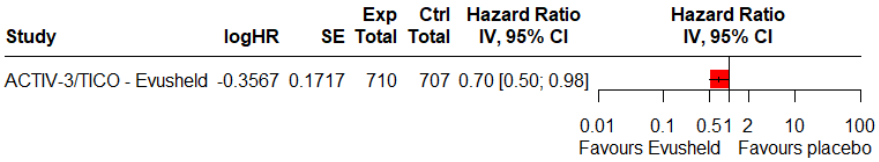


5.11.2.2 *Inpatients*

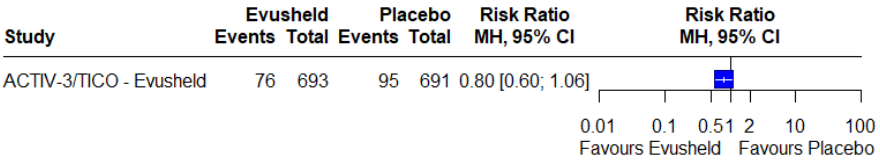
Mortality day 28



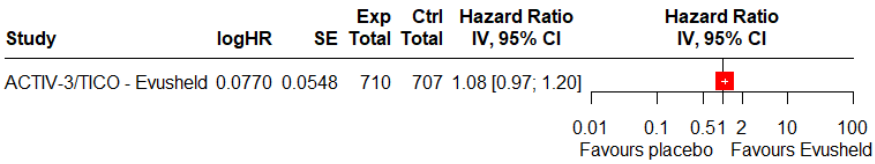
Mortality, day 90



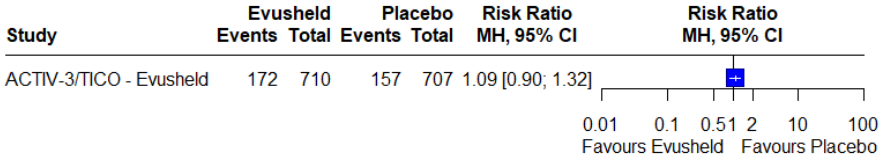
IMV or death by day 28



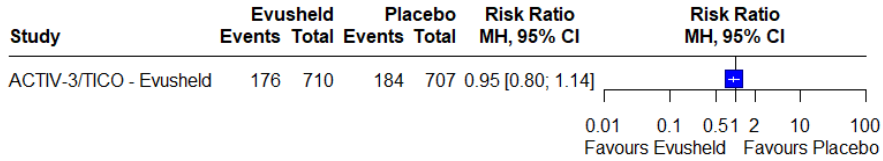
Time to sustained recovery



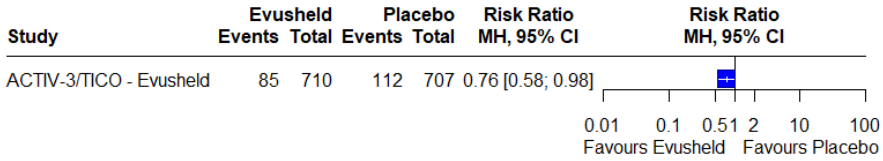
Adverse events, any grade



Adverse events, grade 3 to 4



Serious adverse events by day 90



5.11.3 Referenzen der eingeschlossenen Studien

5.11.3.1 *RCT-Recherche*

- Bender Ignacio RA, Chew KW, Moser C, Currier JS, Eron JJ, Javan AC, et al. Safety and efficacy of combined tixagevimab and cilgavimab administered intramuscularly or intravenously in nonhospitalized patients with COVID-19: 2 randomized clinical trials. JAMA network open. 2023;6(4):e2310039. doi: 10.1001/jamanetworkopen.2023.10039. PubMed PMID: 23119500.
- Hobbs FDR, Montgomery H, Padilla F, Simon-Campos JA, Kim K, Arbetter D, et al. Outpatient treatment with AZD7442 (Tixagevimab/Cilgavimab) prevented COVID-19 hospitalizations over 6 months and reduced symptom progression in the TACKLE randomized trial. Infectious diseases and therapy. 2023. doi: 10.1007/s40121-023-00861-7. PubMed PMID: 23989748.
- Holland TL, Ginde AA, Paredes R, Murray TA, Engen N, Grandits G, et al. Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. The Lancet Respiratory Medicine. 2022;10(10):972-84. doi: 10.1016/S2213-2600(22)00215-6.
- Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Respiratory Medicine. 2022;10(10):985-96. doi: 10.1016/S2213-2600(22)00180-1.

5.11.3.2 *Kohorten-Recherche*

Keine Studien zur Behandlung identifiziert (Prophylaxe mit Evushield war nicht Teil dieser PICO).

5.11.4 Charakteristika der eingeschlossenen Studien

5.11.4.1 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Hobbs 2023; Montgomery, 2022 (TACKLE) outpatients RCT	**Sample size:** N = 903 pts. (1:1) randomized to tixagevimab-cilgavimab or placebo **Enrolment period:** 28.01.2021 to 22.07.2021 USA, Latin America, Europe, and Japan **Inclusion criteria:** · Aged ≥18 years · laboratory-confirmed SARS-CoV-2 infection · World Health Organisation (WHO) Clinical Progression Scale score >1 and 0 and 1 · Dosed within ≤7 days from self-reported onset of COVID-19–related symptoms (mild to Moderatee COVID) or measured fever · ≥1 of the following present within 24 h prior to day 1: cough, sore throat, shortness of breath or difficulties breathing at rest/with activity, myalgia, fatigue, headache, chills, nasal obstruction/congestion/discharge, diarrhea, nw loss of taste/smell · Oxygen saturation of ≥ 92% · All participants were unvaccinated. **Time since symptom onset (mean, range):**	**Experimental:** · tixagevimab–cilgavimab · Dose: 600mg (two consecutive 3ml intramuscular injections, one each of 300mg tixagevimab and 300mg cilgavimab) · N = 452 **Control:** · Placebo (0.9% NaCl, two consecutive 3ml intramuscu	Mortality at longest FU (84 days)	RR 1.00 (95% CI 0.32nto 3.07) Exp: 6/452 Ctrl: 6/451	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: triple blinded, ITT (**low**) 3) Attrition bias: All participants analysed, relatively low drop-out (**low**) **Outcome-specific:** 4) Outcome measurement: high concerns in hospitalisation and admission to ICU due to no consideration of competing events, but low concerns for other outcomes 5) Selective reporting: outcomes were in accordance with the protocol; some concerns in mortality due to incoherence in presentation (**low**) ----------
			Admission to hospital or death (29 days)	RR 0.44 (95% CI 0.27 to 0.73) Exp: 17/413 Ctrl: 40/421	
			IMV or death	Not reported	
			Admission to ICU or death	RR 0.28 (95% CI 0.08, 0.99) Exp: 3/413 Ctrl: 11/421	
			Adverse events, any grade	RR 0.81 (95% CI 0.67 to 0.98) Exp: 132/452 Ctrl: 163/451	
			Infusion-related Adverse events	RR 1.0 (95% CI 0.52 to 1.95) Exp: 15/452 Ctrl: 15/451	
			Serious adverse events	RR 0.61 (95% CI 0.40 to 0.92) Exp: 33/452 Ctrl: 54/451	

	• Exp: 4.9 (SD 1.6) • Ctrl: 5.0 (SD 1.6) **<u>Characteristics</u>** **Age (mean, sd)** • Evushield: 52.9% • Placebo: 47.9% **Serum for SARS-CoV-2 serology negative, n (%)** • Exp: 84.7% • Ctr: 83.4% ***<u>Comorbidities</u>*** **Any** • Exp: 88.7% • Ctrl: 88.7% **Diabetes:** • Exp: 11.7% • Ctrl: 12.4% **Obesity (BMI ≥30 kg/m²)** • Exp: 43.1% • Ctrl: 42.8% **Hypertension** • Exp: 30.3% • Ctrl: 26.8% **Cardiovascular disease** • Exp: 9.3% • Ctrl: 8.4% **Lung diseases** • Exp: 12.8% • Ctrl: 11.1% **Immunosuppressed** • Exp: 4.9% • Ctrl: 5.3%	lar injections) • N = 451 N = mind. eine Dosis und ausgewertet	QoL Incidence of Post-COVID19 condition	Not reported Not reported	6) Overall: **low concerns in (serious) adverse events and infusion; some concerns in mortality; high concerns in hospitalisation and admission to ICU**

	Malignancy • Exp: 4.2% • Ctrl: 3.3% **Kidney disease** • Exp: 2.2% • Ctrl: 2.0%				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ignacio, 2023 (ACTIV-2) outpatient RCT	**Sample size:** N = 229 pts. Randomized (XX pts. planned) **Enrolment period:** 01.02.2021 to 31.03.2021 USA **Inclusion criteria:** · Individuals ≥18 years of age · laboratory-confirmed SARS-CoV-2 infection as determined by any respiratory tract specimen collected ≤240 hours prior to study entry · begin study treatment no more than 8 days from selfreported onset of COVID-19 related symptoms · One or more of the following signs/symptoms present within 24 hours prior to study entry: subjective fever, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, nausea or vomiting,	**Experimental:** · Intravenous Tixagevimab-cilgavimab · Dose: 300mg (150mg of each component admixed) infused over approximately 15 minutes · N = 58 **Control:** · Placebo infused over approximately 15 minutes · N = 56 N = (mind. eine Dosis und ausgewertet)	Mortality/death from any cause (28 days) Mortality at longest FU IMV or death Admission to hospital or death (28 days) Admission to ICU or death Discharged alive Symptom resolution (at least 2 days) Adverse events Grade 3 or higher (28 days) Infusion-related AE Serious adverse events (28 days) QoL Incidence of Post-COVID19 condition	Exp: 0/58 Ctrl: 0/56 Not reported Not reported Exp:0/58 Ctrl: 4/56 Not reported Not reported Exp: 36/58 Ctrl: 38/56 Exp: 3/58 Ctrl: 7/56 Exp: 0/106 Ctrl: 1/117 Exp: 0/58 Ctrl: 4/56 Not reported Not reported	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: ITT, triple masking (**low**) 3) Attrition bias: low concerns (**low**) **Outcome-specific:** 4) Outcome measurement: outcome was measured appropriately, same for both allocated arms (**low**) 5) Selective reporting: analyses were in accordance with the protocol (**low**)

	diarrhea, documented temperature >38°C · Oxygenation saturation of ≥92% **Time since symptom onset (median, IQR):** · Exp: 6 (4-7) · Ctrl: 6 (4-7) ≤ 5 days · Exp: 44.3% · Ctrl: 45.3% **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 43 (33 – 51) · Ctrl: 46 (35 – 58) **Serum for SARS-CoV-2 serology negative, n (%)** · Exp: NR · Ctrl: NR ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: NR · Ctrl: NR **Obesity (BMI ≥30 kg/m²)** · Exp: median BMI 34 (26 – 37) · Ctrl: median BMI 31 (27 – 36) **Hypertension** · Exp: NR · Ctrl: NR				---------- -- 6) Overall: **low concerns for risk of bias**

	Cardiovascular disease · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR **Immunosuppressed** · Exp: NR · Ctrl: NR **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease** · Exp: NR · Ctrl: NR ·				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ignacio, 2023 (ACTIV-2) Outpatient RCT	**Sample size:** N = 229 pts. Randomized **Enrolment period:** 01.02.2021 to 31.03.2021 USA **Inclusion criteria:** · Individuals ≥18 years of age · laboratory-confirmed SARS-CoV-2 infection as determined by any respiratory tract specimen collected ≤240 hours prior to study entry · begin study treatment no more than 8 days from selfreported onset of COVID-19 related symptoms · One or more of the following signs/symptoms present within 24 hours prior to study entry: subjective fever, cough, shortness of breath or difficulty breathing at rest or with activity, sore throat, body pain or muscle pain/aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, nausea or vomiting,	**Experimental:** · intramuscular Tixagevimab-cilgavimab · Dose: 600mg (300mg in 3 mL of each component, 1 component delivered to each lateral thigh) minutes · N = 106 **Control:** · IM saline Placebo · N = 117 N = (mind. eine Dosis und ausgewertet)	Mortality/death from any cause (28 days)	Exp: 0/106 Ctrl: 0/117	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: ITT, triple masking (**low**) 3) Attrition bias: low concerns (**low**) **Outcome-specific:** 4) Outcome measurement: outcome was measured appropriately, same for both allocated arms (**low**) 5) Selective reporting: analyses were in accordance with the protocol (**low**) ----------
			Mortality at longest FU	Not reported	
			IMV or death	Not reported	
			Admission to hospital or death (28 days)	Exp:4/106 Ctrl: 7/117	
			Admission to ICU or death	Not reported	
			Discharged alive	Not reported	
			Symptom resolution (at least 2 days)	Exp: 72/106 Ctrl: 82/117	
			Adverse events Grade 3 or higher (28 days)	Exp: 9/106 Ctrl: 7/117	
			Infusion-related AE	Exp: 2/58 Ctrl: 1/56	
			Serious adverse events (28 days)	Exp: 4/106 Ctrl: 7/117	
			QoL	Not reported	

	diarrhea, documented temperature >38°C · Oxygenation saturation of ≥92% **Time since symptom onset (median, range):** · Exp: 6 (4-7) · Ctrl: 6 (4-7) ≤ 5 days · Exp: 44.3% · Ctrl: 45.3% **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 40 (32 – 48) · Ctrl: 38 (29 – 48) **Serum for SARS-CoV-2 serology negative, n (%)** · Exp: NR · Ctrl: NR ***<u>Comorbidities</u>*** **Any** · Exp: NR · Ctrl: NR **Diabetes:** · Exp: NR · Ctrl: NR **Obesity (BMI ≥30 kg/m²)** · Exp: median BMI under 30 · Ctrl:median BMI under 30 **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease**		Incidence of Post-COVID19 condition	Not reported	6) Overall: **low concerns for risk of bias**

	• Exp: NR • Ctrl: NR **Lung diseases** • Exp: NR • Ctrl: NR **Immunosuppressed** • Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease** • Exp: NR • Ctrl: NR				

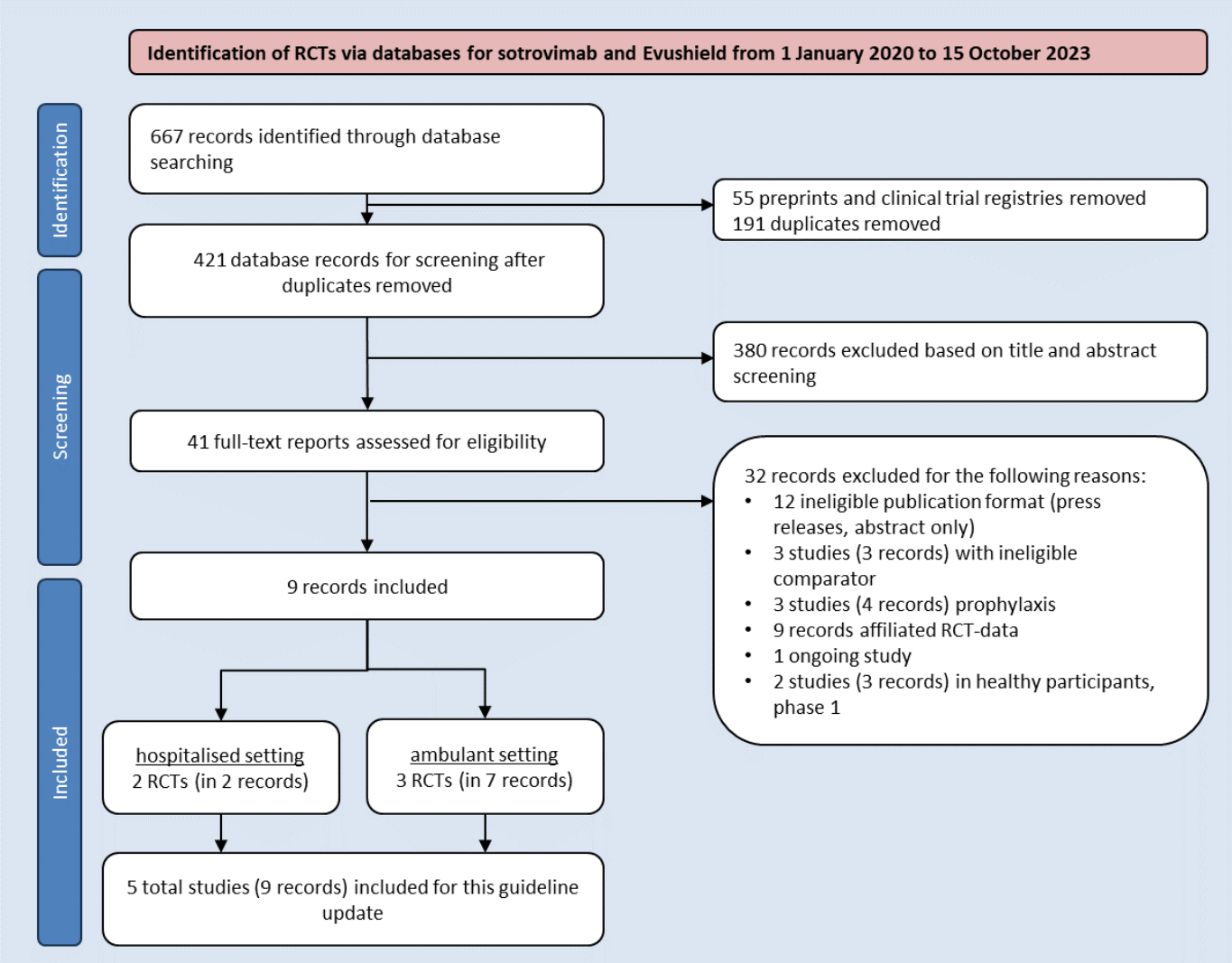
Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group, 2022 RCT	**Sample size:** N = 1455 pts. (1:1) randomized to Tixagevimab–cilgavimab or placebo **Enrolment period:** 10.02.2021 to 30.09.2021 USA, Europe, Uganda, Singapore **Inclusion criteria:** · Age ≥ 18 years · SARS-CoV-2 infection, documented by a nucleic acid test (NAT) or equivalent testing within 3 days prior to randomization OR documented by NAT or equivalent testing more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator · Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator **Time since symptom onset (median, range):** · Exp: 8 (6 – 10) · Ctrl: 8 (6 – 10)	**Experimental:** · Intravenous tixagevimab–cilgavimab · Dose: 600mg (300mg of each component) administered as a single intravenous infusion over a 30-min period · N = 710 **Control:** · Placebo · N = 707 N = (mind. eine Dosis und ausgewertet)	Mortality	HR 0.62 (0.42 – 0.92) Exp: 41/710 Ctrl: 65/707	**For all outcomes:** 1) Randomisation and allocation concealment: low concerns (**low**) 2) Blinding: study participants, site study staff, investigators, and clinical providers were blinded (**low**) 3) Attrition bias: missing outcome data was low (**low**) **Outcome-specific:** 4) Outcome measurement: low concerns (**low**) 5) Selective reporting: analyses was in accordance with the protocol (**low**) --- 6) Overall: **low concerns for risk of bias**
			Mortality at longest FU (90 days)	HR 0.70 (0.50 – 0.97) Exp: 61/710 Ctrl: 86/707	
			IM V or death	Exp: 76.23/693 Ctrl: 94.667/691	
			Admission to hospital or death	Not applicable	
			Admission to ICU or death	Not reported	
			Symptom resolution (90 days)	RR 1.08 (0.97 – 1.2) Exp: 617/710 Ctrl: 595/707	
			Adverse events (any grade) (28 days)	Exp: 172/710 Ctrl: 157/707	
			Adverse events (grade 3-4) (28 days)	Exp: 176/710 Ctrl:184/707	
			Serious adverse events (90 days)	Exp: 85/710 Ctrl: 112/707	
			QoL	Not reported	

	<u>Characteristics</u> **Age (median, IQR)** · Exp: 55 (44 – 66) · Ctrl: 55 (44 – 66) **Serum for SARS-CoV-2 serology negative, n (%)** · Exp: 525/710 (74%) · Ctrl: 516/707 (73%) ***<u>Comorbidities</u>*** **Any** · Exp: 415/710 (40%) · Ctrl: 445/707 (63%) **Diabetes:** · Exp: 183/710 (26%) · Ctrl: 187/707 (26%) **Obesity (BMI ≥30 kg/m²)** BMI 30 – 39.9 · Exp: 281/710 (40%) · Ctrl: 268/707 (38%) BMI ≥ 40 · Exp: 102/710 (14%) · Ctrl: 106/707 (15%) **Hypertension** · Exp: 292/710 (41%) · Ctrl: 300/707 (42%) **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** Asthma · Exp: 68/710 (10%) · Ctrl: 70/707 (10%)		Incidence of Post-COVID19 condition	Not reported	

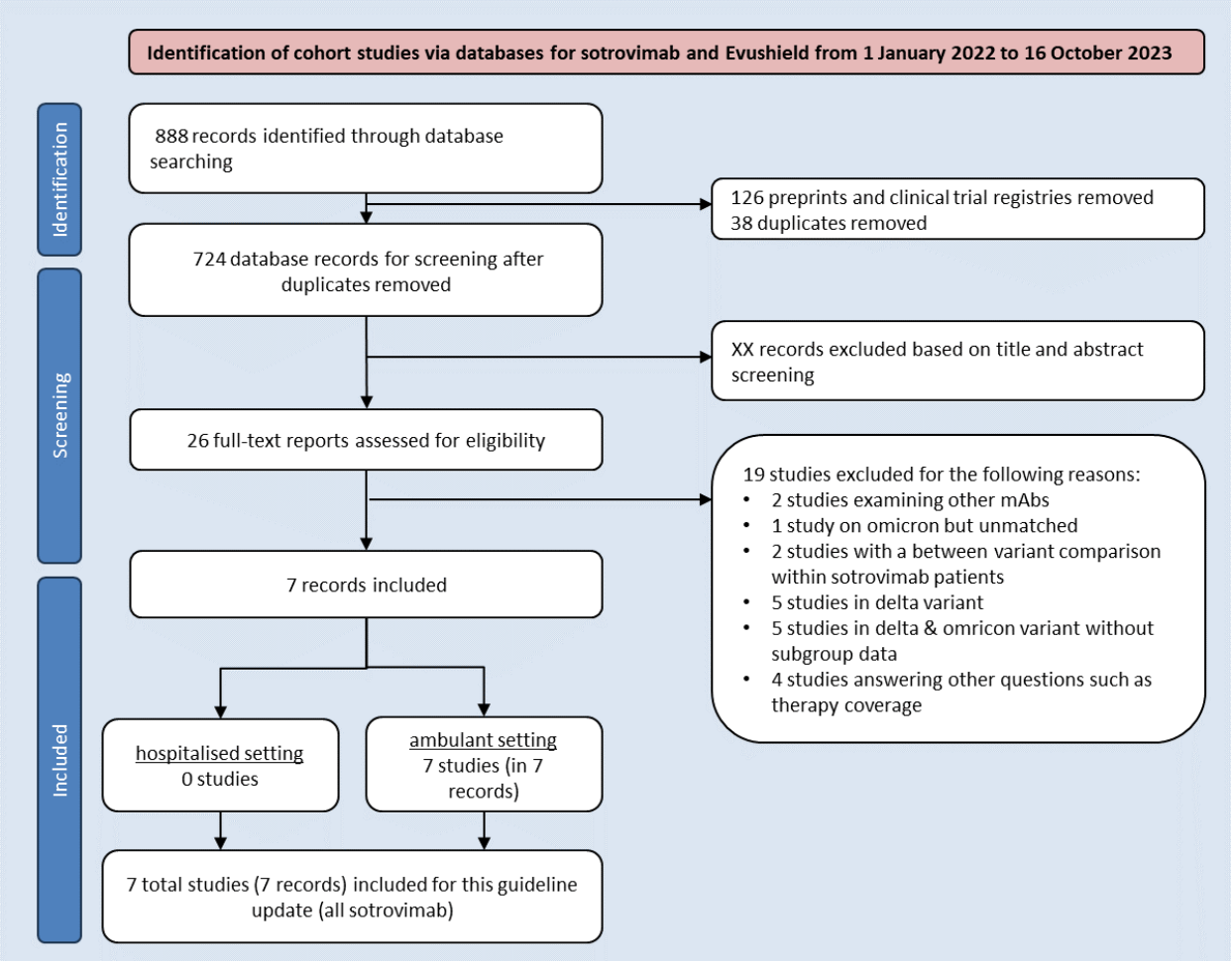
	COPD · Exp: 44/710 (6%) · Ctrl: 42/707 (6%) **Immunosuppressed** · Exp: 57/710 (8%) · Ctrl: 71/707 (10%) **Malignancy** · Exp: NR · Ctrl: NR **Kidney disease (renal impairement)** · Exp: 63/710 (9%9 · Ctrl: 70/707 (10%)				

5.11.5 Studienselektion: Flow Chart 6a & b

5.11.5.1 *Flow chart für die RCT-Recherche*



5.11.5.2 *Flow Chart für die Kohorten-Recherche*



5.11.6 Literaturrecherche 6a & b

5.11.6.1 *Literaturrecherche für RCTs*

Date of search for all databases: 15.10.2023			
Database/Register	**Search**	**Update Search**	**Update Search**
CCSR	281 references, 49 studies		
Scopus	268		
WHO COVID-19 DB*	118		
Total	667		
Total (after deduplication)	616		

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Cochrane COVID-19 Study Register

Search string:

VIR7831* or "VIR-7831" or GSK4182136* or "GSK-4182136" or sotrovimab* or xevudy* or AZD7442* or "AZD-7442" or AZD8895* or "AZD-8895" or tixagevimab* or "COV2-2196" or COV22196* or AZD1061* or "AZD-1061" or cilgavimab* or "COV2-2130" or COV22130* or evusheld* or "antibody combination" or "antibodies combination" or "mab combination" or "mabs combination" or "antibody combinations" or "mab combinations" or "antibody cocktail" or "antibody cocktails" or "covid-19 cocktail" or "covid-19 cocktails" or "mab treatment" or "mab treatments" or "antibody treatment" or "antibody treatments" or "antibodies treatment" or "mab therapy" or "mab therapies" or "mabs therapy" or "mabs therapies" or "antibody therapy" or "antibodies therapy" or "antibody therapies" or "antibodies therapies" or "antibody administration" or "antibodies administration" or "mab administration" or "mabs administration" or "antibody regimen" or "antibody regimens" or "mab regimen" or "mab regimens" or "antibodies target" OR "two mab" or "two mabs"

Results available: report results

Study characteristics:

1) "Intervention assignment": "Randomised"; "Quasi-Randomised" OR "Unclear"

2) "Study design": "Parallel/Crossover" OR "Unclear"

Scopus (via Elsevier)

TITLE-ABS (vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "antibodies combination" OR "mab combination" OR "mabs combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "antibody cocktails" OR "covid-19 cocktail" OR "covid-19 cocktails" OR "mab treatment" OR "mab treatments" OR "antibody treatment" OR "antibody treatments" OR "antibodies treatment" OR "mab therapy" OR "mab therapies" OR "mabs therapy" OR "mabs therapies" OR "antibody therapy" OR "antibodies therapy" OR "antibody therapies" OR "antibodies therapies" OR "antibody administration" OR "antibodies administration" OR "mab administration" OR "mabs administration" OR "antibody regimen" OR "antibody regimens" OR "mab regimen" OR "mab regimens" OR "antibodies target" OR "two mab" OR "two mabs")

AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

AND LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023)

AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "antibodies combination" OR "mab combination" OR "mabs combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "antibody cocktails" OR "covid-19 cocktail" OR "covid-19 cocktails" OR "mab treatment"

OR "mab treatments" OR "antibody treatment" OR "antibody treatments" OR "antibodies treatment" OR "mab therapy" OR "mab therapies" OR "mabs therapy" OR "mabs therapies" OR "antibody therapy" OR "antibodies therapy" OR "antibody therapies" OR "antibodies therapies" OR "antibody administration" OR "antibodies administration" OR "mab administration" OR "mabs administration" OR "antibody regimen" OR "antibody regimens" OR "mab regimen" OR "mab regimens" OR "antibodies target" OR "two mab" OR "two mabs")

AND (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

5.11.6.2 *Literaturrecherche für Kohortenstudien*

Date of search for all databases: from 01.01.2022 to 16.10.2023				
Database/Register	**Search**	**Update Search**	**Update Search**	**Update Search**
CCSR	545 references, 477 studies			
Scopus	184			
WHO COVID-19 DB*	159			
Total	888			
Total (after deduplication)	724 (includes 126 CT.gov und preprints)			

**The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.*

Cochrane COVID-19 Study Register

Search string:

VIR7831* or "VIR-7831" or GSK4182136* or "GSK-4182136" or sotrovimab* or xevudy* or AZD7442* or "AZD-7442" or AZD8895* or "AZD-8895" or tixagevimab* or "COV2-2196" or COV22196* or AZD1061* or "AZD-1061" or cilgavimab* or "COV2-2130" or COV22130* or evusheld* or "antibody combination" or "antibodies combination" or "mab combination" or "mabs combination" or "antibody combinations" or "mab combinations" or "antibody cocktail" or "antibody cocktails" or "covid-19 cocktail" or "covid-19 cocktails" or "mab treatment" or "mab treatments" or "antibody treatment" or "antibody treatments" or "antibodies treatment" or "mab therapy" or "mab therapies" or "mabs therapy" or "mabs therapies" or "antibody therapy" or "antibodies therapy" or "antibody therapies" or "antibodies therapies" or "antibody administration" or "antibodies administration" or "mab administration" or "mabs administration" or "antibody regimen" or "antibody regimens" or "mab regimen" or "mab regimens" or "antibodies target" OR "two mab" or "two mabs"

Results available: report results

Study characteristics:

1) "Study design": case series/case control/cohort

Scopus (via Elsevier)

TITLE-ABS (vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR

"AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "mab combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "covid-19 cocktail" OR "mab treatment" OR "monoclonal antibody treatment" OR "mab therapy" OR "monoclonal antibody therapy" OR "monoclonal antibody administration" OR "mab administration" OR "monoclonal antibody regimens" OR "mab regimens" OR "two mabs")

AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS ((control AND study) OR group OR groups OR (time AND factors) OR program OR survey* OR cohort OR comparative AND stud* OR "evaluation studies" OR follow-up*) AND LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023) AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

(vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "mab combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "covid-19 cocktail" OR "mab treatment" OR "monoclonal antibody treatment" OR "mab therapy" OR "monoclonal antibody therapy" OR "monoclonal antibody administration" OR "mab administration" OR "monoclonal antibody regimens" OR "mab regimens" OR "two mabs") AND (control AND study) OR group OR groups; limit to year 2022 and 2023

(vir7831* OR "VIR-7831" OR gsk4182136* OR "GSK-4182136" OR sotrovimab* OR xevudy* OR azd7442* OR "AZD-7442" OR azd8895* OR "AZD-8895" OR tixagevimab* OR "COV2-2196" OR cov22196* OR azd1061* OR "AZD-1061" OR cilgavimab* OR "COV2-2130" OR cov22130* OR evusheld* OR "antibody combination" OR "mab combination" OR "antibody combinations" OR "mab combinations" OR "antibody cocktail" OR "covid-19 cocktail" OR "mab treatment" OR "monoclonal antibody treatment" OR "mab therapy" OR "monoclonal antibody therapy" OR "monoclonal antibody administration" OR "mab administration" OR "monoclonal antibody regimens" OR "mab regimens" OR "two mabs") AND ((time AND factors) OR program OR survey* OR cohort OR comparative stud* OR evaluation studies OR follow-up*); limit to year 2022 and 2023

5.12 Schlüsselfrage 5b: Sotrovimab und SoC vs. SoC alone

Autor*innen: Caroline Hirsch, Nina Kreuzberger

5.12.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Outpatients with confirmed SARS-CoV-2 infection (and at least one risk factor for severe disease)

Intervention: Sotrovimab plus standard of care

Vergleichsintervention: Placebo plus standard of care

5.12.1.1 *Evidenzprofil 1: Outpatients*

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo + SOC	Sotrovimab + SOC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Mortality, day 28 day 28	Relative risk: 0.2 (CI 95% 0.01 - 4.16) Based on data from 1057 patients in 1 studies[1]	**4** per 1000	**1** per 1000 Difference: **3 less per 1000** (CI 95% 4 less - 13 more)	**Very low** Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether sotrovimab plus standard of care improves or worsen mortality by day 28 during the omicron VOC.
Mortality, day 60	Relative risk (CI 95% -)	per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)		
IMV or death, day 60	Relative risk: 0.08 (CI 95% 0.0 - 1.36) Based on data from 1057 patients in 1 studies[3]	**11** per 1000	**1** per 1000 Difference: **10 less per 1000** (CI 95% 11 less - 4 more)	**Very low** Due to serious imprecision, Due to very serious indirectness[4]	We are uncertain whether sotrovimab plus standard of care improves or worsens the incidence of IMV or death by day 60 during the omicron VOC.
Admission to ICU or death, day 60	Relative risk: 0.05 (CI 95% 0.0 - 0.81) Based on data from 1057 patients in 1 studies[5]	**19** per 1000	**1** per 1000 Difference: **18 less per 1000** (CI 95% 19 less - 4 less)	**Very low** Due to serious indirectness, Due to serious imprecision[6]	We are uncertain whether sotrovimab plus standard of care improves or worsens the incidence of admission to hospital or death by day 60 during the omicron VOC.
Hospital admission (> 24h) or death, day 29	Relative risk: 0.2 (CI 95% 0.08 - 0.48) Based on data from 1057 patients in 1 studies[7]	**57** per 1000	**11** per 1000 Difference: **46 less per 1000** (CI 95% 52 less - 30 less)	**Low** Due to very serious indirectness[8]	Sotrovimab plus standard of care may decrease hospital admission or death by day 29.
Adverse events, any grade	Relative risk: 0.93 (CI 95% 0.74 - 1.17) Based on data from 1057 patients in 1 studies[9]	**234** per 1000	**218** per 1000 Difference: **16 less per 1000** (CI 95% 61 less - 40 more)	**Low** Due to very serious indirectness[10]	Sotrovimab plus standard of care may decrease the incidence of any grade adverse events.
Symptom resolution by day 14	Relative risk: 1.58 (CI 95% 1.27 - 1.96) Based on data from 1057 patients in 1 studies[11]	**197** per 1000	**311** per 1000 Difference: **114 more per 1000** (CI 95% 53 more - 189 more)	**Low** Due to very serious indirectness[12]	Sotrovimab plus standard of care may increase symptom resolution by day 14.
Adverse events, grade 3-4	Relative risk: 0.42 (CI 95% 0.23 - 0.76) Based on data from 1057 patients in 1 studies[13]	**68** per 1000	**29** per 1000 Difference: **39 less per 1000** (CI 95% 52 less - 16 less)	**Low** Due to very serious indirectness[14]	Sotrovimab plus standard of care may decrease the incidence of grade 3 to 4 adverse events.

Infusion-related reactions	Relative risk: 1.01 (CI 95% 0.33 - 3.1) Based on data from 1057 patients in 1 studies[15]	**11** per 1000 **11** per 1000 Difference: **0 less per 1000** (CI 95% 7 less - 23 more)	**Low** Due to very serious indirectness[16]	Sotrovimab plus standard of care may have little or no difference on infusion-related reactions.
Serious adverse events	Relative risk: 0.35 (CI 95% 0.18 - 0.68) Based on data from 1057 patients in 1 studies[17]	**61** per 1000 **21** per 1000 Difference: **40 less per 1000** (CI 95% 50 less - 20 less)	**Low** Due to very serious indirectness[18]	Sotrovimab plus standard of care may decrease the incidence of serious adverse events.
Incidence of Post COVID19 Condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at incidence of post covid19 condition.
Quality of life	Measured with Scale: - Higher is better	Mean Mean Difference: **MD**		No studies were found that looked at quality of life.

1. Primary study [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
2. Risk of bias: keine. No concerns regarding risk of bias.; Inkonsistenz: keine. No concerns regarding inconsistency.; Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals due to very low number of events.;
3. Systematic review with included studies: [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
4. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals, Low number of events;
5. Primary study [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
6. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals, Low number of events;
7. Primary study [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
8. Indirectness: very serious.
9. Primary study [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
10. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
11. Primary study. Baseline/comparison intervention Control arm from the reference for intervention arm [24]
12. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
13. Primary study [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
14. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;
15. Primary study [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
16. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;

17. Systematic review with included studies: [24] Baseline/comparison intervention Control arm from the reference for intervention arm.
18. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.;

5.12.1.2 *Evidenzprofil 2: Inpatients*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection (WHO 4 to 9)

Intervention: Sotrovimab, 500 mg plus standard of care

Vergleichsintervention: Placebo plus standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo + SOC	Sotrovimab + SOC	**Certainty of the Evidence** (Quality of evidence)	**Summary**
28-day mortality 28 days	Hazard ratio: 0.97 (CI 95% 0.39 - 2.41) Based on data from 360 patients in 1 studies[1]	**51** per 1000	**50** per 1000 Difference: **1 less per 1000** (CI 95% 31 less - 68 more)	**Low** Due to very serious imprecision[2]	Sotrovimab may have little or no effect on 28-day mortality.
Time to hospital discharge absolute effect calculated for day 10	Hazard ratio: 1.13 (CI 95% 0.93 - 1.37) Based on data from 360 patients in 1 studies	**145** per 1000	**162** per 1000 Difference: **17 more per 1000** (CI 95% 9 less - 48 more)	**Moderate** Due to serious imprecision[3]	Sotrovimab probably has little or no effect on time to hospital discharge.
Need for IMV or death 5 days	Relative risk: 0.49 (CI 95% 0.09 - 2.65) Based on data from 359 patients in 1 studies	**23** per 1000	**11** per 1000 Difference: **12 less per 1000** (CI 95% 21 less - 38 more)	**Very low** Due to very serious imprecision, Due to serious indirectness[4]	There were too few who experienced an event to determine whether sotrovimab has an effect on clinical status assessed by need for intubatioin or death by day 5.
90-day mortality 90 days	Hazard ratio: 1.02 (CI 95% 0.48 - 2.17) Based on data from 360 patients in 1 studies[5]	**73** per 1000	**74** per 1000 Difference: **1 more per 1000** (CI 95% 37 less - 79 more)	**Low** Due to very serious imprecision[6]	Sotrovimab may have little or no effect on 90-day mortality.
Adverse events, any grade 28 days	Relative risk: 1.05 (CI 95% 0.77 - 1.45) Based on data from 360 patients in 1 studies	**287** per 1000	**301** per 1000 Difference: **14 more per 1000** (CI 95% 66 less - 129 more)	**Low** Due to very serious imprecision[7]	Sotrovimab may have little or no effect on adverse events, any grade by day 28.
Serious adverse events or death 28 days	Relative risk: 0.86 (CI 95% 0.44 - 1.67) Based on data from 360 patients in 1 studies	**96** per 1000	**83** per 1000 Difference: **13 less per 1000** (CI 95% 54 less - 64 more)	**Low** Due to very serious imprecision[8]	Sotrovimab may have little or no effect on serious adverse events or death by day 28.

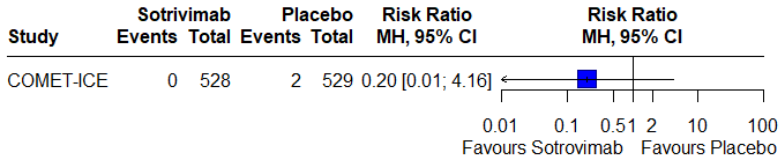
Time to sustained recovery through day 90 day 90	Hazard ratio: 1.12 (CI 95% 0.91 - 1.37) Based on data from 360 patients in 1 studies[9]	**848** per 1000 **879** per 1000 Difference: **31 more per 1000** (CI 95% 28 less - 76 more)	**Very low** Due to serious imprecision, Due to very serious indirectness[10]	We are uncertain whether sotrovimab plus soc improves or worsen time to sustained recovery through day 90.
Serious adverse events or death 90 days	Relative risk: 0.9 (CI 95% 0.53 - 1.52) Based on data from 360 patients in 1 studies	**140** per 1000 **126** per 1000 Difference: **14 less per 1000** (CI 95% 66 less - 73 more)	**Low** Due to very serious imprecision[11]	Sotrovimab may have little or no effect on serious adverse events or death by day 90.
Infusion-related reactions day 1	Relative risk: 1.26 (CI 95% 0.65 - 2.45) Based on data from 360 patients in 1 studies	**79** per 1000 **100** per 1000 Difference: **21 more per 1000** (CI 95% 28 less - 115 more)	**Low** Due to very serious imprecision[12]	Sotrovimab may increase the occurence of infusion-related reactions.
Post-Covid19 condition	Relative risk (CI 95% -)	per 1000 per 1000 Difference: **less per 1000**		No studies were found that looked at post-covid19 condition.
Quality of life				No studies were found that looked at quality of life.

1. Primary study [25] Baseline/comparison intervention Control arm from the reference for intervention arm.
2. Indirectness: keine. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals, Low number of patients and events.;
3. Indirectness: keine. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Low number of patients;
4. Indirectness: very serious. The outcome time frame in studies were insufficient, only 5-day follow-up ; Imprecision: very serious. Wide confidence intervals, Low number of patients and events.;
5. Primary study [25] Baseline/comparison intervention Control arm from the reference for intervention arm.
6. Indirectness: keine. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals, Low number of patients and events.;
7. Imprecision: very serious. Low number of patients, Optimal information size (OIS) criterion not met;
8. Imprecision: very serious. Wide confidence intervals, Low number of patients;
9. Primary study [25] Baseline/comparison intervention Control arm from the reference for intervention arm.
10. Indirectness: very serious. Differences between the population of interest and those studied: Participants were recruited during the alpha/delta VOC (August 2020 through March 2021). Participants were not yet immunised.; Imprecision: very serious. Wide confidence intervals;
11. Imprecision: very serious. Wide confidence intervals, Low number of patients;
12. Imprecision: very serious. Wide confidence intervals, Low number of patients;

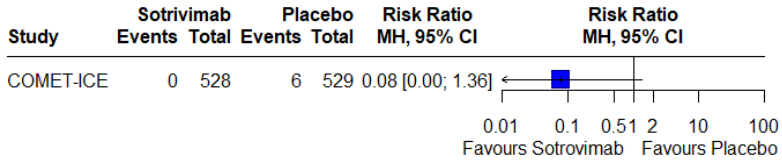
5.12.2 Analysen / Forest Plots

5.12.2.1 *Outpatients*

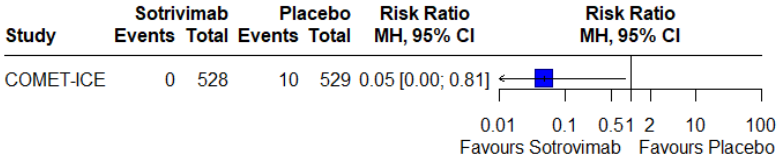
Mortality, day 28



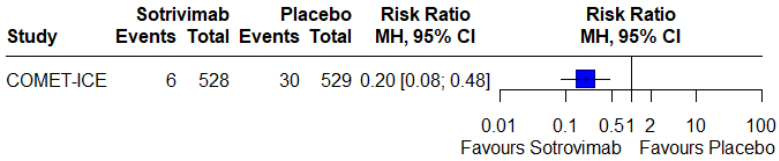
IMV or death, day 60



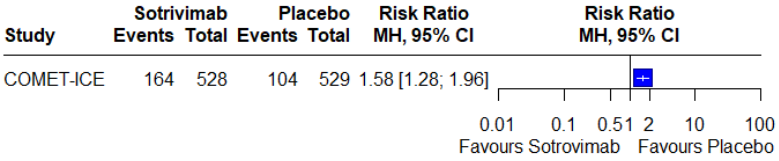
ICU admission or death, day 60



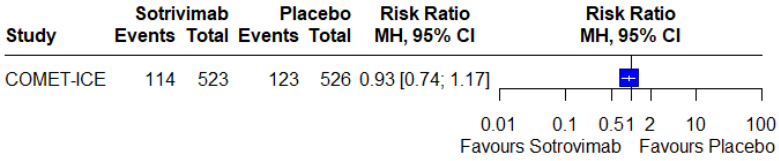
ICU admission (>= 24 h) or death



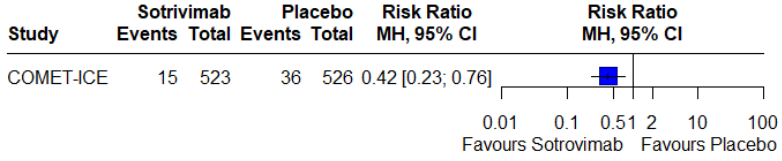
Symptom resolution by day 14



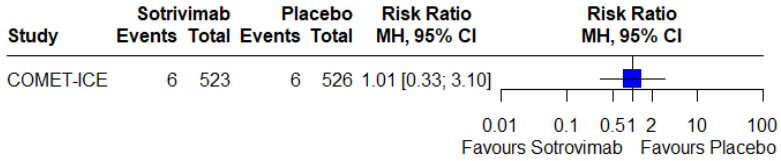
Adverse events, any grade



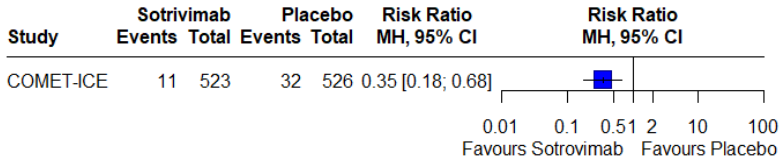
Adverse events, grade 3-4



Infusion-related events

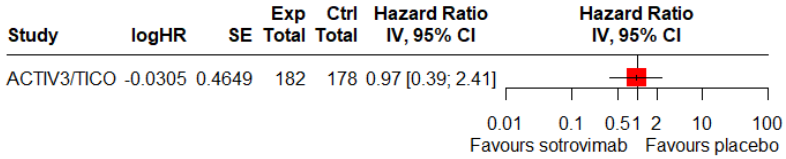


Serious adverse events

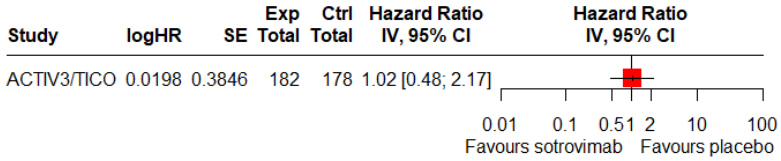


5.12.2.2 *Inpatients*

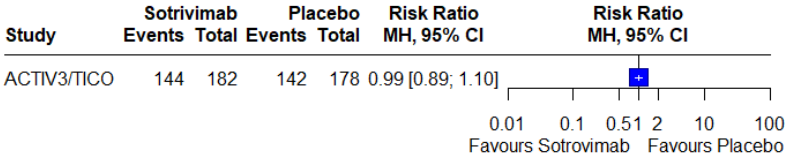
Mortality, day 28



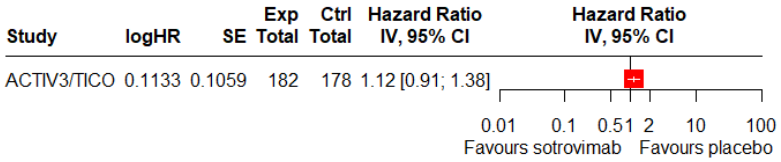
Mortality, day 90



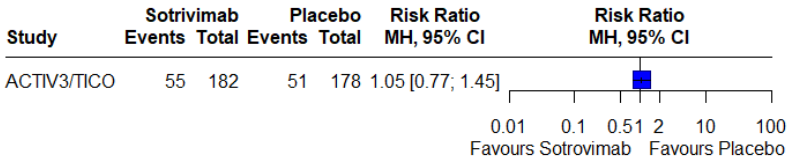
Discharged alive, day 14



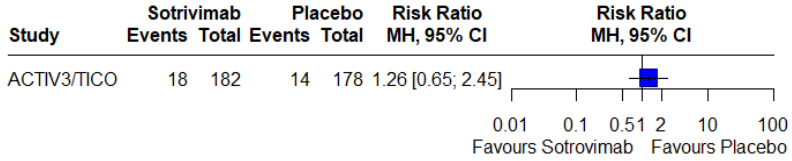
Symptom resolution, here defined as sustained recovery through day 90



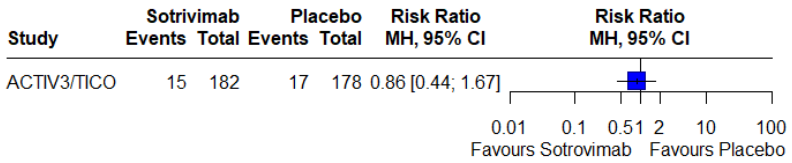
Adverse events, any grade



Infusion-related events



Serious adverse events



5.12.3 Referenzen der eingeschlossenen Studien

5.12.3.1 *RCT-Recherche*

- ACTIV-3/Therapeutics for Inpatients with COVID-19 Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. The lancet Infectious diseases. 2022;22(5):622-35. doi: 10.1016/S1473-3099(21)00751-9. PubMed PMID: 19576625.
- Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. New Engl J Med. 2021;385(21):1941-50. doi: 10.1056/NEJMoa2107934. PubMed PMID: 19158404.
- Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Rodrigues Falci D, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to Moderatee COVID-19: a randomized clinical trial. JAMA. 2022;327(13):1236-46. doi: 10.1001/jama.2022.2832. PubMed PMID: 20415675.
- Lokhandwala T, Acharya M, Farrelly E, Coutinho AD, Bell CF, Svedsater H. Within-trial economic analysis of resource use from COMET-ICE: a phase 3 clinical trial evaluating sotrovimab for the treatment of patients with COVID-19 at high risk of progression. Journal of managed care & specialty pharmacy. 2022;28(11):1261-71. doi: 10.18553/jmcp.2022.28.11.1261. PubMed PMID: 21970543.
- Satram S, Ghafoori P, Reyes CM, Keeley TJH, Birch HJ, Brintziki D, et al. Assessment of symptoms in COMET-ICE, a phase 2/3 study of sotrovimab for early treatment of non-hospitalized patients with COVID-19. Journal of patient-reported outcomes. 2023;7(1):92. doi: 10.1186/s41687-023-00621-8. PubMed PMID: 23941529.

5.12.3.2 *Kohorten-Recherche*

- Aggarwal NR, Beaty LE, Bennett TD, Carlson NE, Mayer DA, Molina KC, et al. Change in effectiveness of sotrovimab for preventing hospitalization and mortality for at-risk COVID-19 outpatients during an Omicron BA.1 and BA.1.1-predominant phase. International Journal of Infectious Diseases. 2023;128:310-7. Epub 2022/10/14. doi: 10.1016/j.ijid.2022.10.002. PubMed PMID: 36229005; PubMed Central PMCID: PMCPMC9549713.
- Ambrose N, Amin A, Anderson B, Barrera-Oro J, Bertagnolli M, Campion F, et al. Neutralizing monoclonal antibody use and COVID-19 infection outcomes. JAMA Network Open. 2023;6(4):e239694. doi: 10.1001/jamanetworkopen.2023.9694. PubMed PMID: 23098879.
- Cheng MM, Reyes C, Satram S, Birch H, Gibbons DC, Drysdale M, et al. Real-world effectiveness of sotrovimab for the early treatment of COVID-19 during SARS-CoV-2 delta and omicron waves in the USA.

Infectious Diseases and Therapy. 2023;12(2):1-15. doi: 10.1007/s40121-022-00755-0. PubMed PMID: 22411921.

- Evans A, Qi C, Adebayo JO, Underwood J, Coulson J, Bailey R, et al. Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study. Journal of Infection. 2023. doi: 10.1016/j.jinf.2023.02.012. PubMed PMID: 22626237.
- Kikuchi K, Nangaku M, Ryuzaki M, Yamakawa T, Ota Y, Hanafusa N, et al. Efficacy of molnupiravir and sotrovimab in Japanese dialysis patients with COVID-19 in clinical practice during the Omicron (BA.1 and BA.2) pandemic. Therapeutic Apheresis and Dialysis. 2023. doi: 10.1111/1744-9987.14033.
- Miyashita N, Nakamori Y, Ogata M, Fukuda N, Yamura A, Ishiura Y, et al. Clinical efficacy of the neutralizing antibody therapy sotrovimab in patients with SARS-CoV-2 Omicron BA.1 and BA.2 subvariant infections. Viruses. 2023;15(6). doi: 10.3390/v15061300.
- Zheng B, Green ACA, Tazare J, Curtis HJ, Fisher L, Nab L, et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform. BMJ (Clinical research ed). 2022;379:e071932. doi: 10.1136/bmj-2022-071932. PubMed PMID: 22119283.

5.12.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
ACTIV-3 2021 Inpatients RCT	**Sample size:** N = 546 (2:1:2:1) randomised to sotrovimab, placebo, BRII-196/BRII-198, placebo · Sotrovimab: N = 184 · Placebo: N = 183; placebo groups pooled for analysis **Enrolment period:** 16.12.2020 to 01.03.2021 USA, Denmark, Switzerland, and Poland **Most important inclusion criteria:** · ≤12 days since SO · SARS-CoV-2 infection, documented by NAT or equivalent testing within 3 days prior to randomization OR more than 3 days AND progressive disease suggestive of ongoing infection · Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19 **Time since symptom onset (median, range):** · 8 days **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 61 (50 to 74) · Ctrl: 60 (49 to 70)	**Experimental:** · intravenous sotrovimab plus standard of care (SOC) · Dose: 500 mg · N = 182 **Control:** · Placebo (saline) plus standard of care (SOC) · N = 178	Mortality (day 28)	RR: 0.98 (0.40 to 2.41) Sotrovimab: 9/182 Placebo: 9/178	**<u>For all outcomes:</u>** 1) Randomisation and allocation concealment: No concerns 2) Blinding: blinding of the participant, clinical staff and outcome assessor by covering infusion bags 3) Attrition bias: low concern, low percentage of drop-out **<u>Outcome-specific:</u>** 4) Outcome measurement: low for all outcomes 5) Selective reporting: low concern for all outcomes, protocol-specified outcomes and time-points analysed --- 6) Overall: low concerns for risk of bias.
			Mortality (day 60)	Not reported	
			Mortality (day 90)	RR: 1.05 (0.51 to 2.18) Sotrovimab: 14/182 Placebo: 13/178	
			Time to hospital discharge	HR: 1.13 (0.93 to 1.37)	
			IMV requirement or death (day 5); no other timings reported	RR: 0.49 (0.09 to 2.65) Sotrovimab: 2/181 Placebo: 4/178	
			Adverse events, any grade (day 28)	RR: 1.05 (0.77 to 1.45) Sotrovimab: 55/182 Placebo: 51/178	
			Serious adverse events or death	RR: 0.90 (0.53 to 1.52) Sotrovimab: 23/182 Placebo: 25/178	
			Infusion reactions	RR: 1.26 (0.65 to 2.45) Sotrovimab: 18/182 Placebo: 14/178	
			QoL	Not reported	

	Comorbidities **Any** · Exp: 74% · Ctrl: 76% **Diabetes:** · Exp: 39% · Ctrl: 35% **Obesity (BMI ≥30 kg/m²)** · Exp: 56% · Ctrl: 56% **Hypertension** · Exp: 57% · Ctrl: 58% **Heart failure** · Exp: 7% · Ctrl: 4% **Lung diseases (Asthma)** · Exp: 10.4% · Ctrl: 9.6% **Lung diseases (COPD)** · Exp: 7.1% · Ctrl: 7.3% **Immunosuppressed** · Exp: 5.5% · Ctrl: 6.2% **Malignancy** · Exp: 3.8% · Ctrl: 3.9% **Renal impairment** · Exp: 15% · Ctrl: 11%		Post Covid19 condition	Not reported	

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
COMET-ICE Gupta 2022, final analysis Outpatients RCT	**Sample size:** N = 1057 · Sotrovimab: N = 528 · Placebo: N = 529 **Enrolment period:** 27.08.2020 to 11.03.2021 Brazil, Canada, Peru, Spain, USA **Most important inclusion criteria:** · ≤5 days since SO · Antigen or PCR test · At least 1 symptom · ≥1 Risk factor **Time since symptom onset (median, range):** · Sotrovimab: 59% ≤3 days, 40% 4-5 days · Placebo: 59% ≤ 3 days, 41% 4-5 days **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 53 (41.5-62) · Ctrl: 53 (43-63) ***<u>Comorbidities</u>*** **Any risk factor for progression** · Exp: 99% · Ctrl: 99%	**Experimental:** · intravenous sotrovimab plus standard of care (SOC) · Dose: 500 mg · N = 528 · median duration of follow-up: 103 days (IQR, 79-128 days) **Control:** · placebo plus standard of care (SOC) · N = 529 · Median duration of follow-up: 102 days (IQR, 77-128 days)	Mortality (day 29)	RR: 0.20 (0.01 to 4.17) Sotrovimab: 0/528 Placebo: 2/529	**<u>For all outcomes:</u>** 1) Randomisation and allocation concealment: No concerns 2) Blinding: blinding of the participant, clinical staff and outcome assessor 3) Attrition bias: low concern, most participants were followed up for main outcomes. **<u>Outcome-specific:</u>** 4) Outcome measurement: The timing of IMV requirement/death and ICU admission/death is not entirely clear, as they are inferred from eTable 2. For safety outcomes, the as
			Mortality (day 60)	Not reported	
			Mortality (day 90)	Not reported	
			Hospitalisation or death	RR: 0.20 (0.08 to 0.48) Sotrovimab: 6/528 Placebo: 30/529	
			Admission to ICU or death, day 60	RR: 0.05 (0.00 to 0.81) Sotrovimab: 0/528 Placebo: 10/529	
			IMV requirement or death	RR: 0.08 (0.00 to 1.36) Sotrovimab: 0/528 Placebo: 6/529	
			Sustained symptom alleviation day 14 (also reported for d7 and 21)	RR 1.84 (1.39 to 2.44) Sotrovimab: 164/528 Placebo: 104/529 *in Satram 2023	
			Adverse events, any grade (day 28)	RR: 0.93 (0.74 to 1.17) Sotrovimab: 114/528 Placebo: 123/526 *as treated data set	
			Adverse events, grade 3-4	RR 0.42 (0.23 to 0.76) Sptrovimab: 15/528 Placebo: 36/529	

	Diabetes (req. medication) · Exp: 23% · Ctrl: 21% **Obesity (BMI ≥30 kg/m²)** · Exp: 63% · Ctrl: 64% **Hypertension: NR** **Heart failure** · Exp: <1% · Ctrl: <1% **Lung diseases (Asthma): NR** **Lung diseases (COPD)** · Exp: 6% · Ctrl: 5% **Immunosuppressed: NR** **Malignancy: NR** **Kidney disease** · Exp: <1% · Ctrl: <1%			*as treated data set	treated set was analysed. 5) Selective reporting: Outcomes analysed as defined in protocol --- 6) Overall: **low concern**
			Serious adverse events	RR: 0.90 (0.53 to 1.52) Sotrovimab: 11/523 Placebo: 32/526 *as treated data set	
			Systemic Infusion reactions	RR: 1.01 (0.33 to 3.10) Sotrovimab: 6/523 Placebo: 6/526 *as treated data set	
			QoL	Not reported	
			Incidence of Post-COVID19 condition	Not reported	

5.12.4.1 *Cohort studie overview (finally not used, as the current omicron variant is not comparable to the variant circulation at the*

Study	Study/ database	design	setting	enrolment dates	country	vaccination status	intervention	comparison	Characteristics
Aggarwal 2022	Colorado state-wide data (CDPHE)	propensity-matched ("nearest-neighbor propensity matching with logistic regression to match patients with treatment status as the outcome. The propensity model included age, sex, race/ethnicity, insurance status, obesity status, immunocompromised status, number of other comorbid	outpatient	26.12.2021 to 10.03.2022	USA	>=2 vaccines Sotrovimab: 73.8% Untreated: 70.5%	sotrovimab (within 10 days after positive test)	untreated patients (no antiviral treatment)	well-matched

		conditions, number of vaccinations, and week in the study (categorical)"							
Ambrose 2023	California, Minnesota, texas and Utah	propensity-matched	outpatient, at least 1 risk factor for severe disease (extraction for omicron BA.1 epoch 2022.01)	9.11.2020 to 31.01.2022; omicron analysed separately; January 2022	USA	Fully vaccinated or boosted:* treated: 37.8% untreated: 33.9%	sotrovimab	untreated patients	well-matched
Cheng 2023	FAIR Health National Private Insurance Claims database	Multivariable and propensity score-matched Poisson and logistic regression	outpatients at higher risk of hospitalization and death	01.09.2021 to 30.04.2022; January	USA	Documented COVID-19 vaccine, no. (%) sotrovimab: 20.32% no mAb: 15.17%	sotrovimab	no mAbs	unclear if well-matched after propensity score
Evans 2023	SAIL Databank	adjusted: "Participants' baseline covariates included age, sex, number of comorbidities, Charlson comorbidity index (CCI) score, clinical subgroup (categorized as immunosuppressed conditions including hematological cancers, non-hematological cancers, other high-risk conditions, or unknown), Welsh Index of Multiple Deprivation (WIMD) version 2019 as quintiles mapped from LSOAs, COVID-19 vaccination status (unvaccinated, one to three vaccinations, or four or more vaccinations), and type of treatment received (molnupiravir, nirmatrelvir-ritonavir, or sotrovimab)"	outpatients at higher risk of hospitalization and death	16.12.2021 to 22.04.2022	UK, Wales	1 or more vaccinations (inkl. 4 and more) sotrovimab: 98.5% untreated: 95.6%	sotrovimab	untreated patients (no antiviral treatment)	not matched, but adjusted analysis

Kikuchi 2022	Registry of COVID-19 in Japan	adjusted	both, dialysis patients	01.01.2022 to 26.05.2022	Japan	2 or more vaccinations sotrovimab: 413/453 combination: 216/231 control: 174/193	Sotrovimab (+- Molnupiravir)	untreated	not matched, but adjusted analysis
Miyashita 2023	Japan	propensity score matched	outpatients, within 5 days of symptom onset and at least one risk factor for severe disease	12.2021 to 07.2022, BA.1	Japan	2 or more vaccinations sotrivimab: 83.1% control: 81.3%	sotrovimab	untreated	propensity score matched, well-matched
Miyashita 2023	Japan	propensity score matched	outpatients, within 5 days of symptom onset and at least one risk factor for severe disease	12.2021 to 07.2022, BA.2	Japan	2 or more vaccinations sotrivimab: 64.4% control: 61.4%	sotrovimab	untreated	propensity score matched, well-matched
Zheng 2022	OpenSavely Platform		outpatients, within 5 days of symptom onset and at least one risk factor for severe disease	16.12.2021 to 10.02.2022	UK, England	2 or more vaccinations sotrovimab: 96.4% molnupiravir: 95.5%	sotrovimab	molnupiravir	two ways of control: matching and multivariable modeling

	Mortality				**Hospitalisation**			
Study	Definition	Exp. deaths	Ctrl. Deaths	adjusted effect estimate	Definition	exp. hospitalisations	ctrl hospitalisations	Adjusted effect estimate

Aggarwal 2022	all-cause mortality day 28	1/1542 (0.1%)	7/3663 (0.2%)	adjusted OR: 0.62 (0.07 to 2.78)	All-cause hospitalisation within 28 days of test	39/1542 (2.5%)	116/3663 (3.2%)	adjusted OR: 0.82 (95% CI 0.55 to 1.19)
Ambrose 2023	death by day 30	0.00%	0.20%	OR 0.10 (0.01 to 1.68)	All cause hospitalisation or death	5.10%	2.60%	OR 2.07 (1.05 to 4.09)
Cheng 2023	February 2022				30-day all-cause hospitalisation or facility-reported mortality (by diagnosis month)	4859 (1.85%)	19192 (3.37%)	adjusted and PS-matched RR: 0.33 (0.27 to 0.41)
Cheng 2023	March 2022				30-day all-cause hospitalisation or facility-reported mortality (by diagnosis month)	2329 (3.26%)	9548 (6.9%)	adjusted and PS-matched RR: 0.39 (0.31 to 0.50)
Cheng 2023	April 2022				30-day all-cause hospitalisation or facility-reported mortality (by diagnosis month)	1046 (2.01%)	1046 (4.37)	adjusted and PS-matched RR: 0.38 (0.24 to 0.58)
Evans 2023					all-cause hospitalisation or death by day 30	53/1079 (4.9%)	544/4973 (10.9%)	HR 0.73 (0.55 to 0.98)
Kikuchi 2022	all-cause mortality, day 15			HR 0.446 (0.223 to 0.895)				
Kikuchi 2022, + molnupiravi	all-cause mortality, day 15			HR 0.208 (0.060 to 0.723)				
Miyashita 2023, BA.1	all-cause mortality	0/642	0/642	NR	No. (%) of patients who required oxygen therapy	26/642	56/642	NR
Miyashita 2023, BA.2	all-cause mortality	0/202	0/202	NR	No. (%) of patients who required oxygen therapy	8/202	20/202	NR
Zheng 2022					hospital admission or death by day 28	127/3331	123/2689	0.86 (0.65 to 1.14)

5.13 Schlüsselfrage 7: Anakinra und SoC vs. SoC alone

Autor*innen: Nora Cryns

Es wurden insgesamt 8 RCTs und 1957 Teilnehmende eingeschlossen.

5.13.1 Evidenzprofile / Summary of Findings (MAGICapp)

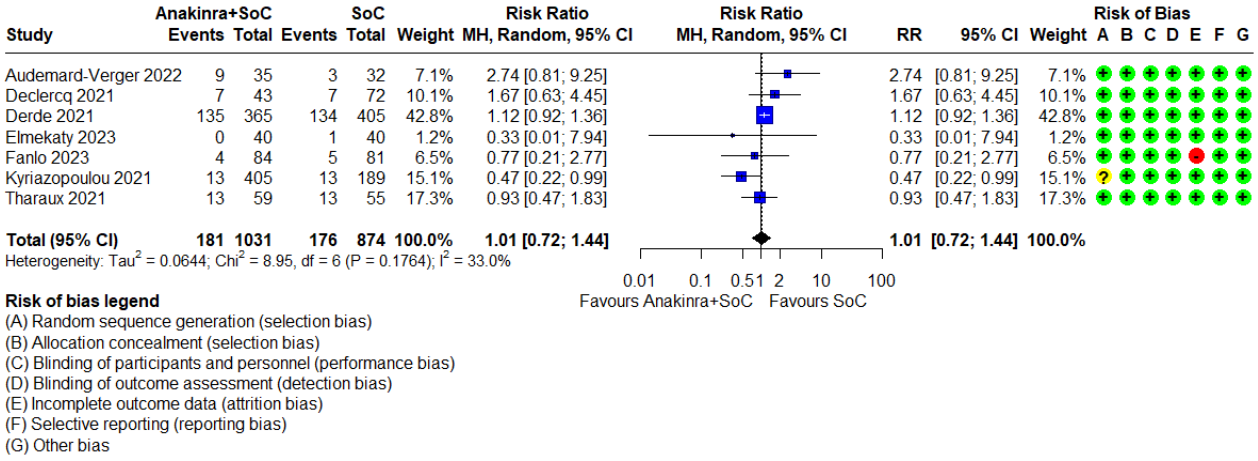
Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** standard care with or without placebo or no treatment	**Absolute effect estimates** Anakinra	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Discharged alive (by day 28-30)	Relative risk: 1.99 (CI 95% 1.21 - 3.29) Based on data from 71 patients in 1 studies	**353** per 1000	**702** per 1000 Difference: **349 more per 1000** (CI 95% 74 more - 808 more)	**Low** Due to very serious imprecision[1]	Anakinra may improve discharged alive (by day 28-30)
28-day mortality	Relative risk: 1.01 (CI 95% 0.71 - 1.44) Based on data from 1905 patients in 7 studies[2]	**201** per 1000	**203** per 1000 Difference: **2 more per 1000** (CI 95% 58 less - 88 more)	**Very low** Due to serious imprecision, Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[3]	We are uncertain whether anakinra improves or worsen 28-day mortality
Admission to ICU	Relative risk: 0.78 (CI 95% 0.48 - 1.29) Based on data from 236 patients in 2 studies	**226** per 1000	**176** per 1000 Difference: **50 less per 1000** (CI 95% 118 less - 66 more)	**Low** Due to serious inconsistency, Due to serious indirectness, Due to very serious risk of bias[4]	Anakinra may improve admission to ICU
Need for invasive mechanical ventilation or death	Relative risk: 0.69 (CI 95% 0.31 - 1.56) Based on data from 709 patients in 2 studies[5]	**138** per 1000	**95** per 1000 Difference: **43 less per 1000** (CI 95% 95 less - 77 more)	**Low** Due to serious inconsistency, Due to serious indirectness, Due to very serious inconsistency[6]	Anakinra may improve need for invasive mechanical ventilation or death
60-day mortality	Relative risk: 1.86 (CI 95% 0.82 - 4.21) Based on data from 115 patients in 1 studies	**125** per 1000	**233** per 1000 Difference: **108 more per 1000** (CI 95% 22 less - 401 more)	**Very low** Due to serious imprecision, Due to very serious imprecision, Due to serious indirectness[7]	We are uncertain whether anakinra improves or worsen 60-day mortality
Serious adverse events	Relative risk: 0.93 (CI 95% 0.75 - 1.14) Based on data from 1150 patients in 6 studies	**258** per 1000	**240** per 1000 Difference: **18 less per 1000** (CI 95% 64 less - 36 more)	**Low** Due to serious inconsistency, Due to serious risk of bias, Due to serious indirectness[8]	Anakinra may have little or no difference on serious adverse events
Adverse events (any grade)	Relative risk: 1.17 (CI 95% 0.82 - 1.68)	**538** per 1000	**629** per 1000	**Low**	Anakinra may have little or no difference on

	Based on data from 556 patients in 5 studies	Difference: **91 more per 1000** (CI 95% 97 less - 366 more)	Due to very serious imprecision, Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness[9]	adverse events (any grade)

1. Imprecision: very serious. Low number of patients, Only data from one study;
2. Systematic review with included studies: [46], [44], [45] Baseline/comparison intervention Control arm from the reference for intervention arm.
3. Risk of bias: very serious. Incomplete data and/or large loss to follow up, baseline differences; Inkonsistenz: very serious. Point estimates vary widely, The direction of the effect is not consistent between the included studies; Imprecision: very serious. Wide confidence intervals;
4. Risk of bias: very serious. Incomplete data and/or large loss to follow up + baseline differences;
5. Systematic review [43] . Baseline/comparison intervention Control arm from the reference for intervention arm.
6. Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2:... %.; Indirectness: keine. Differences between the population of interest and those studied, -> nearly all participants recruited in 2020, Can conclusions be drawn about current Covid variants?;
7. Inkonsistenz: keine. Point estimates vary widely; Indirectness: keine. Differences between the population of interest and those studied, -> nearly all participants recruited in 2020, Can conclusions be drawn about current Covid variants?; Imprecision: very serious. Low number of patients, Only data from one study, Wide confidence intervals, Wide confidence intervals;
8. Risk of bias: very serious. Incomplete data and/or large loss to follow up, baseline differences; Inkonsistenz: very serious. The direction of the effect is not consistent between the included studies; Indirectness: keine. Differences between the population of interest and those studied, -> nearly all participants recruited in 2020, Can conclusions be drawn about current Covid variants?;
9. Risk of bias: very serious. Inkonsistenz: very serious. The magnitude of statistical heterogeneity was high, with I^2:... %.; Indirectness: keine. Differences between the population of interest and those studied; Imprecision: keine. Wide confidence intervals, Low number of patients, Only data from one study;

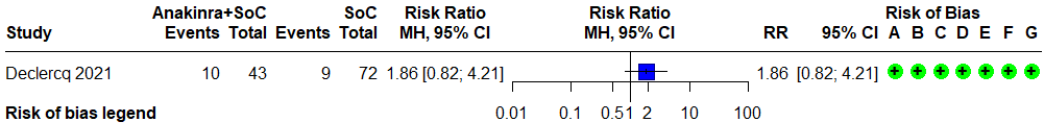
5.13.2 Analysen / Forest Plots

Mortality, day 28



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Mortality, day 60



Risk of bias legend
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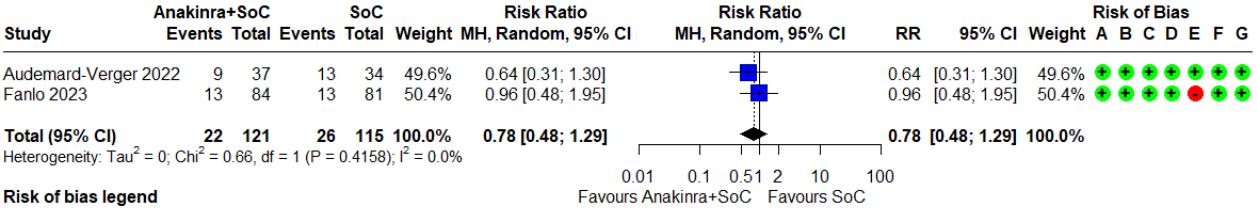
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Admission to ICU



Risk of bias legend
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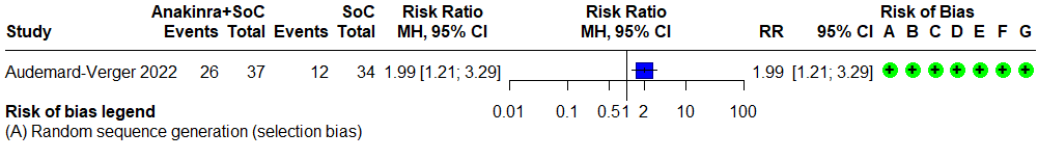
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Discharged alive (by day 28)



Risk of bias legend
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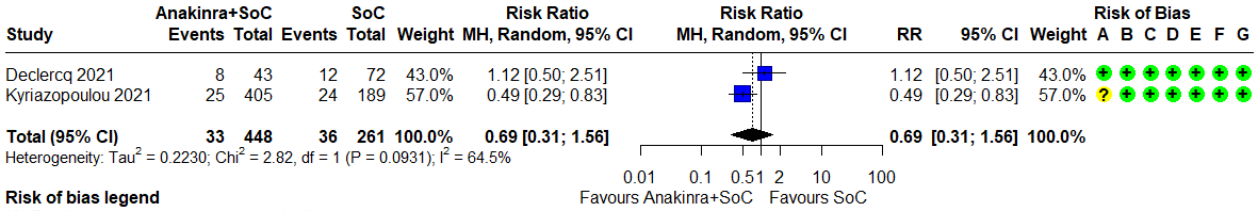
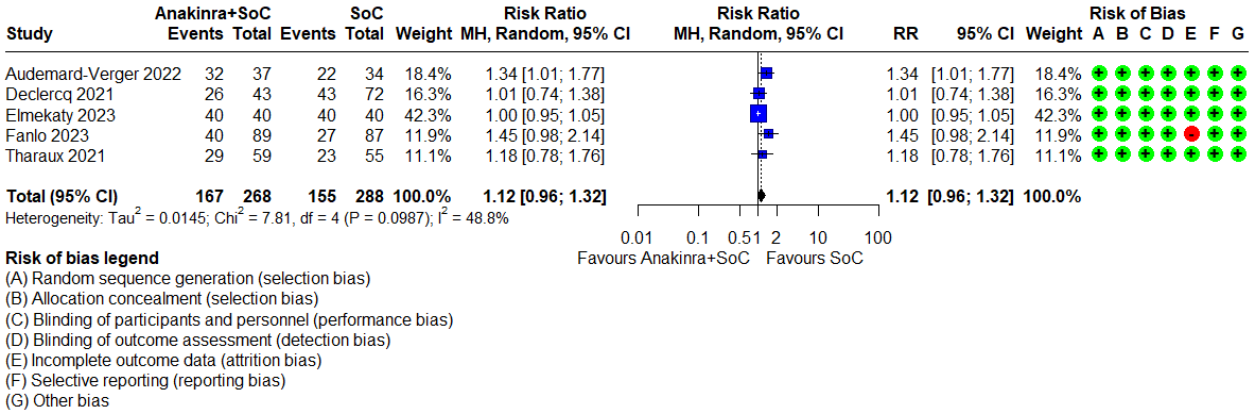
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Need for IMV or death



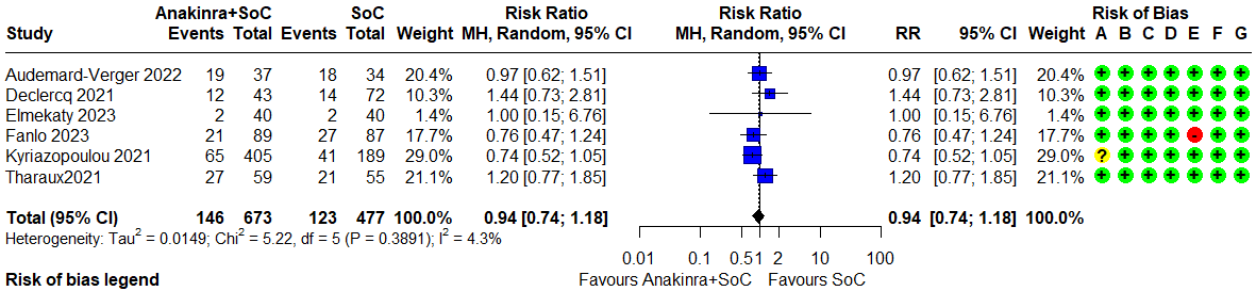
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Any adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Serious adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

5.13.3 Referenzen der eingeschlossenen Studien

- Audemard-Verger, A., Le Gouge, A., Pestre, V., Courjon, J., Langlois, V., Vareil, M. O., ... & Caille, A. (2022). Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial. PLoS One, 17(8), e0269065.
- Dahms, K., Mikolajewska, A., Ansems, K., Metzendorf, M. I., Benstoem, C., & Stegemann, M. (2023). Anakinra for the treatment of COVID-19 patients: a systematic review and meta-analysis. European Journal of Medical Research, 28(1), 1-12.
- Elmekaty, E. Z. I., Maklad, A., Abouelhassan, R., Munir, W., Ibrahim, M. I. M., Nair, A., ... & Al Maslamani, M. (2023). Evaluation of anakinra in the management of patients with COVID-19 infection: A randomized clinical trial. Frontiers in Microbiology, 14, 1098703.
- Fanlo, P., del Carmelo Gracia-Tello, B., Aizpuru, E. F., Álvarez-Troncoso, J., Gonzalez, A., Prieto-González, S., ... & Pardos-Gea, J. (2023). Efficacy and safety of anakinra plus standard of care for patients with severe COVID-19: a randomized phase 2/3 clinical trial. JAMA Network Open, 6(4), e237243-e237243.

5.13.4 Charakteristika der eingeschlossenen Studien

5.13.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference/ Study type	Study characteristics & inclusion	Interventions / Question	Study population	Results (per setting, separate ambulant and inpatient)	Methodischical Notes	Included publications
Dahms, 2023 Systematic review with MA	**Study design** RCTs **Search time frame** Inception of each database to 13.12.2021 **Sources:** Cochrane COVID-19 Study Register (MEDLINE, Embase, · ClinicalTrials.go, · WHO International Clinical Trials Registry Platform, medRxiv, · Cochrane Central Register of Controlled Trials) · WHO COVID-19 Global	**Intervention A** · Anakinra **Intervention B** · Placebo · Standard care alone (SCO)	5 studies on 1627 patients included in meta-analysis **Descriptive statistics (meta-analysis):** · Age: 59.63 · 64% male · comorbidities not reported · vaccination status not reported	**Comparison X:** Number of studies: 5 Number of participants: 1627 **Critical outcomes:** · All-cause mortality (at up to day 28): Anakinra makes little or no difference to all-cause mortality; RR 0.96, 95% CI 0.64–1.45; RD 9 fewer per 1000; 95% CI 84 fewer to 104 more (4 studies, n = 1593) · All-cause mortality (at up tp day 60): Anakinra 233 per 1000 vs. placebo/SCO 125 per 1000; RD 108 more per 1000; RR 1.22 (0.77 – 1.92) (2 studies, n = 115) · In-hospital mortality at up to longest follow-up: Anakinra 404 per 1000 vs. placebo/SCO 331 per 1000; RD 73 more per 1000; RR 1.22 (0.77 – 1.92) (2 studies, n = 889) · Clinical worsening: new need for IMV or death within 28 days: Anakinra 95 per 1000 vs. placebo/SCO 127 per 1000; RD 43 fewer per 1000; RR 0.69	**Methodological quality of included studies assessed using GRADE tool:** **Evidence synthesis:** · Random-effects-Modell **GRADE** · All-cause mortality: low due to serious inconsistency and imprecision · In-hospital mortality: Moderatee due to serious imprecision · Clinical worsening: mow due to serious inconsistency and imprecison · Clinical improvement: low due to serious inconsistency and imprecision · Serious adverse events: low due to serious	Declerq et al. 2021 Derde et al. 2021 Kharazmi et al. 2022 Kyriazopoulou et al. 2021 Tharaux et al. 2021

	literature on coronavirus disease database **Eligibility criteria** **Study type:** · randomized controlled trials reported as full texts, abstract only and unpublished data · Studies comparing treatment with Anakinra to placebo or standard care alone in adult hospitalized patients with SARS-CoV-2 infection			(0.31 – 1.56) (4 studies, n = 1593) · Clinical improvement participants discharges alive at up to day 28: Anakinra 766 per 1000 vs. placebo/SCO 744 per 1000; RD 22 more per 1000; RR 1.03 (0.88 – 1.21) (3 studies, n = 823) · Serious adverse events at up to day 28: Anakinra 246 per 1000 vs. placebo/SCO 241 per 1000; RD 5 more per 1000; RR 1.02 (0.68 – 1.53) (3 studies, n = 823) · Adverse events (any grade) at up to day 28: Anakinra 556 per 1000 vs. Placebo/SCO 520 per 1000; RD 36 more per 1000; RR 1.07 (0.84 – 1.37) (2 studies, n = 229) **Additional outcomes:**	inconsistency and imprecision · Adverse events (any grade): low due to serious inconsistency and imprecision	

5.13.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Audemard-Verger, 2022 RCT	**Sample size:** N = 71 pts. (1:1) randomised to anakrina or optimized standard of care alone (240 pts. planned) **Enrolment period:** 27.04.2020 to 6.10.2020 **Inclusion criteria:** · confirmed SARS-CoV-2 infection: · - positive rRT-PCR and/or typical chest or computed tomographic scan of COVID 19 · - pneumonia and required oxygen therapy: O2 4L/min to maintain Sp02> 92% and respiratory rate ≥ 24/min or O2 ≥n1L/min and increase in oxygen therapy ≥ 2L/min to maintain Sp02> 92% · inflammatory component (reactive C-protein ≥ 50mg/L · treated with antibiotics **Time since symptom onset (median, range):** · Exp: 9 [IQR: 7; 11] · Ctrl: 9 [IQR: 7; 11] **Characteristics** **Age (median, IQR)** · Exp: 71 (15%) · Ctrl: 70 (14%) **Vaccination status** · NR	**Experimental:** · intravenous anakinra plus optimized standard of care (oSOC) · Dose: 400mg/day (100mg every 6 hours) for 3 days; then 200mg/day (100mg every 12 hours) for 7 days · N = 37 **Control:** · optimized standard of care (oSOC) alone · N = 34	All-cause mortality (day 30)	RR 2.74 (0.81 to 9.25) Anakinra: 9/35 SoC: 3/32	For all outcomes: 1) Randomisation and allocation concealment: No concerns 2) Blinding: open-lable trial 3) Attrition bias: Outcome-specific: No concerns, all randomized patients were analyzed. 4) Outcome measurement: No concerns 5) Selective reporting: Outcomes were measured and analysed in accordance to protocol
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	1.99 (1.21 to 3.29) Anakinra: 26/37 SoC: 12/34	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	RR 0.64 (0.31 to 1.30) Anakinra: 9/27 SoC: 13/34	
			Serious adverse events	RR 0.97 (0.62 to 1.51) Anakinra: 19/37 SoC: 18/34	
			Adverse events, any grade	RR 1.34 (1.01 to 1.77) Anakinra: 32/37 SoC: 22/34	
			Hospital-acquired infections	Not reported	

	Country · France ***<u>Comorbidities</u>*** **Any** · NR **Diabetes:** · Exp: 9 (24%) · Ctrl: 6 (18%) **Obesity (BMI ≥30 kg/m²)** · Exp: median BMI under obesity · Ctrl: median BMI under obesity **Hypertension** · Exp: 20 (54%) · Ctrl: 15 (44%) **Cardiovascular disease** · Exp: 2 (5%) · Ctrl: 7 (21%) **Lung diseases** <u>COPD</u> · Exp: 1 (3%) · Ctrl: 6 (18%) <u>Asthma</u> · Exp: 2 (5%) · Ctrl: 1 (3%) **Immunosuppressed** · Exp: 0 (0%) · Ctrl: 1 (3%) **Malignancy** · Exp: 1 (3%) · Ctrl: 1 (3%) **Kidney disease (chronic)** · Exp: 5 (13%)		Quality of life	Not reported	---------- ------- 6) Overall: Low risk of bias

	• Ctrl: 2 (6%)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Fanlo, 2023 RCT	**Sample size:** N = 179 pts. (1:1) randomised to anakinra or optimized standard of care alone (pts. Planned: NR) **Enrolment period:** 08.05.2020 to 01.03.2021 **Inclusion criteria:** · Age 18-80 years · Nasopharyngeal smear with RCP positive for SARS-CoV-2 · X-Rays (or other technique) pulmonary infiltrates compatible with pneumonia. · 1 or more of the following criteria: · - Ambient air oxygen saturation ≤ 94% · - Pa:FiO2 ≤ 300 · - Sa:FiO2 ≤ 350 · High suspicion of CSS that could resemble MAS-like: IL-6 values > 40 pg/mL and/or ferritin >500 ug/L and/or PCR > 30 mg/L and/or LDH >300 UI/L **Time since symptom onset (median, range):** · NR **Characteristics** **Age (mean, IQR)** · Exp: 61.1 (11.7)	**Experimental:** · intravenous anakinra plus optimized standard of care (oSOC) · Dose: 400mg/day (100mg 4 times a day) for a maximum of 15 days · N = 92 **Control:** · optimized standard of care (oSOC) alone · N = 87	All-cause mortality (day 30)	RR 0.77 (0.21 to 2.77) Anakinra: 4/84 SoC: 5/81	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: open-lable trial 3) Attrition bias **Outcome-specific:** Not all patients randomized were analysed, except for the outcomes adverse events and serious adverse events 4) Outcome measurement: No concerns 5) Selective reporting: pre-registration + protocol
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	RR 0.96 (0.48 to 1.95) Anakinra: 13/84 SoC: 13/81	
			Serious adverse events	RR 0.76 (0.47 to 1.24) Anakinra: 21/89 SoC: 27/87	
			Adverse events, any grade	RR 1.45 (0.98 to 2.14) Anakinra: 40/89 SoC: 27/87	

	· Ctrl: 59.8 (SD: 11.3) **Vaccination status** · NR **Country** · Spain ***<u>Comorbidities</u>*** **Any** · NR **Diabetes:** · Exp: 10/89 (11.2%) · Ctrl: 15/87 (17.2%) **Obesity (BMI ≥30 kg/m²)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 34/89 (38.2%) · Ctrl: 36/ 87(41.4%) **Cardiovascular disease (Chronic heart failure)** · Exp: 13/89 (14.6%) · Ctrl: 17/87 (19.5%) **Lung diseases** <u>Chronic pulmonary disease</u> · Exp: 6/89 (6.7%) · Ctrl: 8/87 (9.2%) <u>Asthma</u> · Exp: 9/89 (10.1%) · Ctrl: 9/87 (10.3%) **Immunosuppressed** · Exp: NR · Ctrl: NR		Hospital-acquired infections Quality of life	Not reported Not reported	Outcomes were measured and analysed in accordance to protocol --- 6) Overall: High risk of bias

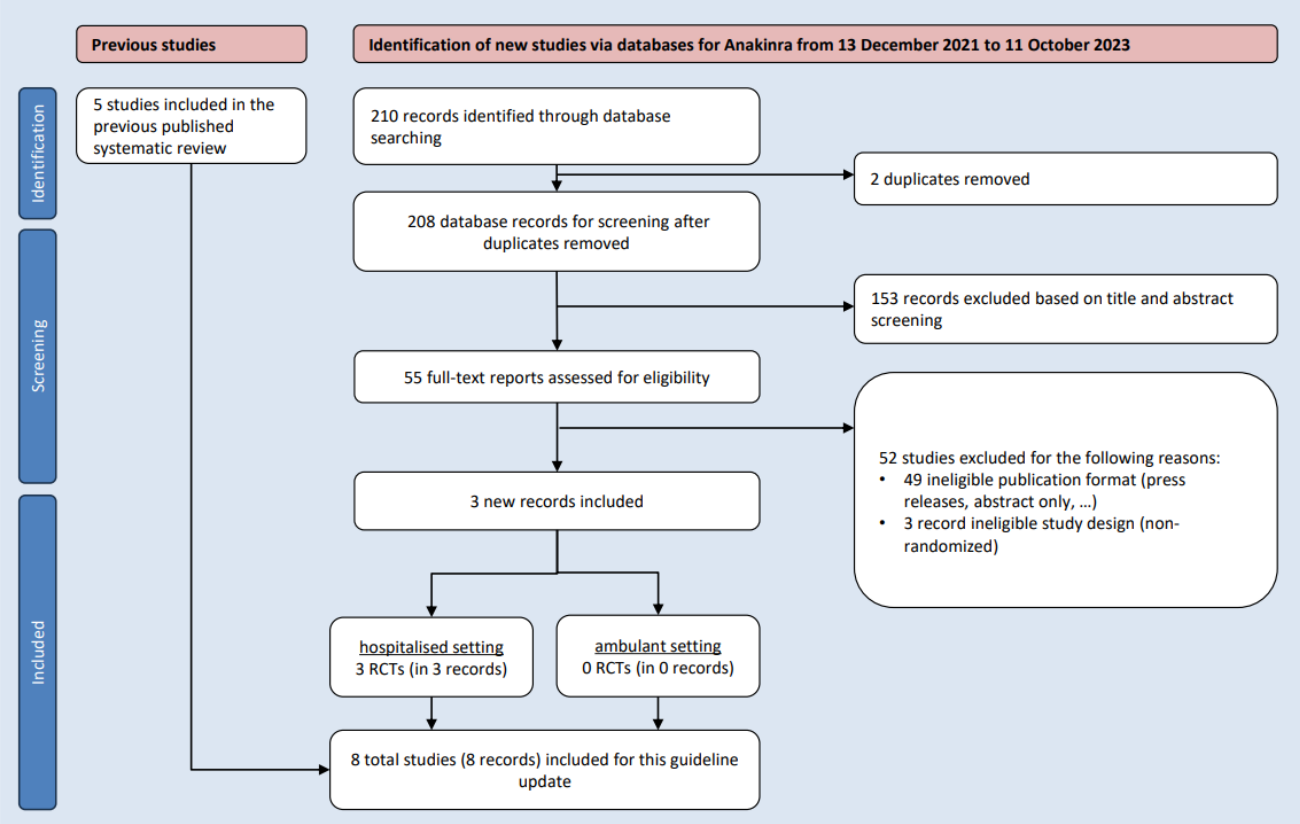
	Malignancy • Exp: NR • Ctrl: NR **Kidney disease** • Exp: 4/89 (4.5%) • Ctrl: 7/87 (8.0%)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Elmekaty, 2023 RCT	**Sample size:** N = 80 pts. (1:1) randomised to anakinra or standard of care alone (327 pts. assessed) **Enrolment period:** 30.10.2020 to 28.02.2021 **Inclusion criteria:** · Confirmed COVID-19 diagnosis · associated presence of respiratory distress: PaO2/FiO2 ≤ 300 mm Hg or respiratory Rate (RR) ≥24 breaths/min or SpO2 ≤ 94% at room air · radiological evidence of pneumonia based on chest X-ray and/or CT · signs of cytokine release syndrome: Ferritin >600 mcg/L at presentation or > 300 mcg/L with doubling within 24h, LDH >250 IU/l, D-dimer >1 mg/L, CRP > 70 mg/L and rising since last 24 h with the absence of bacterial infection, Interleukin-6 level > 10 × UNL (reference range ≤ 7 pg/mL)] **Time since symptom onset (median, range):** · NR **Characteristics** **Age (mean, IQR)** · Exp: 49.5 (SD: 12.2)	**Experimental:** · subcutaneous anakinra plus standard of care (SOC) · Dose: 200mg /day (100 mg every 12 h) for 3 days; then 100 mg/day for 4 days · N = 40 **Control:** · standard of care	All-cause mortality (day 30)	RR 0.33 (0.01 to 7.95) Anakinra: 0/40 SoC: 1/40	**For all outcomes:** 1) Randomisation and allocation concealment: No concerns 2) Blinding: open-label trial 3) Attrition bias **Outcome-specific:** No concerns, all randomized patients were analyzed. 4) Outcome measurement: No concerns 5) Selective reporting: Outcomes were measured and analysed in accordance to protocol --- 6) Overall: Low risk of bias
			All-cause mortality (day 60)	Not reported	
			All-cause mortality (longest follow-up)	Not reported	
			Clinical improvement: discharged alive (day 30)	Not reported	
			Clinical worsening: new need for IMV or death (day 30)	Not reported	
			Admission to ICU or death	Not reported	
			Serious adverse events	RR 1.00 (0.15 to 6.76) Anakinra: 2/40 SoC: 2/40	
			Adverse events, any grade	RR 1.00 (0.95 to 1.05) Anakinra: 40/40	

	• Ctrl: 50.3 (SD: 11.4) **Vaccination status** • NR **Country** • Quatar ***Comorbidities*** **Any** • Exp: 17 (42.5%) • Ctrl: 20 (50.0%) **Diabetes:** • Exp: 17/40 (42.5%) • Ctrl: 18/40 (45.0%) **Obesity (BMI ≥30 kg/m²)** • Exp: median BMI 30.9 (IQR:7.0) • Ctrl: median BMI under 30 **Hypertension** • Exp: NR • Ctrl: NR **Cardiovascular disease (Myocardial infarction)** • Exp: 2/40 (5.0%) • Ctrl: 5/40 (12.5%) **Lung diseases** • Exp: NR • Ctrl: NR **Immunosuppressed** • Exp: NR • Ctrl: NR **Malignancy** • Exp: NR • Ctrl: NR **Kidney disease**	(SOC) alone • N = 40		SoC: 40/40	
			Hospital-acquired infections	Not reported	
			Quality of life	Not reported	

	• Exp: NR • Ctrl: NR				

5.13.5 Studienselektion: Flow Chart



5.13.6 Literaturrecherche

Date of search for all databases: 13.12.2021; Update für LL 11.10.2023		
Database/Register	Search	Update Search
CCSR	92 references (nicht berichten: 70 bisherige, 22 neue)	196 references, 52 studies
Scopus (neue Aufnahme 11.10.2023)		134
WHO COVID-19 DB*	147	32*
Total	239	364
Total (after deduplication)	Total: 204	210

The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.

Search strategies

Cochrane COVID-19 Study Register

Search string:

Anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR Antril OR Kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor"

Study characteristics:

1) "Intervention assignment": “Randomised” OR “unclear” OR
2) "Study design": "Parallel/Crossover" OR “unclear”

Scopus (neue Datenbank seit 11.10.2023)

TITLE-ABS (anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR antril OR kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor") AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") AND PUBYEAR > 2019 AND PUBYEAR < 2024 AND TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") AND PUBYEAR > 2019 AND PUBYEAR < 2024 AND (LIMIT-TO (DOCTYPE , "ar"))

WHO COVID-19 Global literature on coronavirus disease

Title, abstract, subject:
(Anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR Antril OR Kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor") AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

5.14 Schlüsselfrage 8: Antikoagulation

Autor*innen: Stephanie Weibel, Stefanie Reis, Amon Faske

5.14.1 Evidenztabelle / Summary of Findings (MAGICapp)

5.14.1.1 *Evidenzprofil 1*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Standard thromboprophylaxis (low dose)

Vergleichsintervention: No anticoagulation (placebo/SoC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Summary**
		No anticoagulation	Low dose		
All-cause mortality 28 days	Relative risk: 0.7 (CI 95% 0.29 - 1.67) Based on data from 3305 patients in 6 studies	**7** per 1000	**5** per 1000 Difference: **2 less per 1000**	**Low** Due to very serious imprecision[1]	Low dose may have little or no difference on all-cause mortality

		(CI 95% 5 less - 5 more)		
All-cause mortality 90 days	Relative risk: 3.25 (CI 95% 0.13 - 79.03) Based on data from 219 patients in 1 studies	**0** per 1000 **0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)	**Very low** Due to extremely serious imprecision[2]	There were too few who experienced the all-cause mortality, to determine whether low dose made a difference
Any thrombotic event or death up to 28 days	Relative risk: 0.29 (CI 95% 0.06 - 1.37) Based on data from 1284 patients in 1 studies	**11** per 1000 **3** per 1000 Difference: **8 less per 1000** (CI 95% 10 less - 4 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether low dose increases or decreases any thrombotic event or death
Any thrombotic event up to 28 days	Relative risk: 0.44 (CI 95% 0.17 - 1.16) Based on data from 2637 patients in 4 studies	**11** per 1000 **5** per 1000 Difference: **6 less per 1000** (CI 95% 9 less - 2 more)	**Moderate** Due to serious imprecision[4]	Low dose probably has little or no difference on any thrombotic event
Any thrombotic event up to 90 days	Relative risk: 0.51 (CI 95% 0.09 - 2.75) Based on data from 470 patients in 1 studies	**17** per 1000 **9** per 1000 Difference: **8 less per 1000** (CI 95% 15 less - 30 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether low dose increases or decreases any thrombotic event
Clinical worsening: Admission to hospital or death up to 28 days	Relative risk: 0.91 (CI 95% 0.57 - 1.44) Based on data from 2748 patients in 5 studies	**28** per 1000 **25** per 1000 Difference: **3 less per 1000** (CI 95% 12 less - 12 more)	**Moderate** Due to serious imprecision[6]	Low dose probably has little or no difference on clinical worsening: admission to hospital or death
Clinical worsening: Admission to hospital or death up to 90 days	Relative risk: 1.02 (CI 95% 0.45 - 2.3) Based on data from 472 patients in 1 studies	**46** per 1000 **47** per 1000 Difference: **1 more per 1000** (CI 95% 25 less - 60 more)	**Low** Due to very serious imprecision[7]	Low dose may have little or no difference on clinical worsening: admission to hospital or death
Clinical improvement: all initial symptoms resolved at 28 days	Relative risk: 1.16 (CI 95% 0.97 - 1.38) Based on data from 444 patients in 1 studies	**486** per 1000 **564** per 1000 Difference: **78 more per 1000** (CI 95% 15 less - 185 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Thromboprophylaxis may increase improvement of clinical status (asymptomatic according to Gates MRI scale 1) slightly
Major bleeding up to 28 days	Relative risk: 1.49 (CI 95% 0.24 - 9.44) Based on data from 3214 patients in 6 studies	**1** per 1000 **1** per 1000 Difference: **0 less per 1000** (CI 95% 1 less - 8 more)	**Very low** Due to extremely serious imprecision[9]	There were too few who experienced the major bleeding, to determine whether low dose made a difference
	(CI 95% -)			No study was found that looked at clinically

Clinically relevant non-major bleeding up to 28 days		Difference: **less**		relevant non-major bleeding
Serious adverse events up to 28 days	Relative risk: 0.3 (CI 95% 0.06 - 1.43) Based on data from 449 patients in 1 studies	**30** per 1000 **9** per 1000 Difference: **21 less per 1000** (CI 95% 28 less - 13 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether thromboprophylaxis increases or decreases serious adverse events
Any grade adverse event up to 28 days	Relative risk: 1.16 (CI 95% 0.83 - 1.64) Based on data from 668 patients in 2 studies	**154** per 1000 **179** per 1000 Difference: **25 more per 1000** (CI 95% 26 less - 99 more)	**Low** Due to serious risk of bias, Due to serious imprecision[11]	Low dose may have little or no difference on any grade adverse event
Any grade adverse event up to 90 days	Relative risk: 1.37 (CI 95% 0.8 - 2.35) Based on data from 219 patients in 1 studies	**167** per 1000 **229** per 1000 Difference: **62 more per 1000** (CI 95% 33 less - 225 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether low dose increases or decreases any grade adverse event
Quality of life				No study was found that looked at quality of life

1. Imprecision: very serious. Low number of events, Wide confidence intervals;
2. Imprecision: extremely serious. Wide confidence intervals, Low number of events.;
3. Risk of bias: very serious. One study with overall some concern of bias; Imprecision: very serious. Wide confidence intervals, Low number of events;
4. Imprecision: very serious. Low number of patients;
5. Risk of bias: very serious. one study with overall some concern of bias; Imprecision: very serious. Wide confidence intervals, Low number of events.;
6. Imprecision: very serious. Wide confidence intervals;
7. Imprecision: very serious. Only data from one study, Wide confidence intervals;
8. Risk of bias: very serious. one study with overall some concern of bias; Imprecision: very serious. Only data from one study;
9. Imprecision: extremely serious. Wide confidence intervals, Low number of events.;
10. Risk of bias: very serious. one study with overall some concern of bias; Imprecision: very serious. Wide confidence intervals, Low number of patients and few events;
11. Risk of bias: very serious. two studies with overall some concern of bias; Imprecision: very serious. Wide confidence intervals;
12. Risk of bias: very serious. one study with overall some concern of bias; Imprecision: very serious. Only data from one study, Wide confidence intervals;

5.14.1.2 *Evidenzprofil 2*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Therapeutic dose anticoagulation

Vergleichsintervention: No anticoagulation (placebo/SoC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No anticoagulation	 Therapeutic dose	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality 28 days	Relative risk: 1.0 (CI 95% 0.06 - 15.85) Based on data from 328 patients in 1 studies	**6** per 1000	**6** per 1000 Difference: **0 less per 1000** (CI 95% 6 less - 89 more)	**Very low** Due to extremely serious imprecision[1]	There were too few who experienced the all-cause mortality, to determine whether therapeutic dose made a difference
Any thrombotic event or death up to 28 days	(CI 95% -)		Difference: **less**		No study was found that looked at any thrombotic event or death
Any thrombotic event up to 28 days	Relative risk: 1.0 (CI 95% 0.06 - 15.85) Based on data from 328 patients in 1 studies	**6** per 1000	**6** per 1000 Difference: **0 less per 1000** (CI 95% 6 less - 89 more)	**Very low** Due to extremely serious imprecision[2]	There were too few who experienced the any thrombotic event, to determine whether therapeutic dose made a difference
Clinical worsening: Admission to hospital or death up to 28 days	Relative risk: 0.63 (CI 95% 0.21 - 1.87) Based on data from 328 patients in 1 studies	**49** per 1000	**31** per 1000 Difference: **18 less per 1000** (CI 95% 39 less - 43 more)	**Very low** Due to extremely serious imprecision[3]	We are uncertain whether therapeutic dose increases or decreases clinical worsening: admission to hospital or death due to an effect of important benefit, with possibility of important harm
Clinical improvement: all initial symptoms resolved[5] at 28 days	(CI 95% -)		Difference: **less**		No study was found that looked at clinical improvement (all initial symptoms resolved)
Clinically relevant non-major bleeding up to 28 days	(CI 95% -) Based on data from 328 patients in 1 studies		Difference: **less**		No study was found that looked at clinically relevant non-major bleeding
Serious adverse events up to 28 days	(CI 95% -)		Difference: **less**		No study was found that looked at serious adverse events
Any grade adverse event up to 28 days	(CI 95% -)		Difference: **more**		No study was found that looked at any grade adverse events

Quality of life	Gemessen mit: Skala: -	Difference: **null kleiner**		No study was found that looked at quality of life
Major bleeding up to 28 days	Based on data from 328 patients in 1 studies			There were too few (zero events) who experienced major bleeding, to determine whether therapeutic dose made a difference

1. Imprecision: extremely serious. Wide confidence intervals, Only data from one study;
2. Imprecision: extremely serious. Low number of patients, Wide confidence intervals, Only data from one study.
3. Imprecision: extremely serious. Wide confidence intervals, Only data from one study.

5.14.1.3 *Evidenzprofil 3*

Population: Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease, according to the WHO clinical progression scale (WHO 2 to 3)

Intervention: Therapeutic dose anticoagulation

Vergleichsintervention: Standard thromboprophylaxis (low dose)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Low dose	 Therapeutic dose	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality 28 days	Relative risk: 3.02 (CI 95% 0.12 - 73.55) Based on data from 329 patients in 1 studies	**0** per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)	**Very low** Due to extremely serious imprecision[1]	There were too few who experienced the all-cause mortality, to determine whether therapeutic dose made a difference
Any thrombotic event or death up to 28 days	(CI 95% -)	Difference: **less**			No study was found that looked at any thrombotic event or death
Any thrombotic event up to 28 days	Relative risk: 3.02 (CI 95% 0.12 - 73.55) Based on data from 329 patients in 1 studies	**0** per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)	**Very low** Due to extremely serious imprecision[2]	There were too few who experienced the any thrombotic event, to determine whether therapeutic dose made a difference
Clinical worsening: Admission to hospital or death up to 28 days	Relative risk: 1.01 (CI 95% 0.3 - 3.41) Based on data from 329 patients in 1 studies	**30** per 1000	**30** per 1000 Difference: **0 less per 1000** (CI 95% 21 less - 72 more)	**Very low** Due to extremely serious imprecision[3]	We are uncertain whether therapeutic dose increases or decreases clinical worsening: admission to hospital or death

Clinical improvement: all initial symptoms resolved[5] at 28 days	(CI 95% -)	Difference: **less**		No study was found that looked at clinical improvement (all initial symptoms resolved)
Clinically relevant non-major bleeding up to 28 days	(CI 95% -)	Difference: **less**		No study was found that looked at Clinically relevant non-major bleeding
Serious adverse events up to 28 days	(CI 95% -)	Difference: **less**		No study was found that looked at serious adverse events
Any grade adverse event up to 28 days	(CI 95% -)	Difference: **more**		No study was found that looked at any grade adverse event
Quality of life	Gemessen mit: Skala: -	Difference: **null kleiner**		No study was found that looked at quality of life
Major bleeding up to 28 days	Based on data from 329 patients in 1 studies			There were too few (zero events) who experienced major bleeding, to determine whether therapeutic dose made a difference

1. Imprecision: extremely serious. Wide confidence intervals, Only data from one study, Low number of patients;
2. Imprecision: extremely serious. Wide confidence intervals, Only data from one study;
3 Imprecision: extremely serious. Wide confidence intervals, Only data from one study

5.14.1.4 *Evidenzprofil 4*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection and with Moderatee to severe disease, according to the WHO clinical progression scale (WHO 4 to 9)

Intervention: Therapeutic dose anticoagulation

Vergleichsintervention: Standard thromboprophylaxis (low dose/intermediate dose))

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Low dose/intermediate dose	Therapeutic dose	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**

All-cause mortality (WHO 4 to 9) 28 days	Relative risk: 0.8 (CI 95% 0.65 - 0.98) Based on data from 5935 patients in 12 studies	**108** per 1000 **86** per 1000 Difference: **22 less per 1000** (CI 95% 38 less - 2 less)	**Moderate** Due to serious risk of bias[1]	Therapeutic dose probably decreases all-cause mortality (WHO 4 to 9)
All-cause mortality (subgroup WHO 4 to 5) 28 days	Relative risk: 0.65 (CI 95% 0.48 - 0.88) Based on data from 4209 patients in 6 studies	**73** per 1000 **47** per 1000 Difference: **26 less per 1000** (CI 95% 38 less - 9 less)	**Moderate** Due to serious risk of bias[2]	Therapeutic dose probably decreases all-cause mortality (subgroup WHO 4 to 5)
All-cause mortality (subgroup WHO 6 to 9) 28 days	Relative risk: 0.82 (CI 95% 0.64 - 1.04) Based on data from 619 patients in 4 studies	**332** per 1000 **272** per 1000 Difference: **60 less per 1000** (CI 95% 120 less - 13 more)	**Low** Due to very serious risk of bias[3]	Therapeutic dose may decrease all-cause mortality (subgroup WHO 6 to 9)
All-cause mortality (WHO 4 to 9) 90 days	Relative risk: 0.83 (CI 95% 0.51 - 1.33) Based on data from 634 patients in 2 studies	**116** per 1000 **96** per 1000 Difference: **20 less per 1000** (CI 95% 57 less - 38 more)	**Low** Due to very serious imprecision[4]	Therapeutic dose may have little or no difference on all-cause mortality (WHO 4-9)
All-cause mortality (WHO 4 to 9) in hospital	Relative risk: 0.97 (CI 95% 0.79 - 1.19) Based on data from 3344 patients in 3 studies	**180** per 1000 **175** per 1000 Difference: **5 less per 1000** (CI 95% 38 less - 34 more)	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Therapeutic dose may have little or no difference on all-cause mortality (WHO 4 to 9)
Any thrombotic event or death (WHO 4 to 9) up to 28 days	Relative risk: 0.84 (CI 95% 0.73 - 0.97) Based on data from 8075 patients in 8 studies	**162** per 1000 **136** per 1000 Difference: **26 less per 1000** (CI 95% 44 less - 5 less)		Significant subgroup difference (p=0.007) between WHO 4-5 and WHO 6-9. Pooled estimate not considered.
Any thrombotic event or death (subgroup WHO 4 to 5) up to 28 days	Relative risk: 0.72 (CI 95% 0.6 - 0.86) Based on data from 5865 patients in 5 studies	**94** per 1000 **68** per 1000 Difference: **26 less per 1000** (CI 95% 38 less - 13 less)	**Hoch**	Therapeutic dose decreases any thrombotic event or death (subgroup WHO 4 to 5)
Any thrombotic event or death (subgroup WHO 6 to 9) up to 28 days	Relative risk: 0.98 (CI 95% 0.86 - 1.12) Based on data from 1262 patients in 3 studies	**400** per 1000 **392** per 1000 Difference: **8 less per 1000** (CI 95% 56 less - 48 more)	**Moderate** Due to serious imprecision[6]	Therapeutic dose probably has little or no difference on any thrombotic event or death (subgroup WHO 6 to 9)
Any thrombotic event (WHO 4 to 9)[13] up to 28 days	Relative risk: 0.6 (CI 95% 0.49 - 0.74) Based on data from 5458 patients in 9 studies	**83** per 1000 **50** per 1000 Difference: **33 less per 1000** (CI 95% 42 less - 22 less)	**Hoch**	Therapeutic dose decreases any thrombotic event (WHO 4 to 9)

Any thrombotic event (WHO 4 to 9) up to 90 days	Relative risk: 0.64 (CI 95% 0.13 - 3.1) Based on data from 300 patients in 1 studies	**30** per 1000 **19** per 1000 Difference: **11 less per 1000** (CI 95% 26 less - 63 more)	**Very low** Due to extremely serious imprecision[7]	We are uncertain whether therapeutic dose increases or decreases any thrombotic event (WHO 4 to 9) due to an effect of important benefit, with possibility of important harm
Worsening of clinical status: Progression to intubation or death (WHO 4 to 5) 28 days	Relative risk: 0.9 (CI 95% 0.72 - 1.14) Based on data from 2231 patients in 1 studies	**121** per 1000 **109** per 1000 Difference: **12 less per 1000** (CI 95% 34 less - 17 more)	**Low** Due to serious risk of bias, Due to serious imprecision[8]	Therapeutic dose may have little or no difference on worsening of clinical status: progression to intubation or death (WHO 4 to 5)
Worsening of clinical status: Admission to ICU or death (WHO 4 to 5) up to 28 days	Relative risk: 0.75 (CI 95% 0.51 - 1.1) Based on data from 465 patients in 1 studies	**211** per 1000 **158** per 1000 Difference: **53 less per 1000** (CI 95% 103 less - 21 more)	**Very low** Due to extremely serious imprecision[9]	We are uncertain whether therapeutic dose increases or decreases worsening of clinical status: admission to ICU or death (WHO 4 to 5) due to an effect of important benefit, with possibility of important harm
Improvement of clinical status: participants discharged alive (WHO 4 to 9) 28 days	Relative risk: 0.96 (CI 95% 0.9 - 1.02) Based on data from 614 patients in 1 studies	**882** per 1000 **847** per 1000 Difference: **35 less per 1000** (CI 95% 88 less - 18 more)	**Moderate** Due to serious imprecision[10]	Therapeutic anticoagulant probably has little or no difference on improvement of clinical status (participants discharged alive) at day 28 (WHO 4 to 9)
Improvement of clinical status: survival until hospital discharge without receiving organ support (WHO 4 to 5) hospital discharge	Relative risk: 1.05 (CI 95% 1.0 - 1.1) Based on data from 2219 patients in 1 studies	**764** per 1000 **802** per 1000 Difference: **38 more per 1000** (CI 95% 0 less - 76 more)	**Moderate** Due to serious risk of bias[11]	Therapeutic dose probably increases improvement of clinical status: survival until hospital discharge without receiving organ support (WHO 4 to 5)
Major bleeding (WHO 4 to 9)[21] up to 28 days	Relative risk: 1.79 (CI 95% 1.25 - 2.56) Based on data from 9107 patients in 12 studies	**12** per 1000 **21** per 1000 Difference: **9 more per 1000** (CI 95% 3 more - 19 more)	**Moderate** Due to serious risk of bias[12]	Therapeutic dose probably increases major bleeding (WHO 4 to 9)
Major bleeding (subgroup WHO 4 to 5)[23] up to 28 days	Relative risk: 1.74 (CI 95% 0.95 - 3.19) Based on data from 6507 patients in 8 studies	**6** per 1000 **10** per 1000 Difference: **4 more per 1000** (CI 95% 0 less - 13 more)	**Low** Due to very serious risk of bias[13]	Therapeutic dose may increase major bleeding (WHO 4 to 5)

Major bleeding (subgroup WHO 6 to 9) up to 28 days	Relative risk: 1.85 (CI 95% 1.09 - 3.14) Based on data from 1652 patients in 4 studies	**25** per 1000 **46** per 1000 Difference: **21 more per 1000** (CI 95% 2 more - 54 more)	**Moderate** Due to serious risk of bias[14]	Therapeutic dose probably increases major bleeding (WHO 6 to 9)
Adverse events (any grade) during the study period	(CI 95% -)	Difference: **less**		No study reported any adverse events
Quality of life at longest follow-up available	Based on data from 240 patients in 1 studies			One study reported EQ-5D-5L score. No difference between groups (reported as median with IQR).
Serious adverse events during the study period	Based on data from 65 patients in 1 studies			There were too few (zero events) who experienced serious adverse events, to determine whether therapeutic dose made a difference

1. Risk of bias: very serious. Five studies with overall some concerns of bias and two studies with overall high risk of bias. Six studies with low risk of bias (effect estimate excluding biased studies RR 0.83 (0.52; 1.34)).;
2. Risk of bias: very serious. Three studies with overall some concern of bias. Three studies with overall no concern of bias. (effect estimate excluding biased studies RR 0.48 (0.19; 1.18)).;
3. Risk of bias: very serious. Two studies with overall high risk of bias and one study with overall some concern of bias. One study with overall no concern of bias. (effect estimate excluding biased studies RR 0.90 (0.52; 1.57)).;
4. Imprecision: very serious. Wide confidence intervals;
5. Risk of bias: very serious. three studies with overall some concern of bias; Imprecision: very serious. Wide confidence intervals;
6. Imprecision: very serious. Wide confidence intervals;
7. Imprecision: extremely serious. Wide confidence intervals, Only data from one study;
8. Risk of bias: very serious. one study with overall some concern of bias; Imprecision: very serious. Wide confidence intervals;
9. Imprecision: extremely serious. Only data from one study, Wide confidence intervals (effect of important benefit, with possibility of important harm);
10. Imprecision: very serious. Wide confidence intervals;
11. Risk of bias: very serious. one study with overall some concern of bias;
12. ISTH criteria
13. Risk of bias: very serious. One study with overall high risk of bias and eight studies with overall some concern of bias. Five studies with overall no concern of bias. (effect estimate excluding biased studies RR 1.45 (0.73; 2.84)).;
14. ISTH criteria
15. Risk of bias: very serious. Six sudies with overall some concern of bias. Two studies with overall no concern of bias. (effect estimate excluding biased studies RR 0.70 (0.20; 2.49)).;
16. ISTH criteria
17. Risk of bias: very serious. One study with overall high risk of bias, two studies with overall some concern of bias. One study with overall no concern of bias. (effect estimate excluding biased studies RR 7.63 (0.42; 137.36)).;

5.14.1.5 *Evidenzprofil 5*

Population: Hospitalised patients with confirmed SARS-CoV-2 infection and with Moderatee to severe disease, according to the WHO clinical progression scale (WHO 4 to 9)

Intervention: Intermediate dose anticoagulation

Vergleichsintervention: Standard thromboprophylaxis (low dose)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Low dose	Intermediate dose	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality (WHO 4-9) 28 days	Relative risk: 1.02 (CI 95% 0.85 - 1.22) Based on data from 1137 patients in 4 studies	**265** per 1000	**270** per 1000 Difference: **5 more per 1000** (CI 95% 40 less - 58 more)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Intermediate dose may have little or no difference on all-cause mortality (WHO 4-9)
All-cause mortality (subgroup WHO 4-5) 28 days	Relative risk: 5.87 (CI 95% 0.29 - 119.44) Based on data from 111 patients in 1 studies	**0** per 1000	**0** per 1000 Difference: **0 less per 1000** (CI 95% 0 less - 0 less)	**Very low** Due to extremely serious imprecision[2]	There were too few who experienced the all-cause mortality (subgroup WHO 4-5), to determine whether intermediate dose made a difference
All-cause mortality (subgroup WHO 6-9) 28 days	Relative risk: 1.06 (CI 95% 0.88 - 1.29) Based on data from 629 patients in 2 studies	**377** per 1000	**400** per 1000 Difference: **23 more per 1000** (CI 95% 45 less - 109 more)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Intermediate dose may have little or no difference on all-cause mortality (subgroup WHO 6-9)
All-cause mortality (WHO 4-9) 90 days	Relative risk: 1.07 (CI 95% 0.9 - 1.27) Based on data from 1011 patients in 3 studies	**286** per 1000	**306** per 1000 Difference: **20 more per 1000** (CI 95% 29 less - 77 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Intermediate dose may have little or no difference on all-cause mortality (WHO 4-9)
All-cause mortality (WHO 4-9) in hospital	Relative risk: 1.17 (CI 95% 0.43 - 3.18) Based on data from 124 patients in 1 studies	**103** per 1000	**121** per 1000 Difference: **18 more per 1000** (CI 95% 59 less - 225 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether intermediate dose increases or decreases all-cause mortality in hospital (WHO 4-9)
Any thrombotic event or death (WHO 4-9) up to 28 days	Relative risk: 0.73 (CI 95% 0.33 - 1.59) Based on data from 814 patients in 2 studies	**385** per 1000	**281** per 1000 Difference: **104 less per 1000** (CI 95% 258 less - 227 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[6]	Intermediate dose may decrease any thrombotic event or death (WHO 4-9)
Any thrombotic event or death (subgroup WHO 4-5) up to 28 days	(CI 95% -)	Difference: **less**			No studies were found that looked at any thrombotic event or death (subgroup WHO 4-5)
Any thrombotic event or death	Relative risk: 1.03 (CI 95% 0.86 - 1.24)	**429** per 1000	**442** per 1000	**Low**	Intermediate dose may have little or no difference on any thrombotic event

(subgroup WHO 6-9) up to 28 days	Based on data from 590 patients in 1 studies	Difference: **13 more per 1000** (CI 95% 60 less - 103 more)	Due to serious risk of bias, Due to serious imprecision[7]	or death (subgroup WHO 6-9)
Any thrombotic event (WHO 4-9) up to 28 days	Relative risk: 0.53 (CI 95% 0.14 - 1.94) Based on data from 790 patients in 2 studies	**83** per 1000 **44** per 1000 Difference: **39 less per 1000** (CI 95% 71 less - 78 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[8]	Intermediate dose may decrease any thrombotic event (WHO 4-9)
Any thrombotic event (subgroup WHO 4-5) up to 28 days	(CI 95% -)	Difference: **less**		No studies were found that looked at any thrombotic event (subgroup WHO 4-5)
Any thrombotic event (subgroup WHO 6-9) up to 28 days	Relative risk: 1.02 (CI 95% 0.43 - 2.42) Based on data from 566 patients in 1 studies	**35** per 1000 **36** per 1000 Difference: **1 more per 1000** (CI 95% 20 less - 50 more)	**Low** Due to serious risk of bias, Due to serious imprecision[9]	Intermediate dose may have little or no difference on any thrombotic event (subgroup WHO 6-9)
Any thrombotic event (WHO 4-9) up to 90 days	Relative risk: 1.08 (CI 95% 0.2 - 5.77) Based on data from 287 patients in 1 studies	**20** per 1000 **22** per 1000 Difference: **2 more per 1000** (CI 95% 16 less - 95 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[10]	Intermediate dose may have little or no difference on any thrombotic event (WHO 4-9)
Worsening of clinical status: Progression to intubation or death (WHO 4 to 5) up to 28 days	(CI 95% -)	Difference: **less**		No study reported worsening of clinical status (progression to intubation or death)
Worsening of clinical status: Admission to ICU or death[17] up to 28 days	(CI 95% -)	Difference: **less**		No study reported worsening of clinical status (admission to ICU or death)
Improvement of clinical status: participants discharged alive without clinical deterioration or death up to 28 days	(CI 95% -)	Difference: **less**		No study reported improvement of clinical status (participants dicharged alive without clincial deterioration or death)
Improvement of clinical status:	(CI 95% -)			No study reported improvement of clinical status (survival until

Survival until hospital discharge without receiving organ support up to 28 days		Difference: **less**		hospital discharge without receiving organ support)
Major bleeding (WHO 4-9) up to 28 days	Relative risk: 1.48 (CI 95% 0.66 - 3.33) Based on data from 1137 patients in 4 studies	**17** per 1000 **25** per 1000 Difference: **8 more per 1000** (CI 95% 6 less - 40 more)	**Low** Due to very serious imprecision[11]	Intermediate dose may increase major bleeding (WHO 4-9)
Serious adverse events during the study period	(CI 95% -)	Difference: **less**		No study reported serious adverse events
Adverse events (any grade) during the study period	(CI 95% -)	Difference: **less**		No studies were found that looked at adverse events (any grade)
Quality of life at longest follow-up available	Based on data from 334 patients in 1 studies			One study reported EQ-5D-5L score. No difference between groups (reported as median with IQR).

1. Risk of bias: very serious. One study with overall some concern of bias. Three studies with overall no concern of bias (effect estimate excluding biased studies RR 0.85 (0.54; 1.33)).; Imprecision: very serious. Wide confidence intervals;
2. Imprecision: extremely serious. Wide confidence intervals, Only data from one study, Low number of events;
3. Risk of bias: very serious. One study with overall some concern of bias. One study with overall no concern of bias. (effect estimate excluding biased studies RR 2.25 (0.25; 20.46)).; Imprecision: very serious. Wide confidence intervals;
4. Risk of bias: very serious. Two studies with overall some concern of bias. One study with overall no concern of bias. Effect estimate excluding biased studies (RR 1.75 (0.30; 10.23)); Imprecision: very serious. Wide confidence intervals;
5. Risk of bias: very serious. One study with overall some concern of bias; Imprecision: very serious. Wide confidence intervals, Only data from one study, Low number of events;
6. Risk of bias: very serious. One study with overall somce concern of bias. One study with overall no concern of bias. Effect estimate excluding biased studies RR 0.47 (0.26; 0.83).; Inkonsistenz: very serious. I^2=85%, The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.;
7. Risk of bias: very serious. One study with some concern of bias; Imprecision: very serious. Wide confidence intervals;
8. Risk of bias: very serious. One study with overall some concern of bias. One study with overall low risk of bias. Effect estimate excluding biased study RR (0.27 (0.11; 0.64).; Inkonsistenz: very serious. The magnitude of statistical heterogeneity was high, with I^2=78%;
9. Risk of bias: very serious. One study with some concern of bias; Imprecision: very serious. Wide confidence intervals, Only data from one study;
10. Risk of bias: very serious. One study with overall somoe concern of bias; Imprecision: very serious. Wide confidence intervals, Only data from one study, Low number of events;

11. Imprecision: very serious. Wide confidence intervals, Low number of events;

5.14.1.6 *Evidenzprofil 6*

Population: Post-discharge COVID-19 patients

Intervention: Standard thromboprophylaxis (low dose)

Vergleichsintervention: No anticoagulation (placebo/SoC)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No anticoagulation	**Absolute effect estimates** Low dose	**Certainty of the Evidence** (Quality of evidence)	**Summary**
All-cause mortality 28 days	Relative risk: 0.7 (CI 95% 0.26 - 1.85) Based on data from 1535 patients in 2 studies	**17** per 1000	**12** per 1000 Difference: **5 less per 1000** (CI 95% 13 less - 14 more)	**Very low** Due to extremely serious imprecision[1]	We are uncertain whether low dose increases or decreases all-cause mortality due to an effect of important benefit, with possibility of important harm
Any thrombotic event or death up to 28 days	Relative risk: 0.64 (CI 95% 0.28 - 1.44) Based on data from 1535 patients in 2 studies	**38** per 1000	**24** per 1000 Difference: **14 less per 1000** (CI 95% 27 less - 17 more)	**Very low** Due to extremely serious imprecision[2]	We are uncertain whether low dose increases or decreases any thrombotic event or death due to an effect of important benefit, with possibility of important harm
Any thrombotic event or death up to 90 days	Relative risk: 1.11 (CI 95% 0.58 - 2.12) Based on data from 1217 patients in 1 studies	**28** per 1000	**31** per 1000 Difference: **3 more per 1000** (CI 95% 12 less - 31 more)	**Very low** Due to extremely serious imprecision[3]	We are uncertain whether low dose increases or decreases any thrombotic event or death due to an effect of important benefit, with possibility of important harm
Any thrombotic event up to 28 days	Relative risk: 0.36 (CI 95% 0.13 - 0.97) Based on data from 318 patients in 1 studies	**88** per 1000	**32** per 1000 Difference: **56 less per 1000** (CI 95% 77 less - 3 less)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Low dose may decrease any thrombotic event
Clinical worsening: Admission to hospital or death up to 28 days	(CI 95% -)		Difference: **less**		No study reported worsening of clinical status (admission to hospital or death)
Major bleeding up to 28 days	Relative risk: 1.99 (CI 95% 0.18 - 21.89) Based on data from 1535 patients in 2 studies	**1** per 1000	**2** per 1000 Difference: **1 more per 1000** (CI 95% 1 less - 21 more)	**Very low** Due to extremely serious imprecision[5]	We are uncertain whether low dose increases or decreases major bleeding due to an effect of important harm, with possibility of important benefit
	Relative risk: 0.63 (CI 95% 0.2 - 1.94)	**10** per 1000	**6** per 1000	**Low**	Low dose may have little or no difference on

Clinically relevant non-major bleedings up to 28 days	Based on data from 1535 patients in 2 studies	Difference: **4 less per 1000** (CI 95% 8 less - 9 more)	Due to very serious imprecision[6]	clinically relevant non-major bleedings
Other bleedings up to 28 days	Relative risk: 2.0 (CI 95% 0.18 - 21.84) Based on data from 318 patients in 1 studies	**6** per 1000 **12** per 1000 Difference: **6 more per 1000** (CI 95% 5 less - 125 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[7]	We are uncertain whether low dose increases or decreases other bleedings
Serious adverse events during the study period	Relative risk: 1.05 (CI 95% 0.73 - 1.52) Based on data from 1217 patients in 1 studies	**84** per 1000 **88** per 1000 Difference: **4 more per 1000** (CI 95% 23 less - 44 more)	**Moderate** Due to serious imprecision[8]	Low dose probably has little or no difference on serious adverse events
Any grade adverse events during the study period	(CI 95% -)	Difference: **more**		No study reported any grade adverse events
Quality of life at longest follow-up available	Gemessen mit: Skala: -	Difference: **null Größer**		No studies were found that looked at quality of life

1. Imprecision: extremely serious. Wide confidence intervals;
2. Imprecision: extremely serious. Wide confidence intervals;
3. Imprecision: extremely serious. Wide confidence intervals, Only data from one study;
4. Risk of bias: very serious. Imprecision: very serious. Only data from one study;
5. Imprecision: extremely serious. Wide confidence intervals;
6. Imprecision: very serious. Wide confidence intervals;
7. Risk of bias: very serious. Imprecision: very serious.
8. Imprecision: very serious. Wide confidence intervals;

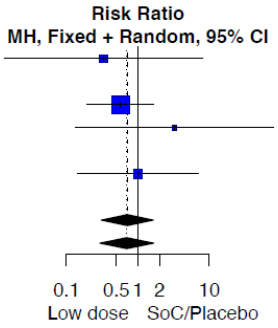
5.14.2 Analysen / Forest Plots

5.14.2.1 *Outpatients: Standard thromboprophylaxis (low dose) versus no anticoagulation (SoC/placebo)*

Mortality, day 28

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV–4B, Connors–2021 (vs placebo)	0	165	1	164	11.7%	7.5%	0.33 [0.01; 8.07]
Ananworanich–2021	0	219	0	230	0.0%	0.0%	
CARE–COALITION VIII, Avezum–2023	5	272	9	280	69.0%	65.2%	0.57 [0.19; 1.68]
ETHIC, Cools–2022	1	105	0	114	3.7%	7.5%	3.26 [0.13; 79.05]
OVID, Barco–2022	0	234	0	238	0.0%	0.0%	
PREVENT HD, Piazza–2023	2	641	2	643	15.5%	19.9%	1.00 [0.14; 7.10]
Total (fixed effect, 95% CI)		**1636**		**1669**	**100.0%**	**--**	**0.71 [0.31; 1.65]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.70 [0.29; 1.67]**

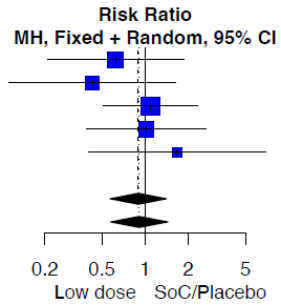
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.37$, df = 3 (P = 0.71); $I^2 = 0\%$



Admission to hospital or death

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV–4B, Connors–2021 (vs placebo)	5	165	8	164	21.4%	17.7%	0.62 [0.21; 1.86]
Ananworanich–2021	3	222	7	222	18.7%	11.8%	0.43 [0.11; 1.64]
ETHIC, Cools–2022	12	105	12	114	30.7%	37.2%	1.09 [0.51; 2.31]
OVID, Barco–2022	8	234	8	238	21.2%	22.9%	1.02 [0.39; 2.66]
PREVENT HD, Piazza–2023	5	641	3	643	8.0%	10.4%	1.67 [0.40; 6.97]
Total (fixed effect, 95% CI)		**1367**		**1381**	**100.0%**	**--**	**0.90 [0.57; 1.41]**
Total (random effects, 95% CI)					**--**	**100.0%**	**0.91 [0.57; 1.44]**

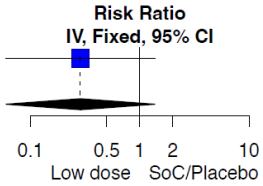
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.64$, df = 4 (P = 0.62); $I^2 = 0\%$



Any thrombotoc event or death

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
PREVENT HD, Piazza–2023	2	641	7	643	100.0%	0.29 [0.06; 1.37]
Total (95% CI)		**641**		**643**	**100.0%**	**0.29 [0.06; 1.37]**

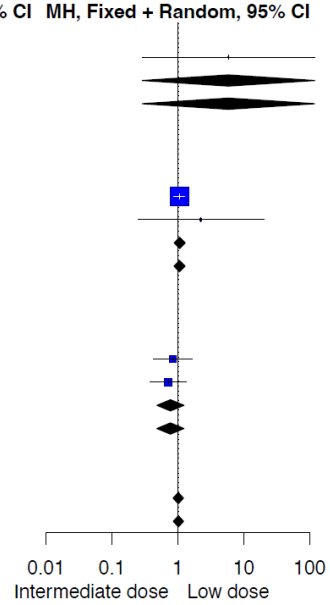
Heterogeneity: $Tau^2 = NA$; $Chi^2 = 0.00$, df = 0 (P = NA); $I^2 = NA\%$



5.14.2.2 *Inpatients: intermediate dose anticoagulation versus standard thromboprophylaxis (low dose)*

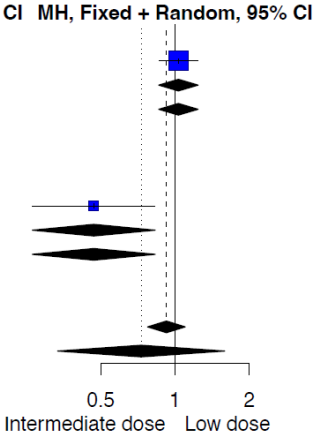
Mortality, day 28

Study or Subgroup	Intermediate Events	Intermediate Total	Low Events	Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Moderate disease (WHO 4 to 5)							
X–COVID, Morici–2021	2	51	0	60	0.3%	0.3%	5.87 [0.29; 119.59]
Total (fixed effect, 95% CI)		51		60	0.3%	—	5.87 [0.29; 119.59]
Total (random effects, 95% CI)					—	0.3%	5.87 [0.29; 119.59]
Heterogeneity: not applicable							
subgroup = Severe disease (WHO 6–9)							
INSPIRATION, Sadeghipour 2021	121	280	117	286	76.6%	84.7%	1.06 [0.87; 1.28]
X–COVID, Morici–2021	3	36	1	27	0.8%	0.7%	2.25 [0.25; 20.46]
Total (fixed effect, 95% CI)		316		313	77.3%	—	1.07 [0.88; 1.30]
Total (random effects, 95% CI)					—	85.3%	1.06 [0.88; 1.29]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.45$, df = 1 (P = 0.50); $I^2 = 0\%$							
subgroup = Mixed moderate to severe disease (WHO 4–9)							
ANTICOVID, Labbé–2023	13	110	16	114	10.4%	6.8%	0.84 [0.43; 1.67]
Perepu–2021	13	87	18	86	12.0%	7.5%	0.71 [0.37; 1.37]
Total (fixed effect, 95% CI)		197		200	22.4%	—	0.77 [0.48; 1.24]
Total (random effects, 95% CI)					—	14.3%	0.77 [0.48; 1.24]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$							
Total (fixed effect, 95% CI)		**564**		**573**	**100.0%**	—	**1.02 [0.85; 1.22]**
Total (random effects, 95% CI)					—	**100.0%**	**1.02 [0.85; 1.22]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.38$, df = 4 (P = 0.50); $I^2 = 0\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 0.57$, df = 2 (P = 0.75); $I^2 = 0\%$							



Any thrombotic event or death, 28 days

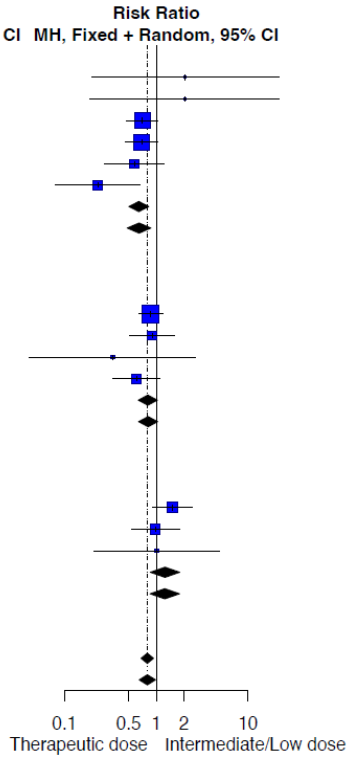
Study or Subgroup	Intermediate Events	Intermediate Total	Low Events	Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Severe disease (WHO 6–7)							
INSPIRATION, Sadeghipour 2021	131	296	126	294	80.6%	56.0%	1.03 [0.86; 1.24]
Total (fixed effect, 95% CI)		296		294	80.6%	—	1.03 [0.86; 1.24]
Total (random effects, 95% CI)					—	56.0%	1.03 [0.86; 1.24]
Heterogeneity: not applicable							
subgroup = Mixed moderate to severe disease (WHO 4–9)							
ANTICOVID, Labbé–2023	14	110	31	114	19.4%	44.0%	0.47 [0.26; 0.83]
Total (fixed effect, 95% CI)		110		114	19.4%	—	0.47 [0.26; 0.83]
Total (random effects, 95% CI)					—	44.0%	0.47 [0.26; 0.83]
Heterogeneity: not applicable							
Total (fixed effect, 95% CI)		**406**		**408**	**100.0%**	—	**0.92 [0.77; 1.10]**
Total (random effects, 95% CI)					—	**100.0%**	**0.73 [0.33; 1.59]**
Heterogeneity: $Tau^2 = 0.2747$; $Chi^2 = 6.81$, df = 1 (P < 0.01); $I^2 = 85\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 0.00$, df = 0 (P = NA); I^2 = NA%							



5.14.2.3 *Inpatients: therapeutic dose anticoagulation versus standard thromboprophylaxis (low and intermediate dose)*

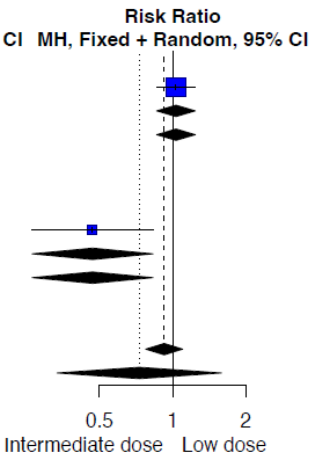
Mortality, day 28

Study or Subgroup	Therapeutic Events	Therapeutic Total	Interm./Low Events	Interm./Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Moderate disease (WHO 4 to 5)							
BEMICOP, Marcos–Jubilar–2022 (bemiparin)	2	32	1	33	0.3%	0.8%	2.06 [0.20; 21.64]
COVID–PREVENT, Rauch–Kröhnert–2023	2	55	1	56	0.3%	0.7%	2.04 [0.19; 21.82]
FREEDOM–COVID, Stone–2023 (apixaban)	54	1121	39	571	18.1%	14.7%	0.71 [0.47; 1.05]
FREEDOM–COVID, Stone–2023 (enoxaparin)	54	1136	39	570	18.2%	14.7%	0.69 [0.47; 1.04]
HEP–COVID, Spyropoulos 2021	9	84	16	86	5.5%	6.0%	0.58 [0.27; 1.23]
RAPID, Sholzberg–2021	4	228	18	237	6.2%	3.4%	0.23 [0.08; 0.67]
Total (fixed effect, 95% CI)		2656		1553	48.8%	—	0.65 [0.50; 0.83]
Total (random effects, 95% CI)					—	40.2%	0.65 [0.48; 0.88]
Heterogeneity: $Tau^2 = 0.0205$; $Chi^2 = 5.8$, df = 5 (P = 0.33); $I^2 = 14\%$							
subgroup = Severe disease (WHO 6 to 9)							
COVID–PACT, Bohula–2022	55	197	62	193	22.0%	19.1%	0.87 [0.64; 1.18]
HEP–COVID, Spyropoulos 2021	16	45	15	38	5.7%	9.7%	0.90 [0.52; 1.57]
HESACOVID, Lemos–2020	1	10	3	10	1.1%	1.0%	0.33 [0.04; 2.69]
Oliynyk–2021	17	84	14	42	6.6%	8.6%	0.61 [0.33; 1.11]
Total (fixed effect, 95% CI)		336		283	35.3%	—	0.81 [0.64; 1.03]
Total (random effects, 95% CI)					—	38.3%	0.82 [0.64; 1.04]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.92$, df = 3 (P = 0.59); $I^2 = 0\%$							
subgroup = Mixed moderate to severe disease (WHO 4 to 9)							
ACTION, Lopes–2021	35	310	23	304	8.2%	11.1%	1.49 [0.90; 2.46]
ANTICOVID, Labbé–2023	14	110	29	224	6.7%	8.8%	0.98 [0.54; 1.78]
COVID–HEP, Blondon–2022	3	79	3	80	1.0%	1.6%	1.01 [0.21; 4.87]
Total (fixed effect, 95% CI)		499		608	15.9%	—	1.25 [0.86; 1.81]
Total (random effects, 95% CI)					—	21.5%	1.24 [0.85; 1.80]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.17$, df = 2 (P = 0.56); $I^2 = 0\%$							
Total (fixed effect, 95% CI)		**3491**		**2444**	**100.0%**	—	**0.80 [0.68; 0.94]**
Total (random effects, 95% CI)					—	**100.0%**	**0.80 [0.65; 0.98]**
Heterogeneity: $Tau^2 = 0.0342$; $Chi^2 = 16.42$, df = 12 (P = 0.17); $I^2 = 27\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 8.89$, df = 10 (P = 0.54); $I^2 = 0\%$							



Any thrombotic event or death, day 28

Study or Subgroup	Intermediate Events	Intermediate Total	Low Events	Low Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
subgroup = Severe disease (WHO 6–7)							
INSPIRATION, Sadeghipour 2021	131	296	126	294	80.6%	56.0%	1.03 [0.86; 1.24]
Total (fixed effect, 95% CI)		296		294	80.6%	—	1.03 [0.86; 1.24]
Total (random effects, 95% CI)					—	56.0%	1.03 [0.86; 1.24]
Heterogeneity: not applicable							
subgroup = Mixed moderate to severe disease (WHO 4–9)							
ANTICOVID, Labbé–2023	14	110	31	114	19.4%	44.0%	0.47 [0.26; 0.83]
Total (fixed effect, 95% CI)		110		114	19.4%	—	0.47 [0.26; 0.83]
Total (random effects, 95% CI)					—	44.0%	0.47 [0.26; 0.83]
Heterogeneity: not applicable							
Total (fixed effect, 95% CI)		**406**		**408**	**100.0%**	—	**0.92 [0.77; 1.10]**
Total (random effects, 95% CI)					—	**100.0%**	**0.73 [0.33; 1.59]**
Heterogeneity: $Tau^2 = 0.2747$; $Chi^2 = 6.81$, df = 1 (P < 0.01); $I^2 = 85\%$							
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 0.00$, df = 0 (P = NA); I^2 = NA%							

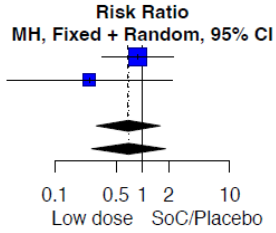


5.14.2.4 *Post-discharge COVID-19 patients: Standard thromboprophylaxis versus standard of care*

Mortality, day 28

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV 4C, Wang–2023	8	610	9	607	69.3%	81.1%	0.88 [0.34; 2.28]
MICHELLE, Ramacciotti–2022	1	159	4	159	30.7%	18.9%	0.25 [0.03; 2.21]
Total (fixed effect, 95% CI)		**769**		**766**	**100.0%**	**–**	**0.69 [0.30; 1.60]**
Total (random effects, 95% CI)					**–**	**100.0%**	**0.70 [0.26; 1.85]**

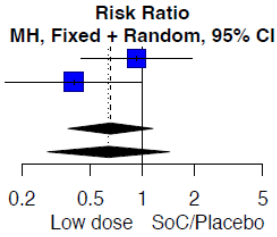
Heterogeneity: $Tau^2 = 0.0721$; $Chi^2 = 1.10$, df = 1 (P = 0.29); $I^2 = 9\%$



Any thrombotic event or death, day 28

Study	Low Events	Low Total	SoC/Placebo Events	SoC/Placebo Total	Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI
ACTIV 4C, Wang–2023	13	610	14	607	48.3%	55.4%	0.92 [0.44; 1.95]
MICHELLE, Ramacciotti–2022	6	159	15	159	51.7%	44.6%	0.40 [0.16; 1.00]
Total (fixed effect, 95% CI)		**769**		**766**	**100.0%**	**–**	**0.65 [0.37; 1.15]**
Total (random effects, 95% CI)					**–**	**100.0%**	**0.64 [0.28; 1.44]**

Heterogeneity: $Tau^2 = 0.1680$; $Chi^2 = 1.92$, df = 1 (P = 0.17); $I^2 = 48\%$



5.14.3 Referenzen der eingeschlossenen Studien

5.14.3.1 *Evidenzprofil 1*

- Ananworanich J, Mogg R, Dunne MW, Bassyouni M, David CV, Gonzalez E, Rogalski-Salter T, Shih H, Silverman J, Medema J, Heaton P : Randomized Study of Rivaroxaban vs Placebo on Disease Progression and Symptoms Resolution in High-Risk Adults With Mild Coronavirus Disease 2019. Clinical Infectious Diseases 2022;75(1):E473-E481
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- Connors JM: Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: the ACTIV-4B Randomized Clinical Trial. JAMA 2021;326(17):1703-1712
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5.14.3.2 *Evidenzprofil 2*

- Connors JM: Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: the ACTIV-4B Randomized Clinical Trial. JAMA 2021;326(17):1703-1712

5.14.3.3 *Evidenzprofil 3*

- Connors JM: Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: the ACTIV-4B Randomized Clinical Trial. JAMA 2021;326(17):1703-1712

5.14.3.4 *Evidenzprofil 4:*

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- Lawler PR, Goligher EC, Berger JS, Neal MD, et al: Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med 2021;385(9):790-802
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- Oliynyk O: Comparison of the Effect of Unfractionated Heparin and Enoxaparin Sodium at Different Doses on the Course of COVID-19-Associated Coagulopathy. Life (Basel, Switzerland) 2021;11(10)
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5.14.3.5 *Evidenzprofil 5*

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5.14.3.6 *Evidenzprofil 6*

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5.14.4 Charakteristika der eingeschlossenen Studien

Study Reference	Study design	Enrollment / Pandemic phase[B]	Randomized patients (n)	Patient status	Intervention	Comparator	Outcomes (Time points as reported)
Inpatient trials							
ACTION, Lopes-2021	RCT, open-label, national, multicenter (Brasil; 31)	Recruitment: 06/2020 - 02/2021 Before Omicron	614	Hospitalized + intensive care unit + ↑ D-dimer; Classified as WHO 4-9, with 85% WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Rivaroxaban 20 mg OD (280 patients, 90%) or enoxaparin 1mg/kg BID for 30 days	Low dose: Enoxaparin 40mg OD, weight and CrCl adjusted, continued until discharge	All-cause mortality (30d), Clinical improvement, any thrombotic event, any thrombotic event or death, major bleeding

ANTICOVID, Labbé-2023	RCT, open-label, national, multicenter (France; 23)	Recruitment: 04/2021 - 12/2021 Before Omicron	339	Hospitalized, WHO ≥5 with hypoxemic COVID-19; Classified as WHO 4-9 Vaccination status n (%): NA	Therapeutic dose: Tinzaparin 175IU/kg OD for 14 days/until discharge, Intermediate dose: Tinzaparin 7000IU OD for 14 days/until discharge	Intermediate dose: Tinzaparin 7000IU OD for 14 days/until discharge Low-dose: Tinzaparin 3500IU OD for 14 days/until discharge	All-cause mortality (28; 90d), any thrombotic event, any thrombotic event or death, major bleeding, QoL
BEMICOP, Marcos-Jubilar-2022	RCT, open-label national, multicenter (Spain; 5)	Recruitment: 10/2020 - 05/2021 Before Omicron	70	Hospitalized, WHO 3-4 +↑ D-Dimer + CURB65 ≤ 2; Classified as WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Bemiparin sc 115IU/kg OD for 10 days (weight adjusted: 50-70 kg: 7,500IU; 70–100 kg: 10,000IU; >100 kg: 12,500IU) 63.6% continued low-dose for a median of 10 additional days	Low dose: Bemiparin 3500IU OD for 10 days 63.6% continued low-dose for a median of 10 additional days	All-cause mortality (30d), any thrombotic event, major bleeding (10d), serious adverse events (10d)
COVID-HEP, Blondon-2022	RCT, open-label, national, multicenter (Switzerland; 4)	Recruitment: 04/2020 - 06/2021 Before Omicron	160	Hospitalized, intermediate care unit (IMCU), or intensive care unit +↑ D-Dimer Classified as WHO 4-9, with max. WHO 7, stratified results according to WHO 4-5 and WHO 6-9 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1mg/kg BID until discharge/clinical improvement/for 30 days	Low or intermediate dose: Enoxaparin, weight adjusted: 40–49.9 kg: 20mg, 50–99.9 kg: 40mg, ≥100 kg: 60mg, Critically ill participants: intermediate dose enoxaparin weight adjusted: 40-99.9 kg: 40mg BID, ≥100 kg: 60mg BID for 30 days	Any thrombotc event or death (30d; WHO 4-5); Any thrombotic event or death (30d; WHO 6-9); 30 day Mortality; Major bleeding (30d; WHO 4-5); Major bleeding (30d; WHO 6-9)
COVID-PACT, Bohula-2022	RCT, open-label, national, multicenter (USA;34)	Recruitment: 08/2020 - 03/2022	672 (382)	Intensive Care Unit Classified as WHO 6-9 with	Therapeutic dose: Enoxaparin 1mg/kg BID for 28 days (median	Low dose: Enoxaparin 40mg OD for 28 days (median	All-cause mortality (30d), any thrombotic event, major bleeding

		Including Omicron		79% and 88% WHO6 Vaccination status n (%): NA	duration 9.9 days)	duration 6.6 days) High crossover rate to therapeutic dose: 34%	
COVID-PREVENT, Rauch-Kröhnert-2023	RCT, open-label, national, multicenter (Germany; 14)	Recruitment: 11/2020 - 05/2021 Before Omicron	111	Ambulatory, Hospitalized +↑ D-Dimer/troponin T + known coronary artery disease/diabetes mellitus/active smoking Classified as WHO 4-5 with 2.7% WHO 6 and 1% WHO 3 Vaccination status n (%): NA	Therapeutic dose: Rivaroxaban 20mg OD for 7 days/until discharge followed by rivaroxaban 10mg OD for 4 weeks	Low dose: Prophylactic dose UFH/LMWH for 7 days/until discharge, no details stated	All-cause mortality (35d), major bleeding
FREEDOM COVID, Stone-2023	RCT, open-label, international, multicentr, in 77 centers in North America (29), South America (26), Asia (13), Europe (8)	Recruitment: 08/2020 - 09/2022 Including Omicron	3398	Hospitalized Classified as WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin sc 1mg/kg BID or Apixaban 5mg BID Until discharge	Low dose: Enoxaparin 40mg OD until discharge	All-cause mortality (30d), any thrombotic event or death, major bleeding
HEP-COVID, Spyropoulos-2021	RCT , open-label, national, multicenter (USA; 12)	Recruitment: 05/2020 - 05/2021 Before Omicron	257	Hospitalized + supplemental oxygen + ↑ D-Dimer or ISTH SIC Score ≥ 4, Classified as WHO 4-9, with 77% ≤WHO 5 Stratified results according to WHO 4-5 and WHO 6-9 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg BID, until discharge	Low/Intermediate dose: Enoxaparin 30-40mg OD/BID until discharge	All-cause mortality, any thrombotic event, any thrombotic event or death, major bleeding

HESACOVID, Lemos-2020	RCT, open-label, national, unicenter (Brasil)	Recruitment: 05/2020 - 05/2021 Before Omicron	20	Intensive Care Unit + ARDS requiring mechanical ventilation + ↑ D-Dimer Classified as WHO 6-9 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg BID for at least 96h and up to 14 days	Low dose: Enoxaparin 40 mg OD for at least 96h and up to 14 days	All-cause mortality (28d), any thrombotic event
INSPIRATION,Sadeghipour-2021	RCT, open-label, national, multicenter (Iran; 10)	Recruitment: 07/2020 - 11/2020 Before Omicron	600	Intensive Care Unit classified as WHO 6-9[A] Vaccination status n (%): NA	Intermediate dose: Enoxaparin 1mg/kg OD for 30 days	Low dose: Enoxaparin 40mg OD	All-cause mortality (30d; 90d), any thrombotic event, any thrombotic event or death, major bleeding
Mohamed-2022	RCT, open-label, national, unicenter (Egypt)	Recruitment: 08/2021 - 10/2021 Before Omicron	124	Intermediate Care Unit (IMCU), pneumonia without hypoxia (SpO2>92%) Classified as WHO 4-5 Vaccination status n (%): NA	Intermediate dose: Enoxaparin 0.5mg/kg BID, duration unclear	Low dose: Rivaroxaban 10mg OD, Duration unclear	All-cause mortality
Oliynyk-2021 (26)	RCT, double-blind, national, unicenter (Ukraine)	Recruitment: 07/2020 - 03/2021 Before Omicron	126	Intensive Care Unit + CAC + ↑ D-Dimer + respiratory failure Classified as WHO 6-9, with 100% WHO 6 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin: 100 Anti-Xa IU/kg BID or UFH: Initial: 80 U/kg/h i.v.; followed by 18 U/kg/h until normalization of D-dimer	Low dose: Enoxaparin 50 Anti-Xa IU/kg QD for 28 days	All-cause mortality (28d)
Perepu-2021	RCT, open-label, national, multicenter (USA; 3)	Recruitment: 04/2020 - 01/2021	173	Hospitalized + Intensive Care Unit and/or mod. ISTH Overt DIC Score ≥3,	Intermediate dose: Enoxaparin 1mg/kg OD until discharge from hospital	Low dose: Enoxaparin 40mg OD, until discharge	All-cause mortality (30d), major bleeding

		Before Omicron		Classified as WHO 5-9, no information on respiratory status reported Vaccination status n (%): NA			
PROTHROMCOVID, Munos-Rivas-2022	RCT, open-label, national, multicenter (Spain; 18)	Recruitment: 02/2021 - 09/2021 Before Omicron	311	Hospitalized + either ↑ D-Dimer, ↑ CRP, ↑ IL6 or SpO_2<94%, Classified as WHO 4-5 Vaccination status n(%): 78 (26) 1-2 doses	Therapeutic dose: Tinzaparin 175IU/kg OD Intermediate dose: Tinzaparin 100 IU/kg OD Until discharge, followed by tinzaparin 4500 IU OD for seven days	Low dose: Tinzaparin 4500IU OD Intermediate dose Tinzaparin 100 IU/kg OD Until discharge	All-cause mortality (30; 90d), any thrombotic event,
RAPID, Sholzberg-2021	RCT, open-label, international, multicenter (28)	Recruitment: 05/2020 - 04/2021 Before Omicron	465	Hospitalized + ↑ D-Dimer, Classified as WHO 4-5, with 6% WHO 6 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg BID For 28 days/until discharge	Low dose: Enoxaparin 40 mg OD, For 28 days/until discharge	All-cause Mortality (28d), any thrombotic event, major bleeding, clinical worsening
REMAP-CAP, ATTAC, ACTIV-4a, Goligher-2021	RCT , open-label, international, multicenter (121)	Recruitment: 04/2020-12/2020 Before Omicron	1207	Intensive care unit Classified as WHO 6-9, with 1.5% WHO 4-5 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg minus 10% BID (received by 77.6%)	Low/Intermediate dose: enoxaparin low dose 40.4%: 40mg OD intermediate dose 51.7%: 0.5mg/kg BID or 40mg BID	All-cause mortality, any thrombotic event, any thrombotic event or death, major bleeding

REMAP-CAP, ATTACC, ACTIV-4a, Lawler-2021	RCT , open-label, international, multicenter (121)	Recruitment: 04/2020 - 01/2021 Before Omicron	2244	Hospitalized classified as WHO 4-5, with 5% WHO 6-7 Vaccination status n (%): NA	Therapeutic dose: Enoxaparin 1 mg/kg minus 10% BID (received by 79.6%)	Low/intermediate dose: enoxaparin low dose 71.7%: 40mg OD intermediate dose 26.5%: 0.5mg/kg BID or 40mg BID	All-cause mortality, any thrombotic event, any thrombotic event or death, major bleeding, clinical worsening, clinical improvement
X-COVID-19, Morici-2021	RCT, open-label, national, multicenter (Italy; 9)	Recruitment: 04/2020 - 04/2021 Before Omicron	186	Hospitalized + Intensive Care Unit Classified as WHO 4-9 with 61% WHO 4-5 and no patients >WHO 7 stratified results according to WHO 4-5 and WHO 6-9 Vaccination status n (%): NA	Intermediate dose: Enoxaparin 40mg BID until discharge	Low dose: Enoxaparin 40mg OD until discharge	All-cause mortality (30d), major bleeding
Post-discharge trials							
ACTIV 4C, Wang-2023	RCT, double-blinded, national, multicenter (USA; 127)	Recruitment: 02/2021 - 06/2022 Including Omicron	1217	Post-discharge Vaccination status n (%): NA	Low dose: Apixaban 2.5mg BID for 30 days	Placebo	All-cause mortality (30d), any thrombotic event or death, major bleeding, non-major clinical relevant bleeding, serious adverse events, QoL
MICHELLE, Ramacciotti-2022 (33)	RCT, open-label, national multicenter (Brasi; 14)	Recruitment: 10/2020 - 06/2021 Before Omicron	318	Post discharge + IMPROVE-Score ≥ 4 or 2-3 + ↑ D-Dimer Vaccination status n (%): NA	Low dose: Rivaroxaban 10mg OD for 35 days	No anticoagulation	All-cause mortality (35d), any thrombotic event, any thrombotic event or death, major bleeding, non-major clinical relevant bleeding,

							other bleedings
				Outpatient trials			
ACTIV 4B, Connors-2021	RCT, double-blind, national, multicenter (USA; 52)	Recruitment: 09/2020 - 06/2021 Before Omicron	657	Symptomatic outpatients Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Apixaban 2.5mg BID for 45 days	Placebo	All-cause Mortality (45d), hospitalization due to cardiovascular events or death within 45 days, thrombotic events within 45 days, severe bleeding within 45 days
Ananworanich-2021	RCT, double-blind, national, multicenter (USA 14)	Recruitment: 08/2020 - 02/2021 Before Omicron	497	Symptomatic outpatients + at least 1 risk factor for severe COVID-19 Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Rivaroxaban 10mg OD for 21 days	Placebo	All-cause mortality (35d), major bleeding, clinical worsening, clinical improvement, serious adverse events
CARE-COALITION VIII, Avezum-2023	RCT, open-label, national, multicenter (Brasil; 33)	Recruitment: 09/2020 - 05/2022 Including Omicron	660	Symptomatic outpatients + at least 2 risk factors for severe COVID-19, Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Rivaroxaban 10mg OD for 14 days	No anticoagulation	All-cause mortality (30d), any thrombotic event, major bleeding
ETHIC, Cools-2022	RCT, open-label, international, multicenter (6; 15)	Recruitment: 10/2020 - 11/2021 Before Omicron	219	Symptomatic outpatients + at least 1 risk factor for severe COVID-19 Classified as WHO 2-3	Low dose: Enoxaparin 40mg OD (BID if >100kg) for 21 days	No anticoagulation	All-cause mortality (21; 50; 90d), major bleeding, clinical worsening, serious adverse events

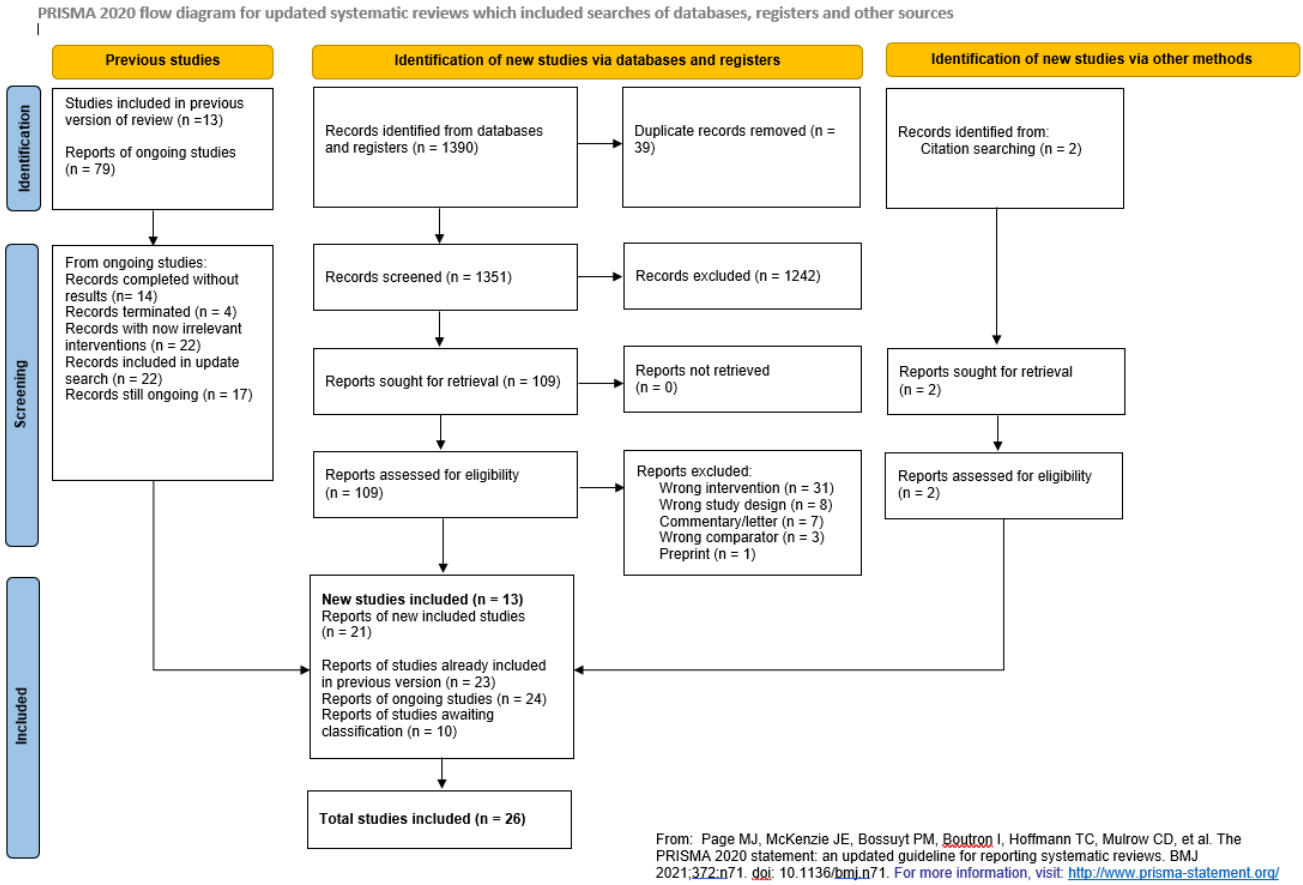
				Vaccination status n (%): 0 vaccinated (exclusion criteria)			
OVID, Barco-2022	RCT, open-label, international; multicenter (2; 9)	Recruitment: 08/2020 - 01/2022 Including Omicron	475	Symptomatic outpatients, Age >50, Classified as WHO 2-3 Vaccination status n (%): NA	Low dose: Enoxaparin 40mg OD for 14 days	No anticoagulation	All-cause mortality (90d), any thrombotic event, major bleeding, clinical worsening Any thrombotic Events (90d) Voci-2023
PREVENT-HD, Piazza-2023	RCT, double-blinded, national, , multicenter (USA; 14)	Recruitment: 08/2020 - 04/2022 Including Omicron	1284	Symptomatic outpatients + at least one risk factor for thrombosis/severe COVID-19 Classified as WHO 2-3 Vaccination status n (%): 27 (2.1) vaccinated	Low dose: Rivaroxaban 10mg OD for 35 days	Placebo	All-cause mortality (35d), 35 day hospitalization, thrombotic events or pulmonary embolism, major bleeding events,

RCT, randomized controlled trial; ↑ D-Dimer, D-Dimer elevation; OD, once daily; BID, twice daily; UFH, unfractionated heparin; CrCl, creatinine clearance, CAC, COVID-19-19 associated coagulopathy,;

[A] Formerly classified as WHO 5-9 with stratified data, now re-classified as WHO 6-9 due to high mortality rate

[B]COVID-19 Pandemic Phases according to the German Robert Koch Institute for public health: Epidemiologisches Bulletin RKI Stand 22.09.2022 (dritte Aktualisierung)

5.14.5 Studienselektion: Flow Chart



5.14.6 Literaturrecherche

5.14.6.1 *Literaturrecherche für CEOsys:*

Search string:

anticoagula* OR antithromb* OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor" OR "Xa inhibitors" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR

Fondaparinux OR Penta OR Quixidar OR Arixtra OR Sulodexid* OR aterina OR "glucuronyl glucosamine glycan sulfate" OR Dociparastat

Study characteristics: "Intervention assignment": Randomised/quasi-randomised/unclear

Date of search: 14.01.2021

Total: 142 studies; 181 Referenzen

Date of search Update: 09.06.2021

Total Update: 332 references (197 studies); new: 151 references

5.14.6.2 *Literaturrecherche für Systematic Review:*

Date of search for all databases: 24.09.2021; update 25.07.2023		
Database/Register	Search	Update Search
CCSR	431 references (245 studies)	786 references (387 stuudies)
WOS (SCI+ECI)	471	1080
WHO COVID-19 DB	250	291*
ResearchSquare	1	-
Total	1153	2157
Total (after deduplication)	1074 (nur Update: 742)	*2184 (nur update 25.07.23:: 1110)*

**Die WHO COVID-19-Forschungsdatenbank ist eine Ressource, die als Reaktion auf die Public Health Emergency of International Concern (PHEIC) geschaffen wurde. Ihr Inhalt ist weiterhin durchsuchbar und deckt den Zeitraum von März 2020 bis Juni 2023 ab. Ab dem 23. Juni 2023 wurden die manuellen Aktualisierungen pausiert, da wir die Notwendigkeit der Fortführung der Datenbank überprüfen.*

Abstract

Search methods:

We searched the Cochrane COVID-19 Study Register (comprising MEDLINE, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, medRxiv, and the Cochrane Central Register of Controlled Trials), Web of Science (Emerging Citation Index and Science Citation Index), WHO COVID-19 Global literature on coronavirus disease, and ResearchSquare to identify completed and ongoing studies to 24 September 2021.

Electronic searches

Our Information Specialist (MIM) conducted systematic searches of the following sources from the inception of each database to 24 September 2021 (date of last search for all databases) and did not place restrictions on the language of publication:

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
  - MEDLINE (PubMed), daily upadates;
  - Embase, weekly updates;
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;

- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates;
- medRxiv (www.medrxiv.org), weekly updates;
- Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates.

- Web of Science Core Collection:
- Science Citation Index Expanded (1945-present);
- Emerging Sources Citation Index (2015-present).

- WHO COVID-19 Global literature on coronavirus disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).
- ResearchSquare (https://www.researchsquare.com/browse)

For detailed search strategies, see Appendix 1.

Searching other sources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews and meta-analyses. In addition, we contacted the investigators of included studies to obtain additional information on the retrieved studies.

We compared our identified studies with results from projects that aim to track COVID-19 intervention research, i.e. www.covid-trials.org, covid-nma.com/dataviz.

Cochrane COVID-19 Study Register

Search string:

anticoagula* OR antithromb* OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor" OR "Xa inhibitors" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat

Study characteristics:

1) "Intervention assignment": “Randomised” OR “quasi-randomised” or “unclear” OR

2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover"

3) "Study type": "Interventional" AND "Study design": "Unclear"

4) "Study type": "Adaptive/Platform"

= 245 studies (431 references)

Web of Science Core Collection (Advanced search)

#1

TI=(anticoagula* OR antithromb* OR "Thrombin Inhibitor*" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor*" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat)

OR AB=(anticoagula* OR antithromb* OR "Thrombin Inhibitor*" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor*" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat)

#2

TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory

syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3

TI=(random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

#4

#1 AND #2 AND #3

Indexes=SCI-EXPANDED, ESCI

= 471

WHO COVID-19 Global literature on coronavirus disease (heißt jetzt anders!)

Search string:

(anticoagula* OR antithromb* OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR Dabigatran OR Pradaxa OR Argatroban OR Novastan OR Acova OR Lepirudin OR Refludan OR Desirudin OR Iprivask OR Revasc OR desulfatohirudin* OR "recombinant HV1 hirudin" OR Bivalirudin OR Hirulog* OR Angiomax OR Angiox OR "Xa inhibitor" OR "Xa inhibitors" OR Xaban* OR Rivaroxaban OR Xarelto OR Apixaban OR Eliquis OR Edoxaban OR Lixiana OR Savaysa OR coumar* OR cumar* OR kumar* OR Benzopyrone* OR Benzopyran* OR Hydroxycinnamic OR "Tonka bean camphor" OR "Vitamin K antagonist" OR "Vitamin K antagonists" OR phenprocoumon* OR henylpropylhydroxycumarin* OR Falithrom OR Fencumar OR Fenprocoumon* OR Liquamar OR Marcoumar OR Marcumar OR Phenprogramma OR Warfarin* OR Warfarat OR Aldocumar OR Warfant OR Brumolin OR Coumefene OR Dethmor OR Dethnel OR Kypfarin OR Marevan OR Panwarfin OR Prothromadin OR Tedicumar OR Zoocoumarin OR Heparin* OR Liquaemin OR Adomiparin OR Ardeparin OR Arteven OR Bemiparin* OR Certoparin OR Clexane OR Klexane OR Clivarin* OR Dalteparin OR Eparina OR Fluxum OR "Fragmin A" OR "Fragmin B" OR Fraxiparin OR Hepathrom OR "Lipo-hepin" OR Liquemin OR Multiparin OR Nadroparin* OR Novoheparin OR Octaparin OR Pabyrin OR Parnaparin* OR Parvoparin OR Pularin OR Reviparin OR Sandoparin OR Semuloparin OR Subeparin OR Sublingula OR Thromboliquine OR Tinzaparin* OR Triofiban OR Vetren OR "Vitrum AB" OR UFH OR LMWH OR Alphaparin* OR "Mono-Embolex" OR Enoxaparin* OR Lovenox OR Danaparoid OR Danaproid OR Orgaran OR Lomoparan OR Fondaparinux OR Penta OR Quixidar OR Arixtra OR sulodexid* OR Aterina OR Luzone OR "glucuronyl glucosamine glycan sulfate" OR "glucuronyl glucosaminoglycan sulfate" OR Dociparastat) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

 excluding databases: MEDLINE, ICTRP, EMBASE, Scopus, PubMed, PMC, Web of Science

= 250 references

ResearchSquare (nicht more nötig da in WHO DB enthalten)

Article type: Research Article

Abstract:

- anticoagulant = 35

- antithrombotic = 2

- thrombin = 2

= selected on page: 1

5.15 Schlüsselfrage 9: Prone positioning vs. standard of care

Autor*innen: Nina Kreuzberger, Caroline Hirsch, Claire Iannizzi

Es wurden insgesamt 16 RCTs eingeschlossen, davon 7 RCTs mit einer Dauer der Wachbauchlagerung von mehr als 5 Stunden.

5.15.1 Evidenztabelle / Summary of Findings (MAGICapp)

Population: Individuals with COVID-19 and ARDS

Intervention: Prone positioning (> 5 hours)

Vergleichsintervention: Any position

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Any position	 Prone positioning (> 5 hours)	**Gewissheit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Intubation or death (day 30)	Relative risk: 0.78 (CI 95% 0.67 - 0.92) Based on data from 830 patients in 2 studies	**491** per 1000	**383** per 1000 Difference: **108 less per 1000** (CI 95% 162 less - 39 less)	**Moderate** Due to serious indirectness[1]	Prone positioning (> 5 hours) probably decreases the number of participants with intubation or death by day 30.
Death (day 30)	Relative risk: 0.93 (CI 95% 0.52 - 1.66) Based on data from 716 patients in 5 studies	**263** per 1000	**224** per 1000 Difference: **12 less per 1000** (CI 95% 80 less - 85 more)	**Low** Due to serious inconsistency, Due to serious imprecision[2]	Prone positioning (> 5 hours) may have little or no effect on the number of deaths byday 30.
Death (day 60)	Relative risk: 0.95 (CI 95% 0.66 - 1.36) Based on data from 400 patients in 1 study Observation time 60 days	**236** per 1000	**224** per 1000 Difference: **12 less per 1000** (CI 95% 80 less - 85 more)	**Low** Due to very serious imprecision[3]	Prone positioning (> 5 hours) may have little or no difference on death by day 60.
Death (day 90)	Relative risk: 1.17 (CI 95% 0.76 - 1.79) Based on data from 40 patients in 1 study	**500** per 1000	**585** per 1000 Difference: **85 more per 1000** (CI 95% 120 less - 395 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether prone positioning (> 5 hours) increases or decreases the number of people with death by day 90.
Intubation (day 30)	Relative risk: 0.77 (CI 95% 0.65 - 0.92)	**363**	**280**	**Moderate**	Prone positioning (> 5 hours) probably decreases

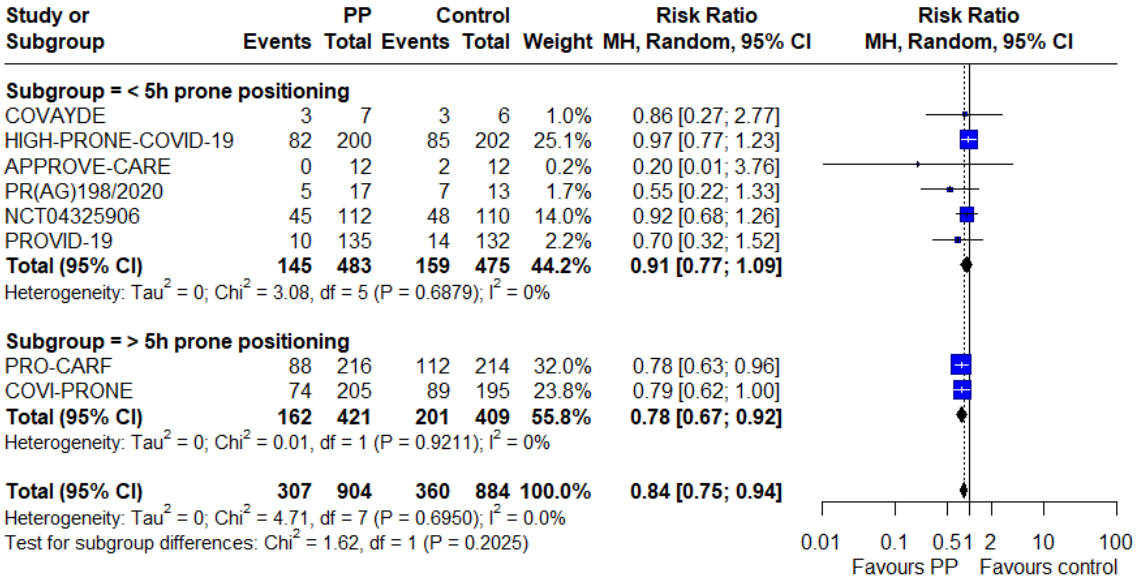
	Based on data from 1116 patients in 6 studies Observation time 30 days	per 1000 per 1000 Difference: **83 less per 1000** (CI 95% 127 less - 29 less)	Due to serious risk of bias[5]	the number of persons requiring intubation by day 30.
Length of hospital stay	Based on data from 60 patients in 1 study	**9.97** **11.53** Days (Mittelwert) Days (Mittelwert) Difference: **MD 1.56 less** (CI 95% 1.65 less - 4.77 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[6]	We are uncertain whether prone positioning (> 5 hours) increases or decreases length of hospital stay.

1. Risk of bias: keine. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Indirectness: very serious. Differences between the intervention/comparator of interest and those studied: The prone positioning was shorter than wished for in COVI-prone (median 5h), no subgroups were provided.;
2. Inkonsistenz: very serious. Point estimates vary widely; Indirectness: keine. Differences between the intervention/comparator of interest and those studied: PP duration varied between studies; e.g., in Jayakumar median around 5h, while PROFLO and PRO-CARF achieved a median around 9h.; Imprecision: very serious. Wide confidence intervals;
3. Imprecision: very serious. Wide confidence intervals, Low number of patients;
4. Risk of bias: very serious. concealment of allocation during randomization process not described, resulting in potential for selection bias. Adherence/drop-out/follow-up of participants not reported.; Imprecision: very serious. Wide confidence intervals, Low number of patients;
5. Risk of bias: very serious. Intubation can have death as competing event. In addition, only one included study had clear intubation criteria (PRO-CARF).;
6. Risk of bias: very serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Imprecision: very serious. Low number of patients;

5.15.2 Analysen / Forest Plots

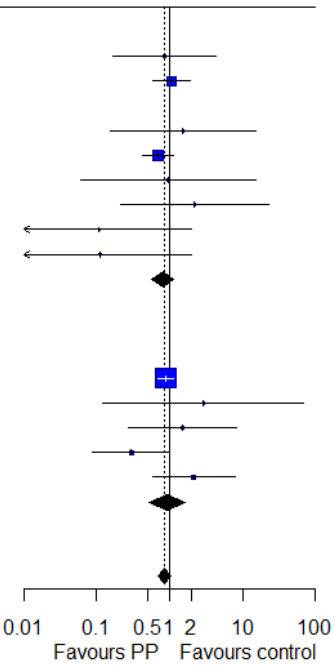
5.15.2.1 *All studies, subgrouped by duration of prone position, cutoff 5h*

Intubation or death by day 30



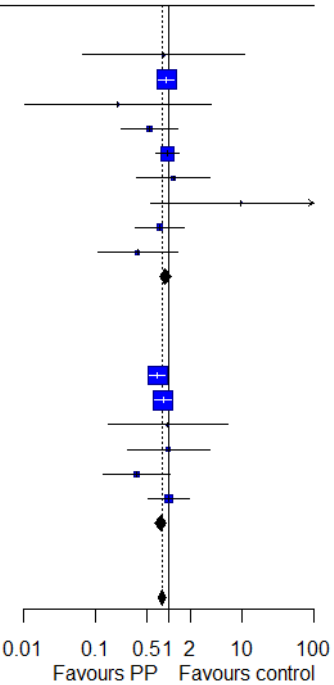
Death by day 30

Study or Subgroup	PP Events	PP Total	Control Events	Control Total	Weight	Risk Ratio MH, Random, 95% CI
Subgroup = < 5h prone positioning						
COVAYDE	2	7	2	6	1.5%	0.86 [0.17; 4.37]
HIGH-PRONE-COVID-19	21	200	20	202	12.0%	1.06 [0.59; 1.89]
APPROVE-CARE	0	12	0	12	0.0%	
PR(AG)198/2020	2	17	1	13	0.8%	1.53 [0.15; 15.09]
NCT04325906	21	112	30	110	16.7%	0.69 [0.42; 1.12]
COVID-PRONE	1	126	1	122	0.5%	0.97 [0.06; 15.31]
EPCoT	2	29	1	32	0.7%	2.21 [0.21; 23.08]
PROVID-19	0	135	4	132	0.5%	0.11 [0.01; 2.00]
Yarahmadi 2022	0	41	4	41	0.5%	0.11 [0.01; 2.00]
Total (95% CI)	**49**	**679**	**63**	**670**	**33.1%**	**0.81 [0.57; 1.15]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 5.92, df = 7 (P = 0.5496); I^2 = 0%						
Subgroup = > 5h prone positioning						
PRO-CARF	71	216	79	214	60.1%	0.89 [0.69; 1.15]
Harris 2024	1	31	0	30	0.4%	2.90 [0.12; 68.58]
Jayakumar 2021	3	30	2	30	1.4%	1.50 [0.27; 8.34]
Nasrallah 2023	3	45	10	45	2.7%	0.30 [0.09; 1.02]
PROFLO	6	36	3	39	2.3%	2.17 [0.58; 8.03]
Total (95% CI)	**84**	**358**	**94**	**358**	**66.9%**	**0.93 [0.52; 1.65]**
Heterogeneity: Tau^2 = 0.1357; Chi^2 = 5.7, df = 4 (P = 0.2223); I^2 = 29.9%						
Total (95% CI)	**133**	**1037**	**157**	**1028**	**100.0%**	**0.87 [0.71; 1.06]**
Heterogeneity: Tau^2 < 0.0001; Chi^2 = 11.83, df = 12 (P = 0.4591); I^2 = 0.0%						
Test for subgroup differences: Chi^2 = 0.16, df = 1 (P = 0.6937)						



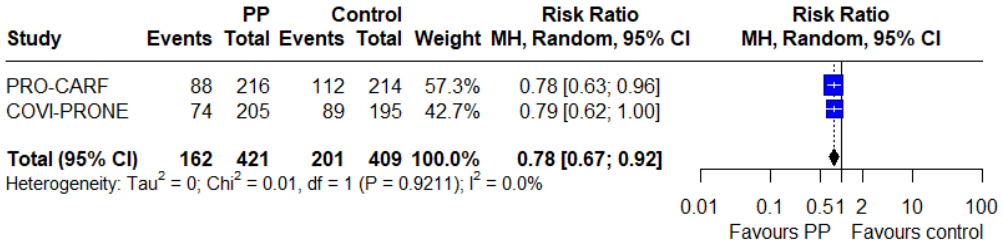
Intubation by day 30

Study or Subgroup	PP Events	PP Total	Control Events	Control Total	Weight	Risk Ratio MH, Random, 95% CI
Subgroup = < 5h prone positioning						
COYADE	1	7	1	6	0.2%	0.86 [0.07; 10.96]
HIGH-PRONE-COVID-19	76	200	82	202	26.1%	0.94 [0.73; 1.19]
APPROVE-CARE	0	12	2	12	0.2%	0.20 [0.01; 3.76]
PR(AG)198/2020	5	17	7	13	2.0%	0.55 [0.22; 1.33]
NCT04325906	38	112	39	110	12.1%	0.96 [0.67; 1.37]
COVID-PRONE	6	126	5	122	1.2%	1.16 [0.36; 3.71]
EPCoT	4	29	0	32	0.2%	9.92 [0.56; 176.44]
PROVID-19	10	135	13	132	2.6%	0.75 [0.34; 1.66]
Yarahmadi	3	41	8	41	1.0%	0.37 [0.11; 1.31]
Total (95% CI)	**143**	**679**	**157**	**670**	**45.6%**	**0.90 [0.75; 1.08]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 7.35, df = 8 (P = 0.4992); I^2 = 0%						
Subgroup = > 5h prone positioning						
PRO-CARF	65	216	92	214	23.8%	0.70 [0.54; 0.90]
COVI-PRONE	70	205	79	195	23.8%	0.84 [0.65; 1.09]
Harris 2024	2	31	2	30	0.4%	0.97 [0.15; 6.44]
Jayakumar 2021	4	30	4	30	1.0%	1.00 [0.28; 3.63]
Nasrallah 2023	4	45	11	45	1.4%	0.36 [0.13; 1.06]
PROFLO	12	36	13	39	3.9%	1.00 [0.53; 1.90]
Total (95% CI)	**157**	**563**	**201**	**553**	**54.4%**	**0.77 [0.65; 0.92]**
Heterogeneity: Tau^2 = 0; Chi^2 = 3.77, df = 5 (P = 0.5832); I^2 = 0%						
Total (95% CI)	**300**	**1242**	**358**	**1223**	**100.0%**	**0.83 [0.73; 0.94]**
Heterogeneity: Tau^2 = 0.0005; Chi^2 = 12.51, df = 14 (P = 0.5651); I^2 = 0.0%						
Test for subgroup differences: Chi^2 = 1.39, df = 1 (P = 0.2377)						

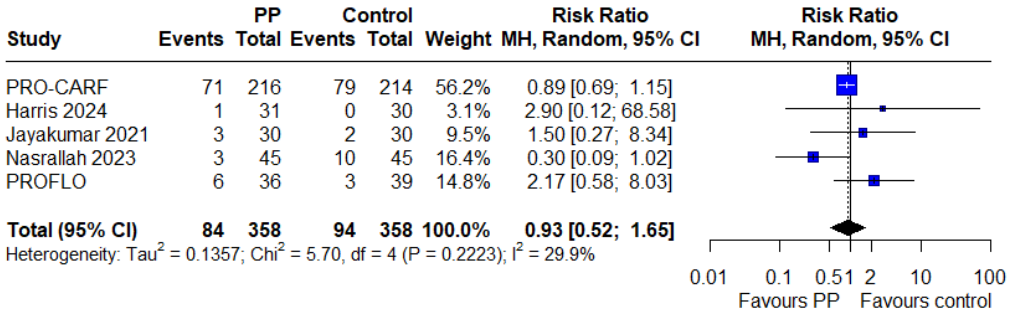


5.15.2.2 *Studies with duration of prone positioning more than 5h*

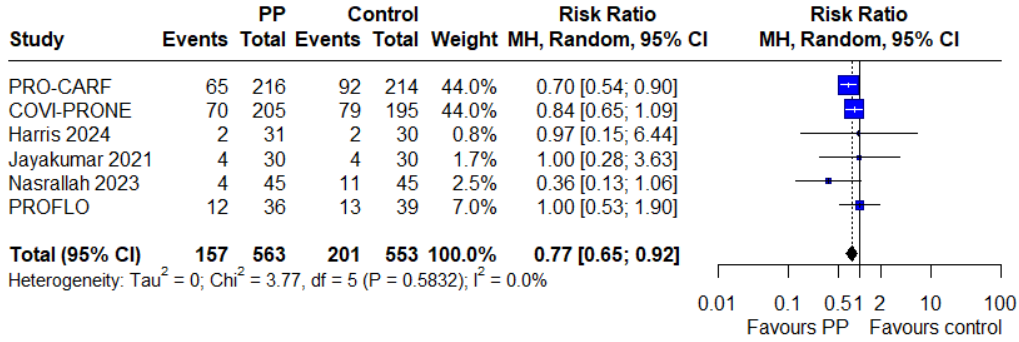
Intubation or death by day 30



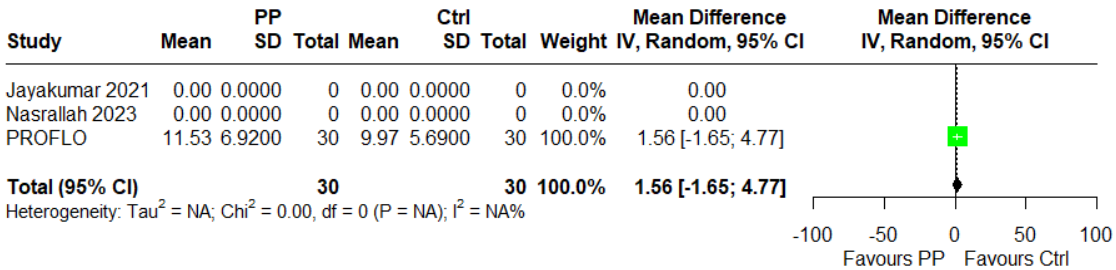
Death by day 30



Intubation by day 30

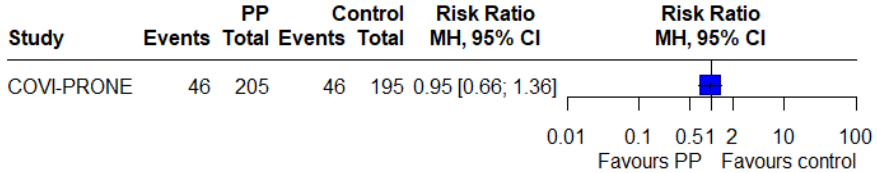


Length of hospital stay

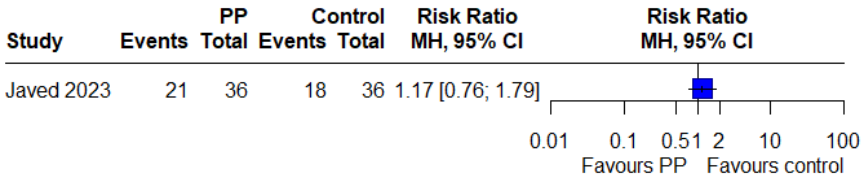


Study entry with 0 means study has reported results, but not as mean (i.e., as median and IQR).

Death by day 60

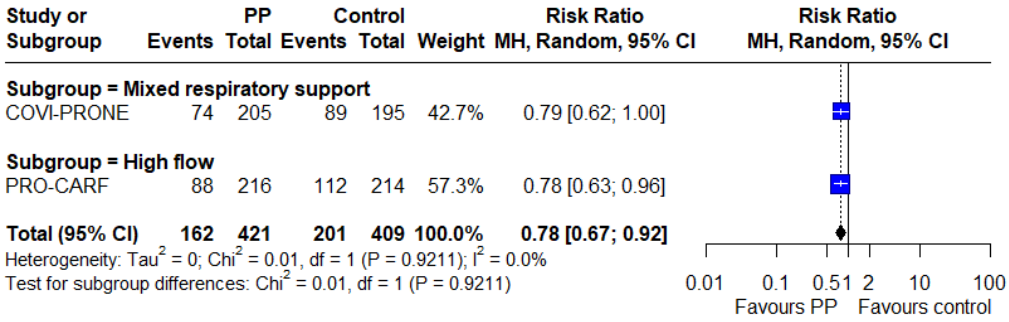


Death by day 90

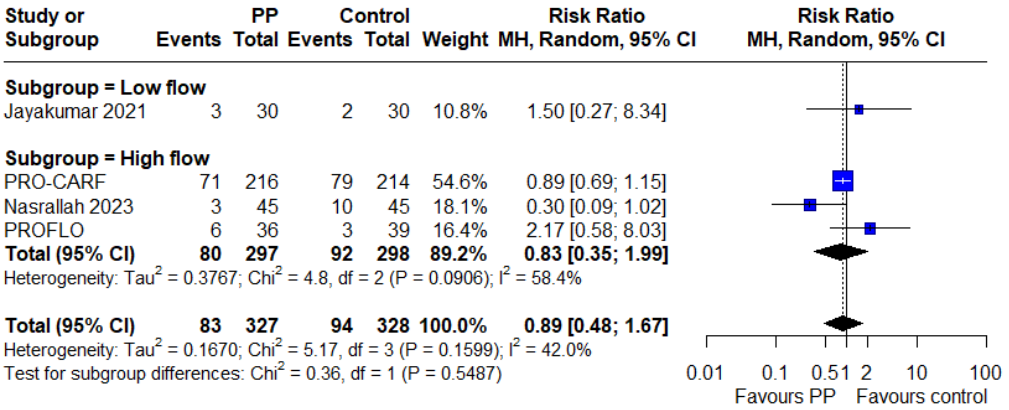


5.15.2.3 *Studies with duration of prone positioning more than 5h, subgroup respiratory support*

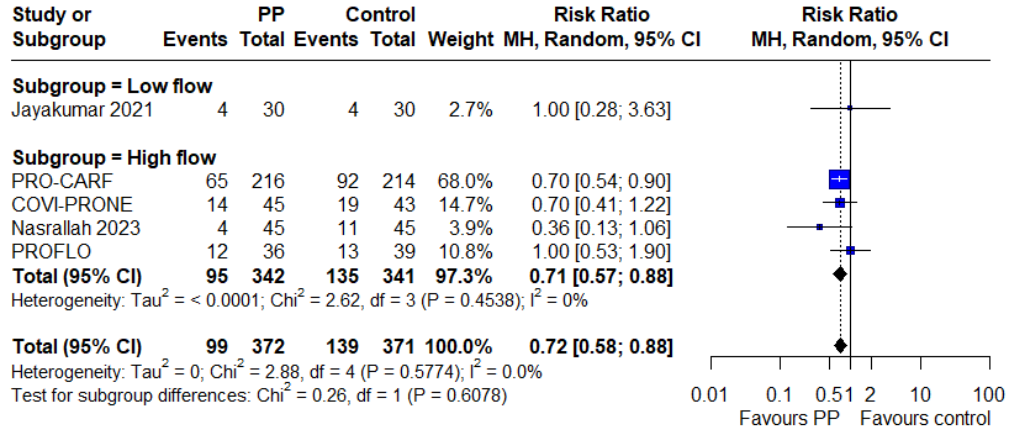
Intubation or death by day 30



Death by day 30

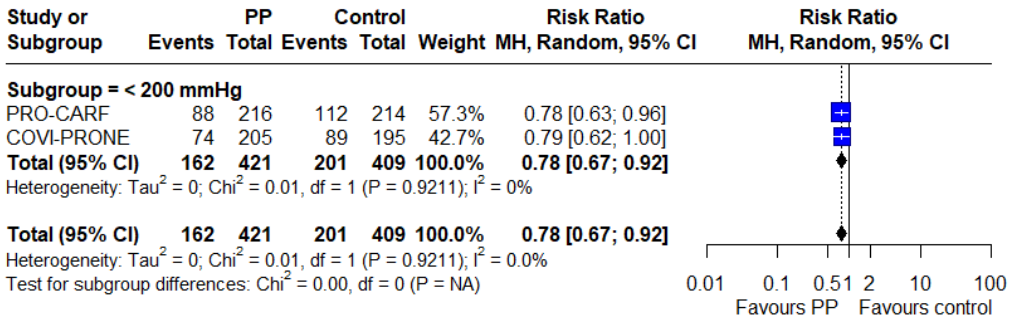


Intubation by day 30

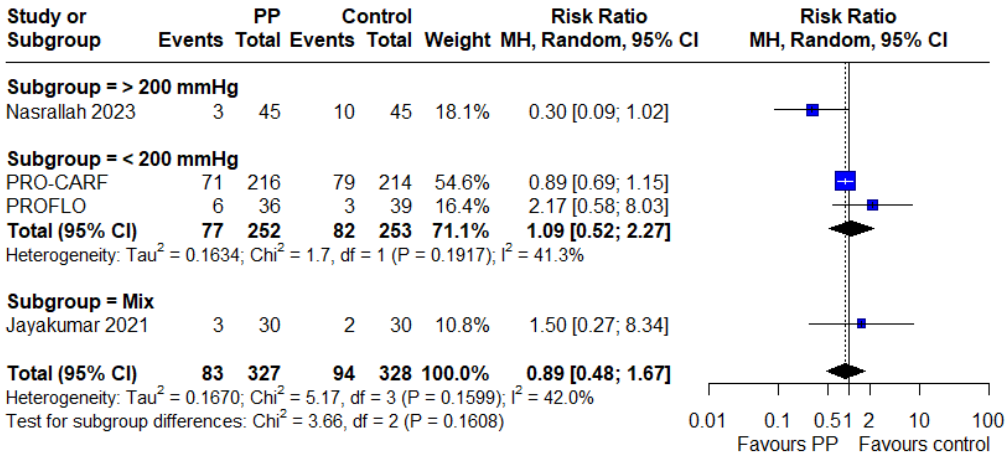


5.15.2.4 *Studies with duration of prone positioning more than 5h, subgroup PaO2/FiO2, cutoff 200 mmHg*

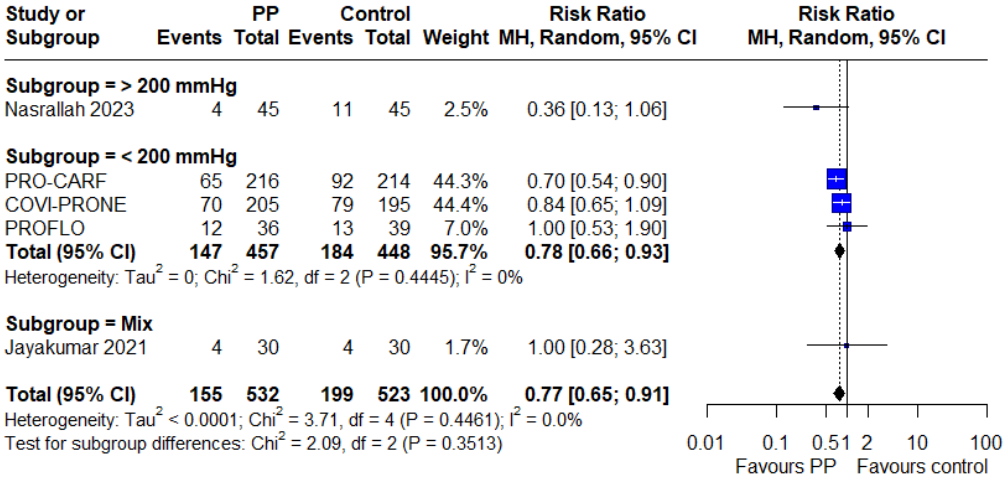
Intubation or death by day 30



Death by day 30



Intubation by day 30



5.15.3 Referenzen der eingeschlossenen Studien

5.15.3.1 *>5h prone positioning*

- Ehrmann S. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet respiratory medicine. 2021;9(12):1387-95. doi: 10.1016/S2213-2600(21)00356-8. PubMed PMID: 18589421.
- Nasrallah BZN, Mahmoud MS, ElGendy HMA, Youssri Mahmoud NM, ElGendy MAEA. Patients self-proning with high-flow nasal cannula improves oxygenation in mild ARDS patients: a randomized clinical trial. Anaesthesia, Pain and Intensive Care. 2023;27(3):351-5. doi: 10.35975/apic.v27i3.2079.
- Rosen J. Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial. Critical care (London, England). 2021;25(1):209. doi: 10.1186/s13054-021-03602-9. PubMed PMID: 17858545.
- Alhazzani W, the Saudi Critical Care Trials G. Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: a Randomized Clinical Trial. JAMA. 2022;327(21):2104-13. doi: 10.1001/jama.2022.7993. PubMed PMID: 20818322.
- Javed H. Effect Of Eight Hours Per Day Of Intermittent Self Prone Positioning For Seven Days On The Severity Of Covid-19 Pneumonia/ Acute Respiratory Distress Syndrome. Journal of Ayub Medical College, Abbottabad. 2023;35(1):68-75. doi: 10.55519/JAMC-01-11069. PubMed PMID: 22673413.
- Jayakumar. Standard Care Versus Awake Prone Position in Adult Nonintubated Patients With Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection-A Multicenter Feasibility Randomized Controlled Trial. Journal of intensive care medicine. 2021;36(8):918-24. doi: 10.1177/08850666211014480. PubMed PMID: 17483494.
- Harris TRE. A randomised clinical trial of awake prone positioning in COVID-19 suspects with acute hypoxemic respiratory failure. Contemp Clin Trials Commun. 2024;39:101295. doi: 10.1016/j.conctc.2024.101295.

5.15.3.2 *<5h prone positioning*

- Nay MA. Prone position versus usual care in hypoxemic COVID-19 patients in medical wards: a randomised controlled trial. Critical care (London, England). 2023;27(1):240. doi: 10.1186/s13054-023-04529-z. PubMed PMID: 23519926
- Yarahmadi S. Effect of Prone Position on Clinical Outcomes of Non-Intubated Patients with Covid-19: a Randomized Clinical Trial. Collegian (Royal College of Nursing, Australia). 2022. doi: 10.1016/j.colegn.2022.12.005. PubMed PMID: 22309020.
- Fezzi M. Early prone positioning does not improve the outcome of patients with mild pneumonia due to SARS-CoV-2: results from an open-label randomised controlled trial - the EPCoT study. ERJ open research. 2023;9(4). doi: 10.1183/23120541.00181-2023. PubMed PMID: 23578942.
- Fralick M. Prone positioning of patients with Moderatee hypoxaemia due to covid-19: multicentre pragmatic randomised trial (COVID-PRONE). BMJ (Clinical research ed). 2022;376:e068585. doi: 10.1136/bmj-2021-068585. PubMed PMID: 20511973.
- Ehrmann S. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet respiratory medicine. 2021;9(12):1387-95. doi: 10.1016/S2213-2600(21)00356-8. PubMed PMID: 18589421.

5.15.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Fralick 2022 COVID-PRONE NCT04383613 *open-label RCT*	**Sample size:** N = 129 (prone positioning), 128 (control group) **Enrolment period:** May 2020 and 31 May 2021 **Countries** · Canada, United States **Inclusion criteria:** · laboratory confirmed or clinically highly suspected diagnosis of covid-19, · needed supplemental oxygen (up to 50% fraction of inspired oxygen), · were able to independently adopt a prone position with verbal instruction. **Time since symptom onset (median, range):** · within 48 hours of admission to hospital, or diagnosed for nosocomial infection in the last 48 hours during their hospital stay	**Experimental:** "were recommended to adopt a prone position four times a day (up to two hours for each session) and encouraged to sleep in prone position overnight. These practices were recommended for up to seven days in hospital, until hospital discharge, or until the patient no longer needed supplemental oxygen (whichever came first)." · Prone positioing · 8h/24h "The median total time spent in prone position up to the first 72 hours was 6 (1.5-12.8) hours; approximately 2.5 hours per day" · N = 129 **Control:** **median 0 (0 to 2) hours**	length of hospital stay	PP: median 5 (IQR 3-9) Control: median 4 (IQR 3-8)	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: · length of hospital stay: some concerns; LoS probably measured appropriately, however staff and participants
			death (any cause)	PP: 1/126 Ctrl: 1/122	
			intubation	PP: 6/126 Ctrl: 5/122	

	<u>Characteristics</u> **Age (median, IQR)** · Exp: 59.5 (45-68) · Ctrl: 54 (44-62) ***<u>Comorbidities</u>*** **Obesity** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 44% · Ctrl: 34% **Cardiovascular disease** · Exp: 3% · Ctrl: 2% **Lung diseases** · Exp: 10% · Ctrl: 12% ***<u>Respiratory support</u>*** **Low flow oxygen** · Exp: 93% · Ctrl: 98% **High Flow Oxygen** · Exp: 4% · Ctrl: 2% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg	· standard of care (oSOC) alone · Instructed not to prone · N = 128			were unblinded, what may have led to differences in hospital discharge decision · death: low concern; · intubation: some concerns; intubation criteria were not really pre-defined, but determined by the team. This may have let to differential initiation of intubation based on group assignment. 5) Selective reporting: No concern. ----------

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Jayakumar 2021 CTRI/2020/12/029702 *open-label RCT*	**Sample size: 60** **Enrolment period:** Not reported **Countries** · India **Inclusion criteria:** · Patients ≥18 years of age · requiring 4 or more LPM of supplemental oxygen to maintain SpO2 ≥ 92% or if ABG was available, PaO2/FiO2 ratio between 100 and 300 mmHg (mild to Moderatee ARDS) with PaCO2 less than 45 mmHg · Patients with AHRF and hemodynamic shock requiring <0.1mcg/kg/min of norepinephrine **Time since symptom onset (median, range):** · unclear **<u>Characteristics</u>** **Age (mean, sd)** · Exp: 54.8 ± 11.1 · Ctrl: 57.3 ± 12.1	**Experimental:** "patients were encouraged by bedside nurses to lie prone for a minimum of 6 hours in a day (cumulative). Additional pillows were provided for comfort to facilitate prone position." · Prone positioing · 6h/24h · · "43% 6 or more hours a day · 70% 4 hours a day" · N = 30 **Control:** · standard of care (oSOC) alone · "Patients randomized to standard care were allowed to change their position as per their comfort (supine, semi	length of hospital stay (ICU)	PP: mean 11.53 (sd 6.92) Control: mean 9.97 (sd 5.69)	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected. Adherence in control group was low, multiple tried PP. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: · length of ICU stay: some concerns; staff and participants were unblinded, what may have
			death (any cause)	PP: 3/30 Ctrl: 2/30	
			intubation	PP: 4/30 Ctrl: 4/30	

	Comorbidities **Obesity (BMI, mean, sd)** · Exp: 28.2 ± 5.7 · Ctrl: 25.8 ± 2.6 **Hypertension** · Exp: 43% · Ctrl: 30% **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: 6.7% · Ctrl: 10% ***Respiratory support*** **Low flow oxygen** · Exp: 90% · Ctrl: 100% **High Flow Oxygen** · Exp: 10% · Ctrl: 0% **Parameters** **PaO2/FiO2** · 201.4 ± 118.8 · 185.6 ± 126.1	sitting, sitting or lateral). If patients in the standard arm wished to lie prone for comfort, this was allowed." · N = 30			led to differences in hospital discharge decision · intubation: some concerns; there were no intubation criteria. There is thus potential for an implicit effect of knowledge of treatment arms. · leath: low concern 5) Selective reporting: No concern. ----------

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Fezzi 2023 EPCoT NCT05008380 open-label RCT	**Sample size:** N = 29 (prone positioning), 32 (control group) **Enrolment period:** 15 August 2021 and 31 May 2022 **Countries** · Italy **Inclusion criteria:** · 18 years and older · positive PCR test for SARS-CoV-2 RNA on a respiratory sample within 7 days of enrolment · at least one of the following conditions: 1) radiological evidence of pneumonia or 2) clinical evidence of respiratory disease, defined as either room air arterial oxygen tension (PaO2 oxygen	**Experimental:** "encouraged to adopt PP for at least three consecutive hours (up to 6 h according to tolerability) twice a day" · Prone positioing · at least 6h/24h, up to 12h/24h · Actual duration: day 1: median 3h (IQR 0-6h) day 3: median 4h (IQR 0-7h) "44.8% and 40.7% maintained pronation for <3 h·day−1 on day 1 and 3, respectively" · N = 29 **Control:** "patients in the control group were free to adopt and maintain any position during the day."; 0h · standard of care (oSOC) alone · Instructed not to prone	length of hospital stay	PP: mean 15.2 (SD 11.0) days Control: mean 12.7 (SD 7.2) days	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: some concerns; intubation can always be affected by death as competing event. · length of hospital stay: some concerns; ascertainment
			death (any cause)	PP: 2/29 Ctrl: 1/32	
			intubation	PP: 4/29 Ctrl: 0/32	

	saturation (SpO2) <94% or need for oxygen supplementation in order to maintain SpO2 > 93% **Time since symptom onset (median, range):** · test within 7 days of enrolment **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 61.0 · Ctrl: 57.5 ***<u>Comorbidities</u>*** **Obesity** · Exp: 6.9% · Ctrl: 6.2% **Hypertension** · Exp: 41.4% · Ctrl: 18.7% **Cardiovascular disease** · Exp: 3.4% · Ctrl: 6.2% **Lung diseases** · Exp: 13.7% · Ctrl: 9.3% ***<u>Respiratory support</u>*** **Low flow oxygen** 98%	· N = 32			was probably not affected, but investigators may have kept those in one group longer than the other. · death: low concerns · intubation: some concerns; intubation criteria have not been reported; therefore, when intubation started could have differered between groups. 5) Selective reporting: Some concern, no protocol reported, intubation and LoS were not listed in clinicaltrials.gov ----------

	High Flow Oxygen 0% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Nay 2023 PROVID-19 NCT04363463 *open-label RCT*	**Sample size: 167** **Enrolment period:** 28 August 2020 to 5 January 2022 **Countries** · France, Monaco **Inclusion criteria:** · hospitalised in medical wards for < 72 h, · 18–85 years old · had laboratory-confirmed COVID-19 pneumonia, · were breathing spontaneously with supplemental oxygen (via standard nasal prongs, mask or high-flow nasal cannula) · were able to selfposition in the prone position or with the assistance of one person. **Time since symptom onset (median, range):** · hospitalised in medical wards for < 72	**Experimental:** "patients assigned to the intervention group had to lie in a prone position for a minimum of two sessions with the goal of a cumulative time of at least 150 min in the prone position during the daytime. Patients were encouraged to lie in the prone position as much as possible. Time and duration of each mobilisation were recorded in a notebook by the patient or a staff member, except at night" · Prone positioing · >150 min/24h · · day 1: 74.8% proned; median time per day proned 138 min [IQR 90 - 176] · N = 135 **Control:** · standard of care (oSOC) alone	length of hospital stay (ICU) Intubation or death (any cause) death Intubation	PP: median 7 (IQR 5 to 11) Control: median 7 (IQR 5 to 12) PP: 10/135 Ctrl: 14/132 PP: 0/135 Ctrl: 4/135 PP: 10/135 Ctrl: 13/132	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern.

	<u>Characteristics</u> **Age (mean, sd)** · Exp: 58.4 (12.1) · Ctrl: 59.2 (11.0) ***<u>Comorbidities</u>*** **Obesity (BMI, mean, sd)** · Exp: 28.6 (4.2) · Ctrl: 28.6 (4.7) **Hypertension** · Exp: 19.3% · Ctrl: 26.5% **Coronary heart disease** · Exp: 6.7% · Ctrl: 3.8% **Lung diseases (COPD, asthma)** · Exp: 4.4%, 8.1% · Ctrl: 0.8%, 6.8% ***<u>Respiratory support</u>*** **Low flow oxygen** · Exp: 96% · Ctrl: 95%% **High Flow Oxygen** · Exp: 4% · Ctrl: 5% **<u>Parameters</u>** **PaO2/FiO2 (median, IQR, mmHg)** · 178 (151–226) · 173 (131–226)	· "Patients randomized to standard care were allowed to change their position as per their comfort (supine, semi sitting, sitting or lateral). If patients in the standard arm wished to lie prone for comfort, this was allowed." · N = 132			----------

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Yarahmadi 2022 IRCT20160126026217N4 *open-label RCT*	**Sample size: 82** **Enrolment period:** August 2020 to April 2021 **Countries** · Iran **Inclusion criteria:** · lack of supportive ventilation · age 35 to 70 · no supportive ventilation · no COPD or asthma · no orthopedic or spine disorder · no thoracic surgery last 6 months **Time since symptom onset (median, range):** · Time gap between onset of symptoms and intervention (Mean (SD)) 1.61 (0.92) **<u>Characteristics</u>** **Age (>=50, %)** · Exp: 61%	**Experimental:** "PP group were asked to lie comfortably in a PP for 90 min and then resume to supine"; "At the end of the 90 min, the participants in the PP group were free to resume the SP or maintain the PP. Still, they were asked to intermittently stay in a PP for a total of 8 h during the 24 h of hospitalisation" · Prone positioing · 8h/24h · Not observed · N = 41 **Control:** · standard of care (oSOC) alone · "asked to lie comfortably in a SP at an angle of 30° for 90 min" · N = 41	length of hospital stay (ICU)	PP: mean 14.970 (sd 0.854) days Control: mean 14.978 (sd 1.104) days	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected. Adherence not measured, there is thus room for performance bias. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: · Length of ICU stay: some concerns; ascertainment
			Intubation or death (any cause)	NR	
			Death (at hospital discharge; survival; at the time of patient discharge to home/ house spice, transfer to the ICU, or patient's death)	PP: 0/41 Ctrl: 4/41	
			Intubation	PP: 3/41 Ctrl: 8/41	

	• Ctrl: 61% ***<u>Comorbidities</u>*** **Obesity (BMI, mean, sd)** • Exp: 24.98 (2.45) • Ctrl: 24.44 (2.50) **Hypertension** • Exp: 51.2% • Ctrl: 17.1% **Coronary heart disease: NR** **Lung diseases: NR** ***<u>Respiratory support</u>*** No oxygen to low flow oxygen **<u>Parameters</u>** **PaO2/FiO2 (median, IQR, mmHg)** • NR				was probably not affected, but investigators may have kept those in one group longer than the other. • death: low concern • intubation: some concerns; there were no intubation criteria. Therefore, it could have been possible to be implicitly affected by group assignment in whether or when to intubate, although this is unlikely. 5) Selective reporting: No concern. ----------

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Alhazzani 2022 COVI-PRONE NCT04350723 Open-label RCT	**Sample size:** N = 205 (prone positioning), 195 (control group) **Enrolment period:** 19 May 2020 to 18 May 2021 **Countries** · Canada, Kuwait, Saudi Arabia, and the US **Inclusion criteria:** · aged 18 years or older · not intubated · suspected or confirmed COVID-19 · required at least 40% oxygen (via	**Experimental:** "target duration of prone positioning was 8 h/d to 10 h/d with 2 to 3 breaks (1-2 hours each), if needed. Daily prone positioning sessions were protocolized to continue until 1 of the following stopping criteria was met: a relative improvement in the FIO2 requirement by 40% from the baseline value that was sustained for 24 hours; endotracheal intubation; or discharge from the ICU or acute care unit" · Prone positioing · at least 8h/24h, up to 10h/24h · Actual duration: · day 1: 5.0 hours (IQR, 2.0-8.0 hours) day 1-4: 4.8 h/d (IQR, 1.8-8.0 h/d) · N = 205 **Control:** "Patients randomized to the control group, and their treating team, were informed of their group assignment. Nurses instructed patients not to position	length of hospital stay	PP: NR Control: NR	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: · length of hospital stay: some concerns; ascertainment was probably not affected, but
			death (any cause)	PP: 46/205 Ctrl: 46/195	
			intubation	PP: 70/205 Ctrl: 79/195	
			Intubation or death	Number of particpants (PP): 74/205 Number of Participants (ctrl): 89/195	

	low- or high-flow oxygen devices) or noninvasive positive pressure ventilation · being treated in an intensive care unit (ICU) or a monitored acute care unit. **Time since symptom onset (median, range):** · time from hospital admission to randomisation was median 1.6 days IQR 0.8 to 3.7 **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 56.8 · Ctrl: 58.3 ***<u>Comorbidities</u>*** **Obesity**	themselves in the prone position."; 0h · standard of care (oSOC) alone · Instructed not to prone · N = 195			investigators may have kept those in one group longer than the other. · death: low concern · intubation criteria: some concerns; were not really pre-defined but determined by the team. This may have let to differential initiation of intubation based on group assignment. 5) Selective reporting: No concern. ----------

	• Exp: NR • Ctrl: NR **Hypertension** • Exp: 46% • Ctrl: 49% **Cardiovascular disease** • Exp: 49% • Ctrl: 52% **Lung diseases** • Exp: 11% • Ctrl: 13% ***<u>Respiratory support</u>*** **Low flow oxygen** • Exp: 22% • Ctrl: 22% **High Flow Oxygen** • Exp: 72% • Ctrl: 68% **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Javed 2023 NCT05405335 open-label RCT	**Sample size:** N = 36 (prone positioning), 36 (control group) **Enrolment period:** 15 October 2021 to 28 February 2022 **Countries** · Pakistan **Inclusion criteria:** · positive COVID-19 PCR or evidence of COVID-19 pneumonia/ ARDS on HRCT chest **Time since symptom onset (median, range):** · unclear **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 56.8	**Experimental:** "Patients who were to be subjected to prone positioning were assisted by experienced staff if the patient requested. The duration of each prone positioning cycle was set for thirty minutes to three hours (duration controlled by the patient) alternating with lying on the right side then on the left side and afterward sitting upright and so on. Total prone positioning duration lasted for eight hours per day for seven days. The duration of each cycle was recorded on the file by the staff." · Prone positioing · 8h/24h · Actual duration: NR · N = 36 **Control:** **Usual care** · standard of care (oSOC) alone · N = 36	length of hospital stay	PP: NR Control: NR	**For all outcomes:** 1) Randomisation and allocation concealment: High concern. Allocation concealment not reported. 2) Blinding: open-label study, high concern. Adherence and drop-out was not reported; as this is an open-label study, performance bias could bias the results. 3) Attrition bias: no concern. **Outcome-specific:** 4) Outcome measurement: no concern. 5) Selective reporting: Some concern, No protocol or SAP available. The clinical trial registry entry does not show mortality as an outcome.
			death (any cause) day 14	PP: 2/36 Ctrl: 10/36	
			death (any cause) day 90	PP: 21/ 36 Ctrl: 18/36	
			death day 30	NR	
			Intubation or death	NR	

	• Ctrl: 58.3 ***<u>Comorbidities</u>*** **Obesity** • Exp: NR • Ctrl: NR **Hypertension** • Exp: NR • Ctrl: NR **Cardiovascular disease** • Exp: NR • Ctrl: NR **Lung diseases** • Exp: NR • Ctrl: NR ***<u>Respiratory support</u>*** **Low flow oxygen** • Exp: NR • Ctrl: NR **High Flow Oxygen** • Exp: NR • Ctrl: NR **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				----------

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ehrmann 2021 COVAYDE NCT04395144 *open-label RCT*	**Sample size:** N = 7 (prone positioning), 6 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** · Canada **Inclusion criteria:** · Covid-19 pneumonia based on the center for disease control guidelines · Presence of acute hypoxemic respiratory failure; · Acute onset within 7	**Experimental:** "PP will be performed before or 1 hour after meal. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. PP will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. PP will be performed minimum twice a day for the first 3 days after the patient's enrolment. Patients will be informed to maintain prone position as long as they can. FIO2 will be adjusted to maintain SpO2 at 90-94%. PP is not protocolized once the patient has been weaned off HFNC. No sedation will be used during the PP. The patients will be monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP session, and at least once for each subsequent session" · Prone positioing · 5/24 (IQR 1.6 to 8.8h)	length of hospital stay* for all studies included in Ehrmann	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, no concern. There were predefined intubation criteria. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern. ----------
			Intubation or death	PP: 3/7 Ctrl: 3/6	
			death (any cause)	PP: 2/7 Ctrl: 2/6	
			intubation	PP: 1/7 Ctrl: 1/6	

	days of insult, or new (within 7 days) or worsening respiratory symptoms; · Bilateral opacities on chest x-ray or computer tomographic scanner not fully explained by effusions, lobar or lung collapse, or nodules; · Cardiac failure not the primary cause of acute respiratory failure · PaO2 / FiO2 ratio <200 mmHg or SO2 / FiO2 < 240 with HFNC at 50 L/min and SpO2	· Actual duration: · median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) · N = 7 **Control:** **"The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."** · standard of care (oSOC) alone · Instructed not to prone · N = 6			

	maintained at 92-95% **Time since symptom onset (median, range):** · Number of days from admission in hospital to enrolment in study: median, IQR: 0.2 (0 to 0.4) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 65.1 · Ctrl: 68.3 ***<u>Comorbidities</u>*** **Obesity** · Exp: 17% · Ctrl: 50% **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 43% · Ctrl: 50% **Lung diseases** · Exp: 29% · Ctrl: 17%				

	Respiratory support · **HFNC** **Parameters** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ehrmann 2021 HIGH-PRONE-COVID-19 France NCT04358939 *open-label RCT*	**Sample size:** N = 200 (prone positioning), 202 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** · France **Inclusion criteria:** · Adult patient suffering from Covid-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected.	**Experimental:** **"depending on tolerance, the objective is to spend as much time as possible, up to 16h and beyond, in prone position per period of 24 hours. At least two sessions of at least 30 minutes each must be performed daily."** · Prone positioing · 5/24 (IQR 1.6 to 8.8h) · Actual duration: · median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) · N = 200 **Control:** **"The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."** · standard of care (oSOC) alone · Instructed not to prone · N = 202	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, no concern. There were predefined intubation criteria. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern.
			Intubation or death	PP: 82/200 Ctrl: 85/202	
			death (any cause)	PP: 21/200 Ctrl: 20/202	
			intubation	PP: 76/200 Ctrl: 82/202	

	· Patient treated by nasal high flow therapy · Moderatee or severe ARDS: bilateral radiological opacities not explained entirely by effusions, atelectasis or nodules; acute hypoxemia with worsening within the 7 previous days, not entirely explained by left ventricular failure; Pa O2 ratio <300 mmHg (or equivalent Sp)./ Fi FiO2 · Written informed				

	consent in France, oral consent in Spain **Time since symptom onset (median, range):** · Number of days from admission in hospital to enrolment in study: median, IQR: 1.5 (1 to 3) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 64.2 · Ctrl: 62.9 ***<u>Comorbidities</u>*** **Obesity** · Exp: 31% · Ctrl: 37% **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 11% · Ctrl: 5% **Lung diseases** · Exp: 14%				

	• Ctrl: 14% ***<u>Respiratory support</u>*** • **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ehrmann 2021 Ireland APPROVE-CARE NCT04347941 *open-label RCT*	**Sample size:** N = 12 (prone positioning), 12 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** · Ireland **Inclusion criteria:** · Suspected or confirmed Covid-19 infection · Bilateral Infiltrates on chest X-ray · SpO2 <94% on FiO2 40% by · either venturi facemask or high flow nasal cannula · Respiratory rate<40 breath/min · Written informed consent **Time since symptom onset (median, range):**	**Experimental:** "Awake prone positioning will be performed before or 1 hour after meal. Call bell will be given to the patient and an oxygen probe will be attached to the patient to monitor spO2 during the procedure. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. Awake prone positioning will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. Patients will be informed to maintain prone position as long as they can. FIO2 will be adjusted to maintain SpO2 at 92-95%. Protocol for sedation and comfort evaluation during PP: No sedation will be used during the PP on ward. The patients are monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP in each day."	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, no concern. There were predefined intubation criteria. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern.
			Intubation or death	PP: 0/12 Ctrl: 2/12	
			death (any cause)	PP: 0/12 Ctrl: 0/12	
			intubation	PP: 0/12 Ctrl: 2/12	

	· Number of days from admission in hospital to enrolment in study: median, IQR: 1 (1 to 2.5) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 62.8 · Ctrl: 59.3 ***<u>Comorbidities</u>*** **Obesity** · Exp: 50% · Ctrl: 67% **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 58% · Ctrl: 33% **Lung diseases** · Exp: 17% · Ctrl: 33% ***<u>Respiratory support</u>*** · **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg	· Prone positioing · 5/24 (IQR 1.6 to 8.8h) · Actual duration: · median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) · N = 12 **Control:** "The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation." · standard of care (oSOC) alone · Instructed not to prone · N = 12			

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ehrmann 2021 Mexico PRO-CARF NCT04477655 open-label RCT	**Sample size:** N = 216 (prone positioning), 214 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** · Mexico **Inclusion criteria:** · Adult patients (18 y) with RT-PCRconfirmed Covid-19 and respiratory distress (regardless of Berlin criteria for ARDS). · Requirement of a FiO2 ≥30% through high-flow nasal cannula (HFNC) to maintain a capillary SpO2 ≥90%.	**Experimental:** "Patients of the experimental group will be also treated with oxygen therapy through high flow nasal cannula (HFNC). Patients will be asked to remain in prone position throughout the day as long as possible, with breaks according to tolerance. Pillows will be offered for maximizing comfort at chest, pelvis and knees. Monitoring of vital signs will not be suspended. Inspired fraction of oxygen will be titrated to maintain a capillary saturation of 92%-95%. Staff intensivist will monitor adherence to protocol and patient's status of both groups on a 24/7 basis." · Prone positioing · 5/24 (IQR 1.6 to 8.8h) · Actual duration: · median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) · N = 216 **Control:** **"The use of awake prone positioning as a so-called rescue**	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, no concern. There were predefined intubation criteria. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern.
			Intubation or death	PP: 88/216 Ctrl: 112/214	
			death (any cause)	PP: 71/216 Ctrl: 79/214	
			intubation	PP: 65/216 Ctrl: 92/214	

	· Written informed consent **Time since symptom onset (median, range):** · Number of days from admission in hospital to enrolment in study: median, IQR: 0.6 (0.4 to 1) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 58.6 · Ctrl: 58.2 ***<u>Comorbidities</u>*** **Obesity** · Exp: 40% · Ctrl: 38% **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 29% · Ctrl: 31% **Lung diseases** · Exp: 8% · Ctrl: 5% ***<u>Respiratory support</u>*** · **HFNC**	**intervention was discouraged in the standard care group and recorded as a protocol violation."** · standard of care (oSOC) alone · Instructed not to prone · N = 214			

	<u>Parameters</u> **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ehrmann 2021 Spain PR(AG)198/2020 NCT04391140 *open-label RCT*	**Sample size:** N = 17 (prone positioning), 13 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** · Spain **Inclusion criteria:** · Adult patient suffering from Covid-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected. · Patient treated by nasal high flow therapy · Moderatee or severe ARDS: bilateral radiological	**Experimental:** "Prone position: depending on tolerance, the objective is to spend as much time as possible, up to 16h and beyond, in prone position per period of 24 hours. At least two sessions of at least 30 minutes each must be performed daily." · Prone positioing · 5/24 (IQR 1.6 to 8.8h) · Actual duration: · median daily duration of awake prone positioning (recorded until day 14) was 5·0 h (IQR 1·6–8·8) · N = 17 **Control:** "The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, no concern. There were predefined intubation criteria. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern.
			Intubation or death	PP: 5/17 Ctrl: 7/13	
			death (any cause)	PP: 2/17 ctrl: 1/13	
			intubation	PP: 5/17 ctrl: 7/13	

	opacities not explained entirely by effusions, atelectasis or nodules; acute hypoxemia with worsening within the 7 previous days, not entirely explained by left ventricular failure; Pa O2 ratio <300 mmHg (or equivalent Sp). / Fi FiO2 · Written informed consent in France, oral consent in Spain **Time since symptom onset (median, range):** · Number of days from admission in hospital to enrolment in study: median, IQR: 1.5 (0 to 4) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 58.1 · Ctrl: 52.4	· standard of care (oSOC) alone · Instructed not to prone · N = 13			

	<u>Comorbidities</u> **Obesity** · Exp: 47% · Ctrl: 39% **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 6% · Ctrl: 8% **Lung diseases** · Exp: 12% · Ctrl: 0% ***<u>Respiratory support</u>*** · **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Ehrmann 2021 USA NCT04325906 *open-label RCT*	**Sample size:** N = 112 (prone positioning), 110 (control group) **Enrolment period:** 2 April 2020 and 26 January 2021 **Countries** · USA **Inclusion criteria:** · Covid-19 pneumonia based on the center for disease control guidelines · Presence of acute hypoxemic respiratory failure; · Acute onset within 7 days of insult, or new (within 7 days) or worsening respiratory symptoms; · Bilateral opacities on chest x-ray or computer tomographic scanner not fully explained by	**Experimental:** "PP will be performed before or 1 hour after meal. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. PP will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. PP will be performed minimum twice a day for the first 3 days after the patient's enrollment. Patients will be informed to maintain prone position as long as they can. F I O will be adjusted to maintain SpO at 92-95%." · Prone positioing · 5/24 (IQR 1.6 to 8.8h) · Actual duration: mean time, SD: 4.4 ± 4.7 · N = 112 **Control:** "The use of awake prone positioning as a so-called rescue intervention was discouraged in the standard care group and recorded as a protocol violation."	length of hospital stay	PP: mean 16.4, sd 10.5 Control: mean 16.5, sd 9.7	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, no concern. There were predefined intubation criteria. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: no concern; intubation can always be affected by death as competing event. 5) Selective reporting: No concern.
			Intubation or death	PP: 45/112 ctrl: 48/110	
			death (any cause)	PP: 21/112 ctrl: 30/110	
			intubation	PP): 38/112 ctrl: 39/110	

	effusions, lobar or lung collapse, or nodules; · Cardiac failure not the primary cause of acute respiratory failure · PaO2 / FiO2 ratio <200 mmHg or SO2 / FiO2 < 240 with HFNC at 50 L/min and SpO2 maintained at 92-95% **Time since symptom onset (median, range):** · Within 7 days from insult; Number of days from admission in hospital to enrolment in study: median, IQR: 0.8 (0.3 to 1.8) **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 62.2 · Ctrl: 62.5 ***<u>Comorbidities</u>*** **Obesity** · Exp: 53% · Ctrl: 56% **Hypertension** · Exp: NR	· standard of care (oSOC) alone · Instructed not to prone · N = 110			

	• Ctrl: NR **Cardiovascular disease** • Exp: 22% • Ctrl: 37% **Lung diseases** • Exp: 10% • Ctrl: 19% ***<u>Respiratory support</u>*** • **HFNC** **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Rosen 2021 PROFLO ISRCTN54917435 open-label RCT	**Sample size:** N = 36 (prone positioning), 39 (control group) **Enrolment period:** 7 October 2020 to 7 February 2021 **Countries** · Sweden **Inclusion criteria:** · ≥ 18 years old · confirmed SARS-CoV-2 · HFNO or NIV for respiratory support · PaO2/FiO2 ≤ 20 kPa **Time since symptom onset (median, range):** · NR **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 66 · Ctrl: 65	**Experimental:** "A protocol targeting at least 16 h APP per day was initiated. Prone and semi-prone positioning was allowed. Flat supine positioning was discouraged and patients were instructed to place themselves in the semirecumbent or lateral position in between proning sessions." · Prone positioing · 16h/24h · Actual duration: median 9.0 [IQR 4.4–10.6] · N = 36 **Control:** "APP was not encouraged but could be prescribed by the attending clinician at his/her discretion." · standard of care (oSOC) alone · N = 39	length of hospital stay	PP: median 16 (IQR 14 to 28) days Control: median 18 (IQR 11 to 30) days	**For all outcomes:** 1) Randomisation and allocation concealment: Low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected. 3) Attrition bias: no concern **Outcome-specific:** 4) Outcome measurement: · length of hospital stay: some concerns; unblinded trial. Those deciding
			death (any cause)	PP: 6/36 ctrl: 3/39	
			intubation	PP: 12/36 ctrl: 13/39	

	Comorbidities **Obesity** · Exp: 23% · Ctrl: 32% **Hypertension** · Exp: 47% · Ctrl: 55% **Cardiovascular disease** · Exp: 17% · Ctrl: 13% **Lung diseases** · Exp: 11% · Ctrl: 26% ***Respiratory support*** **Low flow oxygen** · NR **High Flow Oxygen** · Exp: 86% · Ctrl: 74% **Parameters** **PaO2/FiO2** inclusion P/F >200 mmHg				on discharge may unconsciously be affected by the intervention, however, this is not very likely · death: no concern; intubation can always be affected by death as competing event. · Intubation: some concerns; there were no intubation criteria, therefore, implicitly, knowledge on the intervention arm can have affected the decision to start intubation. 5) Selective reporting: No concern.

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Nasrallah 2023 pactr202204746577792 *open-label RCT*	**Sample size:** N = 45 (prone positioning), 45 (control group) **Enrolment period:** NR, probably from December 2020 (registration date) **Countries** · Egypt **Inclusion criteria:** · ≥ 18 years old · BMI ≤ 30kg/m² · mild ARDS acc. to Berlin criteria · bilateral opacities · Moderatee to severe ARDS (PaO2/FiO2 ratio less than 200) were excluded! **Time since symptom onset (median, range):**	**Experimental:** "Group 2: Patients were subjected to HFNC with a target of SpO2 > 90% with FiO2 ≤ 0.6, and combined with self proning. At first self-proning was applied with HFNC for at least 30 min, if the patient tolerated it well, the position was maintained. The duration of the prone position was 8 h per day" · Prone positioing · 8h/24h · Actual duration: NR · N = 45 **Control:** "Group 1: Patients were subjected to HFNC with a target SpO2 ≥ 90% with FiO2 < 0.6." · standard of care (oSOC) alone · N = 45	length of hospital stay	PP: median 12 (IQR 10 to 12) days Control: median 19 (18 to 21) days	**For all outcomes:** 1) Randomisation and allocation concealment: low concern 2) Blinding: open-label study, some concerns; may affect outcomes that are dependent on physician decision (intubation, length of hospital stay) if there are no clear intubation criteria; death is not affected; adherence not reported for both arms 3) Attrition bias: low concern **Outcome-specific:** 4) Outcome measurement: · Length of hospital stay: some concerns; LoS was probably
			death (any cause)	PP: 3/45 ctrl: 10/45	
			intubation	PP: 4/45 ctrl: 11/45	

	· occurrence within 1 week of a known clinical insult or worsening respiratory symptoms upon admission to ICU **<u>Characteristics</u>** **Age (median, IQR)** · Exp: 62.24 · Ctrl: 58.47 ***<u>Comorbidities</u>*** **Obesity** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung diseases** · Exp: NR · Ctrl: NR ***<u>Respiratory support</u>*** **Low flow oxygen** · NR **High Flow Oxygen** · Exp: NR				measured appropriately, however, knowing the intervention arm may implicitly affect the decision whether to discharge or keep a person in hospital. · death: low concern · intubation: there were no intubation criteria, therefore, implicitly, knowledge on the intervention arm can have affected the decision to start intubation. 5) Selective reporting: some concerns; the clinical trial registry is not very detailed, intubation was named but without a specific time poin and length of stay was not listed.

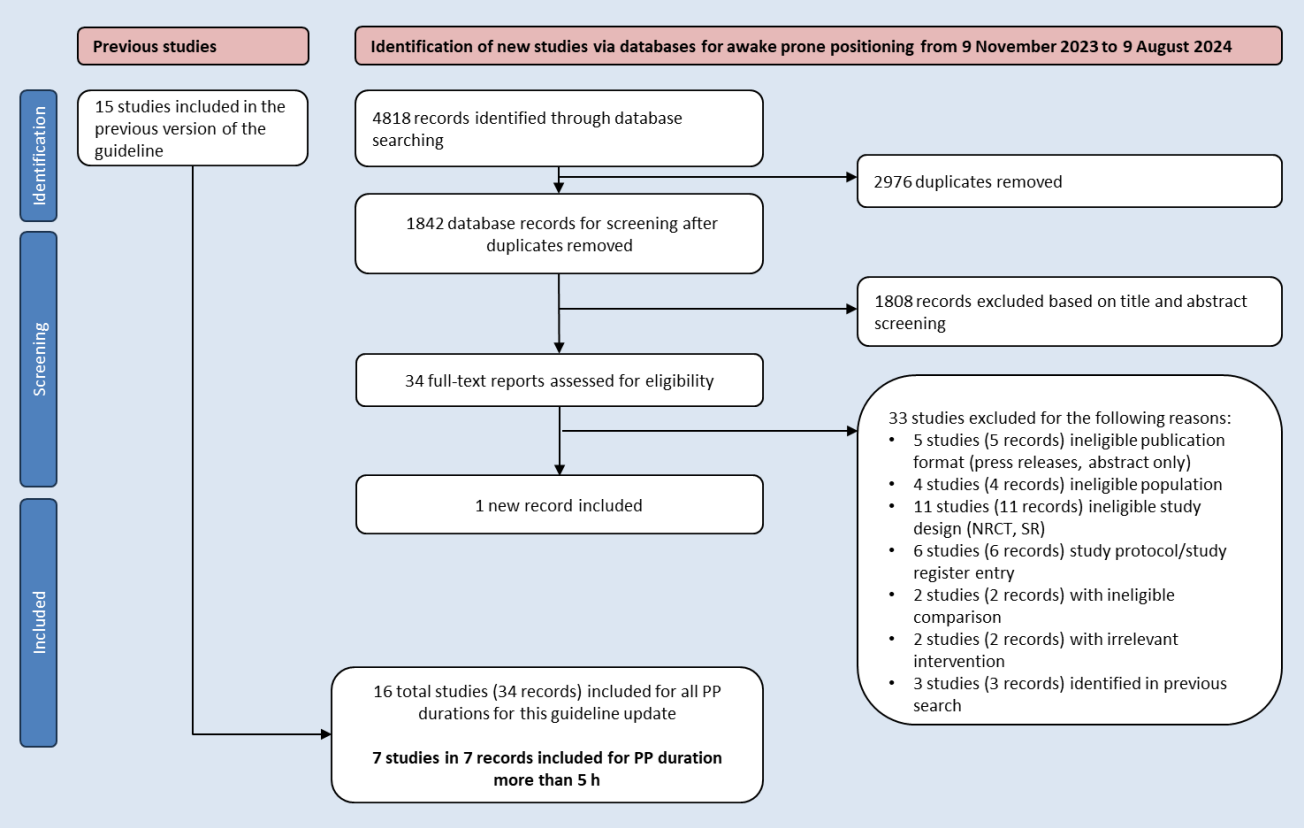
	• Ctrl: NR **<u>Parameters</u>** **PaO2/FiO2** inclusion P/F >200 mmHg				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (RoB-2 domains)
Harris 2024 NCT04853979 *open-label RCT*	**Sample size:** N = 31 (prone positioning), 30 (control group) **Enrolment period:** 9 May to 10 August 2021 **Countries** · Quatar **Inclusion criteria:** · Adult ≥ 18 years with suspected or confirmed COVID 19 pneumonia · Patients who required ≥ 5L supplementary oxygen via face mask (NP, HM, NRB) or NFNC/NIV FiO2 (fraction inspired oxygen) ≥ 0.4 and/or positive end expiratory pressure ≥ 5 cm of water to achieve oxygen saturation (SpO2) measured by pulse oximetry ≥ 94 % · Requiring oxygen therapy initiated within 24 h of hospital	**Experimental:** "Patients were asked to assume APP for as long as possible up to 3 h per session with three sessions per day. Patients received nine sessions over a period equal to three study days. Each session was supervised by a research team member. From day four patients were asked to continue these APP patterns." · Prone positioning · 9h/24h · Actual duration: median 6.2 (IQR 5.2 to 7.7) hours per day, day 1 to 3 · N = 31 **Control:** "The control group were asked to adopt their preferred, comfortable position and not advised about APP."	length of hospital stay	PP: median 11 (IQR 8 to 14) Control: median 12 (IQR 10 to 17)	**For all outcomes:** 1) Randomisation and allocation concealment: low 2) Blinding: some concerns; open-label study, due to the nature of the study intervention, participants, staff and researchers could not be blinded 3) Attrition bias: low **Outcome-specific:** 4) Outcome measurement: · length of hospital stay: some concerns; LoS probably measured appropriately, however staff and participants were unblinded · death: low · intubation: some concerns;
			death (any cause)	PP: 1/31 Ctrl: 0/30	
			intubation	PP: 2/31 Ctrl: 2/30	

	Time since symptom onset (median, range): · within 24 h of hospital admission **<u>Characteristics</u>** **Age (mean, sd)** · Exp: 42.4 (10.9) · Ctrl: 41.2 (9.5) ***<u>Comorbidities</u>*** **Obesity** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 19.4% · Ctrl: 10% **Cardiovascular disease** · Exp: 3.2% · Ctrl: 6.7% **Lung diseases** · Exp: 3.2% · Ctrl: 3.3% ***<u>Respiratory support</u>*** **Low flow oxygen** · Exp: 87% · Ctrl: 77% **High Flow Oxygen** · Exp: 13% · Ctrl: 23% **<u>Parameters</u>**	· standard of care (oSOC) alone · N = 30			there were no intubation criteria. Therefore, it could have been possible to be implicitly affected by group assignment in whether or when to intubate, although this is unlikely. 5) Selective reporting: some concerns; the clinical trial registry is not very detailed, and does not list length of hospital stay, mortality or intubation. ----------

	PaO2/FiO2 (median, IQR) • Exp: NR • Ctrl: NR				

5.15.5 Studienselektion: Flow Chart



5.15.6 Literaturrecherche

Database/Register	Search
CCSR	82
Scopus	130
WHO COVID-19 DB*	80
Total	292
Total (after deduplication)	201

The WHO Covid-19 Research Database is a resource created in response to the Public Health Emergency of International Concern (PHEIC). Its content remains searchable and spans the time period March 2020 to June 2023. Since June 2023, manual updates to the database have been discontinued.

Update Search:

Database/Register	Update Search 15.04.2024	Update Search 09.08.2024
MEDLINE	661	816
CENTRAL	320	346
Embase	855	915
CINAHL	139	155

CT.gov	146	115
ICTRP	156	158
Total	2277	2541
Total (after deduplication)	1599	243 Gesamt von Nov 2023: 1842

5.15.6.1 *Cochrane COVID-19 Study Register*

Search string:
position*
AND
prone* or proning* or pronation*
AND
early or awake or wakefulness* or noninvasive or "non invasive" or nonintubat* or "non intubated" or "non intubation" or nonventilat* or "non ventilated" or "non ventilation" or "face down" or "nasal cannula"

Results available:
reprt results

Study characteristics:
1) "Intervention assignment": “Randomised” OR “unclear” OR
2) "Study design": "Parallel/Crossover" OR “unclear”

5.15.6.2 *Scopus (via Elsevier)*

TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS (position*)

AND TITLE-ABS (prone* OR proning* OR pronation*)

AND TITLE-ABS (early OR awake OR wakefulness* OR noninvasive OR "non invasive" OR nonintubat* OR "non intubated" OR "non intubation" OR nonventilat* OR "non ventilated" OR "non ventilation" OR "face down" OR "nasal cannula")

AND TITLE-ABS (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

AND (LIMIT-TO (DOCTYPE , "ar"))

AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023))

5.15.6.3 *WHO COVID-19 Global literature on coronavirus disease*

Title, abstract, subject:
(position*) AND (prone* OR proning* OR pronation*) AND (early OR awake OR wakefulness* OR noninvasive OR "non invasive" OR nonintubat* OR "non intubated" OR "non intubation" OR nonventilat* OR "non ventilated" OR "non ventilation" OR "face down" OR "nasal cannula") AND (random* OR placebo OR trial OR groups OR "phase 3" OR "phase3" OR p3 OR "pIII")

5.15.6.4 *Ovid MEDLINE(R) ALL*

#	Searches
1	SARS-CoV-2/ or COVID-19/
2	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab.
3	or/1-2
4	Prone Position/ or Patient Positioning/
5	(prone* or proning* or pronation* or reposition*).ti,ab,kf.
6	or/4-5
7	(position* adj2 chang*).ti,ab,kf.
8	position*.ti,ab,kf.
9	wakefulness/ or (early or awake or wakefulness* or noninvasive or non invasive* or nonintubat* or non intubated or non intubation or nonventilat* or non ventilated or non ventilation or face down or (nasal adj2 (canula* or cannula* or oxygen))).ti,ab,kf.
10	8 and 9
11	3 and (6 or 7 or 10)
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	(randomi?ed or placebo).ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.
15	or/12-14
16	exp animals/ not humans/
17	15 not 16*
18	11 and 17
19	(NCT04383613 or NCT04363463 or NCT04395144 or NCT04358939 or NCT04347941 or NCT04391140 or NCT04325906 or NCT04350723 or NCT05405335 or NCT04477655 or IRCT20160126026217N4 or ISRCTN54917435 or pactr202204746577792 or "CTRI/2020/12/029702").af.
20	18 or 19
21	remove duplicates from 20
22	limit 21 to yr="2020 -Current"

*Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins

JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022

5.15.6.5 *Cochrane Central Register of Controlled Trials (CENTRAL) 2024, Issue 3*

ID	Search
#1	[mh "SARS-CoV-2"]
#2	[mh "COVID-19"]
#3	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*):TI,AB
#4	#1 OR #2 OR #3
#5	[mh "Prone Position"]
#6	[mh "Patient Positioning"]
#7	(prone* or proning* or pronation* or repostion*):TI,AB
#8	#5 OR #6 OR #7
#9	(position* NEAR/2 chang*):TI,AB
#10	position*:TI,AB
#11	[mh wakefulness]
#12	(early or awake or wakefulness* or noninvasive or non invasive* or nonintubat* or non intubated or non intubation or nonventilat* or non ventilated or non ventilation or face down or (nasal NEAR/2 (canula* or cannula* or oxygen))):TI,AB
#13	#10 AND (#11 OR #12)
#14	#4 AND (#8 OR #9 OR #13) with Publication Year from 2020 to 2024, in Trials

5.15.6.6 *Ovid Embase*

#	Searches
1	coronavirinae/ or coronaviridae/ or coronaviridae infection/ or coronavirus disease 2019/ or Coronavirus infection/
2	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.
3	exp Severe acute respiratory syndrome coronavirus 2/
4	sars-related coronavirus/ or exp Severe acute respiratory syndrome coronavirus 2/
5	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "Severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab,kw.
6	or/1-5
7	prone position/ or patient positioning/
8	(prone* or proning* or pronation* or repostion*).ti,ab,kw.
9	or/7-8
10	(position* adj2 chang*).ti,ab,kw.
11	position*.ti,ab,kf.

12 wakefulness/ or (early or awake or wakefulness* or noninvasive or non invasive* or nonintubat* or non intubated or non intubation or nonventilat* or non ventilated or non ventilation or face down or (nasal adj2 (canula* or cannula* or oxygen))).ti,ab,kw.

13 11 and 12

14 Randomized controlled trial/

15 Controlled clinical trial/

16 random*.ti,ab.

17 randomization/

18 intermethod comparison/

19 placebo.ti,ab.

20 (compare or compared or comparison).ti.

21 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

22 (open adj label).ti,ab.

23 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

24 double blind procedure/

25 parallel group*1.ti,ab.

26 (crossover or cross over).ti,ab.

27 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

28 (assigned or allocated).ti,ab.

29 (controlled adj7 (study or design or trial)).ti,ab.

30 (volunteer or volunteers).ti,ab.

31 human experiment/

32 trial.ti.

33 or/14-32

34 (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

35 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

36 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

37 (Systematic review not (trial or study)).ti.

38 (nonrandom$ not random$).ti,ab.

39 Random field$.ti,ab.

40 (random cluster adj3 sampl$).ti,ab.

41 (review.ab. and review.pt.) not trial.ti.

42 we searched.ab. and (review.ti. or review.pt.)

43 update review.ab.

44 (databases adj4 searched).ab.

45 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

46 Animal experiment/ not (human experiment/ or human/)

47 or/34-46

48 33 not 47*

49 6 and (9 or 10 or 13)

50 48 and 49

51 remove duplicates from 50

52 limit 51 to yr="2020 -Current"

*Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. Health Info Libr J. 2019 Sep;36(3):264-277.

searched April 15, 2024# Query

S32 S3 AND S30 AND S31

S31 S4 OR S5 OR S6 OR S12

S30 S29 NOT S28

S29 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23

S28 S26 NOT S27

S27 MH human

S26 S24 OR S25

S25 TI animal model*

S24 MH animals+ OR MH animal studies

S23 AB cluster W3 RCT

S22 MH crossover design OR MH comparative studies

S21 AB control W5 group

S20 PT randomized controlled trial

S19 MH placebos

S18 MH sample size AND AB (assigned OR allocated OR control)

S17 TI trial

S16 AB random*

S15 TI (randomised OR randomized)

S14 MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample

S13 MH randomized controlled trials

S12 S7 AND S11

S11 S8 OR S9 OR S10

S10 TI ((nasal N2 (canula* or cannula* or oxygen))) OR AB ((nasal N2 (canula* or cannula* or oxygen)))

S9 TI (early or awake or wakefulness* or noninvasive or non invasive* or nonintubat* or non intubated or non intubation or nonventilat* or non ventilated or non ventilation or face down) OR AB (early or awake or akefulness* or noninvasive or non invasive* or nonintubat* or non intubated or non intubation or nonventilat* or non ventilated or non ventilation or face down)

S8 (MH "Wakefulness")

S7 TI ((position*)) OR AB ((position*))

S6 TI ((position* N2 chang*)) OR AB ((position* N2 chang*))

S5 TI ((prone* or proning* or pronation* or repostion*)) OR AB ((prone* or proning* or pronation* or repostion*))

S4 (MH "Prone Position") or (MM "Patient Positioning")

S3 S1 OR S2

S2 TI ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron*) OR AB ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*)

S1 (MH "COVID-19")

5.15.6.7 *CT.gov*

Search I

COVID-19 | Interventional Studies | (prone OR proning OR pronation OR reposition OR proned)

Search II

COVID-19 AND position | Interventional Studies | (early OR awake OR wakefulness* OR noninvasive OR EXPAND[Concept] "non invasive" OR nonintubat* OR EXPAND[Concept] "non intubated" OR EXPAND[Concept] "non intubation" OR nonventilat* OR EXPAND[Concept] "non ventilated" OR EXPAND[Concept] "non ventilation" OR EXPAND[Concept] "face down" OR EXPAND[Concept] "nasal cannula")

5.15.6.8 *ICTRP*

Search I

(prone OR proning OR pronation OR repostion OR proned) restrict to COVID-19

Search II

position AND (early OR awake OR wakefulness OR noninvasive OR non invasive OR nonintubat* OR non intubated OR non intubation OR nonventilat* OR non ventilated OR non ventilation OR face down OR nasal cannula OR nasal canula OR "nasal oxygen") restrict to COVID-19

5.16 Schlüsselfrage 10: Early vs. late intubation

Autor*innen: Nina Kreuzberger, Caroline Hirsch, Sonja Mahler

Es wurden insgesamt 10 kontrollierte nicht randomisierte Studien (gematcht/gewichtet/adjustiert) eingeschlossen.

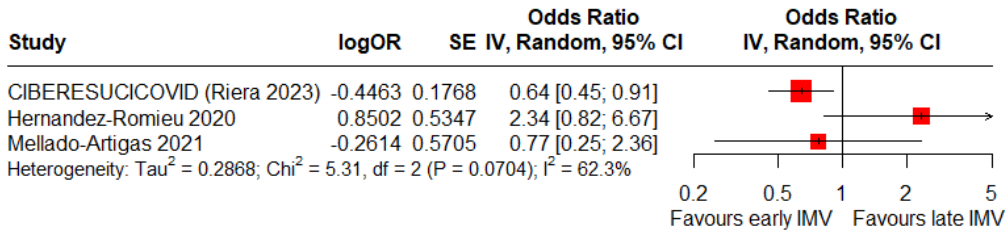
5.16.1 Evidenztabelle / Summary of Findings (MAGICapp)

Für diese Schlüsselfrage wurde keine Empfehlung formuliert und daher keine Evidenztabelle in der MAGICapp angelegt.

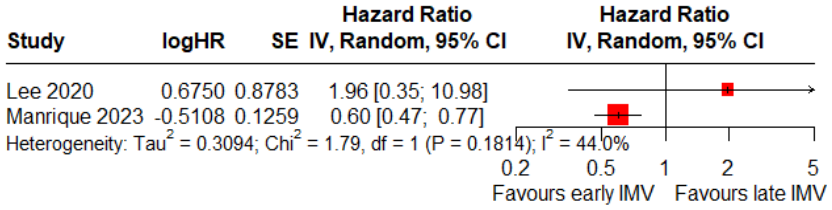
5.16.2 Analysen / Forest Plots

5.16.2.1 *Early intubation < 24h since ARDS onset/ICU admission versus late intubation > 24h since ARDS onset/ICU admission*

Mortality – Odds ratio

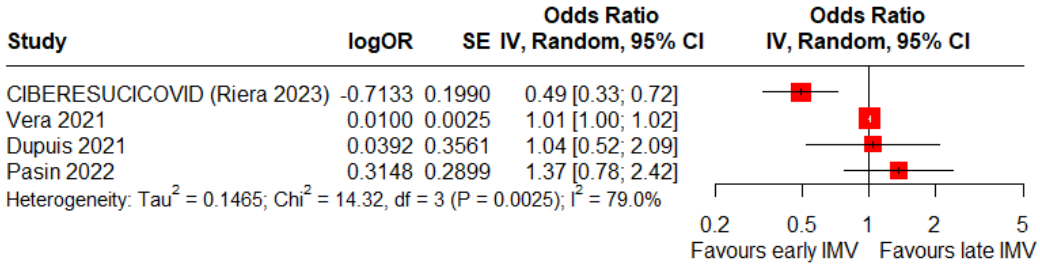


Mortality – Hazard ratio

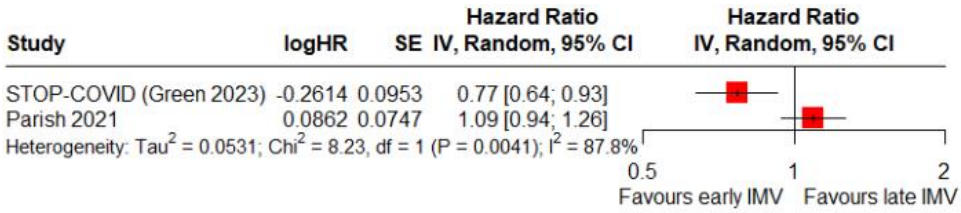


5.16.2.2 *Early intubation < 48h since ARDS onset/ICU admission versus late intubation > 48h since ARDS onset/ICU admission*

Mortality – Odds ratio



Mortality – Hazard ratio



5.16.3 Referenzen der eingeschlossenen Studien

5.16.3.1 *Early intubation < 24h since ARDS onset/ICU admission versus late intubation > 24h since ARDS onset/ICU admission*

- Hernandez-Romieu AC, et al. Timing of Intubation and Mortality Among Critically Ill Coronavirus Disease 2019 Patients: A Single-Center Cohort Study. Crit Care Med. 2020 Nov;48(11):e1045-e1053. doi: 10.1097/CCM.0000000000004600
- Mellado-Artigas R, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Crit Care. 2021 Feb 11;25(1):58. doi: 10.1186/s13054-021-03469-w.
- Riera J, et al. Effects of intubation timing in patients with COVID-19 throughout the four waves of the pandemic: a matched analysis. Eur Respir J. 2023 Mar 2;61(3):2201426. doi: 10.1183/13993003.01426-2022.
- Lee YH, et al. Clinical Significance of Timing of Intubation in Critically Ill Patients with COVID-19: A Multi-Center Retrospective Study. J Clin Med. 2020 Sep 2;9(9):2847. doi: 10.3390/jcm9092847.
- Manrique S, et al. Timing of intubation and ICU mortality in COVID-19 patients: a retrospective analysis of 4198 critically ill patients during the first and second waves. BMC Anesthesiol. 2023 Apr 27;23(1):140. doi: 10.1186/s12871-023-02081-5.

5.16.3.2 *Early intubation < 48h since ARDS onset/ICU admission versus late intubation > 48h since ARDS onset/ICU admission*

- Dupuis C, et al. Association Between Early Invasive Mechanical Ventilation and Day-60 Mortality in Acute Hypoxemic Respiratory Failure Related to Coronavirus Disease-2019 Pneumonia. Crit Care Explor. 2021 Jan 22;3(1):e0329. doi: 10.1097/CCE.0000000000000329.
- Pasin L, et al. Outcomes of COVID-19 Patients with Severe Hypoxemic Acute Respiratory Failure: Non-Invasive Ventilation vs. Straight Intubation-A Propensity Score-Matched Multicenter Cohort Study. J Clin Med. 2022 Oct 14;11(20):6063. doi: 10.3390/jcm11206063.
- Riera J, et al. Effects of intubation timing in patients with COVID-19 throughout the four waves of the pandemic: a matched analysis. Eur Respir J. 2023 Mar 2;61(3):2201426. doi: 10.1183/13993003.01426-2022.
- Vera M, et al. Intubation timing as determinant of outcome in patients with acute respiratory distress syndrome by SARS-CoV-2 infection. J Crit Care. 2021 Oct;65:164-169. doi: 10.1016/j.jcrc.2021.06.008.
- Parish AJ,et al. Early Intubation and Increased Coronavirus Disease 2019 Mortality: A Propensity Score-Matched Retrospective Cohort Study. Crit Care Explor. 2021 Jun 15;3(6):e0452. doi: 10.1097/CCE.0000000000000452.
- Green A, et al. Timing of invasive mechanical ventilation and death in critically ill adults with COVID-19: A multicenter cohort study. PLoS One. 2023 Jun 28;18(6):e0285748. doi: 10.1371/journal.pone.0285748.

5.16.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Parish 2021 *retrospective cohort study; multicenter; propensity score matched*	**Sample size:** N = 1614 **Enrolment period:** 1 March 2020 to 1 December 2020 **Countries:** USA **Inclusion criteria:** · All adult patients, seen in emergency departments (EDs) · tested with a polymerase chain reaction test for SARS-CoV-2 (COVID 19) during their time in the ED and subsequently admitted **Time from symptom onset to intubation (median, IQR):** · NR ***Characteristics*** **Age > 65 (%)** · Exp: 44.7% · Ctrl: 44.5% **Sex (% female)** · Exp: 35.3% · Ctrl: 34.4% ***Comorbidities*** **Obesity (BMI ≥ 30)**	**Experimental:** · Intubated within 48 hours of ED triage · N = 807 **Control:** · All other patients, including those intubated after 48 hours · N = 807 **Intubation cut-off:** 48h since hospital admission **Follow-up:** 60 days	Mortality	HR 1.09 (95% CI 0.94 to 1.26)	**Pre-intervention:** 1) Bias due to confounding: Moderate · matched cohort; SOFA score and PaO2/FiO2 were not matched 2) Bias in selection of participants into the study: Serious · Selection of participants based on characteristics observed after the start of the intervention **At intervention:** 3) Bias in classification of interventions: No information **Post intervention:** 4) Bias due to deviations from intended interventions: No information

	• Exp: 47% • Ctrl: 44.4% **Hypertension** • Exp: 65.3% • Ctrl: 67.7% **Cardiovascular disease** Coronary artery disease • Exp: 12.3% • Ctrl: 12.5% Congestive heart failure • Exp: 11.3% • Ctrl: 11.4% **Lung disease** COPD • Exp: 9.8% • Ctrl: 8.8% Asthma • 14.3% • 13.8% ***<u>Ventilatory support</u>*** **Nasal cannula oxygen** • Exp: 67.5% • Ctrl: 68.3% **Non-rebreather or oxygen mask** • Exp: 53.2% • Ctrl: 55.6% ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** • Exp: NR • Ctrl: NR **APACHE Score (median, IQR)**				5) Bias due to missing data: Low 6) Bias in measurement of outcomes: Low • Mortality is an objective outcome 7) Bias in selection of the reported result: Low --- **Overall risk of bias:** Serious

	• Exp: NR • Ctrl: NR **SOFA Score (median, IQR)** • Exp: NR • Ctrl: NR **PaO2/FiO2 (mmHg)** • Exp: NR • Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Manrique 2023 *retrospective cohort study; multicenter; propensity score matched*	**Sample size:** N = 1369 **Enrolment period:** 22 February 2020 to 11 March 2021 **Countries:** Spain, Andorra, Ireland **Inclusion criteria:** · patients ≥ 15 years old who met the criteria for COVID-19 pneumonia and ARDS according to the Berlin criteria **Time from symptom onset to intubation (median, IQR):** · NR ***Characteristics*** **Age (median, IQR)** · Exp: 64 (56 to 71) · Ctrl: 62 (50 to 70) **Sex (% female)** · Exp: 28% · Ctrl: 28% ***Comorbidities*** **Obesity (BMI ≥ 30)**	**Experimental:** · Intubated <24h after ICU admission · N = 928 **Control:** · Intubated >24h after ICU admission · N = 441 **Intubation cut-off:** 24h since ICU admission **Follow-up:** Up to ICU discharge or death	Mortality (ICU) Mortality (hospital) Length of ICU stay Length of hospital stay	Exp: 293/928 Ctrl: 163/441 Exp: 309/928 Ctrl: 175/441 Exp: median 19 (IQR 12 to 24) Ctrl: median 25 (IQR 8 to 42) Exp: median 35 (IQR 23 to 53) Ctrl: median 41 (IQR 20 to 46)	**Pre-intervention:** 1) Bias due to confounding: Moderate · Matched cohort, but differences in SOFA score, PaO2/FiO2, APACHE II 2) Bias in selection of participants into the study: Serious · Selection of participants based on characteristics observed after the start of the intervention **At intervention:** 3) Bias in classification of interventions: Critical · Intubation decision at discretion of the treating physician **Post intervention:** 4) Bias due to deviations from intended

	· Exp: 38% · Ctrl: 34% **Hypertension** · Exp: 50% · Ctrl: 40% **Cardiovascular disease** Chronic heart failure · Exp: 3% · Ctrl: 4% Ischemic heart disease · Exp: 7% · Ctrl: 4% **Lung disease** Chronic lung disease · Exp: 7% · Ctrl: 5% Asthma · 6% · 6% ***<u>Ventilatory support</u>*** NR ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** · Exp: NR · Ctrl: NR **APACHE II Score (median, IQR)** · Exp: 14 (10 to 17) · Ctrl: 13 (10 to 16) **SOFA Score (median, IQR)** · Exp: 4 (3 to 7) · Ctrl: 3 (2 to 6)				interventions: No information 5) Bias due to missing data: Low 6) Bias in measurement of outcomes: · Low: Mortality; objective outcome · Serious: Length of Stay; the decision to discharge from the ICU/hospital may be influenced by the physician's knowledge of the interventions received. 7) Bias in selection of the reported result: Low --- **Overall risk of bias:** Critical

	PaO2/FiO2 (mmHg) (median, IQR) · Exp: 100 (75 to 148) Ctrl: 116 (90 to 152)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
CIBERESUCICOVID Riera 2023 *secondary analysis of a prospective cohort study; multicenter; propensity score matched*	**Sample size:** N = 614 **Enrolment period:** 29 February 2020 to 31 August 2021 **Countries:** Spain **Inclusion criteria:** · age ≥ 18 years · ICU admission · a confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by real-time reverse transcriptase quantitative PCR testing on nasopharyngeal swabs or lower respiratory tract aspirates **Time to ICU admission (median, IQR):** · Exp: 9 (7 to 11) · Ctrl: 11 (8 to 14)	**Experimental:** · intubated within the first 24h of ICU admission · N = 307 **Control:** · intubated after the first day of ICU admission · N = 307 **Intubation cut-off:** 24h since ICU admission **Follow-up:** Death or hospital discharge or 90 days	Mortality (ICU) Mortality (hospital) Mortality (90 day) Length of ICU stay	Exp: 79/307 Ctrl: 111/307 Exp: 84/307 Ctrl: 114/307 Exp: 85/307 Ctrl: 113/307 Exp: median 17 (IQR 11 to 32) Ctrl: median 27 (IQR 16 to 44)	**Pre-intervention:** 1) Bias due to confounding: Moderate · matched cohort; SOFA score and PaO2/FiO2 were not matched 2) Bias in selection of participants into the study: Serious · Selection of participants based on characteristics observed after the start of the intervention **At intervention:** 3) Bias in classification of interventions: No information **Post intervention:** 4) Bias due to deviations from intended interventions: No information 5) Bias due to missing data: Low

	Characteristics **Age (median, IQR)** · Exp: 64 (56 to71) · Ctrl: 64 (57 to 71) **Sex (% female)** · Exp: 32.5% · Ctrl: 28.3% ***Comorbidities*** **Obesity (BMI ≥ 30)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 53.7% · Ctrl: 54.2% **Cardiovascular disease** Chronic cardiac failure · Exp: 12% · Ctrl: 14.6% **Lung disease** COPD · Exp: 12.3% · Ctrl: 11.4% ***Ventilatory support*** **HFNC** Exp: 71.7% Ctrl: 91.9% **NIV** Exp: 29.7% Ctrl: 41.6% ***Clinical status***				6) Bias in measurement of outcomes: · Low: Mortality; objective outcome · Serious: Length of Stay; the decision to discharge from the ICU/hospital may be influenced by the physician's knowledge of the interventions received. 7) Bias in selection of the reported result: · Moderate: Mortality was defined in the study registry, however at 6 and 12 months of ICU admission · Low: Length of stay --- **Overall risk of bias:** Serious

	Charlston comorbidity index (median, IQR) · Exp: NR · Ctrl: NR **APACHE Score (median, IQR)** · Exp: NR · Ctrl: NR **SOFA Score (median, IQR)** · Exp: 4 (3 to 7) · Ctrl: 3 (2 to 6) **PaO2/FiO2 (mmHg) (at hospital admission) (median, IQR)** · Exp: 214.2 (142.8 to 267.2) Ctrl: 216.6 (114 to 275.7)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Pasin 2022 *retrospective cohort study; multicenter; propensity score matched*	**Sample size:** N = 230 **Enrolment period:** February 2020 to April 2020 **Countries:** Italy **Inclusion criteria:** · adult patients with confirmed SARS-CoV-2 infection, admitted to ICU **days from symptom onset to intubation (median, IQR):** · Exp: 9 (6 to 13) · Ctrl: 8 (6 to 11) ***Characteristics**** *Characteristics in Ctrl beziehen sich auf N=141 (NIV); tatsächlich wurden davon aber nur 89 zu einem späteren Zeitpunkt intubiert **Age (median, IQR)** · Exp: 68 (58 to 75) · Ctrl: 66 (57 to 73) **Sex (% female)** · Exp: 25.5% · Ctrl: 28.4%	**Experimental:** · Straight intubation · N = 141 **Control:** · IMV after NIV failure · N = 89 **Intubation cut-off:** 48h since ICU admission **Follow-up:** NR	Mortality (hospital) Length of hospital stay	Exp: 51/141 Ctrl: 26/89 Exp: median 29 (IQR 15 to 41) Ctrl: median 38 (IQR 18 to 40.75)	**Pre-intervention:** 1) Bias due to confounding: Moderate · matched cohort; unclear whether respiratory rate and PaO2/FiO2 were matched 2) Bias in selection of participants into the study: Serious · Selection of participants based on characteristics observed after the start of the intervention **At intervention:** 3) Bias in classification of interventions: Critical · No clear-cut indication for intubation decision **Post intervention:** 4) Bias due to deviations from intended interventions: No information

	Comorbidities **Obesity (BMI ≥ 30)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** Peripheral vascular disease · Exp: 3.5% · Ctrl: 7.1% **Lung disease** COPD · Exp: 5.7% · Ctrl: 7.1% ***Ventilatory support*** · Ctrl: NR ***Clinical status*** **Charlston comorbidity index (median, IQR)** · Exp: 3 (2 to 5) · Ctrl: 3 (2 to 5) **APACHE Score (median, IQR)** · Exp: NR · Ctrl: NR **SOFA Score (at ICU admission) (median, IQR)** · Exp: 4 (3 to 5) · Ctrl: 4 (3 to 5) **PaO2/FiO2 (mmHg) (at ICU admission) (median, IQR)**				5) Bias due to missing data: Low 6) Bias in measurement of outcomes: · Low: Mortality; objective outcome · Serious: Length of Stay; the decision to discharge from the ICU/hospital may be influenced by the physician's knowledge of the interventions received. 7) Bias in selection of the reported result: Low --- **Overall risk of bias:** Critical

	• Exp: 114 (74.5 to 195.83) Ctrl: 120.71 (83.8 to 181.17)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Mellado-Artigas 2021 *prospective cohort study; multicenter; propensity score matched*	**Sample size:** N = 84 **Enrolment period:** 12 March to 13 August 2020 **Countries:** Spain, Andorra **Inclusion criteria:** · adult patients (≥ 18 years old) · positive confirmatory nasopharyngeal or pulmonary tract sample and received support with either HFNO or intubation on the first day of ICU admission **time to ICU admission (median, IQR):** · Exp: 2 (1 to 4) · Ctrl: 2 (o to 4) ***Characteristics*** **Age (mean, SD)** · Exp: 61 (11) · Ctrl: 63 (9) **Sex (% female)** · Exp: 48%	**Experimental:** · IMV in the first 24 hours of ICU admission · N = 61 **Control:** · HFNO in the first 24 hours of ICU admission · N = 23 **Intubation cut-off:** 24h since ICU admission **Follow-up:** 60 days	Mortality (hospital) Length of ICU stay	Exp: 13/61 Ctrl: 6/23 Exp: median 17 (IQR 12 to 24) Ctrl: median 12 (IQR 9 to 24)	**Pre-intervention:** 1) Bias due to confounding: Moderate · matched cohort; age, sex PaO2/FiO2 were not matched 2) Bias in selection of participants into the study: Serious · Selection of participants based on characteristics observed after the start of the intervention **At intervention:** 3) Bias in classification of interventions: Critical · Intubation decision at descretion of the physician **Post intervention:** 4) Bias due to deviations from intended interventions: No information

	· Ctrl: 39% ***<u>Comorbidities</u>*** **Obesity (BMI ≥ 30)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung disease** · Exp: NR · Ctrl: NR ***<u>Ventilatory support</u>*** · Exp: NR · Ctrl: NR ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** · Exp: NR · Ctrl: NR **APACHE Score (median, IQR)** · Exp: 11 (9 to 14) · Ctrl: 10 (9 to 13) **SOFA Score (at ICU admission) (median, IQR)** · Exp: 5 (3 to 7) · Ctrl: 6 (4 to 8) **PaO2/FiO2 (mmHg) (mean, SD)** · Exp: 117 (51)				5) Bias due to missing data: Low 6) Bias in measurement of outcomes: · Low: Mortality; objective outcome · Serious: Length of Stay; the decision to discharge from the ICU/hospital may be influenced by the physician's knowledge of the interventions received. 7) Bias in selection of the reported result: Low --- **Overall risk of bias:** Critical

	Ctrl: 115 (51)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Hernandez-Romieu 2020 *multicenter; retrospective cohort study*	**Sample size:** N = 175 **Enrolment period:** 6 March 2020 to 7 May 2020 **Countries:** USA **Inclusion criteria:** · all adults (= 18 yr) with a positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction test admitted to one of the COVID-designated ICUs **time from ICU admission to intubation (median, IQR):** · 8.1 (0.3 to 20.1) ***Characteristics*** **Age (median, IQR)** · Exp: <8 hour: 67 (56 to 76); 8-24 hours: 65 (55 to 73) · Ctrl: 67 (57 to 77) **Sex (% female)** · Exp: <8 hour: 50%; 8-24 hours: 40.4%	**Experimental:** · intubated within the first 8 hours of ICU admission N = 76 · intubated between 8 to 24 hours of ICU admission N = 57 **Control:** · IMV after 24 hours of ICU admission · N = 42 **Intubation cut-off:** 24h since ICU admission **Follow-up:** median 12.8 days (IQR, 7.5 to 17.8 days)	Mortality (<8h vs >24h)	OR 2,34 (95% CI 0.73 to 7,44)	**Pre-intervention:** 1) Bias due to confounding: Serious · adjusted model was used, however, not all relevant covariates have been included 2) Bias in selection of participants into the study: Low **At intervention:** 3) Bias in classification of interventions: Moderate · Although this is a prospective cohort study, the intervention could have been categorised after knowing the outcome. **Post intervention:** 4) Bias due to deviations from intended interventions: Low 5) Bias due to missing data: Low

	• Ctrl: 40.5% ***<u>Comorbidities</u>*** **Obesity (BMI ≥ 30)** • Exp: NR • Ctrl: NR **Hypertension** • Exp: <8 hour: 43.3%; 8-24 hours: 45.6% • Ctrl: 42.9% **Cardiovascular disease** • Exp: NR • Ctrl: NR **Lung disease** COPD • Exp: <8 hour: 18.4%; 8-24 hours: 17.5% • Ctrl: 2.4% ***<u>Ventilatory support</u>*** • Exp: NR • Ctrl: NR ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** • Exp: NR • Ctrl: NR **APACHE Score (median, IQR)** • Exp: NR • Ctrl: NR **SOFA Score (at ICU admission) (median, IQR)**				6) Bias in measurement of outcomes: Low • Mortality is an objective outcome 7) Bias in selection of the reported result: Moderate • No protocol --- **Overall risk of bias:** Serious

	• Exp: <8 hour: 10.5 (9 to 12.5); 8-24 hours: 9 (7 to 12) • Ctrl: 7.5 (6 to 9) **PaO2/FiO2 (mmHg) (at first intubation) (median, IQR)** • Exp: <8 hour: 163 (110 to 214); 8-24 hours: 136 (110 to 182) Ctrl: 150 (115 to 192)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Lee 2020 *multicenter; retrospective cohort study*	**Sample size:** N = 39 **Enrolment period:** 17 February 2020 to 23 April 2020 **Countries:** South Korea **Inclusion criteria:** · hospitalized adults (18 years old) with laboratory-confirmed SARS-CoV-2 infection who subsequently were admitted to ICUs · all critically ill patients with COVID-19 who had ARDS during the clinical course were eligible **duration of symptoms before admission, days (median, IQR):** · Exp: 7 (5 to 11) · Ctrl: 5 (4 to 12) ***Characteristics*** **Age (median, IQR)** · Exp: 72 (64 to 76)	**Experimental:** · intubated within 24h since ARDS onset · N = 23 **Control:** · intubated after 24h since ARDS onset · N = 16 **Intubation cut-off:** 24h since ARDS onset **Follow-up:** median 46 days (IQR 24–86 days)	Mortality (hospital)	Exp: 13/23 Ctrl: 7/16	**Pre-intervention:** 1) Bias due to confounding: Serious · Adjusted analysis, but a small number of factors, not all relevant factors considered. 2) Bias in selection of participants into the study: Moderate · No information on start of follow-up **At intervention:** 3) Bias in classification of interventions: Moderate · Intubation decision at descretion of the physician **Post intervention:** 4) Bias due to deviations from intended interventions: Moderate 5) Bias due to missing data: Low

	· Ctrl: 66 (59 to 77) **Sex (% female)** · Exp: 39.1% · Ctrl: 37.5% ***<u>Comorbidities</u>*** **Obesity (BMI ≥ 30)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 43.5% · Ctrl: 50% **Cardiovascular disease** · Exp: 17.5% · Ctrl: 12.5% **Lung disease** · Exp: 13% · Ctrl: 6.2% ***<u>Ventilatory support</u>*** · All patients in the initially nonintubated group received oxygen via high-flow nasal cannula (HFNC) either before intubation or throughout the treatment period. ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** · Exp: NR				6) Bias in measurement of outcomes: · Low: Mortality; objective outcome 7) Bias in selection of the reported result: Moderate · No protocol or study registry --- **Overall risk of bias:** Serious

	• Ctrl: NR **APACHE II Score (median, IQR)** • Exp: 15 (10 to 17) • Ctrl: 14 (8 to 15) **SOFA Score (median, IQR)** • Exp: 3 (2 to 7) • Ctrl: 3 (2 to 4) **PaO2/FiO2 (mmHg) (mean, SD)** • Exp: NR Ctrl: NR				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Dupuis 2021 *multicenter; prospective cohort study*	**Sample size:** N = 162 **Enrolment period:** 15 February 2020 to 1 May 2020 **Countries:** France **Inclusion criteria:** · patients over 18 years · admitted to one of the participant ICUs belonging to the OutcomeRea network and · had at admission an AHRF related to severe COVID-19 pneumonia **time from first symptoms to admission, days (median, IQR):** · Exp: 9 (7 to 12) · Ctrl: 9 (7 to 12) **Time from admission to IMV, days (median, IQR):** · Exp: 1 (1 to 2) · Ctrl: 3 (3 to 4) ***Characteristics***	**Experimental:** · intubated within the first 48 hours since ICU admission · N = 117 **Control:** · intubated after 48 hours hours since ICU admission · N = 45 **Intubation cut-off:** 48h since ICU admission **Follow-up:** 60 days	Mortality (ICU) Length of ICU stay	Exp: 48/117 Ctrl: 18/45 Exp: median 15 (IQR 10 to 21) Ctrl: median 16 (IQR 11 to 22)	**Pre-intervention:** 1) Bias due to confounding: Low · Weight model included all relevant covariates 2) Bias in selection of participants into the study: Low **At intervention:** 3) Bias in classification of interventions: Moderate · Although this is a prospective cohort study, the intervention could have been categorised after knowing the outcome **Post intervention:** 4) Bias due to deviations from intended interventions: Low 5) Bias due to missing data: Moderate · Handling of missing

	Age (median, IQR) · Exp: 61 (52 to 69) · Ctrl: 63 (53 to 70) **Sex (% female)** · Exp: 19.7% · Ctrl: 33.3% ***<u>Comorbidities</u>*** **Obesity (BMI ≥ 30)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: NR · Ctrl: NR **Cardiovascular disease** · Exp: 28.2% · Ctrl: 17.8% **Lung disease** · Exp: 10.3% · Ctrl: 17.8% ***<u>Ventilatory support</u>*** Highest ventilatory support at admission · Exp: IMV 100% · Ctrl: NIPPV 6.67%; CPAP 13.3%; HFNC 66.7%; Others 13.3% ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** · Exp: 1 (0 to 3) · Ctrl: 1 (0 to 3)				confounders by median imputation, which may not be the most ideal way 6) Bias in measurement of outcomes: Low 7) Bias in selection of the reported result: Moderate · No protocol --- **Overall risk of bias:** Moderate

	APACHE Score (median, IQR) • Exp: NR • Ctrl: NR **SOFA Score (median, IQR)** • Exp: NR • Ctrl: NR **PaO2/FiO2 (mmHg) (median, IQR)** • Exp: 110 (80 to 155) Ctrl: 123.3 (90 to 194.5)				

Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Vera 2021 *prospective cohort study*	**Sample size:** N = 183 **Enrolment period:** 17 March 2020 to 31 July 2020 **Countries:** Chile **Inclusion criteria:** · patients with laboratory-confirmed SARS-CoV-2 infection and moderate to severe ARDS · Admission pathways comprised the emergency department and basic ward **Days of symptoms before admission (median, IQR):** · Exp: 7 (4 to 8) · Ctrl: 7 (5 to 10) ***Characteristics*** **Age (median, IQR)** · Exp: 59 (53 to 66) · Ctrl: 64 (55 to 71) **Sex (% female)** · Exp: 29%	**Experimental:** · Intubated within 48h of hospital admission · N = 88 **Control:** · Intubated after 48h of hospital admission · N = 95 **Intubation cut-off:** 48h since ICU admission **Follow-up:** 28 days	Mortality	Exp: 11/88 Ctrl: 21/85 OR 1,01 (95% CI 1 to 1,01)	**Pre-intervention:** 1) Bias due to confounding: Serious · adjusted logistic regression, not adjusted for relevant variables sex, respiratory rate, SOFA 2) Bias in selection of participants into the study: Moderate · No information on start of follow-up **At intervention:** 3) Bias in classification of interventions: Moderate · Although this is a prospective cohort study, the intervention could have been categorised after knowing the outcome. **Post intervention:**

	· Ctrl: 26% ***<u>Comorbidities</u>*** **Obesity (BMI ≥ 30)** · Exp: NR · Ctrl: NR **Hypertension** · Exp: 47% · Ctrl: 48% **Cardiovascular disease** · Exp: NR · Ctrl: NR **Lung disease** · Exp: NR · Ctrl: NR ***<u>Ventilatory support</u>*** · HFNC, non-invasive ventilation, and prone trial in both groups possible ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** · Exp: NR · Ctrl: NR **APACHE Score (within 24h of ICU admission) (median, IQR)** · Exp: 12 (8 to 15) · Ctrl: 13 (8 to 20) **SOFA Score (within 24h of ICU admission) (median, IQR)** · Exp: 6 (4 to 8)				4) Bias due to deviations from intended interventions: Low 5) Bias due to missing data: Low 6) Bias in measurement of outcomes: Low 7) Bias in selection of the reported result: Moderate · No protocol or study registry --- **Overall risk of bias:** Serious

	· Ctrl:4 (2 to 8) **PaO2/FiO2 (mmHg) (at hospital admission) (median, IQR)** · Exp: 123 (82 to 166) Ctrl: 99 (77 to 158)				

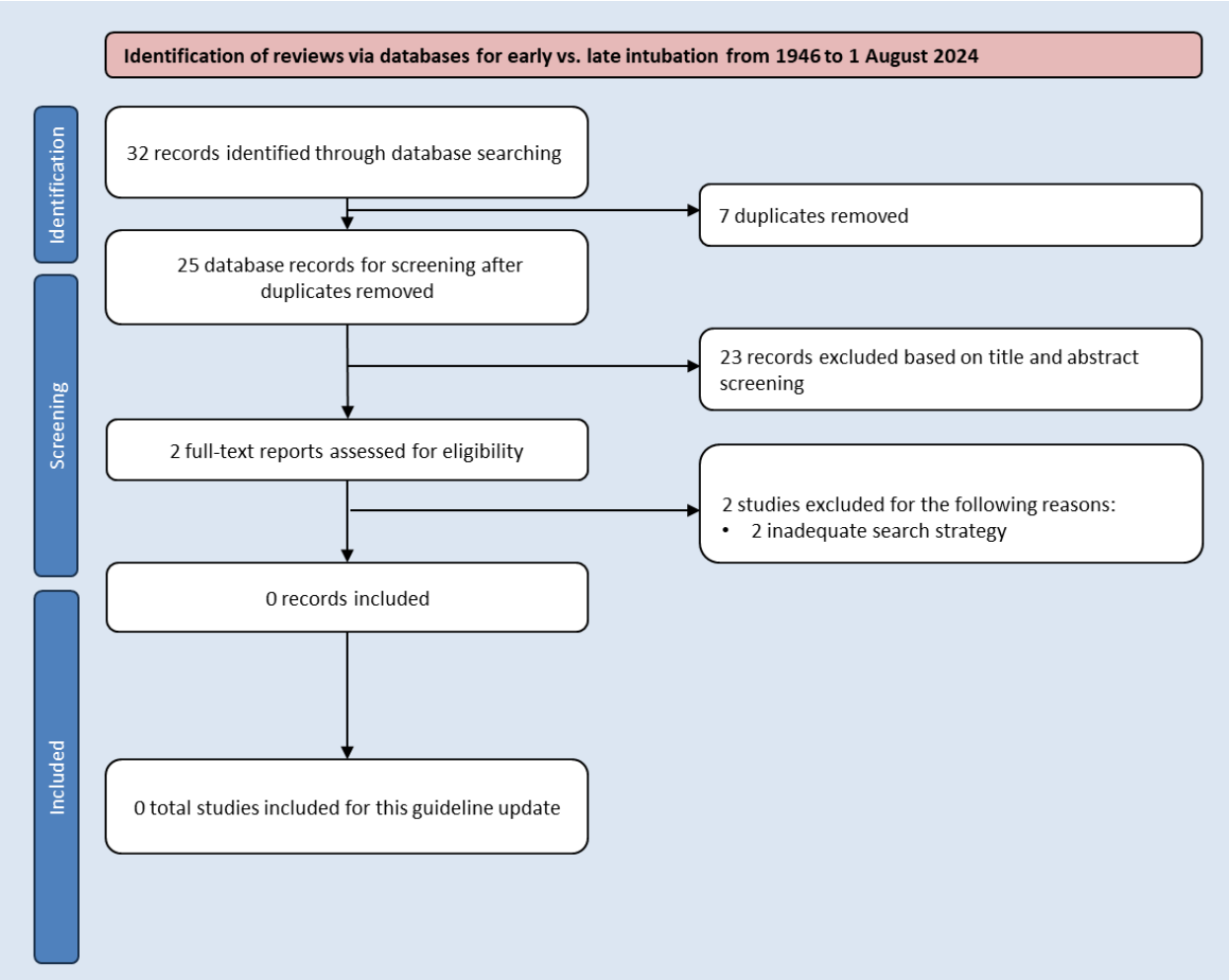
Reference, study design	Population	Interventions	Outcomes and outcome definition	Result per outcome	Risk of Bias (ROBINS-I domains)
Green 2021 *multicenter; prospective cohort study*	**Sample size:** N = 1879 **Enrolment period:** 1 March 2020 to 1 July 2020 **Countries:** USA **Inclusion criteria:** · adult patients (>= 18 years old) with laboratory-confirmed COVID-19 admitted to an ICU **days from symptom onset to ICU admission <=3** · Exp: 22.8% · Ctrl: 27.1% ***Characteristics*** **Age (median, IQR)** · Exp: 63 (53 to 72) · Ctrl: 63 (53 to 73) **Sex (% female)** · Exp: 35.6% · Ctrl: 38.8% ***Comorbidities*** **Obesity (BMI ≥ 30)** · Exp: NR	**Experimental:** · Intubation within 48h of ICU admission · N = 1526 **Control:** · Intubated after within day 3 to 7 of ICU admission · N = 353 **Intubation cut-off:** 48h since ICU admission **Follow-up:** 90 days	Mortality	Exp: 644/1526 Ctrl: 180/353 HR 0.77 (95% CI 0.64 to 0.93)	**Pre-intervention:** 1) Bias due to confounding: Low · Adjusted analysis with a large set of adjustment factors; adjusted and unadjusted effect estimate show a similar effect 2) Bias in selection of participants into the study: Low **At intervention:** 3) Bias in classification of interventions: Moderate · intervention could have been categorised after knowing the outcome **Post intervention:** 4) Bias due to deviations from intended interventions: Low

	· Ctrl: NR **Hypertension** · Exp: 61.3% · Ctrl: 62.9% **Cardiovascular disease** Coronary artery disease: · Exp: 12.3% · Ctrl: 15.9% Congestive heart failure: · Exp: 8.7% · Ctrl: 13.9% **Lung disease** · Exp: 30.9% · Ctrl: 41.4% ***<u>Ventilatory support</u>*** · None ***<u>Clinical status</u>*** **Charlston comorbidity index (median, IQR)** · Exp: NR · Ctrl: NR **APACHE Score (median, IQR)** · Exp: NR · Ctrl: NR **Renal SOFA Score 0** · Exp: 67.7% · Ctrl: 66.9% **PaO2/FiO2 (mmHg)** (>= 300): · Exp: 13.5% Ctrl: 3.8% 200 to 299:				5) Bias due to missing data: Low 6) Bias in measurement of outcomes: Low · Mortality; objective outcome 7) Bias in selection of the reported result: Low --- **Overall risk of bias:** Moderate

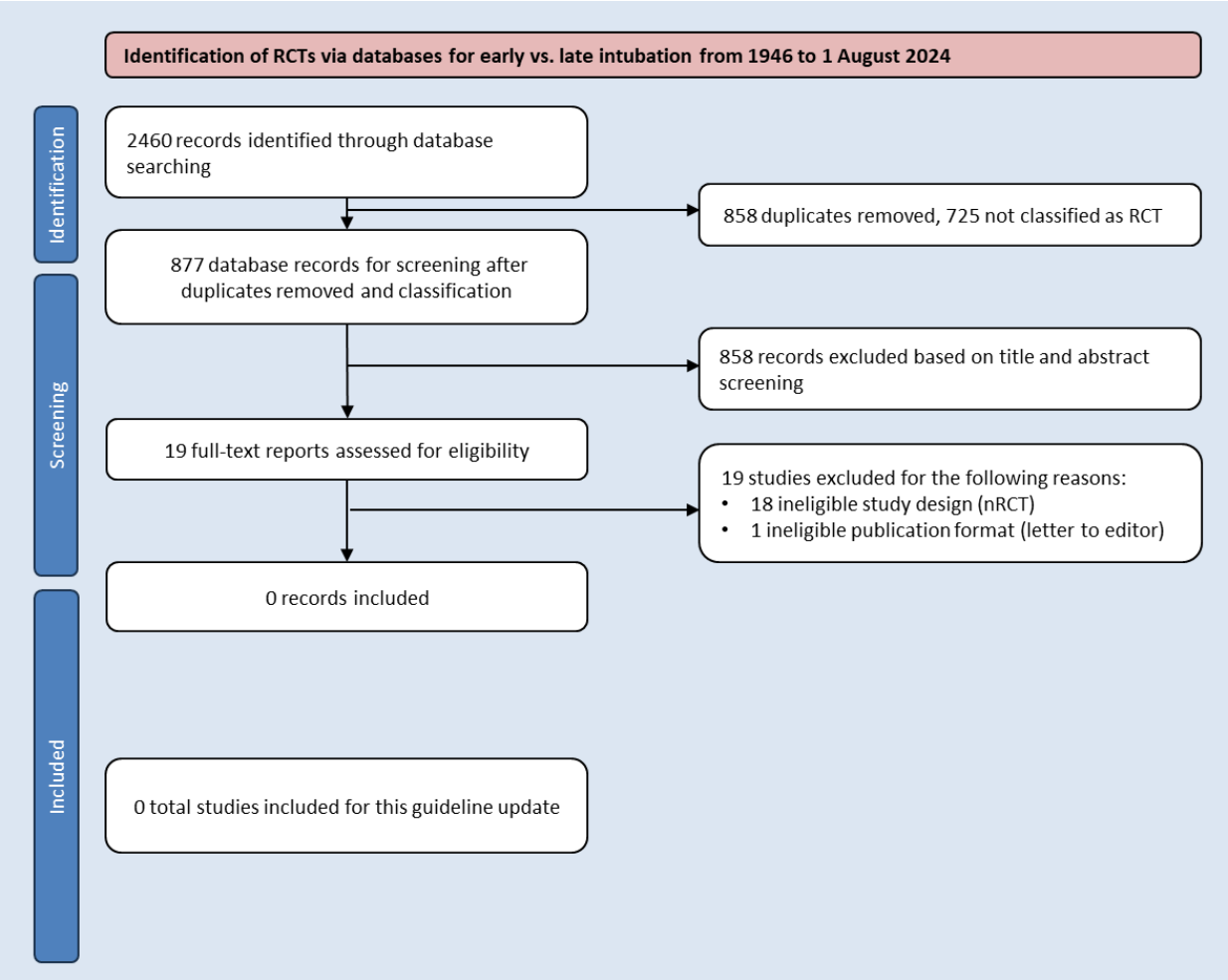
	Exp: 26.1% Ctrl: 10.2% < 200: Exp: 60.3% Ctrl: 86%				

5.16.5 Studienselektion: Flow Chart

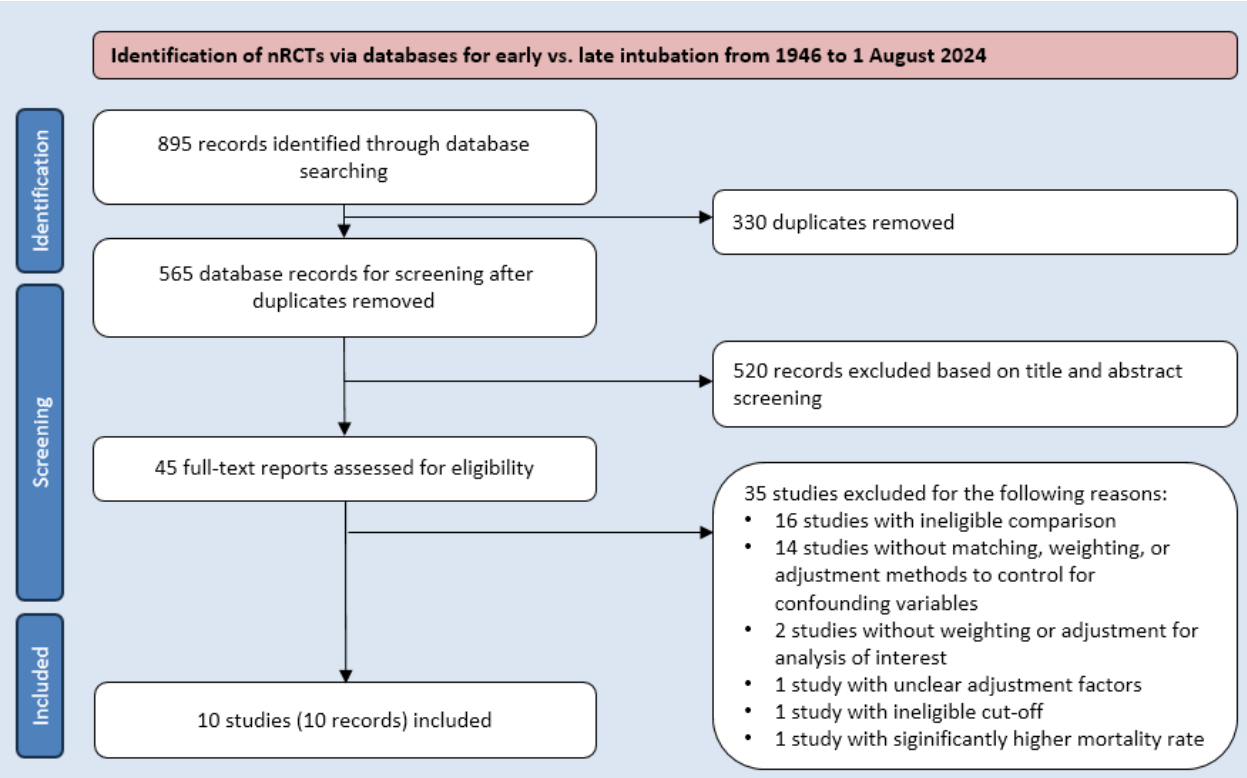
Flowchart für die SR-Recherche



Flowchart für die RCT-Recherche



Flowchart für die nRCT-Recherche



5.16.6 Literaturrecherche

5.16.6.1 *Suche nach SRs*

Date of search for all databases: 02.08.2024	
Database/Register	**Search**
Medline ALL (via OVID) 1946 to July 25, 2023	**22**
EPISTEMONIKOS	**9**
Cochrane Database of Systematic Reviews; Issue 08, 2024 (via Cochrane Library)	**1**
Total	**32**
Total (after deduplication)	**25**

Relevante SRs: ("36517555" or "34540642").ui.

Suchstrategien

MEDLINE (via OVID) ALL 1946 to August 01, 2024

#	Searches
1	SARS-CoV-2/ or COVID-19/

2 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab.

3 or/1-2

4 Respiratory Distress Syndrome/ or Critical Illness/

5 (acute adj2 respirator*).ti,ab.

6 respirator* distress syndrom*.ti,ab.

7 (ARDS or severe respirator* or critical illnes* or criticall* ill).ti,ab.

8 or/4-7

9 exp intubation, intratracheal/

10 (ventilat* or intubat*).ti.

11 or/9-10

12 exp Time-to-Treatment/ or Time Factors/

13 (earl* or hour* or time* or timing*).ti,ab.

14 or/12-13

15 3 and 8 and 11 and 14

16 cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw. or systematic review.pt.

17 15 and 16

18 limit 17 to yr="2020 -Current"

19 remove duplicates from 18

20 ("36517555" or "34540642").ui.

21 19 and 20

Search line 16: (Wong 2006 – systematic reviews filter – high specificity, 90,2 sens / 98,4 spec) Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc. 2006;94(4):451-5.

Epistemonikos

Advanced search and filtered by publication type: systematic review; publication year: 2020 - 2024

(title:(("2019 nCoV" OR 2019nCoV OR coronavir* OR coronovir* OR COVID OR COVID19 OR HCoV* OR "nCov 2019" OR "SARS CoV2" OR "SARS CoV 2" OR SARSCoV2 OR "SARSCoV 2" OR "severe acute respiratory syndrome coronavirus 2" OR omicron* OR omikron*)) OR abstract:(("2019 nCoV" OR 2019nCoV OR coronavir* OR coronovir* OR COVID OR COVID19 OR HCoV* OR "nCov 2019" OR "SARS CoV2" OR "SARS CoV 2" OR SARSCoV2 OR "SARSCoV 2" OR "severe acute respiratory syndrome coronavirus 2" OR omicron* OR omikron*)))

AND (title:("acute respiratory" OR "respiratory distress syndrom" OR ARDS OR "severe respiratory" OR "critical illness" OR "critically ill") OR abstract:("acute respiratory" OR "respiratory distress syndrom" OR ARDS OR "severe respiratory" OR "critical illness" OR "critically ill"))

AND title:(ventilat* OR intubat*)

AND (title:(earl* OR hour* OR time* OR timing*) OR abstract:(earl* OR hour* OR time* OR timing*))

Cochrane Database of Systematic Reviews (via Cochrane Library); Issue 08, July 2024

ID	Search
#1	[mh "Coronavirus Infections"] or [mh Coronavirus] or [mh "SARS-CoV-2"] or [mh "COVID-19"]
#2	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or anti-flu* or anti-influenza* or antiflu* or antinfluenza*):TI,AB,KW
#3	((corona* or corono*) NEAR/1 (virus* or viral* or virinae*)):TI,AB,KW
#4	"severe acute respiratory syndrome coronavirus 2":TI,AB,KW
#5	#1 OR #2 OR #3 OR #4
#6	[mh "Respiratory Distress Syndrome"]
#7	[mh "Critical Illness"]
#8	(acute NEAR/2 respirator*):TI,AB
#9	respirator* distress syndrom*:TI,AB
#10	(ARDS or severe respirator* or critical illnes* or criticall* ill):TI,AB
#11	#6 OR #7 OR #8 OR #9 OR #10
#12	[mh "intubation, intratracheal"]
#13	(ventilat* OR intubat*):TI
#14	#12 OR #13
#15	[mh "Time-to-Treatment"]
#16	[mh "Time Factors"]
#17	(earl* or hour* or time* or timing*):TI,AB,KW
#18	#15 OR #16 OR #17
#19	#5 AND #11 AND #14 AND #18

5.16.6.2 *Suche nach RCTs*

Date of search for all databases: 02.08.2024	
Database/Register	**Search**
Medline ALL (via OVID) 1946 to August 01, 2024	**959**
CENTRAL (via Cochrane Library) Issue 07, 2024	**589***
Scopus	**912**
Total	**2460**
Total (after deduplication)	**1602**
Total (after classified)	**877**

*Records of ICTRP and CT.gov wurden ausgeschlossen.

Suchstrategien

MEDLINE (via OVID) ALL 1946 to August 01, 2024

Search Strategy:

#	Searches
1	SARS-CoV-2/ or COVID-19/
2	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab.
3	or/1-2
4	Respiratory Distress Syndrome/ or Critical Illness/
5	(acute adj2 respirator*).ti,ab,kf.
6	respirator* distress syndrom*.ti,ab,kf.
7	(ARDS or severe respirator* or critical illnes* or criticall* ill).ti,ab,kf.
8	or/4-7
9	exp intubation, intratracheal/
10	(ventilat* or intubat*).ti,ab.
11	or/9-10
12	exp Time-to-Treatment/ or Time Factors/
13	(earl* or hour* or time* or timing*).ti,ab.
14	or/12-13
15	3 and 8 and 11 and 14
16	exp randomized controlled trial/
17	controlled clinical trial.pt.
18	drug therapy.fs.
19	(randomi?ed or placebo or randomly or trial or groups).ab.
20	or/16-19
21	exp animals/ not humans.sh.
22	20 not 21
23	15 and 22
24	limit 23 to yr="2020 -Current"
25	remove duplicates from 24

#16 - #22: Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated October 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh "Coronavirus Infections"] or [mh Coronavirus] or [mh "SARS-CoV-2"] or [mh "COVID-19"]

#2 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or anti-flu* or anti-influenza* or antiflu* or antinfluenza*):TI,AB,KW

#3 ((corona* or corono*) NEAR/1 (virus* or viral* or virinae*)):TI,AB,KW

#4 "severe acute respiratory syndrome coronavirus 2":TI,AB,KW

#5 #1 OR #2 OR #3 OR #4

#6 [mh "Respiratory Distress Syndrome"]

#7 [mh "Critical Illness"]

#8 (acute NEAR/2 respirator*):TI,AB,KW

#9 respirator* distress syndrom*:TI,AB,KW

#10 (ARDS or severe respirator* or critical illnes* or criticall* ill):TI,AB,KW

#11 #6 OR #7 OR #8 OR #9 OR #10

#12 [mh "intubation, intratracheal"]

#13 (ventilat* OR intubat*):TI,AB,KW

#14 #12 OR #13

#15 [mh "Time-to-Treatment"]

#16 [mh "Time Factors"]

#17 (earl* or hour* or time* or timing*):TI,AB,KW

#18 #15 OR #16 OR #17

#19 #5 AND #11 AND #14 AND #18

Scopus

TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS ("acute respiratory" OR "respiratory distress syndrom" OR ards OR "severe respiratory" OR "critical illness" OR "critically ill")

AND TITLE-ABS (ventilat* OR intubat*)

AND TITLE-ABS (earl* OR hour* OR time* OR timing*) AND TITLE-ABS (random* OR placebo OR trial OR groups)

AND PUBYEAR > 2019 AND PUBYEAR < 2025

AND (LIMIT-TO (DOCTYPE , "ar"))

5.16.6.3 *Suche nach nonRCTs*

Date of search for all databases: 07.08.2024	
Database/Register	**Search**
Medline ALL (via OVID) 1946 to August 06, 2024	**457**

Scopus	**438**
Total	**895**
Total (after deduplication)	**565**

Suchstrategien

Ovid MEDLINE(R) ALL 1946 to August 06, 2024

#	Searches
1	SARS-CoV-2/ or COVID-19/
2	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or "severe acute respiratory syndrome coronavirus 2" or omicron* or omikron*).ti,ab.
3	or/1-2
4	Respiratory Distress Syndrome/ or Critical Illness/
5	(acute adj2 respirator*).ti,ab,kf.
6	respirator* distress syndrom*.ti,ab,kf.
7	(ARDS or severe respirator* or critical illnes* or criticall* ill).ti,ab,kf.
8	or/4-7
9	exp intubation, intratracheal/ and (exp Time-to-Treatment/ or Time Factors/)
10	(mechanic* adj2 ventilat* adj8 (earl* or hour* or time* or timing*)).ti,ab,kf.
11	(mechanic* adj2 respirat* adj8 (earl* or hour* or time* or timing*)).ti,ab,kf.
12	(intubat* adj8 (earl* or "24 h" or hour* or time* or timing*)).ti,ab,kf.
13	or/9-12
14	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
15	((control and study) or group* or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp.
16	or/14-15
17	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
18	hi.fs. or case report.mp.
19	or/17-18
20	16 not 19
21	3 and 8 and 13 and 20
22	limit 21 to yr="2020 -Current"
23	remove duplicates from 22

#14 - #20: controlled NRS filter – high sensitivity, 92.17 sens Waffenschmidt, Siw et al. “Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE.” Research synthesis methods vol. 11,5 (2020): 617-626. doi:10.1002/jrsm.1425

Scopus

TITLE-ABS (covid OR covid19 OR "SARS-CoV-2" OR "SARS-CoV2" OR sarscov2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "novel coronavirus infection" OR "novel corona virus infection" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

AND TITLE-ABS ((acute W/2 respirator*) OR "respirator* distress syndrom*" OR ards OR "severe respirator*" OR "critical illnes*" OR "criticall* ill")

AND TITLE-ABS ((mechanic* W/2 ventilat* W/8 (earl* OR hour* OR time* OR timing*)) OR (mechanic* W/2 respirat* W/8 (earl* OR hour* OR time* OR timing*)) OR (intubat* W/8 (earl* OR "24 h" OR hour* OR time* OR timing*)))

AND TITLE-ABS ((control AND study) OR group* OR (time AND factors) OR cohort OR program OR "comparative stud*" OR "evaluation studies" OR survey* OR follow-up* OR ci)

AND PUBYEAR > 2019 AND PUBYEAR < 2025

AND (LIMIT-TO (DOCTYPE , "ar"))

6 Darlegung von Interessen und Umgang mit Interessenkonflikten

Im Folgenden sind die Interessenerklärungen (Stand Dezember 2024) als tabellarische Zusammenfassung dargestellt sowie die Ergebnisse der Interessenkonfliktbewertung und Maßnahmen, die nach Diskussion der Sachverhalte von der der LL-Gruppe beschlossen und im Rahmen der Konsensuskonferenz umgesetzt wurden. Folgende Kriterien wurden angewendet:

- Geringe Interessenkonflikte: Einzelne Vorträge für Firmen, zu deren Produkten ein thematischer Bezug zur Leitlinie bestehen.
    - Konsequenz: Keine alleinige Leitungsfunktion (Koordination/AG) – Peer.
- Moderate Interessenkonflikte: Advisory Board Tätigkeit für Firmen, zu deren Produkten ein thematischer Bezug zur Leitlinie bestehen oder Managementverantwortung für industriefinanziert Studie.
    - Konsequenz: Keine Teilnahme an Abstimmungen zum Thema oder Doppelabstimmung
- Hohe Interessenkonflikte: Relevanter Aktienbesitz von Firmen zu deren Produkten ein thematischer Bezug zur Leitlinie bestehen oder Anstellung bei der Industrie.
    - Konsequenz: keine Teilnahme an Diskussion und Abstimmung zum Thema.

Als Schutzfaktoren werden für diese Leitlinie die unabhängige Evidenzaufarbeitung durch ein Methodenteam und die neutrale Moderation geltend gemacht.

Leitlinienkoordination: Kluge, Stefan; Peer: Skoetz, Nicole (LL-Methodik)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
Prof. Dr. Bausewein, Claudia	Nein	Nein	diverse Vorträge für Krankenhäuser, Vereine, nicht pharmazeutische Industrie	Nein	Universitätsklinikum Köln, Universität Göttingen HelmHoltz Zentrum München IBE München, King's College London, Nein, Uni Erlangen Uni Halle, Nein, Nein, Nein	Nein	Mitglied: Präsidentin der Deutschen Gesellschaft für Palliativmedizin, Mitglied: Co-Koordinatorin S3 Leitlinie Palliativmedizin für Patienten mit nicht heilbaren Krebserkrankungen, Wissenschaftliche Tätigkeit: Betreuung von Patienten mit Atemnot aufgrund fortgeschrittener Erkrankungen, Wissenschaftliche Tätigkeit: Komplexität und Outcome Messung in der Palliativversorgung, Wissenschaftliche Tätigkeit: Palliativversorgung in Pandemiezeiten, Wissenschaftliche Tätigkeit: Gezielte Sedierung am Lebensende, Wissenschaftliche Tätigkeit: Arzneimitteltherapie in der Palliativmedizin, Klinische Tätigkeit: Palliativversorgung, Beteiligung an Fort-/Ausbildung: Leitung der Christophorus Akademie für Palliativmedizin an der Klinik für Palliativmedizin LMU Klinikum München	Keine
Prof. Dr. Berlit, Peter	Norwegischer Wissenschaftsrat	Nein	Nordrheinische Ärzteakademie	Autor und Herausgeber von mehreren Lehrbüchern	Nein	Nein	Wissenschaftliche Tätigkeit: Vaskulitis Schlaganfall bei jungen Patienten Peripheres Nervensystem Neuroimmunologie COVID-19, Beteiligung an Fort-/Ausbildung: DGN-Zeitschriften DGN-Fortbildungen DGN-Jahreskongress DGN-Facharzttraining Neurologie	COI: keine: keine
Prof. Dr. Bracht, Hendrik	Nein	Philips Medical Advisory Board, Sedana Medical Advisory Board	Nein	Nein	Nein	Nein	Mitglied: Wissenschaftlicher Arbeitskreis Intensivmedizin DGAI Schriftführer, Mitglied: Forschungsgruppenleiter TIFOnet Immunsystem der DGAI, Mitglied: European Society of Intensive Care Medicine (ESICM) Chair Workgroup Antibiotic Use, Mitglied: European Society of Clinical Microbiology and Infectious Diseases (ESMID)	Advisory Board mit Thema Medizintechnik/inhalative Sedierung, kein Themenbezug zu COVID-19 Therapie COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							Secretary Study Group Critically ill patients, Wissenschaftliche Tätigkeit: Sepsis, septischer Schock Infektionsmanagement Management von Delir und Sedierung Theraopeutisches Drugmonitoring, Klinische Tätigkeit: Intensivmedizin Klinische Akut- und Notfallmedizin, Beteiligung an Fort-/Ausbildung: keine, Persönliche Beziehung: keine	
PD Dr. Brandt, Christian	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: Verbund für angewandte Hygiene (VAH) e.V. (Vorstandsmitglied - für DGHM), Wissenschaftliche Tätigkeit: Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM) e.V. - Sprecher der Ständigen Arbeitsgemeinschaft "Allgemeine und Krankenhaushygiene", Klinische Tätigkeit: Universitätsklinikum Frankfurt (AöR) der Goethe-Universität, Berater für Bauhygiene, Beteiligung an Fort-/Ausbildung: Landeskrankenhaus AöR, Andernach (Fachkrankenhaus für Neurologie und Psychiatrie) mit mehreren Standorten in Rheinland-Pfalz. In diesem Rahmen auch Vorträge.	COI: keine: keine
Prof. Dr. Böttiger, Bernd W.	C. R. Bard GmbH TTM in den Guidelines15 , C. R. Bard GmbH TTM 2018 ⁄ was kommt auf uns in der Praxis zu?	Nein	McMaster International Review Course in International Medicine How can we improve survival after cardiac arrest: focus on postresuscitation care, Laerdal Medical GmbH Webinar KIDS SAVE LIVES,	Georg Thieme Verlag KG Mitautor Kapitel Lungenembolie, Georg Thieme Verlag KG Mitautor Kapitel Reanimation, MWV Medizinisch Wissenschaftliche	Nein	Nein	Mitglied: Bernd W. Böttiger ist Schatzmeister und Immediate Past Director Science and Research des European Resuscitation Council (ERC); Vorstandsvorsitzender des Deutschen Rates für Wiederbelebung / German Resuscitation Council (GRC), Mitglied im Präsidium der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI), Gründer der Deutschen Stiftung Wiederbelebung, Bundesarzt des Deutsches Roten Kreuz (DRK), , Wissenschaftliche Tätigkeit: Herz-Kreislaufstillstand	Berater-/Gutachtertätigkeit, Vortragstätigkeit zum Thema Wiederbelebung, kein thematischer Bezug zu COVID-19 Therapie COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			Telefonreanimation, Cardiac-Arrest-Zentren et al., deutscher und europäischer Reanimationskongress im September 2017 in Freiburg, Forum für medizinische Fortbildung FomF GmbH Vortrag Reanimationsleitlinien, Forum für medizinische Fortbildung FomF GmbH Wissenschaftliche Leitung, Vorsitz, Moderation, Vorträge Kardiopulmonale Reanimation 2017 / KIDS SAFE LIVES /NAWIB, Robert-Müller-Stiftung Vortrag Update Wiederbelebung, VDBW e.V. Verband Deutscher Betriebs- und Werksärzte e.V Vortrag	Verlagsgesellschaft mbH Co. KG Co-Herausgeber DIVI Jahrbuch 2019/2020, Deutscher Ärzteverlag GmbH Mitherausgeber Zeitschrift DIVI				

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			Laienreanimation • welchen Beitrag Betriebsärzte leisten können, Zoll Medical Deutschland Vortrag UPDATE 2017 • ERC Resuscitation Guidelines 2015 • Ein starkes Statement zum Targeted Temperature Management, Baxalta Deutschland GmbH Vorsitz Gerinnungsstörungen in der Intensivmedizin: komplexe Fälle schnell diagnostiziert, Forum für medizinische Fortbildung FomF GmbH Vortrag Reanimationsleitlinien, Klinikum der Stadt Ludwigshafen Vortrag Cardiac-Arrest-Zentren					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			• Tool or Toy?, GS Elektromedizinische Geräte G. Stemple GmbH Vorsitz und Vortrag CPR per App • Technologien retten Leben. Leben retten: vom Laien bis zur Intensivstation • Der Erfolg ist Gemeinschaftssache, McMaster International Review Course in International Medicine Vortrag Cardiac arrest and resuscitation: 2018 update., Forum für medizinische Fortbildung FomF GmbH Wissenschaftliche Leitung, Vorsitz, Moderation, Vorträge Kardiopulmonale Reanimation / KIDS SAFE LIVES / und Postreanimationsversorgung, C. R.					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			Bard GmbH Moderation, Vorsitz, Vorträge Klinische und ökonomische Evidenz für nicht-invasives, Bio-Feedback gesteuertes Temperaturmanagement., Zoll Medical Deutschland+ Vorsitz Temperaturmanagement ? Ja, aber TTM1, TTM2 oder TTH48?!, Novartis Pharma GmbH Vortrag Cardiac-Arrest-Zentren – Tool or toy? Warum immer noch 2 Jumbojets pro Tag abstürzen., C. R. Bard GmbH Beratung, Moderation und Vorträge TTM Teaching Course – From Proof to Practice, C. R. Bard GmbH Beratung und Moderation					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			TTM 2019 • the circle of survival, Forum für medizinische Fortbildung FomF GmbH Wissenschaftliche Leitung, Vorsitz, Moderation, Vorträge Kardiopulmonale Reanimation und Postreanimationsphase 2019 • KSL /WRAH /GRC / ERC / ILCOR et. Al., Lücke Kongress GmbH Vortrag Outcome nach Herzstillstand, Philips GmbH Market DACH Vortrag Leben retten durch Frühwarnsysteme. Wie weit sind Krankenhäuser und Technik? • Wie umgehen mit unterwünschten Ereignissen auf Normalstation: Das sagen die Leitlinien, Lücke Kongress GmbH Vortra					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			g KIDS SAVE LIVES schnell vor Ort mit Mut, Zoll Medical Deuschland Vortag Epidemiology of cardiac arrest, C. R. Bard GmbH Vortrag TTM Symposium in Bremen, Forum für medizinische Fortbildung FomF GmbH Moderation/Vortrag Kadiopulmonale Reanimation und Porsteanimations-phese Udate im Jahr der neuen Leitlinien 2020 , mekontor GmbH Co. KG, Akademie für Ärztliche Fortbildung – Ärzteakademie c/o Asklepios Klinik St. Georg, Bard Limited , Forum für medizinische Fortbildung – FomF GmbH, Bard Limited, Springer Medien Verlag GmbH,					

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
			C.T.I GmbH, Lücke Kongress GmbH, Zoll Medical Deutschland GmbH, Forum für medizinische Fortbildung – FomF GmbH, Forum für medizinische Fortbildung – FomF GmbH, Zoll Medical Deutschland GmbH, Forum für medizinische Fortbildung – FomF GmbH, Lücke Kongress GmbH, C.R. Bard GmbH, Beiersdorf AG, Barmherzige Brüder, Klinikum St. Elisabeth, Straubing, Becton Dickinson S.A.U., Ärztekammer Nordrhein, Fundacja Polski Instytut Evidence Based Medicine, Forum für medizinische Fortbildung FomF GmbH, Nein					
Cryns, Nora	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: systematische Reviews und Evidenz-basierte Leitlinienerstellung	COI: keine: keine
Faske, Amon	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: Nein, Wissenschaftliche Tätigkeit: Nein, Klinische Tätigkeit: Nein, Beteiligung an Fort-/Ausbildung: Nein,	COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							Persönliche Beziehung: Nein	
Goldkuhle, Marius	-	-	-	Keine Veröffentlichungen mit Bezug zur Leitlinie	Keine Forschungsvorhaben mit Bezug zur Leitlinie	-	Mitglied: Deutsches Netzwerk Evidenz-basierte Medizin e.V., Wissenschaftliche Tätigkeit: Methodik von Meta-Analysen, GRADE, Cochrane Reviews zu Hämato-Onkologischen Fragestellungen, Klinische Tätigkeit: -, Beteiligung an Fort-/Ausbildung: -, Persönliche Beziehung: -	COI: keine: keine
Haase, Reiner	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Hirsch, Caroline	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Prof. Dr. Hoffmann, Florian	---	---	PAEDSIM e.V. - Simulationstraining für Kindernotfälle	Kindernotfall-ABC (Springer) Kinderchrirugie für Pädiater Springer)	Nein	Nein	Mitglied: Mitgliedschaft /Funktion in Interessenverbänden - Schriftführer der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI) und Leiter der Sektion Pädiatrische Intensiv- und Notfallmedizin - Leiter der Arbeitsgruppe Paediatric Life Support des German Resuscitation Councils (GRC) - Mitglied Paediatric science and educational committee (SEC) des European Resuscitation Councils (ERC) - Vorstandsmitglied der Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin (GNPI), Wissenschaftliche Tätigkeit: Optimierung der Versorgungsqualität kritisch kranker Kinder, pädiatrische Reanimation, Kinderintensivmedizin, Klinische Tätigkeit: Oberarzt interdisziplinäre Kinderintensivstation (100%), Beteiligung an Fort-/Ausbildung: PAEDSIM e.v. Teamtraining für Kindernotfälle (pädiatrische Simulationskurse), Persönliche Beziehung: nein	COI: keine: keine
Dr. Iannizzi, Claire	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: Methodische Expertise, Meta-Analyen,	COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							systematische Übersichtsarbeiten	
Prof. Dr. Janssens, Uwe	Keine	Keine	Keine	Keine	Keine	Keine, Nein	Mitglied: Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin; Generalsekretär, Mitglied: Deutsche Gesellschaft für interdisziplinäre Intensivmedizin und Notfallmedizin (DIVI); Präsident / PAst Präsident / Generalsekretär, Mitglied: Deutsche Gesellschaft für Innere Medizin; Mitglied, Mitglied: Deutsche Gesellschaft für Kardiologie; Mitglied, Wissenschaftliche Tätigkeit: Intensivmedizin; Ethik, Klinische Tätigkeit: Kardiologie/Innere Medizin/Intensivmedizin, Beteiligung an Fort-/Ausbildung: DIVI/DGIIN/DGIM, Persönliche Beziehung: keine	COI: keine: keine
Dr. Jarczak, Dominik	nein	nein	nein	nein	nein	nein	Mitglied: Mitglied: DGIIN, DIVI, Wissenschaftliche Tätigkeit: nein, Klinische Tätigkeit: nein, Beteiligung an Fort-/Ausbildung: nein, Persönliche Beziehung: nein	COI: keine: keine
Prof. Dr. Karagiannidis, Christian	Nein	Bayer AG , Xenios	Nein	Nein	Nein	Nein	Mitglied: Präsident DGIIN	Extrakorporale CO2 Elimination, Pegyliertes Adrenomedullin bei ARDS COI: moderat: Stimmenthaltung
Dr. Kersten, Alexander	Jafron Biomedical	Gilead	Edwards, Sedana Medical, Astra-Zeneca	Nein	Jafron Biomedical	Nein	Mitglied: DGK/ESC, Mitglied: DGIIN, Mitglied: DIVI, Mitglied: ESICM, Wissenschaftliche Tätigkeit: Sepsis, ARDS, Klinische Tätigkeit: Intensivmedizin Kardiologie, Pneumologie, ECMO, Persönliche Beziehung: n/a	Advisoryboardtätigkeit Medikamentöse Therapie Remdesivir, Vortragstätigkeit für Astra Zeneca COI: moderat: Stimmenthaltung
Prof. Dr. med. Kluge, Stefan	Nein, Nein	Fresenius, Gilead, MSD, Pfizer, ADVITOS	Biotest, Fresenius, Gilead, MSD, Pfizer, Zoll, Daiichi Sankyo, Mitsubishi Tanabe Pharma ,	Nein	Daiichi Sankyo, Cytosorbents	Nein	Nein	Advisory-Board-Tätigkeit Medikamentöse Therapie, ggf Prophylaxe: Remdesivir, Paxlovid, Studienverantwortung für Antikoagulation Medikation/ggf. Prophylaxe

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			Shionogi					COI: moderat: Stimmenthaltung
Prof. Krawczyk, Marcin	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: Hapatologie, Genetik, Klinische Tätigkeit: Gastroenterologie, Hepatologie	COI: keine: keine Interessenerklärung zur Nachbearbeitung COI: noch nicht bewertet: keine
Kreuzberger, Nina	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: keine, Wissenschaftliche Tätigkeit: systematische Reviews Hämatologie, Onkologie und COVID-19; Leitlinienkoordination (Hodgkin Lymphom), Klinische Tätigkeit: keine, Beteiligung an Fort-/Ausbildung: keine, Persönliche Beziehung: keine	COI: keine: keine
Prof. Dr. Langer, Florian	LEO Pharma , Aspen	LEO Pharma, Bristol-Myers Squibb, Pfizer, Bayer, CSL Behring, SOBI, Roche, BioMarin, Chugai, Shire/Takeda, Alexion, Mitsubishi Tanabe Pharma , AstraZeneca, BioNTech	LEO Pharma, Aspen , Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Bayer, SOBI, Grifols, Shire/Takeda, Alexion, Werfen	Nein	Nein	Keine	Mitglied: Sekretär im Vorstand der Gesellschaft für Thrombose- und Hämostaseforschung (GTH) e.V. , Mitglied: Mitglied der Deutschen Gesellschaft für Hämatologie und Onkologie (DGHO) e.V. , Mitglied: Mitglied der Gesellschaft für Thrombose- und Hämostaseforschung (GTH) e.V. , Mitglied: Mitglied der International Society on Thrombosis and Haemostasis (ISTH) , Mitglied: Mitglied im Berufsverband der Deutschen Hämostaseologen (BDDH) e.V. , Mitglied: Mitglied in der Interessengemeinschaft Hämophiler (IGH) e.V. , Mitglied: Mitglied in der Deutschen Hämophiliegesellschaft (DHG) e.V. , Wissenschaftliche Tätigkeit: Grundlagenwissenschaftliche und klinische Originalpublikationen und Übersichtsarbeiten zu den Themen Thrombose, Hämostase und Vaskuläre Biologie; Co-Autor der GTH Empfehlungen zur Thromboseprophylaxe bei COVID-19 , Klinische Tätigkeit: Leiter der Gerinnungsambulanz und des	Antikoagulation mit Faktor Xa-Hemmern COI: moderat: Stimmenthaltung Prophylaktische und therapeutische orale Antikoagulation/Antikoagulation mit niedermolekularen Heparinen. COI: moderat: Stimmenthaltung

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							Hämophiliezentrums am UKE, hämostaseologischer Konsiliardienst , Beteiligung an Fort-/Ausbildung: Ausrichter (wissenschaftliche Leitung) des jährlich stattfindenden Eppendorfer Gerinnungssymposiums, Co-Kongresspräsident der GTH-Jahrestagung in Bremen 2020 , Persönliche Beziehung: Keine	
Dr. Lund, Natalie	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Dr. Malin, Jakob	MAPLE Health Group, MAPLE Health Group	ATRIVA Therapeutics GmbH, Gilead Sciences, Astra Zeneca, Gilead Sciences, Gilead Sciences, Astra Zeneca, Astra Zeneca, Gilead Sciences	Gilead Sciences, Janssen Cilag, Gilead Sciences, Gilead Sciences	Nein	NIAID / NIH, NIAID/NIH	keine	Mitglied: Deutsche Gesellschaft für Innere Medizin Deutsche Gesellschaft für Infektiologie, Wissenschaftliche Tätigkeit: Therapieansätze bei COVID-19 Antimikrobielle Effekte von small molecule Lipid II Binders HIV , Klinische Tätigkeit: Klinische Infektiologie , Beteiligung an Fort-/Ausbildung: nein, Persönliche Beziehung: nein	Medikamentöse Therapie von COVID-19: Remdesivir, Medikamente von Janssen Cilag, Impfstoff (Astra Zeneca) COI: moderat: Stimmenthaltung
Prof. Dr. med. Marx, Gernot	BBraun Melsungen AG, Adrenomed, 4TEEN4	Nein	Nein	Nein	Nein	Clinomic (Gründer)	Mitglied: DIVI (Präsident elct, Präsident), DGAI (Mitglied des engeren Präsidiums, DG Telemed (Vorstandsvorsitzender), Wissenschaftliche Tätigkeit: Sepsis, Volumentherapie, Telemedizin	Kein Themenbezug zur Leitlinie COI: keine: keine
Monsef, Ina	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Prof. Dr. Müller, Oliver	Europäische Kommission, Schweizer Nationalfonds (SNF), Deutsche Forschungsgemeinschaft (DFG)	Pfizer/BMS, Bayer	Pfizer/BMS, Bayer, Novartis, Daiichi-Sankyo, Berlin-Chemie	Servier	Rheacell, Anthos Therapeutics	Dinaqor AG	Mitglied: Deutsche Gesellschaft für Angiologie, Vorstandsmitglied , Mitglied: Deutsche Gesellschaft für Kardiologie, Nukleusmitglied AG2 und AG40, Mitglied: Gesellschaft für Thrombose und Hämostaseforschung, Mitglied ohne spez. Funktion, Wissenschaftliche Tätigkeit: pAVK, Wissenschaftliche Tätigkeit: Thrombose und Gerinnungsstörungen, Marfan-Syndrom, Kardiomyopathien, Herzinsuffizienz, Klinische Tätigkeit: Angiologie,	Vortrags- und Advisoryboard-Tätigkeit für Pharmazeutische Industrie in Bezug auf Antikoagulation: Prophylaxe/Therapie COI: moderat: Stimmenthaltung

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							Herzinsuffizienz	
Dr. med. Nehls, Wiebke	Nein	Nein	verschiedene Bildungsakademien im Palliativbereich	Nein	Nein	Nein	Mitglied: Deutsche Gesellschaft für Palliativmedizin - Vorstandsmitglied (Mandatsträger für diverse LL) , Wissenschaftliche Tätigkeit: verschiedene pneumologische und palliativmed. Fachzeitschriften, Klinische Tätigkeit: Palliativmedizin und Geriatrie	COI: keine: keine
Dr. med. Nothacker, Monika	keine bezahlten Tätigkeiten	- Versorgungsforschungsprojekt INDiQ (Messung von Indikationsqualität aus Routinedaten - Vergütung wie angegeben - Steuergruppe Nationaler Krebsplan keine Vergütung, IQTIG	Berlin School of Public Health	Nein	German Cancer Aid , Network University Medicine COVID-19, BMG, Network University Medicine for Pandemic Preparedness 2.0 , G-BA Innovationfund	no	Mitglied: - German Network Evidence Based Medicine (member) - German Cancer Society (member until 12/2020) - Guidelines International Network/GRADE Working Group (member), Wissenschaftliche Tätigkeit: Guidelines and Guideline Methodology, Methodology of guidelines based performance measures/quality indicators, Klinische Tätigkeit: no clinical activity or clinical research, Beteiligung an Fort-/Ausbildung: Guideline seminars within Curriculum for guideline developers in Germany , Persönliche Beziehung: no	COI: keine: keine
Prof. Dr. Pfeifer, Michael	Charite Berlin	Boehringer Ingelheim	Boehringer Astra Glaxo Novartis	Nein	Boehringer Janssens	Nein	Mitglied: DGP DGIM DGK, BDI, BDP, ERS, ATS , Wissenschaftliche Tätigkeit: Interstitielle Lungenerrkrankungen, pulmoanle Hypertonie, COPD , Klinische Tätigkeit: Pneumologie und Intensivmedizin , Beteiligung an Fort-/Ausbildung: Pneumoupdate Jahrestagung DGP und DGIM Pneumologisches Kolloqium Regensburg , Persönliche Beziehung: nein	COI: keine: keine
Prof. Dr. Rabe, Klaus F.	Sanofi Regeneron, Boehringer Ingelheim	AstraZeneca, GSK	Novartis, Chiesi Pharmaceuticals, Roche Pharma, Orion Menarini,	Astra Zeneca	Nein, TU München	Nein	Mitglied: DGP, wiss. Beirat, Wissenschaftliche Tätigkeit: Atemwegserkrankungen, Klinische Tätigkeit: Pneumologie	Berater-/Gutachtertätigkeit für Firmen, die Covid-19 Impfstoffe herstellen. Öffentlich geförderte Forschung für die Therapie von

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			Berlin Chemie					COVID-19 ausgelösten Lungenschäden. Kein aktueller thematischer Bezug COI: keine: keine
Reis, Stefanie	Nein	Nein	Nein	Nein	Nein	Nein	Nein	COI: keine: keine
Dr. med. Schorrlepp, Marcel	coliquio GmbH, colquio GmbH	wikoneckt GmbH fresh up Hausarzt Medizin	wikoneckt GmbH fresh up Hausarzt Medizin	keine	keine	keine	Mitglied: DGIM: Sprecher AG Hausärztliche Internisten BDI: Mitglied, Klinische Tätigkeit: Hausärtlicher Internist, Beteiligung an Fort-/Ausbildung: keine, Persönliche Beziehung: keine	COI: keine: keine
Prof. Dr. Schälte, Gereon	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied: DGAI BDA TREMA ESA NAEMT, Wissenschaftliche Tätigkeit: Inflammation Biomarker Airwaymanagement Empfehlungen Atemwegsmanagement bei CoViD-19 Notfallmedizin, Klinische Tätigkeit: Kardioanästhesie Kinderanästhesie ECMO Notfallmedizin	COI: keine: keine
Prof. Dr. med. Skoetz, Nicole	Cochrane, Senior Editor	Scientific Committee Cochrane (bis 03.2023), Editorial Board, GRADE Guidance Group (ab 01.2023)	AWMF	Nein	BMBF, Deutsche Krebshilfe, WHO, Cochrane, DFG, BMG, g-BA	Nein	Mitglied: EbM Netzwerk, Vorstand seit 03.2023 (vorher Mitglied) DGHO, Mitglied WHO Collaborating Center, Leitung (ab 01.2023) GRADE Guidance Group Member (seit 02.2023), vorher Mitglied, Wissenschaftliche Tätigkeit: Systematic Reviews, Cochrane Reviews, GRADE Methodik, Methodik living reviews	COI: keine: keine
Prof. Dr. med. Specker, Christof	Gemeinsamer Bundesausschuss	AbbVie, Boehringer, Novartis, Otsuka, GSK	AbbVie, Boehringer, GSK, Lilly, MSD,	KOOP. RHEUMAZ.R.-R.EV, MED	Nein	Nein	Mitglied: DGRh BDI RHZ-Rhein-Ruhr	Vortragstätigkeiten für Firmen, die COVID-19 Medikamente herstellen.

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			Novartis, Otsuka, Pfizer, Sanofi, Takeda, StreamedUP, AstraZeneca, Medac, Abbvie, Hexal, Rheumaakademie, Rheumaakademie, Lilly	UPDATE, WORTREICH Verlag			G-BA Fachgutachter, Wissenschaftliche Tätigkeit: entzündlich-rheumatische Erkrankungen, immunologische Systemerkrankungen, eHEalth, Klinische Tätigkeit: Rheumatologie klinische Immunologie, Beteiligung an Fort-/Ausbildung: DGRh, Universitäten Düsseldorf und Essen, DGIM, BDI	COI: gering: Limitierung von Leitungsfunktion
PD Dr. Spinner, Christoph	Nein	AstraZeneca, BBraun, Gilead Sciences, GSK, MSD, Janssen-Cilag, Eli Lilly, Molecular Partners, Pifzer, Roche, Formycon, SOBI	AstraZeneca, BBraun, Gilead Sciences, GSK, MSD, Janssen-Cilag, Eli Lilly, Molecular Partners, Pifzer, Roche, Formycon, SOBI	Gilead Sciences	AstraZeneca, BBraun, Gilead Sciences, GSK, MSD, Janssen-Cilag, Eli Lilly, Molecular Partners, Pifzer, Roche, Formycon, SOBI	Keine	Mitglied: Deutsche AIDS-Gesellschaft, Deutsche Gesellschaft für Infektiologie	Advisory Board Tätigkeit für multiple Firmen, die COVID-19 Medikamente herstellen. Studienverantwortung für industriefinanzierte Studien zu medikamentöser COVID-19 Therapie COI: moderat: Stimmenthaltung
Dr. Stegemann, Miriam	Nein	Nein	Deutsche Gesellschaft für Infektiologie, Akademie für Infektionsmedizin, Sandoz	Fachjournale, Autor von Lehrbuch	Nein	Nein	Mitglied: Mitgliedschaft in Fachgesellschaften: Deutsche Gesellschaft für Infektiologie, Deutsche Gesellschaft für Innere Medizin, Deutsche Gesellschaft für Tropenmedizin, European Society of Clinical Microbiology and Infectious Diseases, Wissenschaftliche Tätigkeit: https://www.ncbi.nlm.nih.gov/myncbi/1-eYs7zxJilQ8/bibliography/public/ Antibiotic Stewardship, Infektionsmedizin, Global Health, Klinische Tätigkeit: Antibiotic Stewardship, Infektiologie, Beteiligung an Fort-/Ausbildung: Beteiligung an Fort-/Ausbildung: DGI-Fortbildungen, DGI-Kongress, DGIM-Kongress, Internistisches Facharzttraining, Beteiligung an Erstellung von Therapiehinweisen FG COVRIIN (RKI), Beteiligung an Erstellung der „Living	COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							WHO guideline on drugs to prevent covid-19“ und „Living WHO guideline on drugs for covid-19”	
Prof. Dr. Trummer, Georg	Medela AG	Nein	Nein	Nein	Nein	Resuscitec GmbH	Mitglied: Schriftführer GRC	COI: keine: keine
PD Dr. rer. nat. Weibel, Stephanie	Nein	Nein	Universität Marburg	Nein	NUM CEOsys, GBA, Innofond, S3Cov19live	Nein	Mitglied: Cochrane Anaesthesia, Content Editor, Wissenschaftliche Tätigkeit: Systemtische Übersichtsarbeiten, Meta-Analysen, Cochrane Reviews im Bereich COVID-19, perioperative Medizin und Anästhesie, Beteiligung an Fort-/Ausbildung: Workshops zu Meta-Analysen	öffentlich geförderte Evidenzsynthesen zu COVID-19 COI: keine: keine
Prof. Dr. Weinmann-Menke, Julia	Deutsche Forschungsgesells chaft (DFG	Boehringer Ingelheim, Bayer, Novartis, Chiesi, Novartis, AstraZeneca, GSK, Osuka	Vifor, GSK, medupdate, medupdate, Chiesi, Osuka	GSK	Novartis Boerhinger-Ingelheim GSK Morphopsys Chiesi Astellas	Nein	Mitglied: Deutsche Gesellschaft für Nephrologie, Vorsitzende der Kommission Leitlinien, Pressesprecherin, Mitglied: Deutsche Gesellschaft für Innere Medizin, gewähltes Mitglied des Wissenschaftlichen Beirats, Wissenschaftliche Tätigkeit: Pathogenese der Lupusnephritis NTX-immunologische Mechanismen nach NTX Vaskulitiden (Pathogenese und Therapie), Klinische Tätigkeit: Systemischer Lupus erythematodes Nierentransplantation Glomerulonephritiden chronische Niereninsiffizienz	industriefinanzierte Studien und Advisoryboard-Tätigkeit sowie Vorträge im Bereich Nierenerkrankungen, kein unmittelbarer thematischer Bezug zu COVID-19 Therapie COI: keine: keine
PD Dr. Westhoff, Michael	Nein	Nein	Fa. Löwenstein Medical	Nein	Nein	Nein	Mitglied: Deutsche Gesellschaft für Pneumologie DIVI European Respiratory Society American College of Chest Physicians, Wissenschaftliche Tätigkeit: Aussatemluftforschung Beatmungsmedizin Schlafmedizin Intensivmedizin, Klinische Tätigkeit: Beatmungsmedizin	industriefinanzierte Vorträge über nichtinvasive Beatmung bis 2020. COI: keine: keine

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungs-tätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie, Einstufung bzgl. der Relevanz, Konsequenz
							Schlafmedizin Intensivmedizin, Beteiligung an Fort-/Ausbildung: Ausbildung Atmungstherapeuten Vorlesungen an Uni Witten-Herdecke Kongresse DIVI, DGSM, DGP	
Zorger, Ana-Mihaela	Nein	Nein	Nein	Nein	Nein	Nein	Wissenschaftliche Tätigkeit: Onkologie, Infektiologie, Leitlinienerstellung und Implementierung	COI: keine: keine

04.07.2025: Gültigkeit der Leitlinie nach inhaltlicher Überprüfung durch das Leitliniensekretariat verlängert bis 27.02.2026

Versionsnummer: **11.0**

Erstveröffentlichung: **03/2020**

Überarbeitung von: **02/2025**

Nächste Überprüfung geplant: **12/2025**