Updated S2k Clinical Practice Guideline on Non-alcoholic Fatty Liver Disease (NAFLD) issued by the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS)

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-Fetoprotein
AHA	American Heart Association
AI	Artificial Intelligence
ALD	Alcohol-related Liver Disease
ALT	Alanineaminotransferase
API	Active pharmaceutical ingredient
APASL	Asian Pacific Association for the Study of the Liver
APRI	AST/platelet ratio
ASH	Alcoholic Steatohepatitis
AST	Aspartate aminotransferase
ATI	Attenuation Imaging
AUC	Area under the curve
AUROC	Area under the Receiver Operating Characteristic (ROC) Curve
BMI	Body-Mass-Index
CAP	Controlled Attenuation Parameter
CDT	Carbohydrate-Deficient Transferrin
CHE	Cholinesterase
CIL	Cilofexor
CMV	Cytomegalovirus
CT	Computed Tomography
CVC	Cenicriviroc
DECT	Dual-Energy CT
DM	Duodenal Mucosa
DPP4	Dipeptidyl Peptidase 4
%EWL	Percentage Excess Weight Loss
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr Virus
ELF	Enhanced Liver Fibrosis
ELIVATE	Study of Efficacy, Safety and Tolerability of the Combination of Tropifexor & Licogliflozin and Each Monotherapy, Compared with Placebo in Adult Patients with NASH and Liver Fibrosis.
EPA	Ethyl Eicosapentaenic Acid
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESG	Endoscopic sleeve gastroplasty
EtG	Ethylglucuronid
F1–F4	Stages of Liver Fibrosis 1–4

FASCINATE	Study of TVB-2640 in Subjects with Nonalcoholic Steatohepatitis (NASH)
FASN	Fatty Acid Synthase
FF	Fat Fraction
FGF	Fibroblast Growth Factor
FIR	Firsocostat
FLI	Fatty Liver Index
FLINT	The Farnesoid X Receptor (FXR) Ligand Obeticholic Acid in NASH Treatment Trial
FLIGHT-FXR	Study of Safety and Efficacy of Tropifexor (LJN452) in Patients with Non-alcoholic Steatohepatitis
FPG	Fasting Plasma Glucose
FXR	Farnesoid X Receptor
γ-GT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP-1	Glucagon-like Peptide 1
GOT	Glutamic-Oxaloacetic Transaminase
GPT	Glutamate-Pyruvate Transaminase
HA	Hyaluronic Acid
HAV	Hepatitis A Virus
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HIS	Hepatic Steatosis Index
Histo	Histology
HOMA	Homeostasis Model Assessment
HOMA-IR	Homeostasis Model Assessment – Insulin Resistance
HVPG	Hepatic-Venous Pressure Gradient
iCCa	Intrahepatic Cholangilocarcinoma
IDF	International Diabetes Federation
IQR	Interquartile Range
LDL	Low-Density Lipoprotein
LFS	Liver Fat Score
LSG	Laparoscopic Sleeve Gastrectomy
LT	Liver Transplantation
MAFLD	Metabolic Dysfunction-Associated Fatty Liver Disease
MDB	Mallory-Denk-Bodies
Met	Metformin
mo	Month
MRCP	Magnetic Resonance Cholangiopancreatography
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
n3 PUFA	n-3 Polyunsaturated Fatty Acid
NAFLD	Non-Alcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NFS	NAFLD Fibrosis Score
NASH	Non-Alcoholic Steatohepatitis
NASH CRN	NASH Clinical Research Network
NHLBI	National Heart, Lung and Blood Institute
NPV	Negative Predictive Value
OAGB	One-Anastomosis Gastric Bypass
OCA	Obeticholic Acid
OGTT	Oral Glucose Tolerance Test
OTC	Over the Counter
Pat.	Patient
PCOS	Polycystic ovary Syndrom
PDFF	Proton Density Fat-Fraction
PEth	Phosphatidylethanol
PIIINP	Procollagen III peptide
Pio	Pioglitazone
PMID	PubMed Identifier
p. o.	per os
PPAR	Peroxisome Proliferator-Activated Receptor
PPV	Positive Predictive Value
Prosp.	Prospective
PUFA	Polyunsaturated Fatty Acids
RYGB	Roux-Y Gastric Bypass
SCD-1	Stearoyl-CoA Desaturase 1
SG	Sleeve Gastrectomy
SGLT2	Sodium Dependent Glucose Co-transporter 2
SWE	Shear-Wave Elastography
%TWL	Percentage Total Weight Loss
T2DM	Type 2 Diabetes mellitus
TANDEM	Study of Safety, Tolerability, and Efficacy of a Combination Treatment of LJN452 and CVC in Adult Patients ith NASH and Liver Fibrosis
TBWL	Total Body Weight Loss
TE	Transient Elastography
TG	Triclyceride
THRß	Thyroid Hormone Receptor-Beta
TIMP-1	Tissue Inhibitor of Metalloproteinase-1
TZD	Thiazolidindione
UDCA	Ursodeoxycholic Acid
US	Ultrasound
VCTE	Vibration-Controlled Transient Elastography
Vit C	Vitamin C
Vit E	Vitamin E

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1. Information on the Guideline

Editors

Lead Medical Society

German Society of Gastroenterology, Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankrankheiten, **DGVS**)

Scope and purpose

According to the current guidelines of the DGVS (German Society of Gastroenterology, Digestive and Metabolic Diseases), EASL (European Association for the Study of the Liver, 2016), AASLD (American Association for the Study of Liver Diseases, 2018), APASL (Asian Pacific Association for the Study of the Liver, HCC Guideline, 2017) and the World Gastroenterology Organisation, 2012), the entity "non-alcoholic fatty liver disease" (NAFLD) includes the categories of non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), NASH fibrosis and NASH cirrhosis. New nomenclatures (e. g. metabolic dysfunction-associated fatty liver disease, MAFLD) have been proposed, but are not universally established to date.

The progression of NAFLD and particularly NASH is associated with liver cell stress, consecutive inflammation and fibrosis, potentially leading to liver cirrhosis, portal hypertension and end-stage liver disease. NASH is also a relevant risk factor for the development of hepatocellular carcinoma (HCC). The pathogenesis and natural course of NAFLD are becoming increasingly better understood. However, the heterogeneity of the patients and the disease's multifactorial genesis encumber the assessment of the precise prognosis of affected individuals. In the near future, patients with NASH-associated end-stage liver disease are expected to represent the highest proportion listed for liver transplantation. Despite being modified by genetic factors, the disease is believed to primarily result from hyperalimentation and a hepatic manifestation of metabolic syndrome. The clinical presentation of non-cirrhotic NAFLD is usually non-specific. With a global prevalence of around 25 %, NAFLD is now the leading cause of chronic liver disease worldwide and a growing public health challenge. Given the current obesity epidemic, a further increase in the prevalence of NAFLD is to be expected, especially among adolescents and younger patients. Changes in lifestyles, demographic shifts and the increasing complexity of pharmacological therapies are causes for this rise. Medical healthcare professionals and patient advocate organizations must deal with this collectively and individually. The previous German S2k Guidelines on NAFLD expired in February 2020.

The current revision was needed to incorporate all recent scientific evidence on disease management. The guideline is intended to provide practical guidance on diagnosis, therapy and surveillance of people living with NAFLD, including lifestyle modification and pharmacological treatment. Diagnostic and therapeutic algorithms based on metabolic comorbidities and fibrosis stage are provided to improve its general applicability. The present Guideline aims to offer a compilation on the qualified and effective diagnosis and management of NAFLD that reflects the current state of scientific knowledge, thereby improving the targeted care of NAFLD patients.

Overarching aim of these Clinical Practice Guidelines

This Clinical Practice Guideline is designed to provide easy practical applicability for primary care physicians, internists, clinical nutritionists, surgeons, radiologists, cardiologists, pediatricians and gastroenterologists. Above and beyond that goal, this Guideline intends to set a "corridor of action" for taking common decisions.

The patient target population comprises patients with NAFLD of all ages.

Health care settings

Inpatient and outpatient, primary care, general practice, clinical nutrition/nutritional therapy, surgery, radiology, pediatrics, internal medicine and gastroenterology.

Target users/target audience

These Guidelines target all professional groups involved in the diagnosis and management of NAFLD: Internists, gastroenterologists, endocrinologists, diabetologists, obesity specialists, surgeons, clinical nutritionists, radiologists, specialists in pediatrics and adolescent medicine, pathologists, cardiologists, transplant physicians, patient representatives/advocacy groups as well as affected parties, family members and serves as information for benefits providers (health insurers, pension insurance funds). The German College of General Practitioners and Family Physicians (DEGAM) was invited to collaborate but declined to participate. Nevertheless, we deem these Guidelines to be equally relevant for general practitioners and family physicians.

Constitution of the Guideline Development Group: Stakeholder involvement

This development of these Guidelines was led by the German Society of Gastroenterology (DGVS), which commissioned Professor Ali Canbay, Bochum, Professor Elke Roeb, Giessen, and Professor Frank Tacke, Berlin to be the coordinators. The following were responsible for methodology: Dr. Petra Lynen Jansen, University Lecturer, and Ms. Pia Lorenz, DGVS Administrative Offices, Berlin. Throughout the process, Dr. Nothacker, Association of the Scientific Medical Societies in Germany (AWMF), Berlin, provided methodological advice and support and moderated the consensus conference as a neutral guideline expert. Torsten Karge was available to support the guideline portal and technically supported the consensus conference.

The guideline project was disseminated in the journal "*Zeitschrift für Gastroenterologie*" and published on the AWMF website to enable additional scientific medical societies/representatives to offer their collaboration. Letters were sent to the scientific medical societies and patient groups relevant to this specialty asking them to nominate mandate holders.

Representativeness of the Guideline Development Group: Scientific medical societies and associations involved

- Obesity Working Group in Childhood and Adolescence (*Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter*, **AGA**)
  S. Wiegand (Berlin)
- German Obesity Society (*Deutsche Adipositas-Gesellschaft e. V.*, **DAG**)
  S. Engeli (Greifswald), S. Wiegand (Berlin)
- German Diabetes Society (*Deutsche Diabetes Gesellschaft e. V.*, **DDG**)
  M. Roden (Düsseldorf), N. Stefan (Tübingen)
- German Society for Ultrasound in Medicine (*Deutsche Gesellschaft für Ultraschall in der Medizin e. V.*, **DEGUM**)
  T. Bernatik (Ebersberg), T. Karlas (Leipzig)
- German Society for General and Visceral Surgery (*Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie e. V.*, **DGAV**)
  B. Müller (Heidelberg), K. Rheinwalt (Cologne)
- German Society of Surgery (*Deutsche Gesellschaft für Chirurgie e. V.*, **DGCH**)
  D. Seehofer (Leipzig)
- German Society of Endocrinology (*Deutsche Gesellschaft für Endokrinologie e. V.*, **DGE**)
  J. Bojunga (Frankfurt am Main)
- German Society for Nutritional Medicine (*Deutsche Gesellschaft für Ernährungsmedizin e. V.*, **DGEM**)
  S. Bischoff (Stuttgart), M. Plauth (Dessau)
- German Society for Combating Lipid Metabolism Disorders and their Consequential Diseases DGFF (Lipid League) (*Deutsche Gesellschaft zur Bekämpfung von Fettstoffwechselstörungen und ihren Folgeerkrankungen*, **DGFF** (*Lipid-Liga*) *e. V.*)
  J. Bojunga (Frankfurt am Main),
- German Society of Internal Medicine (*Deutsche Gesellschaft für Innere Medizin e. V.,* **DGIM**)
  R. Günther (Kiel)
- German Cardiac Society (*Deutsche Gesellschaft für Kardiologie*, **DGK**)
  M. Lehrke (Aachen)
- German Society of Pathology (*Deutsche Gesellschaft für Pathologie e. V.*, **DGP**)/Federal Association of German Pathologists (*Bundesverband Deutscher Pathologen e. V.*, **BDP**)
  H. Baba (Essen), T. Longerich (Heidelberg), A. Tannapfel (Bochum)
- German Roentgen Society (*Deutsche Röntgengesellschaft e. V.*, **DRG**)
  K. Ringe (Hannover), A. Schreyer (Brandenburg)
- German Transplantation Society (*Deutsche Transplantationsgesellschaft e. V.*, **DTG**)
  M. Sterneck (Hamburg)
- German Society for Pediatric Gastroenterology and Nutrition (*Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e. V.*, **GPGE**)
  J. de Laffolie (Giessen), P. Gerner (Freiburg), C. Hudert (Berlin), D. Weghuber (Salzburg)
- German Society of Pediatrics and Adolescent Medicine (*Deutsche Gesellschaft für Kinder- und Jugendmedizin e. V.*, **DGKJ**)
  J. de Laffolie (Giessen), R. Ganschow (Bonn), C. Hudert (Berlin)

The German College of General Practitioners and Family Physicians (DEGAM) was invited to collaborate on these Guidelines, but was unable to support the guideline project due to staff bottlenecks; the same applied to the German Hypertension League (*Deutsche Gesellschaft für Hypertonie und Prävention – Deutsche Hochdruckliga e. V.,* **DHL**). The German Psychological Society (*Deutsche Gesellschaft für Psychologie e. V.*, **DGPs**) was similarly invited to collaborate, but did not respond. The German Society for Interventional Radiology and Minimally Invasive Therapy (*Deutsche Gesellschaft für Interventionelle Radiologie und minimalinvasive Therapie*, **DeGIR**) applied to collaborate. However, their participation was declined in light of the previously planned guideline contents. Topics relating to interventional radiology had already been addressed in the guidelines "Complications of Liver Cirrhosis" and "Hepatocellular Carcinoma" and will therefore not be discussed in these Guidelines.

Representativeness of the Guideline Development Group: Patient participation

Mr. I. van Thiel (Cologne) of the German Liver Patients Association (*Deutsche Leberhilfe*)

Besides the Steering Committee (▶ **Table 1**), eight working groups were constituted that were each headed by two leads (▶ **Table 2**). Working group 4 – "Management" is divided into three subgroups. In the working groups, the proportion of university to non-university-based physicians, hospital-based clinicians to private practitioners was well balanced. Participants in the working groups included gastroenterologists, endocrinologists, diabetologists, obesity specialists, pediatricians, specialists in pediatrics and adolescent medicine, pathologists, cardiologists, transplant physicians, clinical nutritionists/nutritional therapists, radiologists and surgeons.

▶ **Table 1** Steering Committee.

Name	City	Responsibility
A. Canbay	Bochum	DGVS
E. Roeb	Gießen	DGVS
F. Tacke	Berlin	DGVS
H. Bantel	Hannover	DGVS
J. Bojunga	Frankfurt am Main	DGFF/DGE
M. Demir	Berlin	DGVS
A. Geier	Würzburg	DGVS
W. Hofmann	Berlin	DGVS
J. Schattenberg	Mainz	DGVS
A. Tannapfel	Bochum	DGPathologie/BDP

2. Methodology

2.1 Methodological principles

Literature search

Each working group performed their literature searches individually. The search and selection details are presented in guideline report.

Scheme of grading of recommendations

The strength of recommendation is derived from the formulation used (Should/Ought to/May be considered) in line with the grading illustrated in ▶ **Table 3**. The strength of consensus was established according to ▶ **Table 4**.

Statements

Statements are defined as descriptions or explanations of specific facts or key questions without direct calls to action. As part of a formal consensus procedure, statements are adopted according to the procedures in the recommendations and can be based on either study results or expert opinions.

3. External review and adoption

Adoption by the chairpersons of the publishing scientific medical societies/organizations

The full and complete Guideline was reviewed by all participating scientific medical societies and agreed on by consensus after a consultation version was posted on the DGVS and the AWMF website to be commented on by the professional community for 4 weeks in February 2022 (02.02. bis 28.02.2022). Commentaries were requested through the DGVS newsletter. All proposed changes are presented in the guideline report.

Editorial independence and guideline funding

These Clinical Practice Guidelines were developed according to the principle of editorial independence. The DGVS provided the funding for the use of the guideline portal, the online kick-off meeting and the online consensus conference. No third parties were in involved in the funding. The work done by the mandate holders and experts was exclusively on an honorary basis.

Disclosing and managing conflicts of interest

In line with the AWMF manual's guidance on managing conflicts of interest, all participants submitted their declarations completed on the corresponding AWMF standard form (form sheet 2018). The conflicts of interest forms were reviewed by the guideline coordinators and Dr. Nothacker (AWMF), then categorized according to the AWMF criteria as low, moderate and high in relation to the individual recommendations. Afterwards, they were presented to the Guideline Development Group prior to commencement of the consensus conference which, in turn, performed a mutual appraisal of the declarations of conflicts of interest.

Financial connections to industrial companies, for whose products no recommendations are issued in these Guidelines, were not appraised as conflicts of interest; this relates, among other things, to drugs under development. Lectures for manufacturers of diagnostics or therapeutics for NAFLD were appraised as low-level direct conflicts of interest. Activities on a scientific advisory board/work as consult or expert for a company in the health industry with a thematic connection to the guideline recommendations and the corresponding stock ownership were ranked as moderate direct conflicts of interest. The companies Siemens Healthcare, Echosens and GE Healthcare are ranked as relevant in terms of diagnostic procedures as are TECOmedical as the manufacturer of the CK18/M30 ELISA and Novo Nordisk as the manufacturer of antidiabetics. Patents were ranked as high conflicts of interest. As a result, eight experts were appraised to have moderate conflicts of interest. Moderate conflicts of interest produced an abstention during the voting and/or duplicated votes (once without, once with the affected parties, anonymous voting). Furthermore, the interdisciplinary and representative composition of the Guideline Development Group as well as the structured consensus development led by a neutral moderator are factors that help protect against bias. The declarations of interests submitted by all experts are listed in the Guideline Report.

4. Dissemination and implementation

Concept for dissemination and implementation

In addition to the journal "*Zeitschrift für Gastroenterologie*", these Guidelines will be disseminated on the AMBOSS knowledge platform and via the homepages of the DGVS (www.dgvs.de) and AWMF (www.awmf.de). An English short version of the Guideline will likewise be published in the "*Zeitschrift für Gastroenterologie*".

▶ **Table 2** Members of the Guideline Development Group.

Working Group 1: Definition	Working Group Lead	E. Roeb, Giessen (DGVS) A. Tannapfel, Bochum (DGPathologie/BDP)
	Working Group Members	M. Bahr, Lübeck (DGVS) S. Hohenester, Munich (DGVS) T. Longerich, Heidelberg (DGPathologie/BDP)
Working Group 2: Screening for NAFLD	Working Group Lead	M. Demir, Berlin (DGVS) M. Krawczyk, Homburg (DGVS)
	Working Group Members	T. Bernatik, Ebersberg (DEGUM) P. Buggisch, Hamburg (DGVS) C. F. Dietrich, Bern (DGVS) C. G. Dietrich, Wiesbaden (DGVS) M. Lehrke, Aachen (DGKardiologie) K. Ringe, Hannover (DRG)
Working Group 3: Diagnostic features	Working Group Lead	H. Bantel, Hannover (DGVS) A. Canbay, Bochum (DGVS)
	Working Group Members	H. Baba, Essen (DGPathologie/BDP) T. Karlas, Leipzig (DEGUM) S. Mueller, Heidelberg (DGVS) S. Rossol, Frankfurt (DGVS) A. Schreyer, Brandenburg (DRG)
Working Group 4a: Management – Non-pharmacological conservative therapy	Working Group Lead	J. Bojunga, Frankfurt am Main (DGFF/DGE) J. Schattenberg, Mainz (DGVS)
	Working Group Members	S. Bischoff, Stuttgart (DGEM) S. Engeli, Greifswald (DAG) H. Hinrichsen, Kiel (DGVS) M. Plauth, Dessau (DGEM) I. van Thiel, Cologne (German Liver Patients Association)
Working Group 4b: Management – Pharmacological therapy	Working Group Lead	A. Geier, Würzburg (DGVS) F. Tacke, Berlin (DGVS)
	Working Group Members	V. Keitel-Anselmino, Magdeburg (DGVS) A. Kremer, Erlangen (DGVS) M. Roden, Düsseldorf (DDG) N. Stefan, Tubingen (DDG)
Working Group 4c: Management – Interventional therapy (endoscopic procedures, bariatric surgery, liver transplantation)	Working Group Lead	U. Denzer, Marburg (DGVS) M. Sterneck, Hamburg (DTG)
	Working Group Members	J. Kluwe, Hamburg (DGVS) B. Müller, Heidelberg (DGAV) K. Rheinwalt, Cologne (DGAV) H. Schmidt, Essen (DGVS) D. Seehofer, Leipzig (DGCH)
Working Group 5: Monitoring and long-term management	Working Group Lead	W. Hofmann, Berlin (DGVS) T. Lüdde, Düsseldorf (DGVS)
	Working Group Members	R. Günther, Kiel (DGIM) A. Pathil-Warth, Frankfurt am Main (DGVS) M. Rau, Wurzburg (DGVS) K. Stein, Magdeburg (DGVS)
Working Group 6: NAFLD/NASH in children (pediatrics)	Working Group Lead	J. de Laffolie, Giessen (DGKJ/GPGE) C. Hudert, Berlin (DGKJ/GPGE)
	Working Group Members	R. Ganschow, Bonn (DGKJ) P. Gerner, Freiburg (GPGE) D. Weghuber, Salzburg (GPGE) S. Wiegand, Berlin (AGA/DAG)
Coordinators		A. Canbay, Bochum (DGVS) E. Roeb, Giessen (DGVS) F. Tacke, Berlin (DGVS)

▶ **Table 3** Grid for grading recommendations.

Description	Syntax
Strong recommendation	Should
Recommendation	Should
Open	Can

▶ **Table 4** Classifying the strength of consensus.

Consensus	% Agreement
Strong consensus	≥ 95
Consensus	≥ 75–95
Majority consensus	≥ 50–75
No Consensus	< 50

Period of validity and update processes

The guideline shall remain valid for around five years (until 30 September 2026). The revision will be initiated by the guideline coordinators of the DGVS. The Steering Committee will review the need for updating the Guideline annually. Ms. Lorenz (leitlinien@dgvs.de) at the DGVS Administrative Offices is available as contact partner.

Editorial note

Gender neutrality

In order to improve legibility, gender-specific terminology has not been used in this document. All personal designations are therefore to be understood as gender neutral.

Participatory decision-making

All recommendations contained in this guideline are to be understood as recommendations intended to be discussed and implemented within a participatory decision-making process involving the physician and the patient and/or the patient's family members.

Special note

Medicine is subject to a continuous development process, so that all information, in particular on diagnostic and therapeutic procedures, can only correspond to the state of knowledge at the time of printing of the guideline. The greatest possible care has been taken with regard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are urged to consult the manufacturers' package inserts and expert information for verification and, in case of doubt, to consult a specialist. Any discrepancies should be reported to the DGVS. The user himself remains responsible for any diagnostic and therapeutic application, medication and dosage. In this guideline, registered trademarks (protected trade names) are not specially marked. It can therefore not be concluded from the absence of a corresponding reference that it is a free trade name. The work is protected by copyright in all its parts. Any use outside the provisions of copyright law without the written consent of DGVS is prohibited and punishable by law. No part of the work may be reproduced in any form without written permission. This applies in particular to reproductions, translations, microfilming and the storage, use and exploitation in electronic systems, intranets and the Internet.

Preamble

According to the current guidelines issued by the DGVS (German Society for Gastroenterology), EASL (European Association for the Study of the Liver), AASLD (American Association for the Study of Liver Diseases), APASL (Asian Pacific Association for the Study of the Liver) and the World Gastroenterology Organisation, non-alcoholic fatty liver disease (NAFLD) includes the spectrum of NAFL (non-alcoholic fatty liver), NASH (non-alcoholic steatohepatitis), NASH fibrosis and NASH cirrhosis. New nomenclatures, such as metabolic dysfunction-associated fatty liver disease, have been proposed, but are not universally established to date. The progression of NAFLD and particularly NASH is associated with liver cell stress, consecutive inflammation and fibrosis, potentially leading to liver cirrhosis, portal hypertension and end-stage liver disease. NASH is also a relevant risk factor for the development of hepatocellular carcinoma (HCC). The pathogenesis and natural course of NAFLD are becoming increasingly better understood. However, the heterogeneity of the patients and the disease's multifactorial genesis encumber the assessment of the precise prognosis of affected individuals. In the near future, patients with NASH-associated end-stage liver disease are expected to represent the highest proportion listed for liver transplantation. Despite being modified by genetic factors, the disease is believed to primarily result from hyperalimentation and a hepatic manifestation of metabolic syndrome. The clinical presentation of non-cirrhotic NAFLD is usually non-specific. With a global prevalence of around 25 %, NAFLD is now the leading cause of chronic liver disease worldwide and a growing public health challenge. Given the current obesity epidemic, a further increase in the prevalence of NAFLD is to be expected, especially among adolescents and younger patients. Changes in lifestyles, demographic shifts and the increasing complexity of pharmacological therapies are causes for this rise. Medical healthcare professionals and patient advocate organizations must deal with this collectively and individually. The previous German S2k Guidelines on NAFLD expired in February 2020.

1. Definitions

NAFL, NASH, NAFLD, Steatosis

STATEMENTS

Hepatic steatosis or steatohepatitis can be triggered by numerous diseases or causes. However, the cause cannot always be clarified.
Strong consensus

Alcohol-related liver disease (ALD) is caused by harmful alcohol consumption (for definition and threshold for harmful consumption, see Chapter "Differentiation between NAFLD and ALD").
Strong consensus

In the broadest sense, non-alcoholic fatty liver disease (NAFLD) is caused by metabolic factors.
Strong consensus

NAFLD can also occur in nonobese individuals (body mass index, BMI < 25 kg/m² in adults or percentile equivalent in children and adolescents). *Strong consensus*

Non-alcoholic steatohepatitis (NASH) can lead to liver fibrosis, even to liver cirrhosis and hepatocellular carcinoma (HCC) or, less commonly, to intrahepatic cholangiocarcinoma (iCCa).
Strong consensus

There are differences between pediatric and adult NAFLD patients. These include etiology, epidemiology and pathology (see Chapter "Pediatrics").
Strong consensus

Commentary

Hepatic steatosis (liver cell steatosis) is characterized by the storage of fat in hepatocytes. Steatohepatitis is present if inflammation and hepatocyte damage can be detected in conjunction with hepatic steatosis [1]. Although a diet-related and alcoholic pathogenesis of steatosis and steatohepatitis is the most common cause, their differential diagnosis, covers a broad spectrum of possible causes for steatosis-associated liver damage (see ▶ **Table 6** Chapter "Diagnostics"). These causes should be investigated in the medical history and taken into account in the final interpretation of the patient's liver damage. The acronym for non-alcoholic fatty liver disease is NAFLD.

Both alcoholic (ASH) and non-alcoholic steatohepatitis (NASH) are characterized by steatosis and lobular inflammation with ballooning of hepatocytes, resulting in wire mesh fibrosis (which progresses if the disease persists). A reliable differential diagnosis of ASH vs. NASH cannot generally be based on histological criteria alone. The differences between ALD and NAFLD identified in cohort comparisons are of a gradual nature and therefore not sufficiently reliable to typify the individual case (cave: Lifestyle modification prior to liver biopsy). Steatosis and the formation of glycogenated nuclei are often more pronounced in NASH, while the inflammatory activity and the detection of Mallory-Denk bodies (MDB) and satellitosis (granulocytic demarcation of a hepatocyte with MDB) is observed more frequently in ASH [2]. The mere evidence of sclerosing hyaline necrosis, which can develop as a result of extensive perivenular hepatocellular necrosis, was not regarded to be a result of NASH, meaning that sclerosing hyaline necrosis excludes a sole non-alcoholic origin of liver damage [3].

Most patients with NAFLD have central obesity and other components of metabolic syndrome. However, NAFLD can also develop in non-obese patients (referred to as lean NAFLD, comprising approx. 20 % of cases). It is assumed that these patients show less inflammatory activity and therefore have a better prognosis [4, 5] Due to the frequent association with metabolic syndrome, a consensus panel suggested that NAFLD be referred to as metabolic dysfunction associated fatty liver disease (MAFLD) [6]. Indeed, this term excludes some entities. On the one hand, lean NAFLD is poorly defined; on the other, metabolic disorders (e. g. mitochondriopathies, glycogenosis) represent separate pathogenetic and therapeutic entities. Further analyses are required to assess the acceptance for and the positive and negative consequences of renaming NAFLD to MAFLD [7]. Based on current knowledge, the term MAFLD should therefore not be used synonymously given its terminological imprecision [8]. The panel has decided to stick to the established term NAFLD, for which the vast majority of scientific evidence exists. The international European and US hepatological associations will hold a consensus meeting on this issue in the near future.

When diagnosed, NASH is considered a precancerous condition/lesion, implying that hepatocellular cancer (HCC) and, or less often, intrahepatic cholangiocarcinoma (iCCA; ratio: 5–7 HCC/1 iCCA) can develop and that surveillance should take place according to the corresponding S3 guideline [9–12]. The HCC incidence in NASH patients without liver cirrhosis is reported at 0.02 % per year and increases up to 1.5 % per year in the presence of liver cirrhosis [9]. The specific aspects of NAFLD/NASH in children are discussed in the Chapter "Pediatrics".

RECOMMENDATIONS

The histological diagnosis of simple steatosis (NAFL) should be made if > 5 % fatty hepatocytes are detected and the NASH criteria are not met.
Strong recommendation, strong consensus

Commentary

Detection of hepatocellular steatosis of up to 5 % is considered normal [13]. A significantly increased accumulation of triglycerides in the liver cells is called hepatic steatosis. A rule of thirds has been established for grading steatosis in the context of NAFLD (low: up to 33 %, moderate: 33–66 %, severe: > 66 % macrovesicular steatosis) [14, 15]. Although the conventional scoring systems mentioned below put the percentage of steatosis in relation to the number of hepatocytes, this approach is so impractical that the parenchymal area affected by macrovesicular steatosis usually tends to be estimated instead [16]. The NAFLD Activity Score (NAS) according to Kleiner not only evaluates lobular inflammation and hepatocellular ballooning but also steatosis as a subcomponent of inflammatory activity (grading) [15].As shown for bland steatosis, liver cell steatosis alone is not an independent risk factor

for progression to liver fibrosis and is therefore unsuitable as a surrogate marker for the inflammatory activity of NAFLD [15]. Evidence of liver cell steatosis typifies the disease (steato-), while inflammatory activity is characterized by the extent of lobular inflammation and hepatocellular ballooning [10, 17].

STATEMENTS

Disease stage and prognosis are determined by the extent of liver fibrosis. See also Chapter 2.

Strong consensus

Liver biopsy is superior to non-invasive methods (laboratory values, imaging, elastography) for the detection of early stages of fibrosis, necroinflammatory activity and hepatocellular ballooning.

Strong consensus

Commentary

The most important factor predicting the prognosis of NAFLD patients is the stage of fibrosis. A meta-analysis of five studies on 1495 biopsy-proven NAFLD patients and a follow-up of 17,452 patient-years showed that, compared to NAFLD patients without fibrosis (F0), those with fibrosis had an increased risk for both overall and liver-specific mortality, which increased continuously with the fibrosis stage. There was an exponential increase in risk in terms of liver-specific mortality [18]. The greatest risk of liver-specific, but also overall morbidity and mortality in NAFLD was demonstrated for advanced fibrosis (F3) and liver cirrhosis (F4). The following event rates were registered over an average observation period of 5.5 years: 8 % all-cause mortality, 8 % liver transplants, 19 % first-time hepatic decompensation, 9 % HCC, 3 % vascular events and 7 % non-hepatic malignancies. The transplant-free 10-year survival was 94 % for F3 and 45.5 % for F4. In stage F3, there were higher cumulative incidences of vascular events (7 % vs. 2 %) and non-hepatic malignancies (14 % vs. 6 %). By contrast, the frequency of hepatic decompensation and the development of HCC were increased in patients with liver cirrhosis: 44 % vs. 6 % and 17 % vs. 2.3 % [19]. These data suggest that cardiovascular and non-hepatic morbidity and mortality are more common in non-cirrhotic NAFLD patients, while complications of advanced liver disease determine the further prognosis in patients with manifest liver cirrhosis.

Xiao et al. conducted a meta-analysis of over 13,000 subjects to determine the best method for diagnosing liver fibrosis in NAFLD. In their comparison of APRI, FIB-4, BARD score, NAFLD fibrosis score (NFS), vibration-controlled transient elastography (VCTE), shear-wave elastography (SWE) and magnetic resonance elastography (MRE), the methods MRE and SWE showed the highest diagnostic accuracy for staging fibrosis. NFS and FIB-4 showed the best performance in detecting advanced fibrosis among the four non-invasive simple indexes [20]. According to current meta-analyses, complex biomarker panels and elastography can identify NAFLD-related fibrosis with moderate accuracy in obese individuals, but these methods have not yet been well validated [21]; also see Chapter “Diagnostics”.

Histological Grading and Staging

RECOMMENDATIONS

The histological diagnosis of steatohepatitis (NASH) should be named if hepatocellular ballooning and lobular inflammation can be detected in addition to steatosis (> 5 %).

Strong recommendation, strong consensus

The disease stage (staging) should be indicated using the NASH-CRN histological scoring system (defined by the same criteria as for the NAFLD Acitivity Score (NAS) and steatosis, activity, fibrosis (SAF) scores).

Strong recommendation, strong consensus

The inflammatory activity (grading) of the disease can be determined histologically using the SAF score (FLIP algorithm [14, 22]) or the NAS [15]).

Strong recommendation, strong consensus

Ballooning is used to describe enlarged, rounded hepatocytes with a pale cytoplasm. *Strong recommendation, strong consensus*

When quantifying lobular inflammation, all inflammatory foci (mean values) counted in the core biopsy specimen should be considered.

Strong recommendation, strong consensus

Commentary

Macrovesicular steatosis of > 5 % suggests fatty liver disease. Steatohepatitis is said to be present if (steatosis-associated) inflammatory foci and hepatocellular ballooning are found concomitant with steatosis [14, 15]. Ballooning is defined as swelling and rounding of the hepatocytes. It is caused by a change in the intermediate filaments of the cytoskeleton, often with associated small lipid droplet accumulation and a dilatation of the endoplasmic reticulum. Immunohistologically, ballooned hepatocytes show a loss of keratin 8/18 expression in the hepatocytes [23]. Cytoplasmic inclusions in the form of Mallory Denk Bodies can also be detected in ballooned liver cells. Further typical but diagnostically unnecessary histomorphological characteristics of NAFLD are the detection of glycogenated nuclei and lipogranulomas. The fibrosis that occurs as a result of steatohepatitis often begins (in adults) in the center of the lobule in the form of perivenular and perisinusoidal fiber deposits (chicken wire type). Over the further clinical course, portal fibrosis develops with formation of bridging (portoportal and portocentral) septa that can ultimately lead to liver cirrhosis as the disease progresses [14, 15].

Two scoring systems (NAS and SAF) have been established for assessing inflammatory activity. While the SAF score allows the diagnosis of NASH ($S_{\geq 1}A_{\geq 2}F_{every}$), NAS was initially developed for use as a semi-quantitative scoring system in clinical trials in ordeto map the spectrum of the natural course of the disease [14, 15]. Both scoring systems have advantages and disadvantages. As with all graded histological parameters, the grading of ballooning is subject to a certain intra- and interobserver variability [24, 25]. In order to achieve the most comparable assessment possible, when using the NAS or the SAF score for grading the inflammatory activity, it is important to ensure that the scoring systems are used as per definition. To evaluate lobular inflammation, the

mean value of all inflammatory foci counted in the core biopsy specimen per 200x magnification field is calculated, rather than just assessing the field of view with the highest number of inflammatory foci.

Whereas the inflammatory activity gives a snapshot of the current liver damage in the core biopsy specimen, the extent of the fibrotic parenchymal remodeling (staging) is used to define the disease stage. The staging provides an indication of the potential for regression and, in the case of repeated liver biopsies, of the dynamics of the liver damage. The histopathological staging systems grade the extent of the fibrosis and require a defined scale value (0–4). Therefore, these results cannot always be equated with the metric, continuous values of non-invasive fibrosis detection methods. A major advantage of histopathological staging is the detection of early stages of fibrosis, where there is a high chance of complete reversibility.

Metabolic Syndrome

DEFINITION/STATEMENT

NAFLD is regarded as the hepatic manifestation of metabolic syndrome, but it can also occur independently.

Strong consensus

Metabolic syndrome consists of several components (see ▶ **Table 5**). These are pathophysiologically related and represent a risk constellation for metabolic, cardiovascular and hepatobiliary health.

Strong consensus

Commentary

According to the International Diabetes Federation (IDF), the components of metabolic syndrome consist of obesity, insulin resistance, dyslipidemia and hypertension. Even before the criteria for diagnosing diabetes mellitus have been met, episodes of hyperglycemia and associated changes in blood lipids (increase in triglycerides and decrease in HDL cholesterol) can increase the risk of cardiovascular damage. The more components of metabolic syndrome are present, the higher is the cardiovascular mortality rate [26]. NAFLD is viewed by gastroenterological and diabetological societies as a hepatic manifestation of metabolic syndrome. According to the IDF consensus, metabolic syndrome exists if central obesity (defined as an enlarged waist circumference) plus two other criteria listed in ▶ **Table 5** can be demonstrated (https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metablic-syndrome.html:). At BMI > 30 kg/m², central obesity can be assumed and waist circumference does not need to be measured additionally [27].

Minimum requirements for liver biopsy (technique, evaluation)

RECOMMENDATIONS

The choice of the biopsy technique should depend on the locally available expertise, possible existing comorbidities, ascites, platelet count and the coagulation function.

Strong recommendation, strong consensus

A percutaneous liver biopsy should be performed in adults with a ≤ 16G needle (i. e.
with a caliber of at least 1.6 mm).

Recommendation, consensus

A core biopsy specimen measuring at least 2 cm in length should be obtained for the histopathological diagnosis of NAFLD.

Recommendation, strong consensus

Two core specimens can be obtained to reduce the sampling error.

Strong open, strong consensus

▶ **Table 5** Criteria for the clinical diagnosis of metabolic syndrome.

Measurands	Cutoff points
Enlarged waist circumference *	Population and country specific definitions
Elevated triglycerides (or drug treatment for hypertriglyceridemia †)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (or drug treatment for reduced HDL-C †)	< 40 mg/dL (1.0 mmol/L) for men; < 50 mg/dL (1.3 mmol/L) for women
Elevated blood pressure (or medication to lower blood pressure and a history of hypertension)	Systolic > 130 mmHg and/or diastolic > 85 mm Hg
Increased fasting glucose ‡ (or drug treatment for hyperglycemia)	≥ 100 mg/dL or previously diagnosed type 2 diabetes mellitus (T2DM). If the level is above 5.6 mmol/L or 100 mg/dL, OGTT is urgently recommended but is not required to define the presence of the syndrome.

HDL-C = high-density lipoprotein cholesterol.

* Until further data are available, it is recommended to use the IDF cutoffs (waist circumference male ≥ 94 cm, female ≥ 80 cm) also for non-Europeans and either the IDF or the AHA/NHLBI cutoffs (male ≥ 102 cm, female ≥ 88 cm) for persons of European origin.

† Fibrates and niacin are very frequently used drugs for hypertriglyceridemia and reduced HDL-C. A patient taking any of these drugs can be assumed to have high triglycerides and low HDL-C. High doses of omega-3 fatty acids assume high triglycerides.

‡ According to these criteria, most patients with T2DM have metabolic syndrome.

Commentary

Liver biopsy is an invasive diagnostic method and associated with – albeit very low – morbidity and mortality [28]. The choice of access route (e. g. percutaneous, transjugular, laparoscopic, transgastral) should take into account the locally available expertise and the biopsy should be performed under optical guidance. Given the direct relationship between biopsy size and number of portal fields recorded [29], the core specimen should not be < 15 mm in length. When a needle caliber ≥ 1.6 mm (≤ 16G, ≤ 16 gauge) is used, this core specimen length ensures the presence of > 10 assessable portal fields [30–32]. Thinner needle calibers (< 1.6 mm) reduce the diagnostic accuracy [33–37]. In prospective studies, the use of larger needles was not associated with a higher risk of bleeding [38, 39]. The recommendation to take a core biopsy measuring at least 20 mm in length using a ≤ 16G needle is based on international consensus [31, 40, 41].

When taking liver biopsies, sampling errors can reduce the diagnostic accuracy of a liver biopsy. In NAFLD, this applies to both percutaneous and intraoperative samples taken under direct vision [42–45]. In this context, taking two biopsies was able to reduce the sampling error [42, 46]. Taking more than two biopsies is associated with an increased risk of complications [47–49].

Minimum criteria for inclusion in the histology report

RECOMMENDATIONS

For NAFLD, the following information should be included on the histology report:

- Biopsy quality (size, number of portal fields, artifacts)
- Steatosis grade (according to the rule of thirds)
- Comments on ballooning and lobular inflammation
- Comments on inflammation (grading, e. g. SAF score or NAS) and on fibrosis stage (staging, by NASH-CRN/SAF)

Recommendation, strong consensus

Commentary

The report on histopathological findings should include a statement on the assessability of the biopsy (good, sufficient, borderline, inadequate). Factors that are taken into account here are the size of the biopsy (length, diameter), the number of portal fields assessed and the degree of fragmentation. Heavily fragmented biopsies can indicate liver cirrhosis, but are exactly what make it more difficult to assess the extent of fibrosis. The liver biopsy report should systematically describe all morphologically detectable changes in the portal fields, liver lobule and vessels. This ensures traceability within the framework of quality assurance measures.

According to the current definition, hepatocellular ballooning and lobular inflammation lead to the diagnosis of NASH [14, 15, 22] and must therefore be described on the histology report. They can be combined using established scoring systems like NAFLD Activity Score (NAS)/NASH-CRN [15] or the SAF/FLIP algorithm [14, 22]. When diagnosing NASH, information on the stage of the fibrosis is essential for further clinical management. For this, the definition of the fibrosis stages according to NASH-CRN/NAS is available, which is similarly used in the SAF Score/FLIP algorithm. As the histopathological findings should always be interpreted in the context of the overall clinical situation and take differential diagnoses into account, a description of all other histological abnormalities is desirable, or, in the context of NASH, also the absence thereof (such as MDB, apoptotic bodies or microvacuolar steatosis).

Indication, timing and performance of liver biopsies

RECOMMENDATIONS

If a reliable differentiation between NAFL and NASH is required, a histological examination should be performed.

Strong recommendation, strong consensus

If exact staging of liver fibrosis is sought, a liver biopsy should be performed.

Strong recommendation, consensus

A liver biopsy should be performed in NAFLD if comorbid constellations need to be detected or excluded.

Recommendation, consensus

The indication for a liver biopsy can be rendered according to the algorithm for NAFLD risk stratification shown in ▶ **Fig. 2** and ▶ **Fig. 4** (see Chapters “Diagnostics” and “Pediatrics”).

Recommendation open, strong consensus

Registration and initial processing of the biopsy

RECOMMENDATIONS

The liver biopsy should be fixed in neutral-buffered formalin immediately after collection.

Strong recommendation, strong consensus

The liver biopsy should be sent in for analysis with a structured examination request form (including the clinical information).

Strong recommendation, strong consensus

Commentary

In addition to the indication for liver biopsy (see also Chapter “Diagnostics”), further processing must be conducted scrupulously. Immediately after collection, the liver biopsy should be transferred to neutral-buffered formalin (6.25–10 % formalin, corresponding to 2.5–4 % formaldehyde in phosphate buffer, pH7) and fixed for a sufficiently long time (optimally overnight) [50, 51]. This prevents any decomposition processes from taking place (e. g. autolysis). All examinations necessary for cytological diagnostics of fine-needle aspirates can be carried out on the formalin-fixed paraffin-embedded biopsy tissue. In addition, this material can be used for reliable investigations at the nucleic acid level (DNA/RNA) (with appropriate differential diagnostic considerations) [51]. Inflammatory manifestations of NASH are not evenly distributed around the liver tissue, which is why liver biopsy carries the risk of sampling error [42]. In addition, any possible comorbid conditions (e. g. primary biliary cholangitis) can manifest

heterogeneously and segmentally. Therefore, a sufficient number of slices (at least 8) should be examined histologically.

The liver has a limited range of responses to damage. Therefore, histologically similar presentations or similar damage patterns can have different causes (e. g. ALD vs. NAFLD). For the optimal interpretation of liver biopsies, knowledge about the relevant clinical history as well as the relevant serological parameters (in relation to the differential diagnostic question) is essential. Here, a structured form, accompanying the liver biopsies has proven useful (an example is shown in the Appendix 1). In some situations, it can be useful to collect an additional core biopsy specimen, fixed in glutaraldehyde (especially in hereditary/childhood liver diseases) for electron microscopic examination or as native dry preparation (e. g. quantitative copper determination).

See Appendix 1

Differentiation of NAFLD from ALD

Differentiation of NAFLD from other hepatic steatoses

RECOMMENDATION/STATEMENT

Statements

The threshold dose for a hepatotoxic alcohol effect varies from person to person and depends on individual cofactors and comorbidities. A reliable differential diagnosis between NAFLD and ALD cannot be made on the basis of histological criteria alone.

Strong consensus

Recommendations

To differentiate NAFLD from ALD or mixed forms, a daily alcohol limit of 10 g for women and 20 g for men should be set.

Recommendation, strong consensus

For hepatic steatoses that are not due to alcohol abuse or are not components of metabolic syndrome, a term in the nomenclature that describes both the cause and the resulting pathology, e. g. “steatosis induced by parenteral nutrition” or “tamoxifen-induced steatohepatitis” should preferably be used.

Recommendation, strong consensus

Commentary

Recommendations and statements on the amount of alcohol were taken from the NAFLD guideline from 2015 [52] and are confirmed by the National Institutes of Health NASH clinical research network and the Asia Pacific Working Party on NAFLD Guidelines 2017 [53]. ALD cannot be ruled out with certainty in the case of higher daily alcohol consumption. Ethyl glucuronide (EtG) in urine or in the hair and phosphatidylethanol (PEth) in the blood are mainly used to confirm alcohol abstinence. By measuring EtG in the hair, alcohol consumption can be estimated retrospectively over a period of several months. EtG in urine is a suitable parameter for alcohol withdrawal or drinking withdrawal programs as well as for abstinence tests before liver transplantation (LT) or for inclusion on the waiting list.

The biochemical parameters ALT, AST and γGT can be used to identify existing alcoholic liver damage. However, the specificity is comparatively low. A combination of different biomarkers is advisable because they differ in their underlying pathomechanisms. GOT/AST, γGT, Hb and ferritin can provide clues for differentiating between ALD and NAFLD [54, 55]. The definition of harmful alcohol consumption is not uniform. In clinical trials on NASH, the definition of an average of no more than 14 units of alcohol per week for women and 21 for men was used [56]. In their meta-analysis, Larsson et al. found that approx. 12 g of alcohol correspond to approx. one drink and that studies use the following categories: Light (< 1 drink/day), moderate (1–2 drinks/day) and high (> 2–4 drinks/day) alcohol consumption [57]. According to the Royal Medical Colleges, studies on alcohol-related harm in women indicate that the level of consumption at which the relative mortality risk increases is around 16 g alcohol/day or around 2 drinks/day [58]. Aberg et al. observed a J-shaped association between alcohol consumption and mortality with alcohol consumption of 0–9 g/day compared to lifelong abstainers. However, these benefits have only been seen in non-smokers. Alcohol consumption > 30 g/day resulted in an increased mortality risk compared to lifelong abstainers [59]. Data from the National Health and Nutrition Examination Survey III have associated alcohol consumption with increased mortality in participants with fatty liver and metabolic syndrome. These findings suggest an overlap between NAFLD and ALD [60].

2. Prognosis & Screening

Incidence

STATEMENT

The annual incidence of NAFLD in the general population is estimated at 28–51 cases per 1000 person-years, depending on region and age.

Strong consensus

Commentary

The incidence of NAFLD has so far only been investigated in a few population-based studies. A meta-analysis from Asia of 237 studies and 13,044,518 individuals found a pooled annual NAFLD incidence rate of 50.9 cases per 1000 person-years (95 % CI 44.8–57.4) [61]. According to a meta-analysis for western countries, the annual incidence rate is 28 per 1000 person-years (95 % CI, 19.34–40.57), with only data from Israel being included [62]. A population-based study from the USA with 3,869 NAFLD patients and 15,209 controls found that the NAFLD incidence increased five-fold from 62 to 329 in 100,000 person-years between 1997 and 2014. There was a 7-fold increase in the group of 18–39 year-olds [63]. To date, there is no accurate information on the incidence of NAFLD in the general population.

Prevalence

STATEMENTS

The prevalence of NAFLD in the general adult population is around 25 % worldwide and varies depending on the population studied, the region and the diagnostic modality used. In Germany, it is around 23 %.

Strong consensus

The global prevalence of NASH is estimated at 3–5 %. In Germany, it is around 4 %.

Strong consensus

There is little data on the prevalence of NASH cirrhosis in the general population.

Strong consensus

Commentary

Studies on the point prevalence of NAFLD in the general population show great variability. This is due, among other things, to regional differences, the different diagnostic modalities and the underlying definition of NAFLD, since liver biopsy as the gold standard in diagnosis cannot be used in population-based studies. A meta-analysis of 86 studies from 22 countries (n = 8,515,431) showed a global prevalence of NAFLD of 25.24 % (95 % CI: 22,10–28,65). The published prevalence rates were lowest for Africa at 13.48 % (95 % CI, 5.69–28.69) and highest for the Middle East (31.79 %; 95 % CI, 13.48–58.23) and South America (30.45 %; 95 % CI, 22.74–39.44) [62]. For Germany, the NAFLD prevalence was around 23 % in 2016 and is mathematically projected to be around 26 % in 2030 [64].

There are no population-based studies on the prevalence of NASH, as this requires obtaining a liver histology. The pooled NASH prevalence in "clinically indicated" NAFLD biopsies was 59.10 % globally (95 % CI: 47.55–69.73). In patients "without a NAFLD-related indication" such as before a living liver donation, the NASH prevalence was between 6.67 % (95 % CI: 2.17–18.73) in Asia and 29.85 % (95 % CI: 22.72–38.12) in North America [62]. For Germany it is estimated at 4.1 %, with a model based projected increase to 6 % in 2030 [64].

There is little data on the prevalence of NASH cirrhosis in the general population. Analysis of a population-based cohort from the USA during the periods 1999–2002 and 2009–2012 using surrogate markers for fibrosis showed a significant increase in the prevalence of NASH cirrhosis of 0.178 % in the period 2009–2012 compared to 0.072 % in the period 1999–2002 ($p < 0.05$). The prevalence of NAFLD with advanced fibrosis (F3) increased from 0.84 to 1.75 % ($p < 0.001$) over the same period. This corresponds to a 2.5-fold increase in the prevalence for NASH cirrhosis and a doubling of NAFLD-associated advanced fibrosis [65]. An analysis of the FLAG cohort with 507 NAFLD patients mainly from secondary care settings in Germany, using the FIB-4 score (modified cut-off of > 2.67 for ≥F3), showed a 10 % prevalence of advanced fibrosis or cirrhosis [66]. In contrast, a mathematical model estimated the prevalence of advanced fibrosis or cirrhosis (≥F3) in NAFLD in Germany to be 3.3 %, which corresponds to the number of cases totaling 600,000 [64].

Risk factors and prognosis

DEFINITION/STATEMENT

Metabolic risk factors, especially (visceral) obesity and type 2 diabetes mellitus (T2DM), are associated with the presence of NAFLD.

Strong consensus

NAFLD and T2DM are mutually associated in terms of incidence and prognosis.

Strong consensus

Older age, being male and of Hispanic descent are associated with the presence of NAFLD.

Strong consensus

NAFLD has a relevant genetic predisposition.

Strong consensus

NAFLD is associated with increased mortality in the general population. This is due to cardiovascular diseases, cancers and the liver disease itself.

Strong consensus

The stage of fibrosis (staging) is decisive for the prognosis.

Strong consensus

Commentary

Liver-related morbidity and mortality: Although histological NASH is generally considered the progressive form of NAFLD, it has repeatedly been shown that NAFLD can also take a progressive course [67–70]. In a meta-analysis of 11 studies with paired biopsies, the fibrosis progression by one stage was 14.3 years for NAFLD and 7.1 years for NASH [67]. In another large study (n = 646), the mean time to developing end-stage liver cirrhosis was investigated using biopsy-confirmed NAFLD over an observation period of 20 years. This showed for F0: 33.4; F1: 34.1; F2: 22.7; F3: 11.8 and F4: 5.6 years, respectively. The presence of NASH had no significant influence on these estimates (likelihood ratio test > 0.05 for all fibrosis stages) [69]. Nevertheless, the most important factor for prognosis in NAFLD is the underlying stage of fibrosis [18]. The greatest risk of both liver-specific and overall morbidity and mortality of NAFLD was found to be advanced fibrosis (F3) and liver cirrhosis (F4). The following event rates were registered over an average observation period of 5.5 years: 8 % all-cause mortality, 8 % LT, 19 % first-time hepatic decompensations, 9 % HCC, 3 % vascular events and 7 % non-hepatic malignancies. The transplant-free 10-year survival was 94 % for F3 and 45.5 % for F4. In F3, there were higher cumulative incidences of vascular events (7 % vs. 2 %) and non-hepatic malignancies (14 % vs. 6 %). In contrast, the proportion of hepatic decompensations and HCC was increased in patients with liver cirrhosis: 44 % vs. 6 % and 17 % vs. 2.3 % [19].

These data suggest that cardiovascular and non-hepatic morbidity and mortality are more common in non-cirrhotic NAFLD patients, while complications of advanced liver disease determine the further prognosis in cases of established liver cirrhosis. The latter includes the risk of developing HCC. Depending on the region and study population, the prevalence rates range between 0.8 % and 34 % [19, 71–75]. The major challenge is that, even in

the non-cirrhotic liver, the risk of NAFLD developing into HCC is 20–50 % [72, 74, 76, 77]. NAFLD is increasingly becoming an indication for LT. In the USA, it is currently the second most common LT indication with an increase of 167 % in the period 2003–2014; in Germany, this trajectory is constantly upwards [78, 79].

Cardiovascular and non-hepatic morbidity and mortality: Depending on the stage of fibrosis, patients with NAFLD have an increased liver-related mortality and all-cause mortality compared to healthy controls [18, 19, 62]. The main causes of death are cardiovascular related [62, 80]. In a retrospective analysis of 619 NAFLD patients over the period 1975–2005 and a median follow-up of 12.6 years, cardiovascular disease was the most common cause of death (38 %), followed by non-hepatic cancer (19 %) and complications of liver cirrhosis (8 %) [71]. Similar data were reported in two prospective studies from Sweden with a follow-up of up to 33 years: cardiovascular causes of death 43 % and 48 %, non-hepatic tumors 23 % and 22 % and liver-related mortality 9 % and 10 %, respectively [81, 82].

Extrahepatic tumors: A meta-analysis of 6,263 patients showed that NAFLD is associated with colorectal adenomas (OR 1.74; 95 % CI: 1.53–1.97) [83]. In one historical cohort study on 25,497 participants observed over 7.5 years, patients with NAFLD, particularly those with advanced fibrosis, showed an increased incidence of colorectal cancer in men and breast cancer in women, in addition to the known risk of HCC [84].

Screening

RECOMMENDATIONS

Screening for NAFLD in adults cannot be recommended for the general population.
Recommendation open, strong consensus

Whenever any risk factors for the development of NASH exist, (non-invasive) diagnosis should be carried out. Therefore, patients with T2DM, metabolic syndrome, overweight/obesity or arterial hypertension should undergo a screening examination.
Recommendation, strong consensus

Patients with persistently or repeatedly elevated liver enzyme should similarly be examined for underlying NAFLD.
Recommendation open, strong consensus

Screening should be carried out by general practitioners or primary care physicians (including pediatricians, internists in primary care).
Recommendation open, strong consensus

Diabetologists, endocrinologists and cardiologists should also evaluate patients from risk groups for NAFLD.
Recommendation, strong consensus

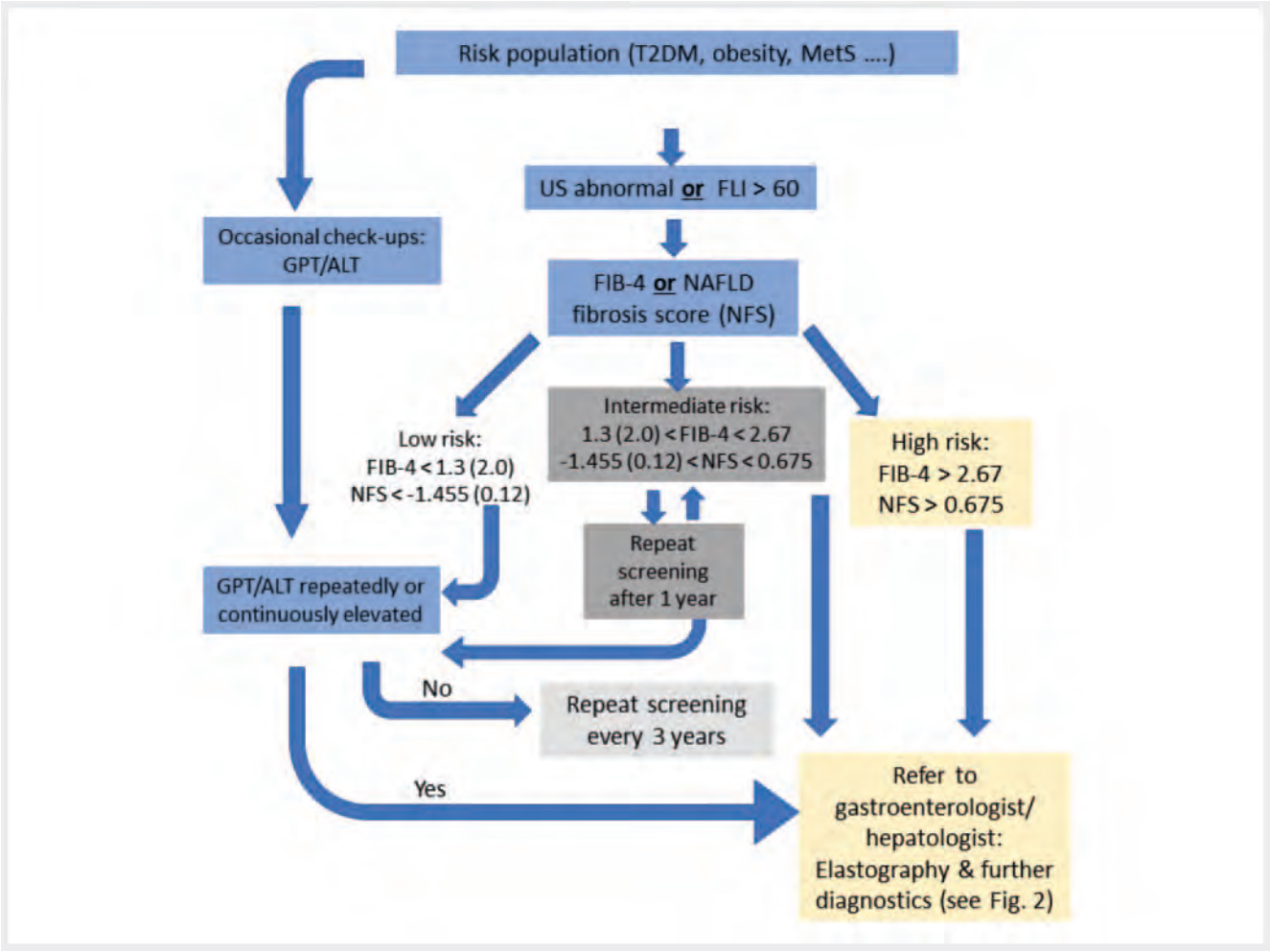
Screening should be carried out using ultrasound and non-invasive scores calculated from routine parameters (e. g. routinely available laboratory parameters, anthropometric measurements such as BMI, waist circumference, etc.).
Recommendation, strong consensus

Patients with continually or repeatedly significant elevations in GPT/ALT should be referred to a gastroenterologist/hepatologist for further diagnostic clarification, regardless of the screening results.
Strong recommendation, strong consensus

Commentary

NAFLD usually has an asymptomatic course and is often diagnosed incidentally [85]. Despite an NAFLD prevalence of 20–30 %, the progression to NASH and NASH fibrosis is not high enough to recommend a screening for NAFLD in the general population [86, 87]. This makes screening all the more important in the group of patients with an increased risk. Elevated liver enzyme levels alone are not a sufficient screening criterion, as NAFLD can also be present at normal transaminase levels. T2DM and obesity are independent risk factors for developing NASH-related fibrosis [88, 89]. Several studies show a clear association with factors related to metabolic syndrome [90–92]. If these risk factors are present, the NAFLD prevalence increases to 60–75 % and thus justifies screening [86]. In German cohorts, the above-mentioned risk factors were observed in patients with NAFLD plus age > 50 years [66, 93]. When several other diseases are present, NAFLD should be diagnostically clarified. There is a reciprocal correlation with coronary artery disease. NAFLD should also be considered in diseases such as polycystic ovarian syndrome (PCO), sleep apnea, hypothyroidism, depression and renal insufficiency [32, 94]. A general screening of relatives does not appear to be justified. Screening in the presence of the aforementioned factors has proven cost-effective, at least in the USA, by preventing liver-specific diseases and endpoints [95]. A decision to implement screening is determined more by the care structures of a particular health care system than by the availability of particular screening procedures. Nevertheless, the design of a screening algorithm must be aligned with the capabilities of those performing the screening (see Recommendation below) [96–98]. In Germany, almost all patients are primarily cared for by general practitioners. A proportion of the patients defined in the risk population (see previous Recommendation) are assigned to specialists (diabetologists/endocrinologists, cardiologists). However, large numbers of patients with T2DM, obesity and arterial hypertension are treated exclusively by general practitioners (e. g. as part of disease management programs).

Due to access to patients, comprehensive risk population screening in Germany can only be in the hands of primary care physicians, possibly supported by diabetologists and cardiologists. This group of physicians is particularly suited to broadly identify the major risk diseases for NAFLD and thus to determine the individual NAFLD risk in these patients [99]. This assessment is also in line with existing EASL recommendations [100, 101] and consistent with a recently developed algorithm for general practitioners and diabetologists [102]. Since screening should mainly be carried out by general practitioners see previous recommendation), screening tools must be widely available, inexpensive and non-invasive in order to increase acceptance [94, 98, 99, 101]. A two-step design with verification of steatosis and fibrosis risk improves the specificity (and in some cases even the sensitivity) of the screening [97, 103]. Positively screened patients must be



▶ **Fig. 1** Screening algorithm [rerif].

transferred to a gastroenterologist/hepatologist for further evaluation. Patients with prolonged or repeated elevations in GPT/ALT should be referred for further evaluation as they are generally at increased risk for liver disease [104–106]. Assuming that at least moderate steatosis is relevant, the fatty liver index (FLI) and NAFLD liver fat score (LFS) perform best, with the highest AUROC values at a positive predictive value (PPV) of 99 %, but without reliable exclusion of steatosis below the respective cutoff [107–109]. FLI can be determined from routine parameters in general practice and should therefore be used if, for example, an ultrasound cannot be performed [100]. Scores using readily available routine parameters for the fibrosis risk include the NAFLD Fibrosis Score (NFS), the FIB-4 Score, the APRI Score, the Forns Score and the BARD Score. The first two (NFS, FIB-4) are superior to the last three (APRI, Forns, BARD) in screening fibrosis in the NAFLD cohort [20, 110] and have also been investigated in Germany [93, 111]. In a recent systematic review, this was confirmed especially for the "hardest" endpoint (mortality) [112]. FIB-4 and NFS are also suitable for screening patients with normal ALT [113] and can be easily determined using internet-based calculators.

In population screening, all scores have noticeable weaknesses [114]. The discriminatory performance of all tests is markedly better in high-risk collectives [114]. Both FIB-4 and NFS have lower specificity in patients > 65 years of age [115], which may increase the referral rate to specialists due to a higher proportion of false-positive screened patients. Data from a screening study on type 2 diabetes patients show that the use of age-adjusted cutoffs on FIB-4 (in delineating negative vs. intermediate) reduces the number of patients tested as intermediate (from 38.3 % to 15.4 % [97].

The screening strategy proposed in ▶ **Fig. 1** is based on recent proposals and takes into account the aforementioned prerequisites for risk screening by general practitioners or primary care practitioners, but may not currently be evidence-based in several areas. This specifically applies to the handling of the intermediate-risk group, the screening interval in low-risk patients and the cost-effectiveness of the entire algorithm. Moreover, this stated screening recommendation requires appropriate training of the general practitioners.

Potential screening algorithm that contains the two main elements (detection of steatosis **and** fibrosis risk), can be modified according to availability and performed in the general practitioner's office. The algorithm corresponds well with the European algorithm of the EASL Clinical Practice Guidelines [101, 116] and a recently proposed approach for general practitioners and diabe-

tologists [102] but is easier to apply. The sequence of fatty liver index and FIB-4 has been specifically studied for screening in a high-risk population of T2DM patients [97]. The application of age-adjusted cutoff points (in brackets) may be useful in order to reduce the high proportion of individuals tested as persons with intermediate risk. How to manage patients with intermediate risk is the subject of discussion and can be structured in various ways (re-screening or direct referral to a hepatologist).

Value of transabdominal sonography of the liver in NAFL

RECOMMENDATION

Transabdominal ultrasound (US) of the liver should be used as primary imaging for screening in patients with suspected NAFLD.

Recommendation, strong consensus

Commentary

Reference is made to the National S3 Guidelines on Hepatocellular [11, 12]. US is a widely available, cost-effective, radiation-free method that allows assessment of hepatic steatosis. Hepatic steatosis results in an increase in the echogenicity of the liver parenchyma. With increasing steatosis, there is a dorsal weakening of the parenchymal signal. US is thus suitable as a screening method for hepatic steatosis: In moderate and severe hepatic steatosis, good sensitivity (approx. 85 %) is achieved with a specificity up to 98 % [117]. The best results are recorded above a liver fat content of 12.5 %. Above this threshold, there was no significant difference in the AUROC values compared to 1H magnetic resonance spectroscopy (MRS) [118]. Nevertheless, sensitivity is markedly worse in mild steatosis and especially in microvesicular steatosis (sensitivity 69 %) [119]. It is therefore not possible to exclude hepatic steatosis using ultrasound. With regard to possible liver fibrosis, US allows neither a definite diagnosis nor reliable staging. US-based shear-wave elastography techniques are useful to rule out advanced liver fibrosis and liver cirrhosis in NASH. See also Chapter “Diagnostics”.

Value of MRI (magnetic resonance imaging) and computed tomography (CT) in NAFLD diagnosis and screening

RECOMMENDATIONS

CT and MRI should not be used as search or screening methods for NAFLD.

Recommendation, strong consensus

If an MRI or CT scan is available for a different indication, these findings can be used to help diagnose NAFLD.

Recommendation open, strong consensus

Commentary

Because of its radiation exposure, CT should not be used as a screening method for the detection of NAFLD. A differentiation between NAFL and NASH is not possible by CT. In terms of methodology, however, CT is a highly reproducible and objective imaging method for visualizing the fat content of the liver. If the density ratio of the liver and spleen on the native CT has a cutoff > 1.1, a diagnosis of at least moderate hepatic steatosis can be rendered [120]. Dual-energy CT (DECT) is a newer imaging technique based on data acquisition at two different energy settings. It can be used to draw conclusions about the composition of tissues. Individual studies on smaller cohorts have produced promising results for quantifying fat content in the liver, even in comparison with magnetic resonance imaging (MRI) [121].

MRI is a radiologic imaging technology without any radiation exposure. In principle, the proportion of water and fat in the liver can be separated using various magnetic resonance techniques. Fundamentally, the sequences are based on fat suppression techniques such as selective fat suppression, selective fat stimulation or the “short-tau inversion recovery” (STIR) sequence. Another approach is “in-phase” and “out of phase” imaging, where signal intensity alterations of fat and water in the tissue are used in the sense of “chemical shift imaging”. Sufficiently large studies are still lacking; individual studies on relatively small populations with histopathological correlation appear promising with regard to an exact fat assessment [122, 123].

According to the literature, magnetic resonance spectroscopy (MRS) has the highest accuracy for fat assessment but is currently limited to research centers due to a lack of standardization of the methodology and high demands on hardware and software. The same is currently true for MR elastography regarding the detection and staging of liver fibrosis [124, 125]. The MR-based quantification of liver fat content using the “proton density fat fraction” (PDFF) is increasingly recognized as the best method by virtue of its high accuracy, easy post-processing and better availability [126]. Compared to histology as the reference standard, PDFF-based determinations deliver high diagnostic accuracy for the detection of steatosis (histological grade 1–3) with an AUROC of 0.99 (05 % CI 0.98–1.00), a sensitivity of 96 % and a specificity of 100 % with a threshold of 3.7 % [127].

The MR-based differentiation of NAFL and NASH using liver-specific contrast media and T1 mapping is presented in publications as very promising. However, it is a method that has not yet become part of routine clinical practice given the small numbers of cases to date [128, 129].

The value of biomarkers in NAFLD screening

RECOMMENDATIONS

The fatty liver index (FLI) can be used for non-invasive determination of liver fat content as part of screening examinations.

Recommendation open, strong consensus

Other non-invasive scores such as FIB-4 or NAFLD Fibrosis Score (NFS), can be used for screening to identify a risk constellation (advanced fibrosis).

Recommendation open, strong consensus
Genetic analyses as part of a screening examination can currently not be recommended.
Recommendation open, strong consensus

Commentary

A wide range of tests and non-invasive algorithms have been developed to diagnose hepatic steatosis and liver fibrosis. The NAFLD Fibrosis Score (NFS) can be easily calculated from standard laboratory parameters using an online input screen (https://nafldscore.com). The following parameters are entered for the calculation: Age, BMI, IGF/diabetes yes/no, AST, ALT, platelets and albumin. A cutoff score below –1.455 excludes advanced fibrosis with 90 % sensitivity. An NFS > 0.676 confirms a diagnosis of advanced fibrosis with 97 % specificity and 67 % sensitivity. FIB-4 is another common algorithm used for non-invasive fibrosis prediction. It is straightforward to calculate from the parameters for AST, ALT, platelets and age of the patient. The analysis is based on two cutoff points: Patients with a cutoff point < 1.3 have a low risk of fibrosis, while patients with a cutoff point ≥ 2.67 have a high risk of advanced fibrosis [130]. Both scores are well suited for use in screening as they are mainly based on routine parameters. Other non-invasive fibrosis scores such as the ratio of AST to platelets (AST/platelet ratio, APRI) or the BARD score show good negative predictive values (NPV) and are therefore suitable for excluding advanced fibrosis. A current meta-analysis of 16 studies showed that the Enhanced Liver Fibrosis (ELF) test is suitable for diagnosing advanced liver fibrosis in NAFLD patients [131]. The test showed a high NPV, especially in populations with a low NAFLD prevalence (e. g. when used in primary care). In contrast to NFS and FIB-4, the ELF test is comprised of a combination of three values that are not measured routinely: Type III procollagen peptide (PIIINP), hyaluronic acid (HA) and tissue inhibitor of metalloproteinase-1 (TIMP1). Therefore, further studies are needed to determine the use of this marker panel in primary care. The fatty liver index (FLI) was developed in 2006 by Bedogni et al. [132]. The calculation is based on BMI, waist circumference, gamma-glutamyl transferase (γGT) and triglycerides. In studies, the FLI has shown a diagnostic value (AUROC) of 0.813 (95 % CI, 0.797–0.830) for the detection of fatty liver [133]. Measuring cytokeratin 18 (K18, neoepitope K18Asp396-NE) in serum is useful in distinguishing between NAFL and NASH: Higher concentrations of K18 fragments were detected in the blood of patients with NASH. K18 in serum can be measured with an M30 ELISA. More recent meta-analyses show a diagnostic accuracy (AUROC) of 0.82 (0.76–0.88) for the detection of NASH patients [134]. To date, a number of different cutoff points for K18 serum concentrations have been published, which makes the use of this biomarker difficult.

Genetic risks (e. g. *PNPLA3*): It is assumed that about 20 % of the total NAFLD risk is caused by individual predisposition and 80 % by environmental factors [135]. In particular, carriers of the *PNPLA3* p.I148 M risk allele have an increased risk of developing a fatty liver. The risk allele also increases the risk of developing liver damage: Carriers are more likely to develop liver fibrosis, cirrhosis and HCC [136, 137]. The *PNPLA3* p.I148 M risk allele is present as a homozygous or heterozygous genotype in about 50 % of all Caucasians and is therefore a common risk factor for hepatic steatosis and fibrosis. Other, rarer variants, e. g. in the *MBOAT7* and *TM6SF2* genes, have been described as causal pathogenetic factors in NAFLD. More recent studies have shown protective effects from gene variants in *MARC1* and *HSD17B13*. A current analysis [138] of patient cohorts from Italy, Germany and the UK Biobank showed that polygenic risk assessments based on the existence of risk variants in the above-mentioned four genes allow a stratification of NAFLD patients with regard to their liver cancer risk. The now low costs for genetic analyses enable genotyping to be used in routine clinical practice. However, routine genotyping of patients with NAFLD cannot yet be justified. A recently published biomarker combination of K18 fragments, C-terminal procollagen type III N-terminal peptide (Pro-C3), *PNPLA3* p.I148 M genotype and acetyl-high mobility group box 1 significantly improved the diagnostic accuracy for NASH in patients with NAFLD (AUROC: = 0.87, sensitivity 0.71, specificity 0.87) [139].

New developments (microbiota, specific imaging, new biomarkers, AI-based algorithms, etc.)

RECOMMENDATION

Systematic stool tests to screen patients for NAFLD cannot be recommended.
Recommendation open, strong consensus

Commentary

Multiple studies indicate that the intestinal microbiome is involved in both the development and progression of NAFLD [140–142]. However, no specific gut microbiota composition can currently be phenotyped for NAFLD [143]. Therefore, stool diagnostics are currently not suitable for screening or diagnosing NAFLD [144].

3. Diagnostics

Initial diagnostics

RECOMMENDATION

Transabdominal ultrasound (US) should be used as primary imaging in patients with suspected NAFLD, but does not allow the exclusion of hepatic steatosis and no distinction between NAFL and NASH.
Recommendation, strong consensus

Commentary

Reference is made here to the National [11, 12], the EASL-EASD-EASO Clinical Practice Guideline NAFLD [116] and current reviews [145]. Ultrasound (US) is a widely available, cost-effective and radiation-free method that allows the diagnosis of hepatic steatosis when the liver parenchyma shows increased echogenici-

ty. With increasing steatosis, there is additionally a dorsal weakening of the parenchymal signal. US is therefore suitable as a screening method for the detection of hepatic steatosis [146]. For the safe use of US diagnostics, knowledge of sound physics and device configuration is required. The examination should therefore be carried out under the guidance of or by experienced examiners. Under these conditions, US has an excellent specificity (> 95 %) for the detection of advanced hepatic steatosis [147], although its sensitivity is insufficient for minor changes (e. g. for grade S1 steatosis 65 %) [119]. It is therefore not possible to exclude hepatic steatosis using ultrasound.

Controlled Attenuation Parameter

RECOMMENDATION

Controlled Attenuation Parameter (CAP) technology can be used in conjunction with liver stiffness measurements for a survey assessment of the extent of hepatic steatosis.
Strong consensus
An accurate non-invasive determination of the degree of steatosis is not possible using CAP. In severe obesity, a critical interpretation of the findings is necessary.
Recommendation, strong consensus

Commentary

Analysis of the ultrasound signal attenuation is a quantitative parameter for assessing the extent of steatosis. Controlled Attenuation Parameter (CAP) technology is a Vibration-Controlled Transient Elastography (VCTE), using software that evaluates the signal attenuation of ultrasound impulses in liver stiffness [148]. CAP was initially only available for the M-probe of the VCTE and has, in numerous histology-controlled studies, shown good diagnostic accuracy for the detection and grading of steatosis in liver diseases of various etiologies [149]. The cut-off for the detection of steatosis was 248 dB/m [149]. However, in patients with NAFLD, who are often obese, an XL probe is needed in many cases. To date, histology-controlled data available on using a XL-CAP probe show a potentially high diagnostic accuracy for the detection of steatosis in suspected NAFLD (sensitivity 80 % and specificity 83 % with a cut-off of 302 dB/m²) [150]. In NAFLD, even with an adequate combination of M and XL tubes, CAP did not show sufficient accuracy to differentiate the individual degrees of steatosis [151]. In a meta-analysis of individual patient data, various quality indicators [152] did not lead to any improvement in the accuracy of CAP [151].

In pilot studies, CAP technology was suitable for assessing steatosis progression, e. g. after bariatric intervention [153]. The prognostic significance of a CAP reduction has not been proven to date [154]. Initial data are available in the comparison of attenuation imaging (ATI) with histology and MRI [155, 156]. The diagnostic accuracy of ATI for detecting steatosis tended to be higher than that of CAP (AUC 0.90 vs. 0.85). The routine clinical use of CAP in NAFLD diagnostics cannot currently be recommended due to the limited amount of data.

Value of magnetic resonance imaging and computed tomography in the diagnosis of NAFLD

RECOMMENDATION

Magnetic resonance-based procedures (MR-PDFF, MR-S) can be performed to quantify fat deposition in the liver. Computed tomography (CT) should not be used in the primary diagnosis of NAFLD.
Recommendation open/Recommendation, strong consensus

Commentary

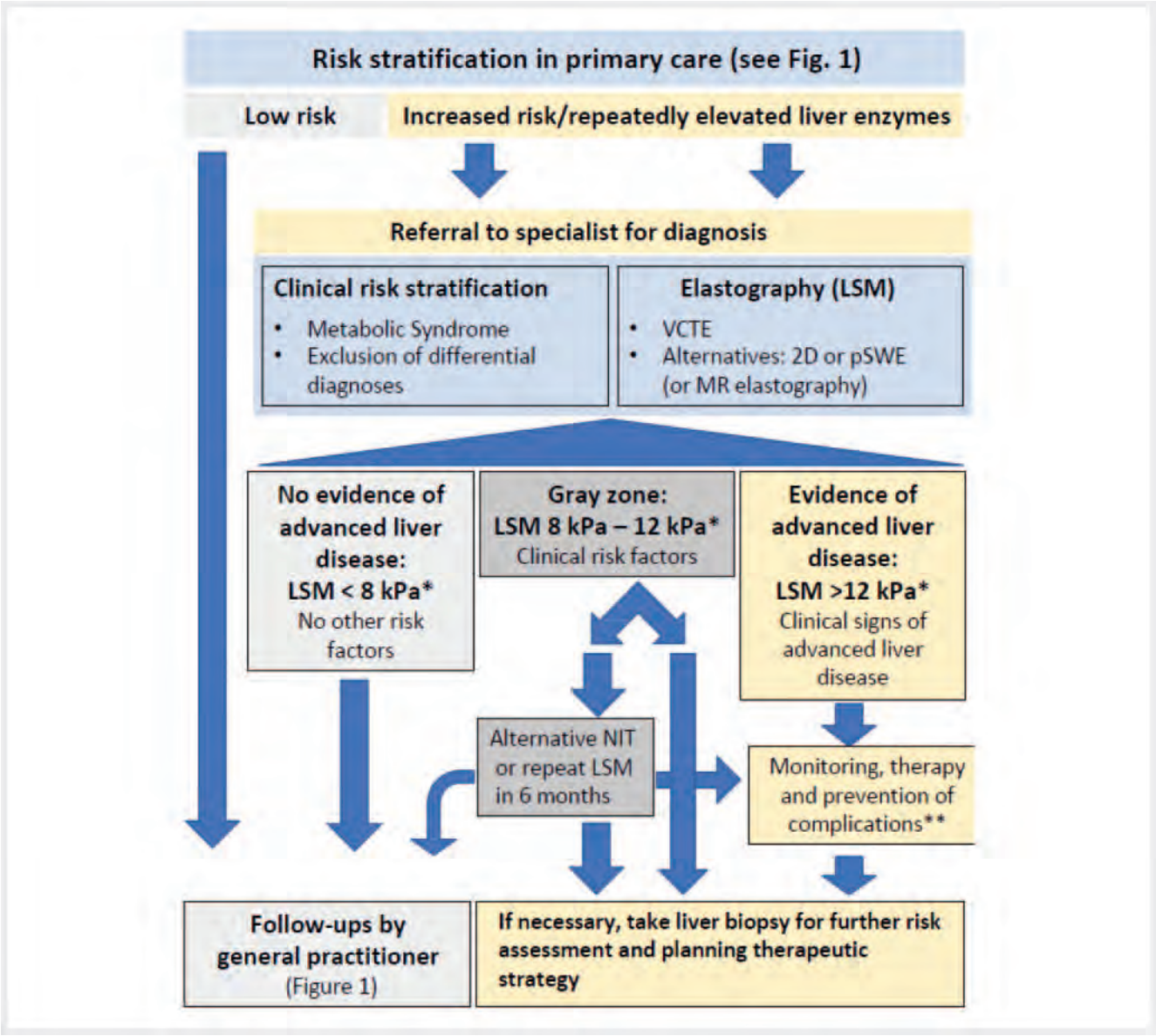
Reference is made to the EASL-EASD-EASO Clinical Practice Guideline NAFLD [116]. Because of its radiation exposure, CT should not be used as the primary diagnostic method for detecting NAFLD. In terms of methodology, however, CT is a highly reproducible and objective imaging method for visualizing the fat content of the liver. Hepatic steatosis can be diagnosed by multiparametric comparisons of parenchymal signal attenuation on native CT. For example, the attenuation of the parenchymal signal of more than 10 Hounsfield units compared to the spleen is a suitable diagnostic criterion. However, the sensitivity for steatosis of mild severity is low [157].

In principle, the proportion of water and fat in the liver can be separated using various magnetic resonance techniques. The Proton Density Fat Fraction (PDFF) method determines the signal ratio of triglyceride protons compared to the total amount of protons (triglycerides and water). The data is given in percent [158]. In several comparative studies, MR-PDFF showed the highest sensitivity and specificity of all non-invasive methods for the detection of hepatic steatosis [145, 159] and is currently the only method that can non-invasively grade the extent of steatosis in NAFLD with reliability. It should be noted that the information is based on the relative triglyceride content, but cannot provide any information about the histological distribution [160]. Due to the diagnostic precision, MR-based methods appear to be suitable as a reference standard for diagnostic and Interventional studies [158, 161]. However, clinical use is currently limited to centers due to low availability and hard- and software requirements. The predictive importance of the steatosis dynamics characterized by means of MR techniques in therapy studies has not yet been finally defined [124, 154].

Diagnostic algorithm

RECOMMENDATIONS

In the initial diagnosis of NAFLD, risk stratification should be carried out in all patients regarding the underlying fibrosis stage. For this, non-invasive tests/scores (NFS, FIB-4) or elastography, possibly also in combination, should be used.
See ▶ **Fig. 2**.
Recommendation, strong consensus
The control intervals for repeating non-invasive test procedures should be based on the initial findings.
Recommendation, strong consensus



▶ **Fig. 2** Diagnostic algorithm in NAFLD for individuals with suspected increased risk of progression (consensus). 2D-SWE: 2 D shear-wave elastography; LSM: Liver stiffness measurement; NIT: Non-invasive (fibrosis) test; pSWE: Point shear-wave elastography; VCTE: Vibration-controlled transient elastography; *The diagnostic cutoffs refer to VCTE. When using a different elastography method, method-specific requirements must be considered. **See Chapter 5 "Monitoring and long-term management of NAFLD" [rerif].

Commentary

Non-invasive fibrosis scores such as FIB-4 or NFS are suitable for risk assessment during the primary diagnostic workup of high-risk patients (e. g. with obesity, T2DM or metabolic syndrome) in whom diagnostic imaging (e. g. by US) confirms hepatic steatosis or where elevated liver enzymes (GOT, GPT and/or γGT) were found and NAFLD is suspected, once other causes have been excluded [32, 116].

Because of the high negative predictive value (NPV) of FIB-4 or NFS (≥ 90 %) [162, 163], advanced fibrosis can be excluded with a high degree of probability, taking into account the lower cutoff point (FIB-4 ≤ 1.3 or NFS <-1.455). In patients with a low risk of fibrosis, the monitoring, e. g. of FIB-4 or NFS and transaminases, can be carried out at regular intervals. For patients with FIB-4 or NFS in the intermediate group (between the two cutoff points) or high group (FIB-4 ≥ 2.67 or NFS> 0.676), an elastography using VCTE is recommended as a further test method after taking relevant comorbidities into account [32, 116, 145]. Alternatively, shear-wave-based elastography methods can be used, taking the manufacturer-specific cut-offs into account [162]. Shear-wave elastography (SWE) technologies are available as software components on many modern ultrasound devices and can therefore be used easily when performing abdominal ultrasound (see Recommendation below). However, compared to VCTE, the SWE procedures are not well evaluated for NAFLD risk stratification and have not yet been considered in the current recommenda-

tions from international specialist societies for clarifying NAFLD (EASL Guideline 2016, AASLD Practice Guidance NAFLD 2018) [32, 116, 145].

Elastography can be invoiced with the OPS Code 3–034 Version 2021 (Complex differential diagnostic sonography using tissue Doppler imaging and tissue deformation analysis). In several studies, the VCTE LSM showed a high NPV for the exclusion of advanced fibrosis, with cutoff values differing only slightly [164, 165]. For this reason, an LSM value of 8 kPa can be regarded as a sensitive threshold value in practice. LSM values in the 12 kPa show a high sensitivity for the presence of liver cirrhosis. If the M and XL probes are used correctly, no adjustments of the cutoffs are necessary [150, 166]. Patients with FIB-4 > 1.3 or NFS ≥ –1455 and an LSM below the low cutoff point (< 8 kPa) can undergo monitoring of, for example, transaminases, FIB-4/NFS and VCTE, at regular intervals. Patients in whom the LSM is between the low and high cutoff value (8–12 kPa) have a medium risk of an underlying advanced fibrosis and require further clarification. Liver biopsy should be considered for these patients. A liver biopsy should also be considered in patients with a high LSM of > 12 kPa, unless there is clear evidence of liver cirrhosis from laboratory parameters, clinical symptoms or diagnostic imaging (▶ **Fig. 2**). Patients with clear evidence of liver cirrhosis, diagnosed with non-invasive procedures, or confirmed advanced fibrosis/cirrhosis, diagnosed with liver biopsy, require regular monitoring for the development of liver-associated complications [11, 12].

Value of elastography and biopsy

RECOMMENDATIONS

Ultrasound-based elastography procedures can be used to rule out advanced liver fibrosis and liver cirrhosis in NAFLD.
Recommendation open, strong consensus

A liver biopsy should be performed if fibrosis is to be reliably detected or ruled out.
(See also Chapter "Definition").
Strong recommendation, strong consensus

Patients with evidence of cirrhosis, diagnosed using non-invasive procedures or histologically, should be monitored regularly for the development of liver-related complications.
See Chapter 5.
Strong recommendation, strong consensus

Commentary

Depending on the risk profile, the use of combined multi-stage methods or repeated elastography can improve the diagnostic accuracy. Parameters of classic B-scan and duplex sonography cannot reliably differentiate between simple NAFL and NASH with fibrosis [145]. In addition, even when using high-frequency probes, B-mode sonography has limited sensitivity for the detection of compensated advanced chronic liver disease (cACLD) [167]. Elastographic methods can better capture the extent of fibrotic changes in the liver parenchyma by measuring the elasticity of the liver tissue and also provide a quantitative assessment. Transient elastography (TE), particularly vibration-controlled TE (VCTE) in a stand-alone device, as well as shear-wave-based methods (SWE) such as point SWE (pSWE) and 2D-SWE, are available [145, 168]. The SWE methods are integrated into ultrasound devices and marketed by manufacturers under different names, e. g. Acoustic Radiation Force Impulse Imaging (ARFI, Siemens), Elast-PQ (Philipps) and Supersonic Shear-Wave Elastography. Strain elastography, which is often used for other organs, has no merits in clinical practice [145, 168, 169].

VCTE and SWE have been evaluated in histology-controlled studies mainly in patients with viral hepatitis [170–172] and showed a high NPV for the exclusion of advanced fibrosis and/or cirrhosis. Quality indicators of liver stiffness measurement using VCTE and pSWE are well established over a longer time [168, 171]. The following VCTE cutoffs have been proposed for the diagnosis of advanced fibrosis in NAFLD: 7.9 kPa with a sensitivity of 91 %; 9.6 kPa with a specificity of 92 %. VCTE using the M-probe is limited in obese patients (BMI > 30 kg/m²) and associated with false-positive results [173]. Meanwhile, the applicability of VCTE has been optimized by the XL probe [164] and its importance in NAFLD has been proven in large studies [150, 174] and meta-analyses [175, 176]. In morbid obesity, valid measurements can only be obtained in approx. 60 % of cases [177]. In the largest prospective multicenter European study with 373 evaluated patients, these cutoffs were established: **8.2 kPa for F ≥ 2**, sensitivity 71 %, spec. 70 %; **9.7 kPa for F ≥ 3**, sensitivity 71 %, spec. 75 %; **13.6 kPa for F4**, sensitivity 85 %, spec. 79 %; F4 Cutoff for 90 % sensitivity 10.9 kPa [150], independent of the probe used (M or XL) [150, 166]. Serial examinations could increase the positive predictive value if parameters were abnormal at both measurement times [178].

Histology-controlled data for use in NAFLD patients are also available for pSWE and 2D-SWE [179, 180]. The advantage of these techniques is the better applicability in obesity [175], whereby anthropometric factors have to be taken into account when interpreting the measurements [181]. Depending on the method, the cut-off points [182] and the diagnostic accuracy [183] in NAFLD patients are in the range of VCTE. A diagnostic superiority compared to VCTE has not yet been proven [184]. VCTE and the SWE-based methods should be carried out by experienced users, whereby technical and patient-related influencing factors must be taken into account [185]. SWE-based methods are more complex to perform than VCTE and should be used by an experienced doctor. Liver stiffness should be determined at least three hours after the last meal in a standardized position, avoiding extreme breathing maneuvers. As acute hepatitis as well as extrahepatic diseases such as right heart failure and obstruction of the biliary tract lead to changes in the elasticity of the liver, these confounders must be recorded and evaluated with appropriate measures. In contrast, the influence of severity of steatosis on liver stiffness measurement is low [186]. For detailed instructions on how to use the individual elastographic methods, please refer to the recommendations of the specialist societies [168, 169, 187]. In particular, manufacturer-specific recommendations and technology-adapted cutoffs must be observed [188, 189].

Analogous to steatosis quantification, MR techniques can also be used to assess liver fibrosis. Compared to the ultrasound methods listed above, MR elastography (MRE) had a somewhat higher

diagnostic accuracy [176, 184] and, in combination with serum markers, showed a high positive predictive value [190].

Fibrosis scores

RECOMMENDATIONS

The NAFLD Fibrosis Score (NFS) and the FIB-4 Index can be used as non-commercial and easy-to-perform tests to rule out advanced liver fibrosis (F3 / F4) in NAFLD.

Recommendation open, strong consensus

In NAFLD, suspected advanced fibrosis (F3 / F4) can also be primarily clarified by elastography.

Recommendation open, strong consensus

Commentary

The diagnostic value of the NFS and FIB-4 index to exclude advanced liver fibrosis is comparable, whereby the FIB-4 is based on fewer parameters. The FIB-4 index is therefore easier to determine, less expensive and should be prioritized.

The NFS includes age, BMI, glucose intolerance/diabetes mellitus, platelet count, albumin and AST/ALT ratio, which can be calculated free of charge using http://nafldscore.com. In a meta-analysis of 64 studies with 13 046 patients, the diagnostic accuracy (AUC) of the NFS for the diagnosis of advanced fibrosis (F ≥ 3) was 0.84 [20]. The NFS takes into account a low and high cutoff value of < –1455 and> 0.676. With an NFS of < –1455, advanced fibrosis could be excluded with a sensitivity of 82 % (exploration cohort, n = 480) or 77 % (validation cohort, n = 253) and NPV of 93 % or 88 % [162].

The **FIB-4 Index** is a cost-free test that can be calculated via http://gihep.com/calculators/hepatology/fibrosis-4-score/ and consists of age, platelet count, AST and ALT. For the FIB-4 index in NAFLD, a low and high cutoff value of 1.3 and 2.67 was identified for the assessment of advanced fibrosis [163]. In a study of 541 NAFLD patients, a NPV of 90 % for excluding advanced fibrosis was found for FIB-4 with a cutoff value of ≤ 1.3 [163]. In the meta-analysis of 64 studies with 13 046 patients, the diagnostic accuracy of the FIB-4 score was comparable to the NFS (AUC = 0.84) [20]. As the specificity of FIB-4 and NFS markedly decreases from ≥ 65 years, an age-adapted cutoff value (from ≥ 65 years) was determined for both. This is 2.0 for FIB-4 and 0.12 for NFS for the exclusion of advanced fibrosis (F3/4). With these cutoff points, the specificity in older patients could be improved to 70 % without reducing sensitivity (FIB-4: Sensitivity 77 % at cutoff 2.0; NFS Sensitivity 80 % with cutoff 0.12). The power of both tests is also markedly limited in young patients < 35 years of age [115]. How far the age-adapted cut-off points for FIB-4 and NFS need to be taken into account must be further evaluated, as their use in individuals ≥ 65 years increases specificity but clearly reduces sensitivity [191].

NFS and FIB-4 were compared to other scoring systems such as APRI (AST/platelet ratio index) and BARD score, BMI, AST/ALT ratio and diabetes mellitus, and for TE using VCTE and evaluated for diagnosing advanced fibrosis in NAFLD. In a multi-center and single-center study of 741 and 323 NAFLD patients, FIB-4 and NFS were superior to the **BARD score** [111, 192] and APRI [192]. In the multi-center study, a comparison with TE using VCTE (cutoff points: < 7.9 kPa and ≥ 9.6 kPa) was also carried out. TE was shown to be superior to non-invasive scores, including NFS and FIB-4, in predicting advanced fibrosis (AUC: TE = 0.86, NFS = 0.77 and FIB-4 = 0.79; NPV: TE = 94 %, NFS = 87 % and FIB-4 = 85 %). The rate of false positive results was higher for TE and the rate of false negative results was higher for NFS and FIB-4 [192]. In another comparative study with 245 NAFLD patients, the TE (cutoff points were: < 7.9 kPa and ≥ 9.6 kPa) significantly better for the diagnosis or exclusion of advanced liver fibrosis (AUC 0.93) compared to the AST/ALT ratio (AUC: 0.66), APRI (AUC 0.74), FIB-4 (AUC: 0.80), NFS (AUC: 0.75) and BARD score (AUC 0.69) [165]. A multicenter study of 452 NAFLD patients from France also demonstrated a higher diagnostic accuracy of TE (0.83) for the detection of advanced fibrosis compared to BARD (0.69), APRI (0.75), FIB-4 (0.78) and NFS (0.73) [110]. The superiority of TE using VCTE (n = 126; cutoff values: 8 kPa) compared to NFS (n = 233), FIB-4 (n = 243) and APRI (n = 243) to diagnose advanced fibrosis was further confirmed in a single-center NAFLD study from Germany (NPV: 97 % versus 92 %, 91 % and 90 %; sensitivity: 91 % versus 69 %, 69 % and 77 %) [93]. Recently, the **Hepamet Fibrosis Score** (HFS), which takes age, gender, HOMA-IR, diabetes mellitus, GOT, albumin and platelets into account, was evaluated in a multicenter cohort of 2452 NAFLD patients and compared to NFS and FIB-4. This score takes into account a low and high cutoff (0.12 and 0.47) for the exclusion or detection of advanced fibrosis (sensitivity 74 %, specificity 97 %, NPV 92 %, PPV 76 %) [193]. The HFS is freely available online (https://www.hepamet-fibrosis-score.eu) and does not require age-adjusted cutoffs. The HFS also showed a high diagnostic value in NAFLD patients with normal weight or normal transaminases and was superior to the NFS or FIB-4.

A blood-based marker panel (NIS4), consisting of HBA1c, alpha2-macroglobulin, YKL-40 and miR-34a-5 p, using a low and high cutoff point (< 0.36 and > 0.63), excluded NASH with significant NAFLD activity (NAS ≥ 4) and fibrosis (≥ F2) with a sensitivity of 81.5 % and an NPV of 77.9 % and confirmed it with a specificity of 87.1 % and a PPV of 79.2 % [194].

Non-invasive diagnostics of inflammatory activity

STATEMENT

There is currently no established imaging method available for the non-invasive assessment of inflammatory activity.

Strong consensus

Commentary

In pilot studies, MR-based technologies as well as a liver stiffness score, attenuation measurement and laboratory parameters showed good diagnostic characteristics for the non-invasive prediction of NASH. Measuring inflammatory activity remains a challenge for imaging techniques. Conventional US diagnostics do not offer any reliable diagnostic criteria for the detection of NASH [145]. Liver stiffness is modulated not only by fibrotic changes but also by inflammatory activity, although the inflammatory

component is moderate in most patients. Therefore, this technology alone does not offer any possibility of further differentiating between fibrosis and inflammatory activity [145]. The additional determination of tissue viscosity during elastographic analysis (dispersion slope) is a new method that shows a clear correlation with lobular inflammation [195, 196].

An algorithm consisting of liver stiffness (surrogate of fibrosis), attenuation measurement (surrogate of steatosis) and AST was, in a multicenter, histology-controlled study, predictive of underlying NASH with significant NAFLD activity (NAS ≥ 4) and fibrosis (≥F2) [197]. This FAST score showed an NPV of 85 % (sensitivity 90 %) with a cutoff of ≤ 0.35 and a PPV of 83 % (specificity 90 %) with a cutoff of ≥ 0.67 %) for the exclusion or confirmation of NASH with NAS ≥ 4 and ≥F2. In bariatric patients, the FAST score correlated with the decrease in inflammatory activity [198].

In addition to the US-based methods, MR-based methods appear to be suitable for differentiating NASH and NAFL [145]. In particular, the determination of the "iron-corrected T1" (cT1) is a promising parameter [199] which, in combination with a liver function test, showed promising results [200].

Individual serum markers

STATEMENT

There are no well-established non-invasive markers for diagnosing NASH.

Consensus

Commentary

Cytokeratin-18 (K18) fragments are released from apoptotic hepatocytes and can be detected in the blood (M30 ELISA) [201–203]. This biomarker for cell death has been evaluated in numerous international studies to assess disease activity in NAFLD [201, 203–207]. In a meta-analysis of 11 studies with 822 patients, the overall sensitivity and specificity of K18 fragments were 66 % and 82 % for the diagnosis of NASH [134]. Another meta-analysis of 9 studies and a total of 856 patients reported an overall sensitivity of 78 % (0.64–0.92) and specificity of 87 % (0.77–0.98) as well as a diagnostic value (AUC) of 0.82 (0.78–0.88) [208]. The detection of K18 fragments showed a close correlation to histological inflammation and hepatocellular ballooning and thus reflected the inflammatory liver damage in NASH [207, 209]. Blood levels for K18 fragments also correlated with fibrosis In NAFLD [207, 209, 210]. Here, an AUC of 0.82 [201], 0.86 [207], 0.93 [209] and 0.88 [205] was determined for the K18 marker. The high diagnostic value of K18 determined in these studies could not be proven in a study on predominantly Latin American NAFLD patients. This showed a sensitivity/specificity of 58 %/68 % and 54 %/85 % with a correspondingly lower AUC of 0.65 and 0.68 for the diagnosis of NASH and fibrosis [210]. A recently published multicenter study of NAFLD patients from Germany showed that when the K18 marker detected false-positive NASH, the majority of patients had an inflammatory activity of at least 1 in the NAS and vice versa; the majority of patients with a false-negative result for NASH showed little or no fibrosis when the K18 marker was used [211]. One limitation of the K18 marker is the lack of a uniform cut-off for the detection of NASH in patients with suspected NAFLD. In several studies, a cutoff value for K18 of around 200 U/L was determined, which enabled a distinction between NASH and NAFL with the best possible sensitivity/specificity [201, 206, 209, 210].

The consideration of the K18 marker in scores such as the CHek-Score [212] or MACK-3-Score [213] is less well evaluated in contrast to its use as an individual parameter for assessing NAFLD activity. The MACK-3 score takes into account K18, GOT and an insulin resistance determined by HOMA (Homeostasis Model Assessment). A MACK-3 score ≤ 0.134 or ≥ 0.550 showed a 90 % sensitivity and 94 % specificity for the diagnosis of fibrotic NASH (NAS ≥ 4 and fibrosis F ≥ 2) [213]. Since the scores mentioned were mainly evaluated in patients with pronounced obesity or metabolic syndrome, their diagnostic value in NAFLD patients without obesity or metabolic syndrome remains unclear at present. Due to the lack of widely available elastography methods in extended primary diagnostics, e. g. in intermediate NFS/FIB-4 (FIB-4: 1.3–2.67 or NFS: -1,455–0,675), the subsequent determination of K18 or K18-based scores can be helpful in identifying patients with possible fibrotic NASH [211]. As an alternative to K18, the above-mentioned NIS4 for detecting fibrotic NASH could be considered in extended primary diagnostics or in prescreening for therapy studies. The determination of this marker panel in everyday clinical practice cannot currently be recommended.

Evaluation of risk factors and comorbidities in NAFLD

RECOMMENDATIONS

NAFLD patients should be evaluated regarding their cardiovascular risk in the same way as other at-risk patients, as per guidelines of the cardiological specialist societies.

Strong recommendation, strong consensus

Because of the close and reciprocal association of NAFLD with metabolic risk factors, the diagnosis of NAFLD should document BMI, abdominal circumference, blood pressure and fasting glucose, HbA1c, triglycerides and LDL and HDL cholesterol.

Strong recommendation, strong consensus

In addition, malnutrition, sarcopenia, physical and mental fitness and medication intake (including OTC* preparations) should be recorded using appropriate examinations or scores.

Recommendation, strong consensus

Commentary

Because of the increased risk of cardiovascular morbidity and mortality in NAFLD, cardiovascular risk stratification should be undertaken. Initially, this should be done using risk scores (e. g. HEART score) and detailed recording of risk factors. Existing diseases should be identified at an early stage and preventive and therapeutic measures initiated. Metabolic risk factors such as arterial hypertension, dyslipidemia and particularly (visceral) obesi-

* OTC, over the counter, medicinal product that does not require a prescription and can be purchased without a doctor's prescription.

ty and T2DM are associated with a higher prevalence of NAFLD [214]. The NAFLD prevalence increases with increasing BMI and was over 95 % in patients undergoing bariatric surgery [215, 216]. Conversely, in a large meta-analysis, the global obesity prevalence in NAFLD was 51.34 % (95 % CI: 41.38–61.20) and with NASH in 81.83 % (95 % CI: 55.16–94.28) [62]. The association between T2DM and NAFLD is bidirectional. On the one hand, the prevalence of NAFLD in T2DM is twice that of the general population. According to a meta-analysis of 80 studies with 49,419 people from 20 countries, it was 55.5 % globally (95 % CI: 47.3–63.7), with the highest reported prevalence of 68 % (95 % CI: 62: 1–73) in Europe [217]. On the other hand, T2DM favors the advanced forms of NAFLD. The global prevalence of NASH in T2DM was 37.3 % (95 % CI: 24.7–50.0 %) and 17 % (95 % CI 7.2–34.8) of patients with NAFLD and T2DM have advanced fibrosis (≥ F3) [217]. The prevalence of NAFLD is also increased in underlying arterial hypertension. A cross-sectional study from Brazil that included 5362 people with normal blood pressure, prehypertension (untreated systolic blood pressure 120–139 mmHg or diastolic blood pressure 80–89 mmHg) and hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or antihypertensive medication) showed significantly different NAFLD prevalence rates of 16.5, 37.5 and 59.3 % ($p < 0.001$) [218]. On the other hand, the global prevalence of hypertension in patients with NAFLD and NASH was 42.54 % (95 % CI: 30.06–56.05) and 70.65 % (95 % CI: 54.64–82.79) [62]. Dyslipidemia, defined as an increase in serum triglycerides (TG) and LDL cholesterol with low HDL cholesterol, is another metabolic risk factor for an increased NAFLD prevalence. A large cross-sectional study from Taiwan with 44 767 individuals showed that those with the highest total cholesterol to HDL and TG to HDL ratios showed a NAFLD prevalence of 78 %, while the NAFLD prevalence for the lowest ratios was 33 % [219]. The global prevalence of dyslipidemia in NAFLD and NASH is 40.74 % (95 % CI: 30.80–51.50) and 83.33 % (95 % CI: 36.87–97.72) [62].

In addition, age, gender and ethnicity influence the prevalence of NAFLD. A population-based study with 2811 participants from the Netherlands, mean age of 76.4 years (65.3–98.7 years) showed a prevalence of NAFLD of 35.1 %, which decreased with increasing age [220]. Being male also seems to be a risk factor for NAFLD [221, 222]. However, there are also data that show a higher NAFLD prevalence in females [223]. Ethnicity and related genetic differences are also likely to influence the prevalence of NAFLD. A meta-analysis from the United States showed that Latin Americans had the highest, while African Americans had the lowest NAFLD prevalence. White Americans are placed in between [224]. Familial accumulation of NAFLD due to genetic factors has been observed, e. g. occurring more frequently in monozygous compared to bizygous twins [225] and in family members of overweight children [226]. A possible genetic factor is a polymorphism in the PNPLA3 gene (adiponutrin). Meanwhile, the association of PNPLA3 SNP rs738 409 (Ile148Met) with steatosis and the progression to NASH fibrosis, cirrhosis and HCC has been confirmed repeatedly [136].

NAFLD is associated with extrahepatic diseases; the odds ratios (OR) obtained from meta-analyses are given below: Chronic renal failure (OR 1.37; (95 % CI: 1.20–1.53)), obstructive sleep apnea (OR 2.37; (95 % CI: 1.59–3.51)), hypothyroidism (OR 1.42; (95 % CI: 1.15–1.77)) and psoriasis (OR 2.15; (95 % CI: 1.57–2.94)) [227–230]. Further associations exist with osteoporosis (prevalence 3.6 % with NAFLD vs. 1.5 % without; $p < 0.005$) and polycystic ovary syndrome (PCOS) with an almost four-fold increase in NAFLD prevalence [231, 232].

Estimating prognosis and risk stratification

RECOMMENDATIONS

The diagnostic measures should aim to determine the severity of the disease and thereby predict the individual prognosis and allow risk stratification.

Strong recommendation, strong consensus

The diagnostics for NAFLD should be structured using clinical, laboratory, imaging and, if necessary, histological methods according to the algorithm in ▶ **Fig. 2**.

Recommendation, strong consensus

Patients with incidentally diagnosed fatty liver should also be characterized in the same way.

Strong recommendation, strong consensus

Commentary

The majority of NAFLD cases show a strong association with obesity and T2DM [233–240], with some studies also reporting a NAFLD prevalence in the normal weight population of 7 %–16 % [4, 241–243]. Corresponding to the obesity-related occurrence of NAFLD, there are further associations with various metabolic dysregulations, which are summarized in ▶ **Table 5** (Definition) and which together define the metabolic syndrome. The presence of NAFLD is an independent risk factor for cardiovascular disease. This association is further strengthened by the occurrence of NASH. However, both disease entities do not form a cardiovascular risk equivalent, so that an individual risk assessment should be carried out taking into account previous cardiovascular diseases, age, gender, cholesterol, blood pressure and lifestyle using validated risk scores (e. g. Heart-SCORE). Additional risk modifiers (▶ **Table 5**) must be considered. In addition, family history of cardiovascular disease, the presence of subclinical atherosclerosis, and socioeconomic status should be considered in the risk assessment.

Differentiation of NAFLD from other liver diseases with steatosis

RECOMMENDATIONS

When diagnosing NAFLD, other secondary causes and accompanying liver diseases should be excluded in addition to alcohol (see ▶ **Table 6**).

Strong recommendation, strong consensus

Other comorbidities such as (subclinical) hypothyroidism, polycystic ovarian syndrome and obstructive sleep apnea syndrome should be taken into account when evaluating NAFLD.

Recommendation, strong consensus

▶ **Table 6** Differential diagnosis of hepatic steatosis (strong consensus).

Differential diagnosis of hepatic steatosis	
Genetic diseases including lipid metabolism disorders	Abetalipoproteinemia Hypobetalipoproteinemia Familiar hyperlipidemia Lipodystrophy Hereditary fructose intolerance LAL deficiency (cholesterol ester storage disease (CESD), Wolmann's disease) Wilson's disease Glycogen storage disease See also Table 2 (Liebe et al., 2021) [249]
Nutrition-related causes	Hyperalimentation acquired lipid metabolism disorders Fatty liver as part of the metabolic syndrome Total parenteral nutrition Malnutrition Acute weight loss (bariatric surgery, fasting) Pancreatectomy
Pregnancy	Acute fatty liver of pregnancy (AFLP)
Medications	**Microvesicular steatosis:** Including, but not limited to valproic acid, tetracyclines, nucleoside analogs, acetylsalicylic acid, didanosine, stavudine, MDMA (amphetamines) **Macrovesicular steatosis (+/– steatohepatitis):** Including, but not limited to amiodarone, tamoxifen, methotrexate, corticosteroids, anti-retroviral therapy, irinotecan, spironolactone, sulfasalazine
Endocrine causes	Type 2 diabetes Hypothyroidism Growth hormone deficiency Pituitary insufficiency Adrenocortical tumors Polycystic ovary syndrome (PCOS)/hyperandrogenism Estrogen deficiency/menopause Male hypogonadism
Chronic hepatitis C virus (HCV) infection	Specifically HCV genotype 3
Small intestinal disease	Celiac disease Bacterial overgrowth of the small intestine Short bowel syndrome (anatomical, functional)
Environmental factors, noxae, toxins	See also Table 1 (Liebe et al. 2021) [249]
Idiopathic diseases	Weber-Christian syndrome

Commentary

NAFLD is associated with various comorbidities. These include cardiometabolic diseases, polycystic ovarian syndrome (PCOS) and sleep apnea syndrome. It has also been shown that subclinical hypothyroidism or low normal thyroid function is associated with progressive NAFLD [244]. Low-normal thyroid function was associated with increased all-cause and cardiovascular-related mortality [245]. Hypothyroidism contributed to triglyceride synthesis and insulin resistance and thus enhanced the development of NAFLD [246, 247]. In PCOS patients it could be shown that the apoptotic cell death detected by K18 fragments was associated with insulin resistance and a high NASH prevalence [248].

Differentiation between NAFLD and ALD

RECOMMENDATION/STATEMENT

The detection of Carbohydrate-Deficient-Transferrin (CDT) is not useful for the differential diagnostic work-up of NAFLD versus ALD due to a lack of sensitivity and specificity

Strong consensus

Alcohol biomarkers (see Commentary) can be used to rule out excessive alcohol consumption (e. g. when required for legal purposes).

Recommendation, strong consensus

If there is a need for reliable evidence of alcohol consumption, the amount of ethyl glucuronide in the urine or hair can be determined.
Recommendation open, strong consensus

Commentary

ALD is characterized by an increased GOT/GPT ratio (as long as there is no cirrhosis) and γGT as well as increased MCV and ferritin, which can be considered in the differential diagnosis to NAFLD However, ALD cannot be proven by an increase of these laboratory parameters. ALD cannot be excluded with certainty using individual methods. The clinical history and structured questionnaires such as the CAGE test or AUDIT (-C) questionnaire on alcohol consumption are important [250, 251]. The threshold dose for liver-toxicity is different for each individual and statistically defined and threshold values do not guarantee that a patient would not sustain liver damage from very low alcohol consumption. Alcohol sensitivity is influenced, among other things, by genetics, ethnicity and gender. According to the European and American guidelines, the upper limit of 20 and 30 g alcohol per day is set for women and men, respectively [169, 252]. Both the Asian and German S2k Guidelines stipulate stricter upper limits of 10 and 20 g alcohol per day for women and men, respectively, also taking into account the carcinogenic effects of alcohol [52, 253].

Although there are slight histological differences between NAFLD and ALD, histology does not allow a reliable differentiation between the two diseases [254]. This also applies to hepatic iron overload that can occur in both diseases [54]. There are typical changes in the transaminases, depending on the etiology and the stage of fibrosis [255]. In a direct comparison of 30 patients with ALD and NAFLD (each matched for gender, fibrosis stage and age), there were differences found between the two diseases [55]. In this study, the γGT, GOT, ferritin and MCV were significantly higher in ALD, as expected, but the Hb was lower. In NAFLD, glucose and BMI were higher but not significantly. For differentiating between NAFLD and ALD, the **NAFLD/ALD index** was developed, which takes MCV, AST/ALT ratio, BMI and gender into account [256]. This score also requires prospective validation in larger cohorts in order to check the diagnostic value for its use in everyday clinical practice. **Carbohydrate-deficient transferrin (CDT)** can be detected in higher alcohol consumption (at least 50 g/day over a period of 1–2 weeks), but is not specific for the diagnosis of ALD and can be false negative in liver cirrhosis. The sensitivity and specificity for the detection of CDT can vary considerably, depending on the assay used 250]. **Ethyl glucuronide (EtG)**, on the other hand, has a high specificity as a direct marker for detecting alcohol and can be found in the urine for up to 80 hours after alcohol consumption. With a cutoff for uEtG of 0.1 mg/L, substantial alcohol consumption can be excluded. EtG can be detected in the hair for even longer, with the detection reflecting alcohol consumption of one month per 1 cm of hair. With a cutoff of < 7 pg/mg, general alcohol abstinence can be assumed [250]. Measuring EtG is costly and is reserved for specific situations, such as the evaluation for listing patients for a liver transplant, which requires long-term abstinence from alcohol.

4. Treatment

4a Non-pharmaceutical therapy

RECOMMENDATIONS

Overweight or obese NAFLD patients should reduce their body weight by at least 5 % in order to achieve an improvement in steatosis, inflammation or transaminase levels.
Strong recommendation, strong consensus

To improve fibrosis, overweight/obese patients should aim for a weight reduction of at least 10 %.
Recommendation, strong consensus

NAFLD patients should practice moderate to moderately intense aerobic exercise for 3 hours a week.
Recommendation, strong consensus

Commentary

Weight loss in overweight or obese NAFLD patients leads to a regression of steatosis [116, 257–259]. The reduction in steatosis and ALT is proportional to the weight loss; there is a clear dose-effect relationship [260–262]. In this context, it is irrelevant how the weight loss was achieved [32, 116, 257, 258].

The evaluation of paired liver biopsies from NASH patients before and after weight reduction show that a weight loss of at least 10 % should be achieved in order to accomplish regression of fibrosis and complete regression of NASH [263–274]. Similar results were also found by systematic reviews [275] and guidelines [32, 116, 258, 276]. They also show that a minor weight loss primarily leads to an improvement in steatosis and transaminase levels [269, 272, 275–280]. A controlled trial showed that 50 % of normal-weight NAFLD patients achieved a remission of steatosis with a weight reduction by 3–5 % [281].

In overweight and obese patients with liver cirrhosis, a 16-week lifestyle intervention with a low-calorie diet and aerobic exercise led to a significant decrease in body weight and portal hypertension; here, a weight reduction of at least 10 % was associated with a 23 % decrease in the hepatic-venous pressure gradient (HVPG) [282]. Regarding the regression of an already existing NASH cirrhosis or the prevention of disease progression with the development of HCC, no results from studies on lifestyle intervention are available to date. All in all, a weight reduction of at least 10 % is extremely effective in the treatment of NASH (90 % cure rate), but this target was only achieved by 10 % of patients in clinical practice [275]. Concepts such as web-based training [283, 284], text messaging [285] or increasing motivation through donations for charitable purposes [286] are new approaches to solving this dilemma.

Physical exercise should be carried out to reduce hepatic steatosis and to potentiate the effect of weight loss on the inflammation. Improvement in the necroinflammatory response has not yet been proven. Measuring liver fat using 1H-MRS shows that aero-

bic exercise without body weight changes led to a decrease in the hepatic fat content [287–290]. Meta-analyses showed that aerobic training and/or isometric training in NAFLD patients also improved transaminase levels and hepatic fat content independently of weight loss [261, 291–294]. Both training concepts are apparently equally effective [261, 292, 294].

RECOMMENDATIONS

Overweight or obese patients with NAFLD should be recommended a weight loss program, using a low-calorie diet as per the recommendations of the German Association for the Study of Obesity (DAG), S3 Guideline "Prevention and Therapy of Obesity" (AWMF 050–001).

Strong recommendation, strong consensus

A Mediterranean diet (MD) should be considered to improve steatosis and insulin sensitivity.

Recommendation, consensus

In normal-weight NAFLD patients (lean NAFLD), physical activity should be promoted in accordance with WHO recommendations aimed at building up muscle mass.

Recommendation, strong consensus

A Mediterranean diet can be recommended to patients with NAFLD and a BMI between > 20 and < 25 kg/m^2.

Recommendation open, strong consensus

Commentary

The rationale for weight loss is an improvement in the risk of comorbidity, transaminase activity and liver histology (necroinflammation); a Mediterranean diet can improve steatosis and insulin sensitivity. Overweight or obese NAFLD patients should be advised about a low-calorie diet in accordance with the guidelines for obesity management (S3 Guideline "Prevention and Therapy of Obesity" AWMF Register No. 050–001) [258, 295, 296]. The caloric target is 1200 kcal/day for women and 1400–1500 kcal/day for men, corresponding to a reduction by –500 to –1000 kcal/day [276]. The combination of a low-calorie diet with aerobic or isometric exercise has a synergistic effect and increases effectiveness in terms of improving steatosis and necroinflammatory activity [268, 269, 279, 297, 298]. When the energy balance was changed to the same extent by either a low-calorie diet alone or by a combination of less restrictive diet and physical activity, the participants in a systematic study achieved the same weight loss (-10 %) and the same improvement in transaminase activity, liver fat and insulin sensitivity [299]. Both interventions are effective on their own if the other variable – weight or physical activity – is kept constant. Aerobic training exercise without changing body weight led to a decrease in hepatic fat content [287–290], as did weight reduction with a low-calorie low-carb or low-fat diet while maintaining an inactive, sedentary lifestyle [280]. NAFLD patients exhibit a low level of physical activity, in diabetic NAFLD patients, physical activity ranks in the lowest quartile [300]. Overweight or obese NAFLD patients show a reluctance to make lifestyle changes; only 10 % actively deal with the subject [301].

The study shows that a specific fat or carbohydrate composition of a low-calorie diet had no advantages with regard to weight reduction or improvement in transaminase activity or histological changes in NAFLD [32, 258, 276]. This also applies to formula diets, referred to as very low-energy diets (VLED), as meal replacement [302, 303]. Consuming a VLED (800 kcal/d), more than 80 % of a Munich cohort achieved a weight loss of at least 10 % in 52 weeks, accompanied by significant improvements in transaminase activity, FLI and NAFLD Fibrosis Score [304]. A high protein diet may be beneficial. In obese patients with T2DM, an isocaloric protein-rich diet led to an improvement in steatosis, insulin sensitivity and BMI after 6 weeks [305].

The rapidly increasing prevalence of obesity over the past few decades has been associated with the increasing consumption of fructose and fructose-containing corn syrup in processed foods and beverages [306–309]. However, meta-analyses did not show that fructose consumption in the context of a normocaloric diet promotes the development or progression of NAFLD [310–312]. In a double-blind study on overweight people, excessive caloric intake, but not fructose compared to isocaloric amounts of glucose, was associated with an increase in the hepatic fat content and transaminases [313].

The results of seven interventional [272, 314–319] and four observational studies [320–323] suggest that a Mediterranean diet (MD) has beneficial effects on body weight, insulin sensitivity and hepatic steatosis. However, the data on the preventive effectiveness of MD with regard to the development of NAFLD is less clear [116, 275, 324, 325]. Data from the Framingham study show a reduced risk of new NAFLD disease in people with high adherence to MD {Ma, 2018 #332. In this context, a high-quality diet like MD was particularly effective when genetic risk factors were present. A Greek study found no association between MD adherence and the presence of NAFLD, but a negative correlation between MD adherence on the one hand and insulin resistance, transaminases, liver stiffness and histologically diagnosed steatosis and fibrosis on the other [321]. MD lowers the risk of cardiovascular disease and new onset T2DM, where obesity and insulin resistance play roles as etiological factors [326]. Compared with general dietary recommendations, an MD improves insulin sensitivity and steatosis even without weight loss [316]. In the CENTRAL study, MD was superior to a low-fat diet in terms of fat mobilization from the liver, heart and pancreas determined by whole-body MRI [327].

Compared with metabolically healthy individuals, the risk of mortality and cardiovascular events is more than threefold in normal weight patients with an underlying metabolic disease – a condition that affects around 20 % of the normal weight population [328, 329]. A controlled study of normal weight (BMI 22.7 kg/m²) NAFLD patients in Hong Kong showed that a low-calorie diet, achieving a weight reduction of 3–5 %, leads to remission of NAFLD in 50 % (measured by the hepatic fat content using ^{1}H-MRS) [281]. Other types of diet have yet to be evaluated [330, 331].

Aerobic or isometric exercise can reduce hepatic fat content and insulin resistance [287–290, 332, 333]. It therefore seems logical to recommend these types of exercise to normal-weight NAFLD patients in order to improve steatosis and insulin sensitiv-

ity. A meta-analysis concluded that both types of exercise are equally effective with regard to hepatological endpoints, while isometric exercise proves less stressful for people with poor cardiorespiratory fitness [294]. The median effective aerobic exercise level was 4.8 MET (metabolic equivalent) provided in three 40-minute training units per week and 3.5 MET in three 45-minute units per week for isometric exercise [294].

According to WHO exercise guidelines of November 25th, 2020, published at https://www.who.int/publications/i/item/9789240015128, patients with NAFLD and a BMI > 20 and < 25 kg/m² should practice a minimum of 150 to 300 minutes of moderate-intensity aerobic physical activity or at least 75–150 minutes of high-intensity aerobic physical activity per week. Alternatively, an equivalent combination of medium and high intensity activity during the week can also be used.

Stimulant foods (alcohol, tobacco, coffee)

RECOMMENDATIONS

NAFLD patients with moderate alcohol consumption should reduce their alcohol intake.

Recommendation, consensus

Patients with NAFLD-associated cirrhosis should abstain from alcohol and nicotine.

Strong recommendation, strong consensus

Commentary

Retrospective studies that showed a favorable effect of moderate alcohol consumption on health must be assessed critically, as they only examined associations and not causalities [334–336]. In addition, prospective data from animal experiments clearly showed a negative effect of alcohol on, for example, diet-induced fatty liver [337–340]. This could also be observed in NAFLD patients who, because of alcohol consumption, showed accelerated fibrosis progression [341]. Finally, a retrospective study showed that patients with NASH cirrhosis who also consume alcohol in small quantities have a significantly higher risk of developing HCC [342]. Alcohol consumption is a meaningful risk factor for the development of liver cirrhosis [343] and, especially in advanced stages of the disease, therefore, social alcohol consumption should be abstained from completely. In these instances, absolute abstinence should be recommended. In a small cohort analysis, patients with moderate, regular alcohol consumption (< 140 g/week) were more likely to have an advanced stage of fibrosis, especially those with T2DM [344].

RECOMMENDATION

Coffee can be recommended for patients with NAFLD.

Recommendation open, consensus

Commentary

Systematic reviews and meta-analyses suggest that drinking coffee leads to a reduction in the risk of HCC. Consuming larger amounts of coffee resulted in a higher risk reduction [345, 346]. However, increased coffee consumption is not associated with a reduced risk of hepatobiliary carcinoma [347]. The protective agents from coffee and the molecular mechanisms of HCC prevention have so far remained unclear.

Positive effects with regard to coffee consumption can be derived from epidemiological studies [348]. These showed a protective effect of coffee consumption in relation to the risk of developing NAFLD and also in relation to the fibrosis stage [349], but no controlled studies are available on this topic. In a pooled meta-analysis with a total of 11 studies, people who drank coffee had a relative risk of 0.77 (95 % CI 0.60–0.98) to develop NAFLD. In addition, there is also a significantly reduced risk of advanced liver fibrosis compared to patients who do not drink coffee (RR 0.68; 95 % CI 0.68–0.79) [349].

RECOMMENDATION

Patients with NAFLD should receive vaccinations according to the current STIKO (German Standing Committee on Vaccination) guidelines.

Recommendation, strong consensus

Commentary

Patients with chronic liver disease fall into a risk group. According to the STIKO recommendations, all patients with chronic liver disease should be vaccinated against hepatitis A, hepatitis B, influenza and COVID-19. Patients who are awaiting organ transplantation or immunosuppressive therapy and immunosuppressed patients, e. g. those with liver cirrhosis, should be vaccinated against pneumococci. Vaccination against varicella is recommended for seronegative patients prior to any planned immunosuppressive therapy or organ transplantation. Vaccination with live vaccines is contraindicated after liver transplantation. Vaccinations should be carried out in accordance with the latest STIKO guidelines (www.rki.de/epidbull).

4b Drug therapy

Drug therapy for NAFLD regardless of comorbidities

RECOMMENDATION/STATEMENT

Statement

At the time of publication of this guideline, there are no approved medications for the treatment of NAFLD.

Strong consensus

Recommendation

Drugs such as ursodeoxycholic acid, pioglitazone, metformin, silymarin or pentoxifylline or dietary supplements such as vitamin E or omega-3 fatty acids should not generally be used, based on currently available data on the treatment of NAFLD.

Strong recommendation, strong consensus

Commentary

The use of antioxidants such as vitamin E in patients with NAFLD fibrosis (≥F2) at a dose of 800 IU/day resulted in a histological reduction in steatosis and inflammation for two years without improving fibrosis [350]. Supplementation with vitamin E cannot be recommended, as some meta-analyses reported an increased all-cause mortality on long-term vitamin E treatment, especially at doses > 400 IU/day [351, 352] and an increased rate of prostate cancer in men [353]. Other dietary supplements such as omega-3 fatty acids, silymarin, polyphenols or drugs such as ursodeoxycholic acid (UDCA) and pentoxifylline did not produce any significant histopathological improvements in patients with NAFLD and can therefore not be recommended for treatment (see Appendix Table 4b-1; randomized controlled trials of off-label drugs and nutritional supplements). Pioglitazone was also evaluated in NAFLD patients without T2DM, for example in the PIVENS study [350]. Pioglitazone improved liver histology, steatosis, ballooning and lobular inflammation, but not fibrosis. In addition, pioglitazone cannot be recommended due to its side effect profile including significant weight gain, increased risk of bone fractures and, rarely, heart failure.

Regarding dietary supplements, most evidence available is on the use of omega-3 fatty acids and other polyunsaturated fatty acids. The WELCOME trial showed no effect on fibrosis stage [354] and a decrease in liver fat content was only found in subgroups [355]. Even smaller studies on omega-3 fatty acids [356] or omega-3 polyunsaturated fatty acids (3 PUFAs) [357] could not find any effect on the liver histology. Meta-analyses showed an improvement in transaminases only after 12 months alongside a decrease in liver fat content [358, 359]. In one study on overweight men, those in the subgroup with increased liver fat content showed no reduction of hepatic steatosis measured by MRI after 12 weeks [360]. Data from randomized trials on supplementation with trace elements in NASH are not available. The NHANES III study showed a lower mortality rate and lower non-invasive markers of fibrosis in NAFLD patients who had elevated serum selenium levels [361]. Controlled data on phytotherapy or "hepatoprotective substances" are scarce. A trial from Hong Kong compared *Phyllanthus urinaria* with placebo over a period of 24 weeks and found no effect on histological inflammation, obesity or fibrosis [362]. In a randomized controlled trial with histological endpoints, silymarin showed no effects on NAFLD [363]. Few clinical trials are available on vitamin D supplementation. Reduced liver values were found over a period of 48 weeks [364]. These effects could not be observed in patients with T2DM [365]. A randomized trial on the supplementation with probiotics combined with prebiotics for one year showed no effect on non-invasive markers in NAFLD. Short studies have observed an effect on the liver enzymes after 12 weeks [366]. Studies on the use of prebiotics, synbiotics and probiotics are limited to small case numbers and mostly only examined liver function tests and ultrasound over a limited period of time [367]. In a randomized trial, combined probiotics and prebiotics supplementation showed a change in the microbiome, but no benefit on liver fat content or liver stiffness as a surrogate for liver fibrosis [368]. In lean NAFLD patients (n = 50), synbiotics showed a benefit in terms of improving non-invasive surrogate markers of hepatic steatosis and fibrosis over 28 weeks [369]. Data on fecal microbiota transplant are not available [370].

See Appendix Table 4b-1

Drug therapy for NAFLD patients with diabetes

RECOMMENDATIONS

Due to the beneficial effects on NASH, non-cirrhotic NAFLD patients with T2DM should be given (metformin plus) glucagon-like peptide 1 (GLP-1) receptor agonists such as liraglutide or semaglutide.

Recommendation, strong consensus

The use of sodium dependent glucose transporter 2 (SGLT2) inhibitors, e. g. empagliflozin and dapagliflozin, or the thiazolidinedione pioglitazone may be considered in these patients.

Recommendation open, strong consensus

Patients with NASH-associated liver cirrhosis and T2DM can receive metformin, if they have compensated Child-A cirrhosis and preserved kidney function.

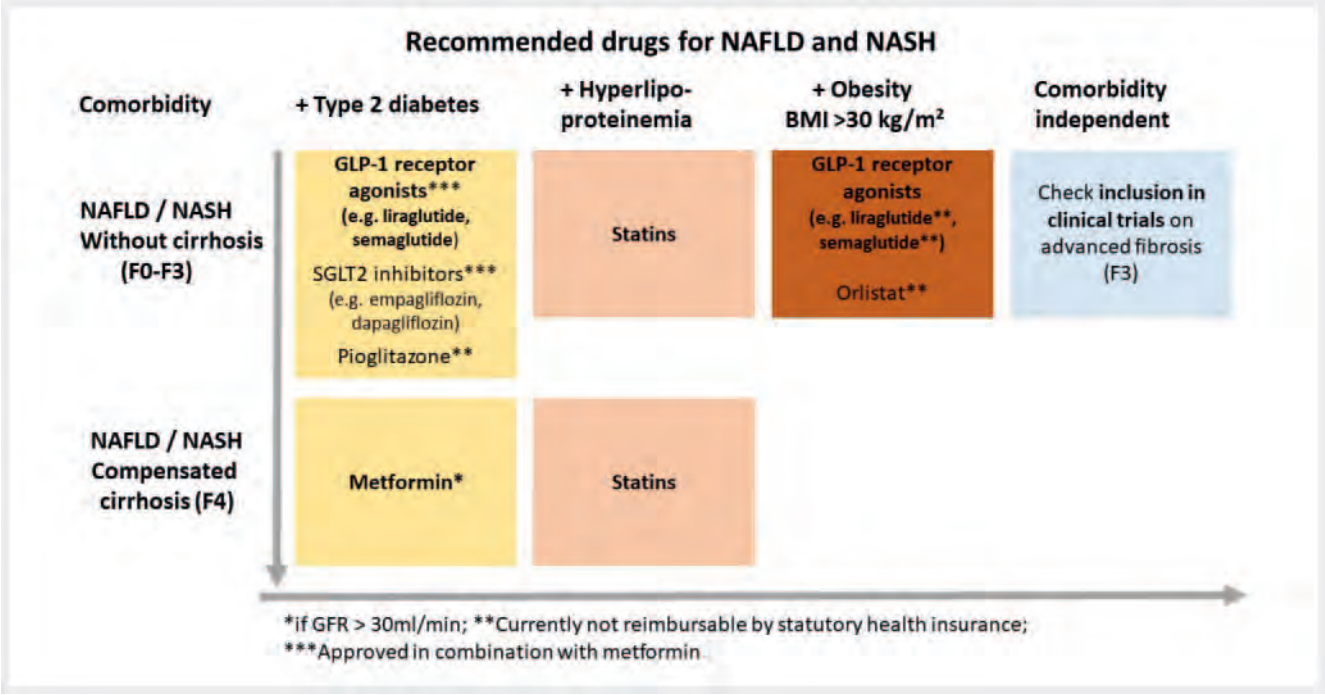
Recommendation open, strong consensus

Commentary

GLP1 analogues are only approved in combination with metformin (or as monotherapy in the case of metformin intolerance) for the treatment of T2DM. The 2020 national care guideline for T2DM suggests a combination therapy of metformin + SGLT2 inhibitors or GLP-1-RA for type 2 diabetes with cardiovascular risk factors and metformin monotherapy for type 2 diabetes without risk factors. The National Disease Management Guideline Type 2 Diabetes (long version, 2nd edition) is available: https://www.awmf.org/uploads/tx_szleitlinien/nvl-001l_S3_Typ_2_Diabetes_2021-03.pdf.

A placebo-controlled study with 52 NASH patients, 33 % of whom had T2DM, showed more resolution of NASH and less fibrosis progression after one year of liraglutide therapy [371]. Treatment with semaglutide for NASH and NASH fibrosis stage F1–F3 (62 % of the patients had T2DM) was associated with a significantly more frequent resolution of NASH, but without significant improvement in fibrosis [372]. The daily injections tested in this phase 2 study, however, correspond to a higher dose than is currently approved in Germany for the treatment of T2DM (in combination with metformin). In addition, GLP-1 analogues showed positive effects in cardiovascular endpoint studies (3P-MACE, cardiovascular death, non-fatal stroke, hospitalization due to heart failure and overall mortality) and have comparatively few contraindications, e. g. underlying or increased risk of pancreatitis, pregnancy or breast feeding. The European Medicines Agency (EMA) has approved semaglutide 2.4 mg/day for the management of obesity (BMI > 30 kg/m² or > 27 kg/m² with serious comorbidities), in conjunction with hypocaloric diet and physical activity, in January 2022.

Therapy with sodium dependent glucose transporter 2 (SGLT2) inhibitors showed a significant improvement in the liver fat content in patients with NAFLD and type 2 diabetes [373–376]. Data from randomized controlled studies on the effect of SGLT2 inhibi-



▶ **Fig. 3** Drug recommendations for NAFLD depending on comorbidities and fibrosis stages (consensus) Please note that the dosing for liraglutide and semaglutide differ dependent on the indication (i. e. obesity treatment or type 2 diabetes therapy) [rerif].

tors on liver histology are currently not available. SGLT2 inhibitors also show positive effects in cardiovascular and renal endpoint studies. The main side effects are genitourinary infection, dehydration and masking symptoms and clinical findings of diabetic ketoacidosis. The lack of histological data explains the overall lower strength of recommendation for SGLT2 inhibitors.

There are also a number of previous studies on the use of pioglitazone in patients with NASH who have either impaired glucose tolerance or T2DM. In a 6-month placebo-controlled study with a reduced-calorie diet, pioglitazone achieved a greater reduction in liver fat content and a significant improvement in NASH (hepatocellular ballooning and lobular inflammation) but not in fibrosis [377]. In an 18-month placebo-controlled study, based on a low-calorie diet of patients with NASH and prediabetes or T2DM, with a subsequent 18-month open-label follow-up, therapy with pioglitazone showed a greater reduction in liver fat content, a more frequent resolution of NASH as well as a greater improvement in fibrosis [378]. However, therapy with pioglitazone is contraindicated in several conditions, particularly in heart failure (NYHA I-IV) and in bladder cancer. Caution is advised in individuals with increased bone fracture risk and severe obesity, as pioglitazone promotes weight gain. These safety concerns justify the overall lower recommendation strength for pioglitazone.

There is currently insufficient experience on the possible use of GLP-1 receptor agonists, SGLT2 inhibitors or pioglitazone in patients with NASH-associated liver cirrhosis. SGLT2 inhibitors may require dose adjustment or discontinuation in case of impaired kidney function.

Other antidiabetic agents such as metformin, dipeptidyl peptidase IV inhibitors or insulin have so far not shown any specific advantages for the treatment of NAFLD. However, large retrospective studies have reported that metformin reduced the risk of developing hepatocellular carcinoma (HCC) in NAFLD patients [379]. Even in patients with NASH-associated Child A stage compensated cirrhosis, the use of metformin for treating diabetes is associated with a reduced risk of hepatic decompensation and HCC; it can therefore be used in compensated liver cirrhosis in a dose of up to 2 g/day, if the renal function is normal [Vilar-Gomez, 2021 #388] [380]. Metformin is contraindicated if the glomerular filtration rate (GFR) is below 30 ml/min. However, there are no prospective controlled studies on the use of metformin in liver cirrhosis.

A placebo-controlled study of patients with NASH and T2DM showed a greater reduction in liver fat content for vitamin E (800 IU/day) and a more frequent reduction in NASH without improvement in fibrosis [381]. The increased mortality and morbidity risk in vitamin E supplementation (see above) limits its use, particularly in patients with diabetes mellitus. In contrast, large studies in patients with T2DM show cardiovascular benefits with pioglitazone [382], liraglutide [383], semaglutide [384] and the SGLT2 inhibitors, such as empagliflozin [385] and dapagliflozin [386], so that these drugs should preferably be used for patients with T2DM.

Drug therapy for lipid metabolism disorders

RECOMMENDATIONS

Lipid metabolism disorders in NAFLD patients should be treated effectively.

Strong recommendation, strong consensus

In view of the overall favorable effects, statins can also be used in NAFLD patients with compensated liver cirrhosis.

Recommendation open, strong consensus

Commentary

There are no high-level studies that have investigated the treatment of NAFLD in lipid metabolism disorders. In underlying NAFLD, lipid metabolism disorders such as familial hypercholesterolemia, hypertriglyceridemia, lipoprotein (a) elevation or isolated HDL cholesterol reduction should be treated effectively, as they present a substantially increased risk for cardiovascular diseases; also, NAFLD increases the risk of cardiovascular diseases, independent of lipid metabolism disorders [233, 387]. There are no controlled studies showing the effectiveness of lipid-lowering agents on liver histology in NAFLD. In large cohorts, the use of statins in NAFLD was associated with a lower risk of liver disease progression [388–390]. Hepatotoxic side effects seem to occur very rarely, even when statins are used in patients with decompensated cirrhosis [391]. Statins also appear to have other benefits in cirrhotic patients. Clinical observations have shown a reduced risk of HCC [392] as well as a reduction in portal hypertension, improved endothelial dysfunction and reduced fibrogenesis [393].

Drug therapy for obesity

RECOMMENDATIONS/STATEMENT

Obesity in NAFLD patients should be managed effectively.

Strong recommendation, strong consensus

In non-cirrhotic NAFLD patients with obesity and an indication for pharmacotherapy for weight loss, glucagon-like peptide 1 (GLP-1) receptor agonists should be used because of their beneficial effects on NASH.

Recommendation, strong consensus

Orlistat, which is approved for the treatment of obesity, can be used in overweight and obese patients with NASH.

Recommendation open, strong consensus

Commentary

If GLP-1 receptor agonists (e. g., liraglutide, semaglutide) or orlistat use is indicated, the treatment can also have a beneficial effect on NAFLD or histologically confirmed NASH. Such data are not available for other approved weight-loss drugs. Although there are no approved drugs for the treatment of NAFLD in obesity, clinical trials in patients with NASH show a beneficial effect of treatment with glucagon-like peptide 1 (GLP-1) receptor agonists, of which semaglutide and liraglutide are approved in the EU for treating obesity [394]. However, there are no studies for GLP-1 agonists that exclusively included NAFLD patients with obesity. In a placebo-controlled study (n = 52) in patients with NASH, with a mean BMI of 35 kg/m², one-year treatment with liraglutide of 1.8 mg/day s. c. more frequently produced a resolution of NASH and at the same time a less frequent progression of the fibrosis [371]. A current study of NASH examined the use of semaglutide, which has been approved in Germany for the treatment of T2DM as well as obesity. Semaglutide was used in patients with NASH and stage F1–F3 fibrosis, who had a mean BMI of 36 kg/m². Therapy with semaglutide was associated with more frequent resolution of NASH without significant improvement in fibrosis [372]. The daily injections tested in this phase 2 study, however, correspond to a higher dose than for the treatment of T2DM (in combination with metformin). In addition, GLP-1 analogues showed beneficial effects in cardiovascular endpoint studies and have comparatively few contraindications (see above).

The drug orlistat, which is approved for the treatment of obesity, also showed positive effects on the course of NASH. In a placebo-controlled study (N = 50) over 36 weeks in patients with NASH and a BMI ≥ 27 kg/m² (mean BMI 36 kg/m²), who were all on a reduced-calorie diet and received 800 IU of vitamin E/day, orlistat therapy improved steatosis, ballooning and inflammation (but not fibrosis), particularly if the weight loss was ≥ 9 % [268]. Such data (favorable influence on NAFLD) are not available for other approved weight-loss drugs.

In addition to these treatment options, the fixed-dose combination of bupropion and naltrexone is also approved for weight reduction in Germany. A recently published post-hoc analysis of the approval data, which was financed by the approval holder, shows minor, clinically irrelevant, improvements in the ALT and the FIB-4 index. It should be noted that a heterogeneous patient group was included with the aim of weight reduction. The study did not aim to include patients with liver changes [395]. The validity of this analysis is therefore low. In the USA, the fixed-dose combination of phentermine and topiramate as well as lorcaserin are also approved for the treatment of weight loss. There is no data for either on the effect of NAFL or NASH [396].

To what extent does liver dysfunction in NAFLD influence therapy with statins, antihypertensives, antidiabetic drugs, anticoagulants and platelet aggregation inhibitors that are, or must be administered, for other indications?

RECOMMENDATIONS/STATEMENT

Statement

At this time, no recommendations can be made on the dose adjustment of drugs for any indication in patients with NAFLD without decompensated cirrhosis.

Strong consensus

Recommendation

For drugs with a narrow therapeutic range and/or life-saving importance, therapeutic drug monitoring can be useful in patients with NAFLD, especially those with impaired liver function.

Recommendation open, strong consensus

Commentary

A variety of enzymes and drug transporters are active in the liver metabolism. Their specific interaction has a decisive influence on the pharmacokinetics of drugs with hepatic metabolism and/or high biliary elimination. Animal and human studies on the changes in gene expression, protein expression and enzyme and transporter activity in NAFLD/NASH have been carried out for the most relevant enzymes of the cytochrome P450 family, the glucuronyl-, sulfo- and glutathione transferases, the influx transporter of the OCT (organic cation transport), OAT (organic anion transport) and OATP (organic anion transporting polypeptides) and the efflux transporter P-glycoprotein, BCRP (breast cancer resistance protein) and the multidrug resistance-associated protein (MRP) [397]. The changes appear to be more pronounced in NASH than in NAFLD. These data are not conclusive, mainly due to the small and heterogeneous database. The dose adjustment of a specific drug, however, cannot be derived from these data. The attempt to use physiologically based pharmacokinetic modeling (PBPK) to predict the kinetics of an individual drug on the basis of pharmacokinetic data in a specific patient population is possible in individual cases, but this also does not allow any general recommendations for clinical practice [398]. In these studies, as well as in those where the change in the area under the plasma drug concentration–time curve was determined for patients with NAFLD or NASH, deviations of ± 30–50 % or less were found [399–401]. Ultimately, the decision to adjust the dose of a drug, undergoing hepatic metabolic elimination and/or biliary elimination, remains an individual decision. Therapeutic drug monitoring is useful for decision-making, but is not established for many drugs or is not available in routine clinical practice. The focus should therefore be on drugs with a narrow therapeutic window and/or lifesaving treatment. In this case, drug monitoring should also be carried out even the information for healthcare professionals does not explicitly recommend it.

Future pharmacological interventions

RECOMMENDATIONS

Until specific NASH drugs are approved, patients with advanced fibrosis (F3) and/or other specific risk constellations (e. g. high NASH activity with F2 fibrosis, cardiometabolic comorbidities) should be considered for clinical trials.

Recommendation, strong consensus

Commentary

At present, the use of novel NASH-specific drugs in fibrosis stage F1 or F2 cannot be assessed conclusively. The benefits and risks of using newly approved NASH-specific drugs in fibrosis stage F4 are currently unclear. New therapeutic approaches that are currently being investigated in clinical trials are very promising and oftentimes focus on advanced fibrosis (F3). So far, however, there has been no scientific evidence that these substances improve long-term outcomes (survival, cardiovascular events, cancer, liver-related complications). As a surrogate for such long-term outcome data, the European Medicines Agency as well as the US Food and Drug Administration accept a significant improvement in liver histology as a result of the intervention, compared to a comparative treatment (currently placebo) for a "conditional approval". It is required that in the follow-up biopsy either the histological features of NASH such as ballooning and inflammation have resolved without worsening of the fibrosis (NASH resolution) and/or the liver fibrosis has improved by at least one severity stage without worsening of the NASH characteristics (fibrosis improvement) [402, 403]. The most important aspect is the significant reduction in the (prognostically relevant) hepatic fibrosis resulting from NASH-specific drug treatment. Since these endpoints are clinically plausible and scientifically accepted, patients with an appropriate risk constellation, i. e. in particular with advanced bridging fibrosis (F3) and/or high disease activity and/or severe cardiometabolic risk factors, should preferably be included in clinical trials that investigate these endpoints. Even if the patients only receive placebo, they generally benefit from the close monitoring and lifestyle advice, as can be derived from the "placebo response rates" for the histological endpoints of 15–35 % [404].

A number of substances are currently being investigated in clinical phase 3 and phase 2 studies [405–408] that act on the pathophysiological processes of glucose metabolism, inhibition of de novo lipogenesis, inflammation or fibrogenesis. The substance classes include agonists of the nuclear receptors FXR (or its downstream mediator fibroblast growth factor/FGF19) and PPAR, chemokine receptor (CCR) inhibitors, thyroid hormone receptor-ß (THR-ß) agonists, inhibitors of lipogenic key enzymes such as FASN and SCD-1 Enterohepatic hormones and their agonists such as glucagon-like-peptide-1 (GLP-1), FGF19 or FGF21. Medicines with a primarily antidiabetic effect such as the group of SGLT2 inhibitors should also be mentioned here.

Obeticholic acid (FXR agonist), resmetirom (THR-ß agonist), lanifibranor (PPAR agonist), semaglutide (GLP-1 receptor agonist) and aramchol (SCD-1 inhibitor) are currently being tested in phase 3 studies) (Appendix, Table 4b-2). An interim analysis showed positive data for obeticholic acid with regard to fibrosis improvement as a co-primary endpoint (REGENERATE Study) [409]. Several substances such as elafibranor (PPARα/δ agonist), cenicriviroc (CCR2/5 inhibitor) and selonsertib (ASK1 inhibitor) did not demonstrate positive efficacy results in phase 3 and are therefore no longer being developed for this indication. Further FXR agonists (tropifexor, cilofexor), recombinant FGF19 (aldafermin), different variants of FGF21 (pegbelfermin, efruxifermin), GLP-1 analogues (liraglutide, semaglutide), pan-PPAR agonists (lanifibranor) showed promising results in phase 2 studies (Appendix, Table 4b-2). Based on the current phase 3 interim analysis, obeticholic acid is the only drug with a significant benefit on fibrosis improvement and is the primary candidate for the first conditional approval; however, this was not granted at the time the guidelines were published [410].

In the future, NASH therapies will possibly consist of a combination of two or more drug classes with complementary effects in order to achieve an optimal therapy response. Such combination treatments are already being investigated in clinical trials (e. g. tropifexor plus cenicriviroc, semaglutide plus FXR agonist); most combinations contain at least an FXR agonist (Appendix, Ta-

ble 4b-2). No statement can currently be made about additive or synergistic pharmacological effects due to the small number of cases available in phase 2 data [407, 408].

It is currently unclear, which patients will be the target population of future NAFLD treatment. Some of the recently conducted phase 3 studies included patients with stage F1 fibrosis and underlying risk factors, while others defined at least F2 or even exclusively F3 as the target population. Primarily, patients with more advanced fibrosis should be considered with a high degree of urgency because liver-associated as well as extrahepatic mortality are significantly increased [411]. It remains to be clarified to what extent patients with earlier stages of fibrosis should receive specific drug therapy or only those with the immediate highest risk of progression in F3. Presently, there are only very few study data (phase 2 or 3) available for pharmacological therapies in NASH cirrhosis [402].

Future personalized therapy concepts are to be expected. This could consist of a targeted "correction" of the intestinal microbiota to reduce NAFLD and cardiometabolic comorbidities [412] or targeted therapies based on genetic risk stratification. The classic example of this would be the single nucleotide polymorphism (SNP) in the patatin-like phospholipase domain-containing 3 gene (PNPLA3), rs738409, which codes for the missense mutation I148 M. Targeted drugs (e. g. antisense oligonucleotides, tyrosine kinase inhibitor momelotinib) could inhibit PNPLA3 levels in 148 M homozygous persons and thus modify a pathomechanism for progression [413, 414].

See Appendix, Table 4b-2

4c Interventional therapy approaches

Indications for bariatric surgery

RECOMMENDATIONS

For grade III obesity (BMI ≥ 40 kg/m²) and NAFLD, bariatric surgery should be recommended, provided there are no contraindications and all conservative measures have been exhausted.

Strong recommendation, consensus

For grade II obesity (BMI ≥ 35 kg/m² and < 40 kg/m²) and NAFLD, bariatric surgery should be recommended, provided there are no contraindications and conservative measures have been exhausted.

Recommendation, strong consensus

With a BMI < 35 kg/m² and NAFLD, bariatric surgery should only be carried out in the context of clinical trials.

Recommendation, strong consensus

Bariatric surgery should not be performed in patients with decompensated cirrhosis and/or portal hypertension.

Strong recommendation, strong consensus

Patients with compensated liver cirrhosis should be assessed for possible underlying portal hypertension prior to bariatric surgery.

Strong recommendation, strong consensus

Bariatric surgery can be performed in patients with portal hypertension after a critical benefit/risk assessment. This should only be done at experienced centers and ideally in the context of clinical trials.

Recommendation open/Strong recommendation, strong consensus

Commentary

Bariatric surgery has been proven to be the most effective therapy for morbid obesity. Furthermore, bariatric surgeries usually lead to an improvement and often to a complete remission of obesity-associated secondary diseases as well [415]. According to the current German S3 guideline of the DGAV from 2018, bariatric surgery is indicated in severe obesity with a BMI ≥ 40 kg/m² (even without concomitant diseases), if conservative weight reduction measures (diet change, exercise and possible behavioral therapy) have failed. Moreover, this procedure should be offered to patients with a BMI ≥ 35 kg/m² and at least one major obesity-related concomitant disease such as NAFLD and NASH, once conservative weight reduction measures alone have failed [415].

It should be noted that NAFLD and NASH are frequent comorbidities in obese patients [75]. Various studies and a current meta-analysis show that bariatric surgery led to high remission rates of NAFLD and NASH in these patients [271]. The highest-quality data come from the "Lille Bariatric Cohort", which showed a high remission rate in histologically confirmed NASH over five years. The study moreover showed that bariatric surgery could lead to long-term improvement in existing liver fibrosis, even though fibrosis progression occurred in a small percentage of patients [416]. This observation is highly relevant since fibrosis is considered the most important risk factor for the progression of NAFLD and NASH to cirrhosis or HCC [18, 69]. Registry-based data suggest that bariatric surgery reduces the risk of HCC and progression to cirrhosis [417, 418]. Finally, a cost-benefit analysis showed an advantage for bariatric surgery, especially in NASH [419].

Although there are studies that demonstrate the positive effects of weight reduction even in normal weight NASH patients [420] and despite the excellent surgical results obtained in prospective and retrospective cohort studies on patients with BMI ≥ 35 kg/m², it cannot generally be recommended to offer metabolic surgery for NAFLD and NASH to patients with BMI < 35 kg/m² and failed conservative therapy. The reasons for this are that the data only stem from non-randomized trials and that no prospective data exist on the effects of metabolic surgery for patients with BMI < 35 kg/m² and NAFLD and/or NASH. However, a recently published network meta-analysis suggests that bariatric surgery is a more effective therapeutic option than drug therapies [421]. Future studies should compare metabolic surgery directly with the most effective drug therapy and in this way investigate the value of metabolic surgery in NAFLD and NASH patients with a BMI < 35 kg/m².

In patients with established liver cirrhosis, bariatric surgery should only be performed in the compensated cirrhosis stage. Mosko et al. have shown that mortality in decompensated cirrhosis and/or previous bleeding increases remarkably due to portal hypertension (compensated cirrhosis: 0.9 %; decompensated cirrhosis: 16.3 %) [422]. Overall, the risk of perioperative complications in patients with compensated liver cirrhosis is markedly in-

creased, but still within an acceptable range [423–425]. Patients with liver disease and signs of portal hypertension should undergo extensive diagnostic evaluation preoperatively [426]. This includes at least one consultation with a gastroenterologist/hepatologist, a preoperative esophagogastroduodenoscopy (EGD) to assess potential esophageal varices and/or hypertensive gastropathy alongside a portal venous CT to evaluate bypass circuits. If necessary, invasive measurement of the portal venous pressure can also be considered. Furthermore, the indication for bariatric surgery in patients with portal hypertension can only be made within the framework of a careful, critical interdisciplinary risk-benefit assessment [427]. At centers with a wealth of experience and maximum care capacity, lowering the portal vein pressure may be considered prior to bariatric surgery [17, 427]. Bariatric surgery can also be performed on well-selected LT candidates at experienced centers highly specialized in liver transplantation and bariatric surgery [428].

Bariatric surgery in NAFLD

RECOMMENDATIONS

In patients with obesity and NAFLD, surgical procedures such as sleeve gastrectomy, Roux-Y gastric bypass (RYGB) and single-anastomotic gastric bypass can be performed.
Recommendation open, strong consensus

The adjustable gastric band should not be used in obesity and NAFLD because of its inferior effectiveness.
Recommendation, strong consensus

Due to the risk of progressive liver failure by malabsorptive procedures (e. g. biliopancreatic diversion, distal gastric bypass and one-anastomotic bypass with a biliopancreatic loop more than 200 cm long), the liver disease severity should be considered very carefully. *Strong recommendation, strong consensus*

Sleeve gastrectomy should be favored in patients with liver cirrhosis.
Recommendation, strong consensus

Commentary

Various surgical procedures have been established, with laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-Y gastric bypass surgery (RYGB) being used most frequently in Germany and worldwide. The use of laparoscopic one-anastomosis gastric bypass (OAGB) is also becoming increasingly popular. Thus far, there has not been a conclusive assessment with regard to the effectiveness and risk-benefit analysis of the various procedures. Randomized controlled trials with a 5-year follow-up comparing sleeve gastrectomy and RYGB produced overall equivalent outcomes. RYGB leads to a marginally better weight loss (approx. 1–2 BMI points after 5 years), while sleeve gastrectomy is associated with fewer complications and re-operations [429, 430]. Nevertheless, sleeve gastrectomy has been linked to a markedly increased risk of *de novo* gastroesophageal reflux with a subsequent risk of developing Barrett's esophagus and associated esophageal cancer [431, 432]. Corresponding long-term data are lacking, thereby making EGD-guided follow-up care in patients with sleeve gastrectomy indispensable. A randomized controlled trial comparing RYGB with 200 cm OAGB showed a comparable effect on weight loss and metabolic outcome after two years of follow-up. In the trial, however, OAGB was associated with a significantly higher rate of deficiency symptoms [431]. Their significance is currently still unclear, as they mainly led to anemia and only a few cases resulted in a relevant protein deficiency, which could be of importance for patients with impaired liver function.

Gastric banding is inferior to the other methods in terms of long-term weight loss and metabolic effects and should therefore only be used in exceptional cases [432]. Although biliopancreatic diversions (Scopinaro and duodenal switch) have the most significant metabolic effects, their use is limited due to side effects, particularly by the occurrence of malnutrition [432].

With regard to the effectiveness of the various surgical procedures in NAFLD and NASH, no concluding assessment is possible due to limited data. Studies using histology, taken during the initial surgery and in the follow-up, show contradicting results. The publications by Froylich et al. and Schönfels et al. compared RYGB with sleeve gastrectomy [433, 434]. While Froylich et al. found no difference between RYGB and sleeve gastrectomy, Schönfels et al. showed a more frequent normalization in liver histology findings after sleeve gastrectomy. When comparing RYGB with adjustable gastric banding, Caiazzo et al. showed the clear superiority of RYGB over adjustable gastric banding in terms of improved liver histology [274]. Further studies with long-term results and histological endpoints are urgently needed to determine the best practice for NAFLD and NASH.

The safety of the various surgical procedures should be considered carefully when used in NAFLD and NASH patients. Liver failure after bariatric surgery is a very rare but serious complication. An analysis of ten patients with liver failure after bariatric surgery showed that this only occurred after bypass procedures (RYGB and OAGB); to date, no such cases have been described in the literature after sleeve gastrectomy or gastric banding [435, 436]. Thus, in patients with severe NAFLD and liver dysfunction with the risk of postoperative liver failure, malabsorptive bypass procedures such as distal RYGB or an OAGB with> 200 cm biliopancreatic leg length should be avoided. Moreover, a recent meta-analysis showed that the perioperative complication risk after sleeve gastrectomy was reduced down to a third compared to RYGB in patients with liver cirrhosis [437]. Sleeve gastrectomy also has the advantage that changes to upper gastrointestinal tract anatomy are minimized and that endoscopic access to the biliary tract remains. This is particularly relevant for potential LT candidates. Thus, sleeve gastrectomy should be the surgical procedure of choice in patients with liver cirrhosis.

Endoscopic procedures in NAFLD (requirements, methods)

RECOMMENDATIONS/DEFINITION

Endoscopic bariatric procedures can be used for patients with NAFLD and obesity, if conservative therapy has failed and a surgical bariatric procedure is rejected or contraindicated.
Recommendation open, strong consensus

When choosing an endoscopic bariatric procedure, based on the available evidence, endoscopic placement of an intragastric balloon (IGB) or endoscopic sleeve gastroplasty (ESG) should be used. *Recommendation, strong consensus*

Endoscopic small bowel interventions (endoscopic duodenojejunal bypass, duodenal mucosa resurfacing, and partial jejunal diversion using an incisionless magnetic anastomosis system) should only be performed for NAFLD patients in the setting of clinical trials.

Recommendation, strong consensus

Commentary

Endoscopic procedures are less effective and long-lasting than surgical procedures in terms of weight reduction but can be used if conservative therapy has failed and surgical bariatric procedure are contraindicated. The AWMF "Clinical Practice Guideline: Obesity Surgery and the Treatment of Metabolic Diseases" from 2018 states a "can be considered" recommendation for endoscopic procedures – mainly in favor of the intragastric balloon as based on the data available at the time that guideline was written [438] (AWMF Register No. 088–001).

The best studied endoscopic procedure is the **intragastric balloon (IGB)**; it is indicated from a BMI of ≥ 30 to 40 kg/m² with an implantation period of 6 months. One recent meta-analysis examined 13 RCTs (endoscopic IGB vs. sham or lifestyle interventions) with 1523 patients and showed a significant advantage for IGB with regard to percentage excess weight loss (%EWL) and percentage total weight loss (%TWL), e. g., of –17.98 % and – 4.40 %, respectively [439]. An older meta-analysis from 2008 [440] of 3698 patients demonstrated a good safety profile for this method with serious complications below 1 % (small intestinal obstruction 0.8 %, gastric perforation 0.1 %) and the need for earlier removal due to pain/sense of pressure in 4.2 % of patients. IGB as bridging intervention in patients with a BMI > 50 kg/m² before bariatric surgery proved to not be significantly effective [441] in a recent meta-analysis with regard to weight loss. Therefore, there is no advantage for bridging with IGB in such severely overweight patients, at least with regard to weight loss.

IGB is also the best studied endoscopic procedure with regard to metabolic and hepatic parameters. Table 4c in the Appendix gives an overview of the studies and results. At 6 months after IGB there was not only a significant decrease in BMI but also a significant decrease in plasma glucose, insulin levels and triglycerides, in addition to a significant decrease in liver enzyme levels (AST, ALT). Two papers examined the effect on liver histology, using the NAFLD activity score, and showed a decrease of 2–3 points [442, 443]. It was also shown in 4 studies that imaging procedures (MRI, CT, US) showed a significant decrease in liver volume [444], steatosis grade [445, 446] and liver fibrosis stage [443].

See Appendix Table 4c

Endoscopic sleeve gastroplasty (ESG) has been established over the last few years in parallel with the introduction of endoscopic suturing. A recent Danish meta-analysis analyzed 23 studies – mainly cohort studies and case series – including 3 non-prospective comparisons versus laparoscopic gastric sleeve (**LSG**), surgical endoluminal sleeve gastroplasty (primary obesity surgery endoluminal procedure, **POSE**) and endoscopic intragastric balloon (**IGB**) [447]. There was a mean weight loss over 12 months of –16.3 %. The intervention was superior to IGB and lifestyle modifications with regard to weight loss and inferior to the surgical procedures, albeit with a lower rate of adverse events than surgery. Two studies investigated ESG (OverStitch technique) with regard to metabolic and hepatic parameters (see Appendix Table 4c). In addition to weight loss, there was a significant decrease in HbA1c [448, 449] and a lowering of the NFS and hepatic steatosis index after 12 and 24 months [449]. At present, there are 2 ongoing prospective randomized studies on the procedure: ESG (OverStitch) + lifestyle modification vs. sham + lifestyle modification in patients with histologically confirmed NASH [NCT 03426111] and ESG versus LSG [NCT04060368].

The third endoscopic approach involves bypassing the proximal small intestine (duodenum), as this is where metabolic processes take place. This has a particularly favorable effect on T2DM and thus can also reduce lipogenesis and lipid storage in the liver. The **endoscopic duodenal-jejunal bypass using EndoBarrier®** consists of a metal stent that is anchored in the duodenal bulb. A plastic tube is attached to it and bridges the duodenum into the jejunum. A meta-analysis of 15 heterogeneous studies, including 5 RCT, demonstrated a more effective weight loss for the EndoBarrier® compared to lifestyle interventions [450]. The improvement in the metabolic parameters HBA1c and fasting glucose did not reach statistical significance. There were 27 adverse events, nausea, vomiting, mucosal laceration and ulceration in the duodenal bulb, 6 of which were severe. A retrospective study from Germany examining hepatic parameters (see Appendix Table 4c) showed improved diabetes control, decreased AST and ALT levels, and elastographically (VCTE) a decrease in liver stiffness and a decrease in hepatic steatosis [451]. The procedure is currently not approved in Germany.

The **duodenal mucosa resurfacing (DMR)** (Revita System) is based on circular thermal ablation of 10 cm duodenal mucosa using an endoscopic balloon catheter. Initial high-quality prospective data published on obese patients with T2DM showed an improvement in diabetic metabolism and a decrease in liver enzyme levels (see Appendix Table 4c) [452, 453]. Further prospective studies on effectiveness, side effects and the influence on steatosis and liver fibrosis in NAFLD are to be expected.

Another endoscopic procedure, the **partial jejunal diversion,** is a partial jejunoileal bypass, which is generated by the endoscopic insertion of 2 magnets (100 cm distal to the Treitz ligament and about 100 cm proximal to the ileocecal valve). Only small feasibility studies are currently available (see Appendix Table 4c) showing a positive influence on the metabolic situation [454]. Further data are expected.

What are the indications for liver transplantation in NAFLD?

RECOMMENDATION

The indication for liver transplantation (LT) should be based on the same criteria as for patients with liver cirrhosis or HCC of other origins.

Strong recommendation, strong consensus

Commentary

Liver transplantation (LT) is an established treatment option for patients with decompensated liver cirrhosis or HCC developing from NASH cirrhosis. When rendering the indication, reference is also made to the S2k Guidelines on Liver Transplantation that is expected to be published in 2022.

Numerous studies have looked at the survival of patients with post-LT NASH compared to patients with other liver diseases. In most studies, the 1-year survival of NASH patients tends to be slightly worse [455, 456]. In a large study by the European Liver Transplant Registry, the 1 and 10-year survival in the 1667 patients with NASH cirrhosis without HCC compared to the 47 063 non-NASH patients without HCC was not significantly different (1 and 10 year -Patient survival: NASH 84.1 % and 62.1 % versus non-NASH 86.2 % and 62.9 %). The same also applied to patients with HCC, although the overall survival of the HCC patients was significantly worse. In the multivariate Cox regression analysis, the patient age > 61 years (HR 2.07) or > 65 years (HR 1.72) was associated with an increased mortality compared to the patient age < 45 years. Furthermore, there was an increased mortality for patients with BMI > 40 kg/m² (HR 1.96) but also with a low BMI < 18.5 kg/m² (HR 4.29) [457]. An analysis of the United Network for Organ Sharing (UNOS) database including patients between 2002 and 2016 showed a comparable patient survival rate between NASH patients and patients with cryptogenic, autoimmune or alcoholic liver cirrhosis [458]. On the other hand, a large meta-analysis that included 37 studies from 11 countries between 1996 and 2016 found a negative effect of obesity on transplant success. Patients with BMI > 30 kg/m² or BMI > 35 kg/m² had a significantly poorer survival rate compared to normal-weight patients (72.6 % and 69.8 % versus 84.2 %; p = 0.02 and p = 0.03, respectively) [459].

In the benefit/risk assessment, the indication for LT in patients with decompensated NASH cirrhosis is emphasized by the fact that waiting list mortality appears to be higher in patients with NASH or obesity than in other patient groups. An analysis of the UNOS database showed that obese patients benefited more from LT than patients of normal weight [460]. However, the BMI is only of limited significance in patients with NASH cirrhosis and hydropic decompensation. No influence of weight on survival was found when weight was corrected for ascites [461]. On the other hand, the BMI does not reflect the existing muscle mass. Sarcopenia, which is associated with poorer survival after transplantation, can also occur in obese patients and can be recorded, for example, by measuring the muscle mass index.

The risk of recurrence of NASH is not per se a contraindication to LT. Although 41–54 % of all NASH patients develop NAFLD again within 1 year after transplantation [462, 463] and 89 % in the long-term course [464], the development of fibrosis appears to be markedly slower than in patients. In a recently published single-center American cohort study with 226 patients, transplanted for NASH cirrhosis, histological NASH recurrence was found in 49 % 3 years after transplantation, but cirrhosis was seen in only 4 patients after 9 years [465]. Another single-center American study, which included 103 patients transplanted for NASH cirrhosis, found advanced fibrosis in 20.6 % (median) by histology after 47 months post-LT and in 26.8 % by transient elastography after 75 months (> F3) [464]. This recent study showed higher recurrence rates of NASH cirrhosis than older, larger studies, in which the cirrhosis recurrence rate was between 4–10 % after approx. 10 years. Nevertheless, the recurrence rate appears to be acceptable compared to other transplant indications and by no means a reason for the rejection of NASH cirrhosis as a transplant indication.

What are the specific risks of LT in NAFLD patients?

RECOMMENDATIONS

Before listing for LT, a multidisciplinary evaluation of the patients should be conducted due to the increased perioperative risk, especially with regard to the increased occurrence of cardiovascular events and infectious complications.

Strong recommendation, strong consensus

After LT, the patient's management and the choice of immunosuppressive medication should take into account the increased risk of recurrence of metabolic syndrome, cardiovascular disease and recurrence of NAFLD.

Strong recommendation, strong consensus

Commentary

At the time of listing for LT, patients with NASH cirrhosis suffered more often from a metabolic syndrome than patients with any other cirrhosis pathogenesis. In addition, it could be shown that NASH patients tend to be older [466]. In LT candidates with NASH cirrhosis, the prevalence of coronary artery disease (CAD) is also markedly higher at 21 %–29 % than in patients with cirrhosis of other etiologies (5–11 %) [466, 467]. This corresponds to the higher complication rate post-LT, proven in numerous studies [468–470]. In the study by Vanwagner et al. [471], cardiovascular events occurred in 26 % of the 115 NASH patients in the 1st year post-LT, but only in 8 % of the 127 patients with ethyl toxic cirrhosis (p < 0.001). In the multivariate analysis, NASH was a significant risk factor for the occurrence of cardiovascular complications, regardless of age, T2DM, nicotine consumption and the presence of a metabolic syndrome. NASH cirrhosis was also associated with high cardiovascular mortality (50 %), with 70 % of events occurring perioperatively. According to a large cohort analysis of the UNOS database on over 32 800 liver transplant patients, the presence of NASH cirrhosis was a risk factor for the occurrence of serious cardiovascular events 30 and 90 days post-LT (OR 1.6) [472]. In the

largest current meta-analysis by M. Barone et al. [473], which included 24 studies, there was a significantly increased mortality risk at 30 days, 1, 2 and 5 years after LT, especially for the subgroup of patients with BMI ≥ 40 kg/m². A BMI > 30 kg/m² already posed an increased risk of postoperative complications. The increased cardiovascular risk should be taken into account when evaluating patients for LT. Hogen et al. [474] therefore suggested that coronary angiography always be performed in patients with NASH cirrhosis, if more than 2 of the following risk factors exist: Age > 50 years, T2DM, hypertension, family history of cardiovascular disease, nicotine consumption or known cardiovascular disease. Patients with 1–2 risk factors can initially be examined using dobutamine stress echo; coronary angiography should only be performed if CAD is suspected.

Furthermore, infectious complications – in particular wound healing disorders – were observed more frequently in patients with NASH cirrhosis than in patients with other transplant indications. This could be explained by the higher prevalence of T2DM. Overall, in some studies, increased perioperative morbidity is also reflected in a longer intensive care and hospital stay after LT. In a study by Malik et al. infections were actually the most common cause of death (57.1 %) post-LT [475].

Due to the increased perioperative risk, patients with NASH cirrhosis should therefore be comprehensively and critically assessed in a multidisciplinary setting as part of the transplant evaluation, including not only gastroenterologists/hepatologists and transplant surgeons, but also cardiologists, anesthetists and diabetologists [476].

As shown above, patients transplanted for NASH cirrhosis are at high risk of recurrence of NAFLD and NASH. Risk factors are insulin-dependent diabetes mellitus before transplantation [463], older age in conjunction with a metabolic syndrome [477], female gender [478], genetic factors [479] alongside severe weight gain and obesity post-transplantation [480]. This should definitely be considered with regard to the management of patients post-LT and when choosing immunosuppressive therapy. Steroids are associated with the occurrence of metabolic syndrome, but both calcineurin inhibitors – tacrolimus and cyclosporine – also have a negative effect on the development of insulin resistance [481]. In contrast, there was no association between the use of everolimus and the occurrence of NAFLD post-LT.

When is liver transplantation contraindicated?

RECOMMENDATION/STATEMENT

Statements

A BMI ≥ 40 kg/m² is regarded as a risk indicator for a poorer treatment outcome post-LT. The determination of the BMI in patients with advanced liver cirrhosis is particularly prone to errors due to fluctuations in the volume status.

Strong consensus

Recommendation

A BMI of ≥ 40 kg/m² alone should not be considered a contraindication for LT but should be viewed in the context of the patient's overall condition and taking into account the comorbidities.

Recommendation, strong consensus

Commentary

NAFLD is often associated with relevant extrahepatic comorbidities that can endanger the therapeutic outcome of LT [233]. Numerous studies associated obesity with a poorer clinical outcome post-LT [457, 459, 468, 473, 476, 482]. Particularly noteworthy is a current European registry study, evaluating over 66,000 liver transplants. The multivariate analysis and, specifically the subpopulation of patients with NASH without HCC, showed a significant association between morbid obesity (BMI ≥ 40 kg/m²) and poorer survival LT [457]. This association has already been documented in earlier registry studies that were, however, evaluated independently of the diagnosis [468, 482, 483]. The older practice guidelines of the American Association for the Study of Liver Diseases (AASLD) therefore defined a BMI ≥ 40 kg/m² (WHO class III) as a relative contraindication to LT [484].

However, it must be noted that there are also studies on larger patient populations that did not identify a higher BMI as an independent risk factor for post-LT mortality [461, 485, 486]. The falsification of BMI due to ascites was a relevant confounding factor for presumed associations between obesity and post-LT prognosis [461]. It is noteworthy that the European transplant registry study not only found an association for morbid obesity (and cachexia) with poorer survival in the NASH cohort, but also for a BMI in the normal weight range (18.5–25 kg/m²) [457]. A plausible explanation for this negative treatment outcome could be that a normal weight BMI in the usually overweight population of NAFLD/NASH patients may indicate a history of muscle wasting and established sarcopenia. Moreover, an older retrospective study of over 25,000 waiting list patients calculated that LT had a relevant survival benefit even in morbidly obese patients that was no less than across other BMI ranges [487].

All of this shows that the BMI is not a universally applicable, sufficiently accurate tool to define a contraindication to LT in NAFLD patients. Although a recent meta-analysis also described a significant association between obesity with BMI ≥ 30 kg/m² and poorer survival post-LT, it was opposed to recommending the use of BMI as an exclusion criterion due to the heterogeneity of the included studies [459]. With that in mind, BMI should be used as a guide to the risk of complications in overweight patients post-LT and not as a categorical exclusion criterion.

Future studies may show that, in patients with NASH cirrhosis, other parameters reflect the chances of success of LT better than BMI and are also associated with survival on the waiting list or post-LT, such as frailty [488], myosteatosis [489] or cardiopulmonary performance capacity [490].

Specific lifestyle interventions and drug therapy while waiting on the list pre-LT

RECOMMENDATIONS

In preparation for an LT, the nutritional status of patients with NAFLD should be assessed.

Strong recommendation, strong consensus

Obese or malnourished patients with NALFD on the LT waiting list should receive nutritional counseling.

Strong recommendation, strong consensus

Obesity should be given special consideration in the context of the psychological evaluation for LT.
Recommendation, strong consensus
Patients on the LT list should be treated according to the recommendations for pharmacological and non-pharmacological therapy for NAFLD.
Strong recommendation, strong consensus

Commentary

A large proportion of patients with NASH cirrhosis are overweight or obese. In a recent European registry study, the mean BMI of patients who had to undergo LT due to NASH was 32.6 kg/m² [457]. As described above, there is abundant evidence that obesity is associated with a poorer post-LT prognosis [459]. In addition to obesity, NASH patients with advanced liver cirrhosis often have prognostically unfavorable disorders such as malnutrition, sarcopenia and myosteatosis. Many patients with liver cirrhosis also suffer from malnutrition and sarcopenia and, in conjunction with obesity, present as combined clinical picture of sarcopenic obesity [489, 491–494]. These clinical conditions can be treated with targeted interventions. In addition to the nutritional recommendations for treating overweight patients with NAFLD, offering a Mediterranean diet with plenty of vegetables, fruit, grains, fish and olive oil as the main source of fat [325, 495], measures such as snacks and late meals, a protein-rich diet, and the addition of branched-chain amino acids [496, 497] can be used. A diet adapted to the energy requirement is likely to have a positive effect on malnutrition [498–501]. A differentiated assessment of the nutritional status and body composition of NASH patients on the transplant waiting list is therefore indicated. A retrospective study indicated that nutritional interventions improve survival and quality of life in patients with liver cirrhosis [502]. Weight reduction should not be recommended for patients with advanced NASH cirrhosis, as this could worsen sarcopenia and malnutrition.

Obesity can be associated with mental illnesses such as eating disorders or depression [503, 504] and vice versa, it can also have psychosocial effects that negatively impact the patient's prognosis [505]. For this reason, and because psychological support can help implement the required lifestyle changes, current obesity guidelines recommend the psychological assessment of obese patients and the integration of psychological interventions into the obesity management strategy [503, 504, 506]. Accordingly, obese patients with NASH cirrhosis should also be given a targeted psychological assessment as part of the LT evaluation focusing on obesity-associated mental illnesses and the need for additional psychotherapeutic treatment.

While it is well established that weight reduction through lifestyle changes lead to a histological improvement in patients with non-cirrhotic NASH [269], little evidence is available on patients with advanced NASH cirrhosis. An uncontrolled pilot study examined the effect of an intensive lifestyle intervention with an individualized low-calorie diet and 60 minutes of physical training per week in 60 overweight or obese patients with compensated NASH cirrhosis and portal hypertension. Significant weight reduction was achieved after 16 weeks that was accompanied by an improvement in portal hypertension. Liver decompensation was not reported during the intervention [282]. Numerous smaller studies also showed that adapted programs of physical exercise did not have any adverse effects in patients with liver cirrhosis but suggested positive effects on aspects such as maximum oxygen capacity (VO2), muscle mass, mobility and quality of life [507–510]. However, the large proportion of Child A cirrhosis patients, included in the studies, must be pointed. Whether lifestyle intervention can bring about clinical improvement in patients with decompensated Child C liver cirrhosis has not yet been investigated in large, controlled studies. However, adapted movement exercises to maintain mobility seems to be sensible.

Indications and contraindications for endoscopic intervention or bariatric surgery in NAFLD patients before, during or after LT

RECOMMENDATIONS

Bariatric surgery can be performed before, during or after LT.
Recommendation open, strong consensus
In the context of LT in patients with BMI > 35 kg/m², the indication for bariatric surgery should be rendered on a case-by-case basis and in close interdisciplinary cooperation between the transplant center and a center for bariatric surgery.
Strong recommendation, strong consensus
Bariatric surgery prior to a planned LT can be considered for compensated cirrhosis.
Recommendation, consensus
Given the paucity of data, pre-LT endoscopic bariatric interventions should be performed on cirrhotic patients only within the framework of clinical studies.
Recommendation, strong consensus
Post-LT, an endoscopic gastric sleeve or intragastric balloon should be the endoscopic therapeutic intervention used.
Recommendation, strong consensus
Endoscopic small bowel interventions post-LT should be only undertaken within clinical trial settings, as the impacts on the absorption of immunosuppressive medication are unclear.
Recommendation, strong consensus

Commentary

A BMI ≥ 40 kg/m² is viewed by many centers as a relative contraindication to LT due to the increased post-LT morbidity and mortality [511]. In addition, cirrhotic patients with a BMI ≥ 40 kg/m² on the waiting list show an increased risk of mortality or an increased risk of being removed from the waiting list [512]. The relationship between a BMI ≥ 40 kg/m² and a deterioration in post-LT outcomes cannot be demonstrated to the same extent in all analyses [513]. Therefore, in patients on the transplant list with severe obesity (BMI > 35 kg/m²) and other prognostically unfavorable factors (e. g. T2DM), obesity surgery should be discussed on an individual basis, after conservative measures have failed [514].

From the data available thus far, no general recommendations for the optimal timing of bariatric surgery (before, during or after LT) can be derived [514], because each time point is impacted by its own specific risks and contraindications [515]. Therapy plan-

ning for patients with a BMI > 35 kg/m² and a possible indication for LT should therefore be carried out individually after a careful risk-benefit assessment [516]. This should be done in centers with experience in bariatric surgery and transplant medicine, as hospital mortality in cirrhotic patients at centers, performing > 100 bariatric surgical interventions per year is markedly lower than at centers with lower case numbers (OR 0.3, p < 0.0001 compared to centers with < 50 operations per year) [422]. LT candidates can also undergo bariatric surgery relatively safely in highly specialized centers for LT and bariatric surgery that possess the corresponding experience [428].

Pre-LT bariatric surgery can be helpful to give patients with morbid obesity access to LT in the first place and at the same time this makes sense in terms of favorably influencing modifiable risk factors for survival post-LT [511]. However, bariatric surgery prior to LT can only be carried out in patients with a low MELD score and acceptable risk with no signs of clinical decompensation. Except in cases of underlying HCC as a transplant indication, patients with well-compensated cirrhosis usually do not qualify for LT. Thus, preoperative bariatric surgery does not play any major role in clinical practice. Furthermore, an increased percentage of patients suspended from the transplant list due to sarcopenia following bariatric surgery has been reported [517].

It could be shown in smaller case series that sleeve gastrectomy in patients with Child A stage compensated cirrhosis is associated with an increased but still low overall complication rate [424, 427, 437]. Decompensated cirrhosis or significant portal hypertension carry a high postoperative complication and mortality rate, meaning that the indication for pre-LT bariatric surgery should no longer be rendered that readily. An analysis of data from the US Nationwide Inpatient Sample based on 3888 obesity surgeries in patients with compensated cirrhosis and 62 with decompensated cirrhosis showed that even with compensated cirrhosis, a longer hospital stay and increased mortality compared to patients without cirrhosis (0.3 % vs 0.9 % OR 2.17). These figures only concern hospital mortality; later decompensation and readmissions were not taken into account. In contrast, the mortality in patients with decompensated cirrhosis was 16.3 % (OR 21.2, CI 5.39–82.9) [422]. With regard to operation type in cirrhotic patients, sleeve gastrectomy has markedly fewer complications than RYGB [437].

Reliable data for a better risk stratification of patients with morbid or severe obesity based on the MELD score, the HVPG or liver function tests are not yet available. In general, the 30-day mortality rate increases linearly with increasing MELD score, namely by 1 % for every MELD point between 8 and 20 and by a further 2 % for every MELD point above 20 [518–520].

It is not clear whether preoperative TIPS implantation in patients with cirrhosis and portal hypertension can reduce the postoperative complication rate for bariatric surgery. However, data on other abdominal interventions suggest that preoperative TIPS can reduce complications from portal hypertension [521, 522].

If transplantation is not an option in patients with decompensated cirrhosis due to morbid obesity alone, the indication for simultaneous obesity surgery and LT can also be considered on an individual basis. Acceptable outcomes for LT with simultaneous sleeve gastrectomy, were reported mainly from single-center case series. It could be shown that a simultaneous sleeve gastrectomy during an LT markedly reduces post-transplantation BMI [523, 524]. On the other hand, simultaneous sleeve gastrectomy increases perioperative morbidity and mortality post-LT In addition, malnutrition can occur in the early phase after transplantation, which can delay convalescence in patients often already suffering from catabolic symptoms (sarcopenic obesity) [525]. On the other hand, successful simultaneous LT with sleeve gastrectomy resulted in permanent weight reduction up to 3 years post-LT (weight loss 34.8 ± 17.3 % after 3 years) and additional longer term advantages with regard to arterial hypertension, insulin resistance and hyperlipidemia [524].

Regarding the choice of procedure, most experience is available for sleeve gastrectomy in the context of LT. Possible advantages of SG for (potential) liver transplant patients are the simpler technical feasibility, the preservation of the endoscopic access to the biliary tract system and the avoidance of malabsorption. The latter also plays a role in terms of the reliable absorption of immunosuppressants.

A third option is potential bariatric surgery after LT if conservative measures fail with persistent or worsening morbid obesity. Conservative treatment of severe obesity and metabolic complications post-LT can be particularly difficult, among other things because side effects of immunosuppression make metabolic control more difficult [526]. Successful case series have also been published on obesity surgery post-LT [527–529]. Overall, the complications are within acceptable limits [527, 530–532]. Because of expected adhesions and the level of immunosuppression, obesity surgery should, if possible, not be carried out before the end of the first year after transplantation. Isolated case reports exist on the use of the IGB in patients with liver cirrhosis or post-LT [533].

NAFLD patients as organ donors

RECOMMENDATIONS

Patients with NAFLD should be generally considered as organ donors.

Strong recommendation, strong consensus

If a higher-grade of hepatic steatosis is suspected in the donor liver, pre-LT rapid section diagnostics of the organ should be carried out in accordance with the standards of the German Organ Transplantation Foundation (DSO).

Recommendation, strong consensus

If higher grades of hepatic steatosis are present in an organ donated after death, the transplant can be conditioned by *ex vivo* machine perfusion.

Recommendation, strong consensus

Patients with low-grade NAFLD can be evaluated as living donors.

Recommendation, strong consensus

Commentary

The problem of accurately evaluating liver function in higher grades of hepatic steatosis in an organ donated after death using ex vivo machine perfusion was discussed in [534]. Patients with NAFLD should always be considered as organ donors. The acceptable degree of hepatic steatosis depends on the type of donation (living vs. cadaveric donors), the type of steatosis (macrovesicular vs. microvesicular) and other donor and recipient factors and must be determined in each individual donor/recipient case. With regard to the accurate evaluation of living liver donation many other factors must be taken into account, not just the steatosis grade alone.

In the context of liver donation after brain dead, macrovesicular steatosis> 30 % is an extended donation criterion. Microvesicular steatosis, on the other hand, is less relevant. A higher grade macrovesicular steatosis of the graft represents an independent risk factor for postoperative complications up to primary graft failure. One of the reasons for this is increased ischemia-reperfusion injury observed in steatotic liver grafts [535]. In addition to macrovesicular steatosis, other factors such as donor age and time of ischemia have a major influence on subsequent transplant function [536]. Recipient factors must also be taken into account in the individual organ acceptance in order to estimate the cumulative risk in the transplantation of organs with extended donor criteria. The procedure regarding organ acceptance of steatotic donor livers does not differ between recipients with and without NASH. There are no data that justify a different approach, especially since steatosis of the transplant is reversible in the early phase after transplantation [116, 515].

A better assessment of the liver function and conditioning of steatotic transplants may be used in the future for regenerating liver tissue ex vivo via machine perfusion. Results based on stronger evidence are mainly available for normothermic perfusion of donor livers. A prospective randomized trial showed that more transplants were used after normothermic machine perfusion and that these showed less graft damage postoperatively than the control group with cold preservation without machine perfusion [537]. In addition, by using normothermic machine perfusion, 22 of 31 (71 %) livers that were initially assessed as unsuitable for transplantation could be transplanted after machine perfusion and testing for functionality. A high proportion of the livers were rejected for transplantation due to underlying steatosis alone or for combined reasons [538]. There are also indications that the ischemia-reperfusion damage may be less pronounced after machine perfusion, which could be of particular advantage in steatotic transplants [539].

If living donation is planned, it is important to rule out relevant steatosis in the potential living donor, both for reasons of donor protection and with regard to a possible initial non-functioning of the liver in the recipient. Therefore, the limits for steatosis in living donation, especially adult recipients, are markedly lower than in post-mortem donation. Living donors with a macrovesicular steatosis of> 30 % are rejected in most centers. The exact extent of acceptable steatosis in living donors depends, among other factors, on the donor's age and the volume of the donor's residual liver after living donation (future liver remnant) [540] and therefore cannot be given in general terms. Potential donors with excessive or borderline hepatic steatosis can use conservative measures (diet, lifestyle change) to help reverse steatosis. This also applies to non-overweight donors with NAFLD [541].

To assess the liver parenchyma of the living donor, a sonography and a VCTE are performed to quantify steatosis using CAP and fibrosis using stiffness measurement. Additional biopsy-guided assessment of the degree of steatosis is necessary, primarily in living donors with an increased BMI, since the prevalence of steatosis in potential donors with a BMI > 28 kg/m2 is as high as 76 % [542]. The same applies if the CAP measurement is increased to > 248 dB/m or a VCTE measurement is increased to > 7 kPa.

5. Monitoring and long-term management

Surveillance (frequency)

RECOMMENDATIONS

Clinical and laboratory follow-ups should be performed in all patients with NAFLD.

Strong recommendation, strong consensus

The extent and intervals should be based on the occurrence of comorbidities as well as on the severity of the liver disease and should be carried out every 6 months, annually or every 2–3 years.

Recommendation, strong consensus

In patients with incident diagnosed NAFLD without advanced fibrosis and without typical comorbidities, follow-up examinations should include the evaluation of metabolic comorbidities.

Recommendation, strong consensus

Commentary

The close association between NAFLD and metabolic diseases must be viewed bidirectionally, i. e. that NAFLD can already precede the development of T2DM by years. Conversely, according to a current multinational meta-analysis, 72 % of patients with NAFLD have a metabolic syndrome and 47 % have T2DM [32, 543, 544]. In addition, the vast majority of NAFLD patients are overweight and have arterial hypertension. The frequency of cardiovascular diseases is higher in NAFLD than in control groups and already lead to cardiovascular events such as myocardial infarction and stroke from the early stages of fibrosis [18, 545].

A recommendation of the follow-up extent and time interval must therefore be adjusted to the heterogeneity of NAFLD with its risk factors and comorbidities. The following factors play a decisive role: Cooperation between primary and secondary care, knowledge of and reference to other national health care guidelines (specifically on obesity, T2DM, CAD, gastrointestinal oncology and HCC) as well as reference to existing preventive screening examinations and cancer prevention in accordance with G-BA guidelines is required.

Surveillance of fibrosis progression

RECOMMENDATIONS

Individual fibrosis progression in patients with NAFLD can be evaluated using repeated non-invasive tests.
Recommendation open, strong consensus
Elastography and/or CAP can be used to assess the clinical course in patients receiving therapeutic interventions.
Recommendation, consensus

Commentary

In general, NAFLD can be regarded as a rather slowly progressing liver disease [408]. As the only histologic feature, liver fibrosis is associated independently with long-term overall mortality, LT and liver-related events [82, 546]. A current meta-analysis, which included 13 studies with a total of 4428 patients and histologically confirmed NAFLD, showed a steadily increasing risk for all-cause mortality in F4 compared to F0 (RR, 3.42 (95 % CI, 2.63–4.46), liver-related mortality (RR, 11.13 (95 % CI,, 4.15–29.84), die LT (RR, 5.42 (95 % CI, 1.05–27.89) and liver-related events (RR, 12.78 (95 % CI, 6.85–23.85) [411].

Measured over a longer period of time, the initial stage of fibrosis correlates with the development of severe liver disease. One retrospective cohort study on 646 liver-biopsied NAFLD, patients were followed for an average of 20 years. Patients with F3 fibrosis developed liver decompensation over a period of 6 years whereas patients with F1 fibrosis took up to 35.6 years [69]. It therefore seems appropriate to also assess the progression of fibrosis over time during long-term monitoring of NAFLD patients in order to identify more equivocally those patients at high risk for clinical endpoints. As paired liver biopsies outside of clinical trials are not acceptable, it makes sense to repeatedly use non-invasive surrogate markers for liver fibrosis, such as the FIB-4 index, the AST/ALT quotient, the NFS or imaging methods (including transient elastography, shear-wave elastography, ARFI). Earlier data on chronic hepatitis C have shown that repeated measurement of liver stiffness and calculation of FIB-4 combined allow a better prediction of clinical endpoints than measuring each parameter alone [547]. The interventional FLINT study with paired liver biopsies showed that, for NAFLD, the non-invasive tests FIB-4 and NFS correlated with an improvement in liver histology [548]. Data from the Swedish population-based AMORIS study (n = 40,729), in which the FIB-4 index was determined at baseline value in the years 1985–1996, with a repeated measurement on average 2.4 years later, suggest that the increase in FIB-4 is associated with an increasing risk of advanced liver disease later on [549]. However, half of the liver-related events also occurred in the permanently "low" FIB-4 group, implying that the sensitivity for the repeated FIB-4 calculation with regard to liver endpoints must be classified as low (sensitivity 10–40 %). It should also be pointed out that increasing age might also be relevant when calculating FIB-4, because age is a parameter in the calculation determining the FIB-4 score [115].

Non-invasive determination of fibrosis progression: A pragmatic recommendation at this point in time may be the calculation of a low-cost score such as the AST/ALT quotient or the FIB-4 repeated every 2–3 years, especially in patients who have one or more risk factors for advanced fibrosis: Age 45–55 year; BMI > 30–32 kg/m^2; T2DM; arterial hypertension. Alternatively, depending on availability, liver stiffness measurements can be repeated every 2–3 years. Future studies will clarify whether new surrogate markers (e. g. NIS4, FAST score) or imaging methods such as MR elastography or MR PDFF can also be used to assess the individual rate of fibrosis progression and the course of NASH [550].

Risk profiles

RECOMMENDATION/STATEMENT

Statement

Patients with NASH and/or NAFLD fibrosis have an increased risk of cardiovascular and tumor-associated morbidity and mortality.
Strong consensus

Recommendation

Over the long-term course, the cardiovascular risk profile should be checked regularly, and patients should be informed about the statutory offers for early detection of cancer.
Recommendation, strong consensus

Commentary

Basic diagnostics for long-term management

- Physical examination with determination of:
  - BMI
  - Waist size
  - Blood pressure
- Clinical laboratory tests:
  - ALT, AST, γ-GT, bilirubin, AP
  - Blood count
  - Lipid status (triglycerides, cholesterol, HDL, LDL cholesterol)
  - Fasting blood sugar, HbA1c

In patients with incident NAFLD without advanced fibrosis and without typical concomitant diseases, these examinations can be carried out every 2–3 years, e. g. as part of the regular health check every 36 months. In patients with advanced fibrosis and/or NASH, baseline examinations should be performed annually.

Two large-scale meta-analyses in recent years have convincingly shown the increased incidence of liver and cardiovascular endpoints in NAFLD patients with an increasing stage of fibrosis [18, 411]. In the recently published meta-analysis by Taylor et al. the unadjusted relative risk for all-cause mortality was between 1.12 (95 % CI 0.91–1.38; for F0 versus F1) and 3.42 (95 % CI 2.63–4.46; F0 versus F4 fibrosis) [411]. Cardiovascular diseases such as myocardial infarction and stroke are the main causes of overall mortality. In a retrospective cohort study from the *German Disease Analyzer Database* (IQVIA), data from 22,048 NAFLD patients followed up at 1262 general practices between 2000–2015 were compared with a control group without NAFLD. The risk of newly emergent cardiovascular diseases was compared between the two groups that were adjusted for the incidence of arterial hyperten-

sion and diabetes mellitus, among others. The *hazard ratio* (HR, 95 % CI) was 1.34 (1.10–1.63) for the occurrence of myocardial infarction, 1.35 (1.25–1.45) for CAD, 1.15 (1.04–1.26) for atrial fibrillation and 1.09 (0.95–1.24) for stroke (n. s.) [545].

Furthermore, current studies have shown the higher incidence of cancers in patients with NAFLD compared to those without NAFLD [551]. One study conducted in the United States on 4722 patients with NAFLD demonstrated an almost doubling of the number of new cancers, especially gastrointestinal tumors, over an average follow-up of 8 years. Further analysis of the German Disease Analyzer Database (IQVIA, (see above) found that tumors of the urogenital system in men with an HR (Hazard Ratio) of 1.26; skin tumors (regardless of gender) with an HR of 1.20 and breast cancer in women with an HR of 1.22 were increased compared to patients without NAFLD [552]. In patients with NASH and/or fibrosis, annual checkups, including the basic examinations (see above), should be carried out as part of long-term management. It should also be ensured that, in addition to preventive measures and interventions (reference Chapter "Therapy"), subject-specific estimations of the individual risk profile (e. g. based on of the S3 Guideline "General practitioner risk advice on cardiovascular prevention"; ESC Pocket Guidelines of the European Society of Cardiology/German Society of Cardiology). Furthermore, patients should be encouraged to participate in the statutory cancer screening program in Germany (e. g. information on cancer screening from the German Federal Joint Committee (G-BA)).

RECOMMENDATIONS

HCC surveillance should be offered to all patients with confirmed NAFLD cirrhosis, provided they could be treated for HCC.
Strong recommendation, strong consensus

The HCC monitoring should involve liver sonography, performed by an experienced examiner with a technically adequate device, every six-months.
Recommendation, strong consensus

Additional determination of alpha-fetoprotein (AFP) can be carried out.
Recommendation open, strong consensus

If the conditions for sonographic examination are inadequate, a supplementary liver MRI can be performed.
Recommendation open, strong consensus

HCC Surveillance in NAFLD cirrhosis

Commentary

The association of NAFLD cirrhosis and HCC development has been well studied and documented over the past few years. Patients with confirmed NAFLD cirrhosis have a markedly higher annual risk of HCC. In two different American cohort studies, the HCC risk was found to be 1.56 % and 2.6 %, respectively; overall, it can be classified at over 1.5 % [342, 553]. This is slightly lower than in patients with HCV-related cirrhosis, in whom the annual incidence of HCC is approximately 4 %. In view of the fact that NAFLD-associated HCC often has a worse prognosis, as they occur more frequently in older and more severely ill patients and are often discovered late, regular surveillance is recommended [554, 555]. In patients with NAFLD cirrhosis, this is cost-effective, since the annual incidence of HCC is more than 1.5 % [556–558]. However, in a large matched case-control study conducted within the U. S. Veterans Affairs healthcare system, no improvement in cancer-associated mortality was obtained in patients with liver cirrhosis who underwent regular screening [559]. These results question the usefulness of the HCC screening in patients with liver cirrhosis and must therefore be examined further in follow-up studies.

Liver ultrasound is a widely available, inexpensive and effective screening method for HCC detection in risk groups [560–562]. Since screening quality depends largely on the examiner's experience and the equipment quality, an experienced examiner with a sufficient number of examinations per year and a device with a quality level analogous to DEGUM II are recommended for screening examinations (http://www.degum.de/) (https://www.leitlinienprogramm-onkologie.de/Leitlinien.7.0.html). If the liver cannot be adequately assessed by ultrasound, an additional MRI can be offered. Two studies on the role of MRI in HCC screening were evaluated in a meta-analysis on HCC screening [563–565]. This showed a pooled sensitivity for HCC detection of 83.1 % (95 % CI 72.0 % –90.5 %) and a specificity of 89.1 % (95 % CI 86.5 % –91.3 %) [565]. One of the two studies showed a significantly better sensitivity and specificity of MRI compared to ultrasound for the detection of HCC in cirrhosis patients [563]. Further studies are necessary to clarify the cost effectiveness of MRI examinations for HCC surveillance.

German and European HCC guidelines do no longer recommend mandatory testing of the tumor marker alpha-fetoprotein (AFP) for HCC surveillance [116, 566], as any unequivocal added benefit to ultrasound alone remained unclear. However, a current meta-analysis on HCC surveillance suggests that the addition of AFP to ultrasound increases sensitivity of HCC detection. In total, 32 studies with 13 367 patients were analyzed. Ultrasound alone had a lower sensitivity of 45 % for HCC detection than the combination with AFP of 63 % (relative risk 0.88; 95 % CI 0.83–0.93 for all stages, in the early stage RR 0.81; 95 % CI 0.71–0.93) [565]. Due to the widely discussed value of AFP alone, several alternative biomarkers or combinations of several biomarkers for HCC screening have been tested in studies in the last few years. In this context, the **GALAD score** has emerged as a promising screening method that determines the HCC risk using the patient's age, gender and the biomarkers α-fetoprotein (AFP), the AFP isoform L3 (AFP-L3) and the des-gamma-carboxy prothrombin (DCP) [567]. Patients with HCC showed an AUC of 0.96.

Various microRNAs were also investigated as biomarkers for HCC. In patients with chronic hepatitis B or C, markedly decreased levels of microRNA-139 were found in HCC [568, 569]. There are discordant results for mircoRNA-182. One study showed an increased risk of HCC due to the upregulation of miR-182, another showed a significant downregulation of the same miR-182 in HCC patients with chronic hepatitis C [570, 571]. MiR150, miR331–3 p or miR193 also seem to be interesting markers for diagnosing or predicting the course of the disease [106, 570, 572]. In total, there is not enough data to make clear recommendations for microRNA testing in the context of screening.

Surveillance in NAFLD without cirrhosis

RECOMMENDATION/DEFINITION/STATEMENT

Statement

A general recommendation for systematic HCC monitoring of NAFLD patients without proven cirrhosis cannot be given.

Strong consensus

Recommendation

Patients with advanced NAFLD hepatic fibrosis and other risk factors can be offered surveillance (as an individualized procedure) consistent with the recommendation for patients with NAFLD cirrhosis.

Recommendation open, strong consensus

Commentary

NAFLD has meanwhile become one of the main risk factors for the development of HCC and will possibly replace viral hepatitis as the main cause in a few years [573]. Regular monitoring of patients with proven NAFLD cirrhosis with regard to the development of HCC is therefore established and recognized (see above). It is much more difficult to evaluate the extremely heterogeneous group of patients with NAFLD without the full clinical picture of cirrhosis. A general HCC surveillance of all NAFLD patients is neither cost effective nor practicable – especially given the high and steadily increasing number of cases – since the annual incidence of HCC in this group is well below 1.5 % [574]. Several studies in the last years have shown that up to 42 % of all cases of NAFLD-associated HCC occur in non-cirrhotic livers [575]. This fact requires the identification of patient groups with an increased risk profile. The following risk factors were identified:

Advanced hepatic fibrosis: A meta-analysis by Dulai et al. identified the NAFLD-associated liver fibrosis as the most important risk factor for mortality in NAFLD [18]. In particular, the risk of liver-specific mortality including HCC was exponentially increased in fibrosis patients and depended on the degree of fibrosis (maximum HR 42.30 (95 % CI 3.51–510.34) in F4. Therefore, a non-invasive determination of the degree of fibrosis should be carried out in all patients with NAFLD (e. g. as a combination of two different test modalities, e. g. fibrosis scores (FIB-4, NFS) and imaging methods (transient elastography, shear-wave elastography, ARFI, etc.) [9]. Further current studies have identified liver fibrosis in NAFLD patients as a risk factor for the development of HCC [76, 576]. An American retrospective cohort study on 296,707 NAFLD patients with the same number of controls found that alongside older age, male sex and T2DM there was an increased risk of HCC from constantly increased FIB-4 above 2.67 in the subgroup of patients without cirrhosis [76, 553]. In the case of NAFLD-associated fibrosis, it therefore makes sense to investigate further risk factors for the development of HCC.

Male sex has meanwhile emerged from many studies on NAFLD patients as an independent risk factor for HCC [76, 553, 577]. A European study investigated 100 patients with NAFLD-HCC and 275 control patients with NAFLD. In the group of HCC patients, 82 % were male, in the control group only 59 % [577]. A similar assessment came from Ioannou et al. on a cohort from within the U. S. Veterans Affairs healthcare system [553].

Several studies have identified elderly patient age as a risk factor for developing HCC [76, 106, 342, 553, 578, 579]. Two studies conducted within the U. S. Veterans Affairs healthcare system diagnosed HCC significantly more often in NAFLD patients who were older than 60 (aHR 2.09) and 65 (0.41 per 1000 PY) years of age [76, 553]. In a Taiwanese cohort, age > 55 years was already a relevant risk factor for HCC in NAFLD patients (HR 7.78 95 % CI 3.12–19.44) [106]. Also in a Japanese cohort of NAFLD patients, age> 60 was one of the risk factors for HCC (HR: 4.27; 95 % CI: 1.30–14.01) [578]. Altogether, it can be said that with increasing age of NAFLD patients, the risk of developing HCC also increases significantly. This leads to the well-known problem that patients with HCC in the context of NAFLD are often older and more seriously ill than patients with HCC of a different etiology and are therefore more difficult to treat.

T2DM A retrospective cohort study from Japan with 6508 NAFLD patients showed T2DM to be an independent risk factor for HCC (HR: 3.21; 95 % CI: 1.09–9.50) [578]. This observation could be confirmed in further recent studies, so that T2DM, frequently occurring in the context of metabolic syndrome in NAFLD patients, is to be regarded as a relevant risk factor for HCC [76, 579].

Elevation of transaminase levels: A persistent inflammatory reaction of the liver could also be identified as a risk factor for developing HCC in NAFLD patients. Several studies found an increase in AST alone (AST> 40 IU/l, HR 8.20; 95 % CI 2.56–26.26) or in ALT (HR 6.80; 95 % CI 3.00–15,42) or AST/ALT ratio or FIB-4 as a risk factor for HCC development [76, 106, 553, 578]. This is consistent with the fact that persistent inflammation in the liver promotes carcinogenesis.

Genetic risk factors: In the last few years several genetic risk factors for the development of NASH cirrhosis have been described. In particular for SNP in the genes PNPLA3, TM6FS2 and MBOAT7, a clear association with increased intrahepatic fat accumulation and fibrosis was shown [136, 580–582]. Additionally, PNPLA3 rs738 409 C>G in patients with F3 fibrosis or cirrhosis was determined to carry a significantly increased HCC risk (HR 2.66; 95 % CI, 1.02–7.13) [576]. Even for these SNP, heterozygous NAFLD patients had an increased risk of HCC and this risk was even 5 times higher in homozygosity for GG compared to CC [577]. For the MBOAT7 variant re641 738 C<T an increased risk of HCC in NAFLD patients was also demonstrated in a current study, especially in pre-existing fibrosis (OR 1.65, 95 % CI 1.08–2.55) [583]. A combination of risk alleles in PNPLA3, MBOAT7 and TM6FS2 led to an increasing risk of HCC for each additional risk allele.

Overall, the study situation is insufficient for a surveillance recommendation. There is no risk score on the basis of which a recommendation for or against HCC surveillance can be made. In summary, the subgroup of NAFLD patients with proven fibrosis and other risk factors (male gender, older age, T2DM, chronic hepatic inflammation, genetic risk factors) have a significantly increased risk of developing HCC. In the absence of an existing risk stratification score in the sense of an individualized treatment concept, HCC screening analogous to the procedure in NAFLD cirrhosis can be offered.

Endoscopic surveillance in NAFLD cirrhosis

RECOMMENDATIONS

Patients with compensated NASH cirrhosis without evidence of varices from the screening endoscopy (see Chapter "Diagnostics") and continued liver damage and/or persistent co-risk factors (e. g. obesity) should be monitored endoscopically every 2–3 year, according to the S2k guideline gastrointestinal bleeding (▶ **Table 7,** Recommendation for varices screening) [584].
Strong recommendation, strong consensus

In patients with compensated NASH cirrhosis and small varices in the screening endoscopy, an annual endoscopic monitoring should be carried out according to the S2k Clinical Practice Guidelines "Gastrointestinal Bleeding" – especially if obesity and/or cofactors such as alcohol consumption persist.
Strong recommendation, strong consensus

After a decompensation event of a previously compensated NASH cirrhosis, the variceal status should be re-checked endoscopically.
Strong recommendation, strong consensus

Commentary

The current recommendations are based on the report of the "Baveno VI Consensus Workshop" on risk stratification and individual treatment of portal hypertension [585], which largely is in line with the AASLD recommendations on portal hypertension and bleeding in cirrhosis [586]. In the Baveno VI recommendations, criteria were also developed to select patients with compensated liver cirrhosis in a subgroup of patients with compensated cirrhosis using non-invasive markers (elastography value < 20 kPa and platelets > 150 000/µL) in whom there is no necessity for initial screening endoscopy, but who should only have the non-invasive tests repeated annually. These recommendations only applied to patients with viral liver disease. However, since a current study was able to validate the Baveno VI criteria in patients with metabolic liver disease [587], future studies could implement non-invasive screening examinations for varices status in patients with compensated NASH cirrhosis and thus reduce the number of unnecessary screening endoscopies in compensated NASH cirrhosis. In this context, recommendations to extend monitoring intervals are defined in the Baveno VI criteria based on the persistence or elimination of underlying liver-damaging diseases (e. g. recovery from viral hepatitis, complete abstinence from alcohol), while no clear recommendations can currently be made in this regard in the context of the NAFLD.

6. Pediatrics

Preamble

Children, adolescents and adults with obesity face an ever-present, persistent form of social stigma. They are often faced with discrimination in the workplace as well as in education and health care. Research shows that weight stigma can damage health, undermine human and social rights, and is unacceptable in modern societies. There is international consensus to consistently avoid stigmatizing language [588]. In this context, "people-first language" is a recognized linguistic standard that is also used in this guideline.

Prevalence and incidence

STATEMENTS

With a prevalence of 3–10 %, NAFLD is the most common chronic liver disease in children and adolescents in industrialized nations.
Strong consensus

The increasing incidence over the past few decades follows the increase in prevalence of overweight and obesity.
Strong consensus

Commentary

As part of the global obesity pandemic, the incidence and prevalence of NAFLD is increasing. The obesity rate has more than tripled since the 1960 s and is now 18.5 % in the USA and affects 13.7 million children and adolescents [589]. In Germany, the latest data from the 2nd wave of the KIGGS study found a prevalence of 15.4 % for overweight and 5.9 % for obesity [590–592].

The prevalence of NAFLD in children and adolescents varies significantly with the screening method used (transaminases, ultrasound, biopsy) and the patient population (regional-ethnic, genetic and environmental differences, gender, other risk factors). Accurate non-invasive biomarkers are missing for the precise recording of the NAFLD prevalence: Estimates range from 3–10 % of all children and adolescents in western industrialized nations [588–590]. In a pooled analysis of over 16,000 children with obesity the prevalence was 34.2 % (Confidence interval [CI] 95 % 27.8–41.2 %) compared to 7.6 % (CI 95 % 5.5–10.3 %) in the general pediatric population [593]. In one autopsy study conducted in San Diego County (USA), a histologically confirmed NAFLD was found in 9.6 % of all children and adolescents examined, with the prevalence in obesity being 38 % [594].

Classification of metabolic syndrome

STATEMENT

NAFLD in childhood and adolescence is closely associated with the metabolic syndrome.
Strong consensus

Commentary

In children and adolescents with obesity and other components of metabolic syndrome, the risk of developing NAFLD increases to 60–70 % [595, 596]. A multicenter study of 675 children with NAFLD showed a prevalence of T2DM of 30 %, whereby these children also had a higher risk of developing NASH [597]. Considering the strong metabolic influencing factor in the etiolo-

gy of the disease, a renaming of the nomenclature to Metabolic (Dysfunction) Associated Fatty Liver Disease (MAFLD) was recently discussed among experts [597].

Natural course of NAFLD

STATEMENT

Insufficient data are available to predict the long-term course of NAFLD in children and adolescents.

Strong consensus

Commentary

Very little high-quality data are available on the long-term course of pediatric NAFLD. This includes the question of the progression of a simple NAFL to NASH, the development of fibrosis in children and adolescents with NASH as well as the rate of NASH-associated cirrhosis and the occurrence of HCC. In adult patients with NASH, mortality is largely determined by the degree of fibrosis [16]. One of a few published case descriptions in children with sequential liver biopsy reports a potentially rapid progression of NASH to cirrhosis within a few years [598]. In a histopathological study, Mann et al. describe portal inflammatory activity as an independent risk factor for progression to advanced fibrosis [599]. This is of particular importance since portal involvement primarily affects younger children (see Chapter "Histopathology"). Ultimately, the question of the capacity of the liver for regression of moderate or advanced fibrosis under adequate therapy remains, especially in childhood and adolescence.

The lifespan, and thus the imminent cumulative risk of progression or the occurrence of complications, is increased in pediatric NAFLD. The latency here can be significant. A large retrospective study examined the relationship between the BMI in 244 464 school children in Copenhagen (born between 1930 and 1989) and the incidence of NAFLD in adulthood. Weight gain in childhood was shown to be an independent risk factor for developing NAFLD and liver cirrhosis later in life. Another Danish study shows a clear association between BMI at the age of 18–20 years and severe liver-related morbidity and mortality 40 years later (increase 5 % per BMI unit over 11.5 kg/m² for cirrhosis, decompensation and liver-associated death) [600]. In a cohort of 66 adolescents (age 13.9 ± 3.9 years), observed over 20 years, the liver transplant-free interval in patients with NAFLD was significantly shorter than in the general US population (standardized mortality ratio 13.6 (95 %) Confidence interval, 3.8–34.8; $p < 0.0001$)), with 2 patients requiring LT due to decompensated liver cirrhosis. [601] Overall, there is concern about an earlier occurrence of serious hepatic or cardiovascular complications in adolescence or early adulthood [602].

Risk factors for developing fibrosis in NAFLD include the presence of other components of metabolic syndrome, such as insulin resistance or dyslipidemia [603]. According to current data, low or moderate alcohol consumption into young adulthood is not, as previously assumed, protective for the development of fibrosis [604, 605]. Important epigenetic influences are the maternal diet and behavior and consequent intrauterine deficiency or overnutrition (high fat diet in animal models [606], epidemiological data [607, 608] and a number of DNA methylation and histone modification profiles as well as microRNA profiles in the liver and blood circulation [609].

Genetics

RECOMMENDATION

Routine PNPLA3 genotyping for clinical risk stratification of NAFLD in childhood and adolescence cannot be recommended.

Recommendation open, strong consensus

Commentary

The PNPLA3 148 M variant is the genetic influencing factor that has been best studied in children and adolescents. It is associated with an increased risk for NAFLD and also with the histological severity of steatosis, inflammation and fibrosis. The minor allele frequency of PNPLA3 is positively associated with the prevalence of NAFLD. Meanwhile, several pediatric studies with histologically proven NAFLD have confirmed the association of the PNPLA3 I148 M variant with a higher degree of steatosis, a higher NASH risk and an increased risk of fibrosis [610–612].

The fact that only a subset of patients with NAFLD develop progressive NASH initially pointed to a multifactorial background of the disease beyond purely lifestyle and environmental factors and it is proved that the individual genetic predisposition plays a decisive role in the phenotype of NAFLD. Numerous genetic risk factors for NAFLD have now been identified. These are clinically relevant, especially in children and adolescents with an early onset of the disease and thus long duration of the disease. In the aforementioned autopsy study by Schwimmer et al. ethnic origin was also examined. After correction for the BMI, children with a Hispanic family background had the highest risk (11.8 %), while children with an African American background were protected (1.5 %) [594]. The increased risk for children with a Hispanic-Mexican background could also be reproduced in population-based studies. It turns out that the minor allele frequency (MAF) of the pathogenic I148 M allele in the Mexican population is markedly elevated at 0.73 compared to Caucasians (0.26–0.32) and African-Americans (0.18) [613].

While the data on TM6SF2 in children does not currently permit a final assessment, a recent meta-analysis showed no effect of MBOAT7 in children and adolescents, in contrast to adults [614]. The study of 685 children and adolescents showed for the protective variant HSD17B13a lower degree of steatosis, lower transaminases and a lower fibrosis score [615]. The study of 685 children and adolescents showed for the protective variant HSD17B13a lower degree of steatosis, lower transaminases and a lower fibrosis score [615]. The interaction of the risk from PNPLA3 1148 M with fructose consumption in children would warrant further investigation into risk stratification. Currently, this does not result in changing advice on lifestyle changes or pharmacological therapy options [616]. In clinical trials, genotyping should be carried out for a more precise evaluation of outcomes.

Screening

RECOMMENDATIONS

In children and adolescents with BMI above the 97th percentile according to Kromeyer Hauschild or a BMI above the 90th percentile and other risk factors such as insulin resistance, diabetes and dyslipidemia, the ALT levels among others should be determined from the age of 8 years.

Recommendation, strong consensus

ALT levels should be compared to gender-specific reference ranges.

Recommendation, strong consensus

Commentary

Chronic liver disease must also be identified promptly in obese children and adolescents. NAFLD progresses in childhood and adolescence and, in exceptional cases, can also lead to liver cirrhosis. Diagnostics enables the exclusion of other chronic liver diseases and an early attempt at therapy [601, 617, 643, 659]. ALT levels should be compared to gender-specific reference ranges [618].

Algorithms for persistent transaminase elevation

RECOMMENDATIONS

If there is clinical evidence of progressive liver disease (e. g. cholestasis or splenomegaly) or if serum transaminases remain elevated for more than 6 months, diagnostic work-up should be carried out in children and adolescents.

Recommendation, strong consensus

Other liver diseases as a cause of increased transaminases should be excluded.

Strong recommendation, strong consensus

Commentary

Since other hepatopathies can present clinically, in laboratory tests, in imaging and histologically with very similarly pictures, the primary goal is not the diagnosis of NAFLD, but the reliable exclusion of other causes for the elevated transaminases (infections, autoimmune diseases, metabolic and endocrinological diseases).

RECOMMENDATIONS

The following parameters should be recorded in the medical history:

Self-reported history: Question about underlying diseases (type 1 diabetes, type 2 diabetes, hepatitis B and C, neurosurgical intervention close to the hypothalamus-pituitary gland, chemotherapy, radiation, autoimmune diseases), ethnic origin, duration of obesity, diet and exercise history, therapeutic attempts with regard to obesity, drugs/toxins, alcohol consumption.

Family history: Family history of overweight, liver diseases, autoimmune diseases.

Recommendation, strong consensus

A medical and neurological examination including height, weight, BMI, and blood pressure should be performed. Special features (e. g. striae distensae, hirsutism, acanthosis nigricans) as well as liver and spleen size should be documented.

Recommendation, strong consensus

In obesity and persistently elevated transaminases, stepwise diagnostics should be carried out according to the following scheme (▶ **Fig. 4**).

Recommendation, strong consensus

Commentary

Basic diagnostic tests for persistently elevated transaminases:

Medical history and clinical findings: Blood pressure should be measured with the correct cuff size.

Screening:

- AST, ALT, γ-GT, AP, bilirubin (direct, indirect), CK, LDH, partial thromboplastin time (Quick-test)
- Ultrasound examination

When warning signs are present, i. e. clinical, laboratory or sonographic evidence of progressive liver disease or in the presence of cholestasis, immediate further diagnostics should be initiated, otherwise follow-up within the infection-free interval after 6–12 weeks.

Basic diagnostic tests (level 1):

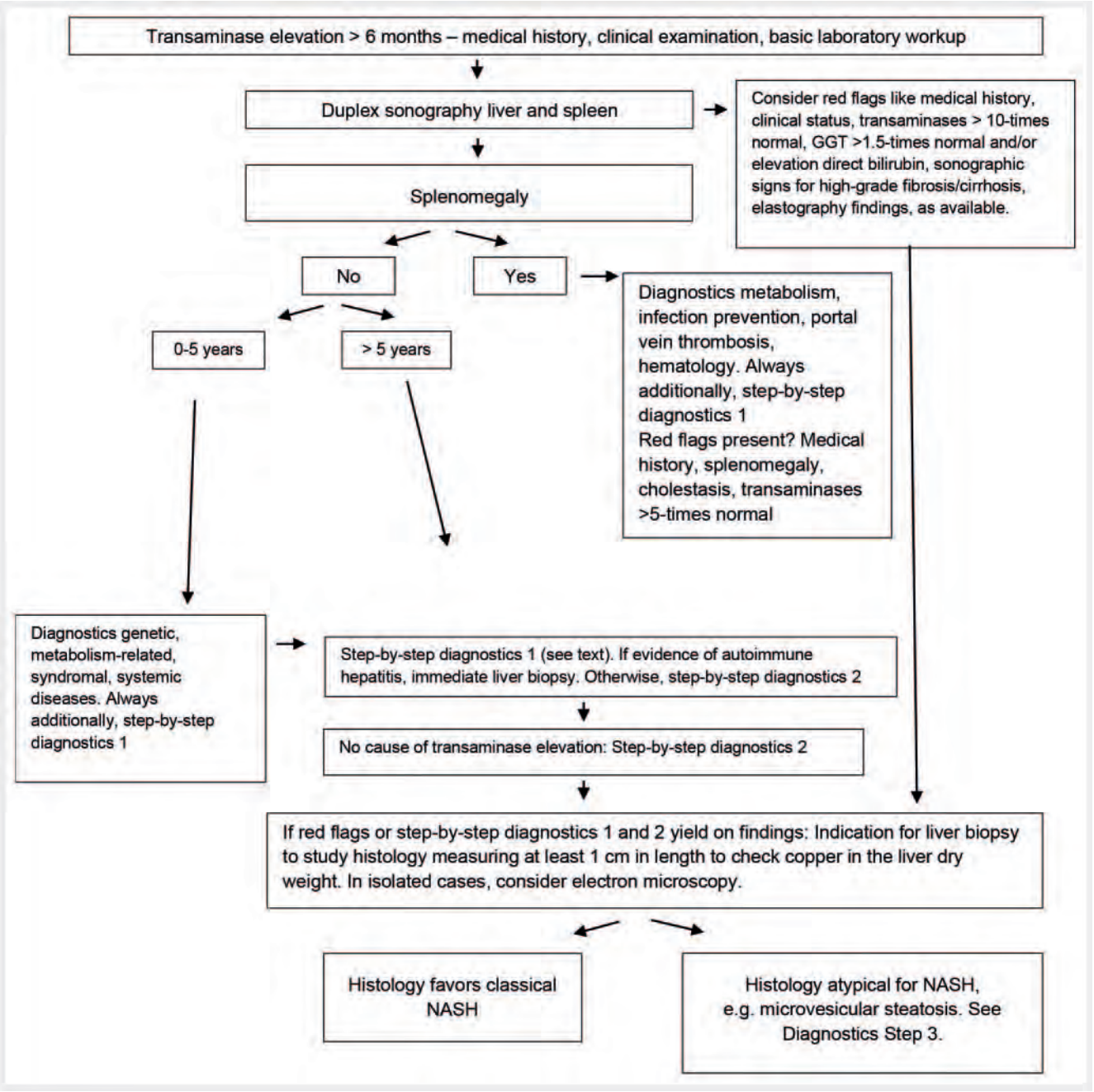
If elevated liver values persist for more than 6 months without "red flag signs" such as splenomegaly, sonographic or clinical signs of high-grade liver fibrosis/cirrhosis, cholestasis, abnormal family or travel history, blood count, Quick, PTT, autoantibodies (ANA, SMA, LKM, SLA), immunoglobulins (IgG, IgA, IgM), transglutaminase-IgA-Ab, serum ceruloplasmin, serum alpha-1-antitrypsin, cholesterol, HDL, LDL, T3, fT4, TSH, virus serology (CMV, EBV, HAV, HBV, HCV, HEV) should be measured.

Extended basic diagnostic tests (level 2):

Copper excretion in the 24-hour urine with or without administration of penicillamine, phenotyping of alpha-1-antitrypsin, if necessary, in borderline results.) LAL-D enzymes, hepatitis E serology.

In addition, special diagnostic procedures such as genetic and metabolic diagnostics such as amino acids in plasma, organic acids in urine, lactate and ammonia in serum, sweat test, echocardiography, etc. can also be helpful.

Ultrasound examination by elevated ALT provides the probably most sensitive method for the early detection of NAFLD. A disadvantage of sonography is the inability to quantify hepatic steatosis.



▶ **Fig. 4** Step-by-step diagnosis by obesity and persistently elevated transaminases: Basic diagnostic tests for persistently elevated transaminases [rerif].

Indication for liver biopsy and extended diagnostics

RECOMMENDATIONS

When warning signs are seen, i. e. based on medical history or clinical evidence of progressive liver disease or cholestasis, the child should undergo extended diagnostics (liver biopsy) in a step-by-step regimen without delay.

Strong recommendation, strong consensus

If there are no warning signs, liver function should be checked after 3–6 months. In overweight individuals, weight reduction should be attempted during this period.

Strong recommendation/recommendation, strong consensus

An extended diagnostics should also be carried out in case of persistently elevated liver function values over a period of 3–6 months. The extended diagnostics should be based on clinical findings, medical history, age of the child and previous results and should be carried out in a step-by-step regimen. See ▶ **Fig. 4**

Recommendation, strong consensus

Sonography of the abdomen, especially the liver and spleen, should be performed as part of extended diagnostics. Ultrasound should be performed by pediatricians, pediatric gastro-

enterologists, or radiologists/gastroenterologists experienced with children.
Strong recommendation, strong consensus
The indication and timing of the biopsy should be determined by pediatric gastroenterologists or pediatricians experienced in gastroenterology as part of a step by step diagnostics.
Recommendation, strong consensus

Commentary

An immediate liver biopsy as part of the initial diagnosis is recommended, if there is suspected progressive liver disease, e. g. with high IgG or positive liver-associated autoantibodies or suspected Wilson's disease (low ceruloplasmin, increased copper excretion in the urine, Kaiser-Fleischer ring).

In cases of radiological evidence of hepatic steatosis, Wilson's disease or other specific hepatopathies cannot be ruled out with certainty without liver biopsy. Patients with normal or only slightly elevated transaminases can already have significant fibrosis. In addition to the puncture-related risks (pain, bleeding, biliary leakage, injury to other organs, pneumothorax), liver biopsy carries a considerable sampling error, especially since the histological picture of NAFLD is not homogeneously distributed in the liver (1: 50 000 sample volume) [46]. Further uncertainty arises from the fact that the histological assessment is dependent on the examiner [619]. The importance of the non-invasive markers is shown in the Chapter "Monitoring".

RECOMMENDATIONS

A liver biopsy should be performed after 18 months at the latest, if persistently elevated liver function values cannot be clearly explained in any other way.
Recommendation, strong consensus

Commentary

NAFLD covers a spectrum of diseases from the NAFL to NASH-associated cirrhosis. The term NAFL is also used in children and adolescents for describing non-alcoholic fatty liver or benign hepatic steatosis. Accordingly, the term NASH is used in pediatrics for the more aggressive form of liver cell steatosis involving hepatocytic degeneration and fibrosis. To diagnose NAFLD in childhood, it is required that at least 5 % of the hepatocytes have macrovesicular fat deposits. In analogy to the diagnosis of hepatic steatosis in adults, there are low-grade (mild) steatosis (less than a third of the hepatocytes affected), moderate (moderate) steatosis (two-thirds of the hepatocytes affected) and high-grade (severe) steatosis (more than two-thirds of the hepatocytes affected). If, during the diagnostic process, there is evidence of a different liver disease, the diagnosis should be sought immediately, if necessary with a liver biopsy.

Differential diagnostics

RECOMMENDATION/DEFINITION

Weighing a potential risk (from the puncture) against the expected benefit (diagnosis of a previously unrecognized potentially dangerous hepatopathy, e. g. Wilson' disease, possibility of differentiating NAFL versus NASH; in the latter case intensifying obesity therapy, etc.) should be discussed with parents and, if feasible, the patient.
Strong recommendation, strong consensus
For the differential diagnosis of NAFLD, children and adolescents should be given access to specialized pediatric care.
Recommendation, strong consensus
A differential diagnosis should be carried out to rule out other causes.
Recommendation, strong consensus

Commentary

Differential diagnoses for NAFLD in childhood and adolescence:

- *Nutritional disorders:* Acute or chronic malnutrition, parenteral nutrition,
- *Hepatopathies:* Infectious hepatitis, autoimmune diseases (autoimmune hepatitis, primary sclerosing cholangitis PSC, inflammatory bowel disease, celiac disease), metabolic diseases (lysosomal acid lipase deficiency, Wilson's disease, α1-antitrypsin deficiency, glycogen storage disease, familiar hyperlipoproteinemia, abetalipoproteinemia, oxidation- urea cycle disorders, hemochromatosis), endocrine diseases (after CNS surgery near the pituitary gland or chemotherapy, hypothyroidism, pituitary insufficiency),
- Disease syndromes: e. g. Bardet Biedl syndrome, Prader Willi syndrome, lipodystrophy,
- Hepatotoxic drugs: e. g. amiodarone, methotrexate, steroids, L-asparaginase, vitamin A, zidovudine and other "highly active antiretroviral therapy" (HAART) for HIV, valproate.

Ethical considerations for inclusion in clinical trials:

Participation in a study is very desirable; non-participation has no effect on the therapy. Avoiding (repeated) liver biopsies in childhood using validated non-invasive markers is an important goal in order to be able to treat as many children as possible in studies. No non-invasive marker is currently sufficiently validated to adequately replace liver biopsy. Another goal of clinical trials is to develop new drug targets.

Histopathology of pediatric NAFLD

STATEMENT

The histopathological changes of NASH in children are comparable to those in adults, with different degrees of steatosis, inflammation and fibrosis. In general, the histopathological changes are less pronounced in children, cirrhosis is less common, and boys are more likely to develop the disease.
Strong consensus

Commentary

Schwimmer and coworkers have described two different forms of NASH in children [620]. Type 1 shows a picture comparable to that of NAFLD in adults. This form is characterized by steatosis in zone 3 (centrilobular) frequently associated with hepatocellular ballooning and the development of perisinusoidal fibrosis. It seems to be more common among adolescents.

Type 2 of childhood NAFLD is more common in younger children and shows a pronounced, partly panacinar steatosis in zone 1. The largest fat vacuoles are found periportally. Hepatocellular ballooning and perisinusoidal fiber deposits are usually absent, or these features are only mild. Although a milder lobular inflammation was initially described, the analysis of a larger cohort showed no statistically significant difference between the two variants of hepatic steatosis in children. Mallory bodies are very rarely found. However, children with periportal steatosis more pronounced in zone 1 have fibrosis emanating from the portal field. This occurs more often than in NASH with zone 3 steatosis already with septa present, and thus shows a potential for progression [620, 621]. Already in the original work by Schwimmer et al. as in other studies, an overlap between these two types of NAFLD in children could be demonstrated, which is why the classification does not seem practicable. In addition, the available data derive from cross-sectional studies, making it impossible to assess whether the two types of steatosis are prognostically relevant. It seems important that there are distinct steatosis phenotypes (in contrast to adults) and that NAFLD can also be progressive in children, although the formal criteria for diagnosing NASH (fat + ballooning + inflammatory foci) are not met.

In the differential diagnosis, Wilson's disease, other, also rare, hepatic metabolic diseases or weight loss due to diarrhea in the context of chronic inflammatory bowel diseases with liver involvement must be considered. The diagnostic differentiation from viral hepatitis is particularly important.

▶ **Table 7** Histopathological criteria of infantile NAFLD.

Population	Children	Adolescents
Steatosis	Zone 1 up to panacinar	Zone 3 up to panacinar
Inflammation	More portal than intra-acinar inflammation, especially in the early stages	Intraacinar inflammation dominant
Extensive ballooning	Rare or absent, no Mallory-Denk bodies	In zone 3
Fibrosis	Incipient periportal fibrosis	Perisinusoidal fibrosis, in zone 3

Treatment: Prevention, lifestyle therapy/obesity therapy

RECOMMENDATIONS

Children and adolescents with NAFL/NASH should receive a multimodal lifestyle intervention if they are overweight or obese. This should be in line with the guideline of the Working Group for Obesity in Children and Adolescents of the German Obesity Society. (AWMF 050–002)

Strong recommendation, strong consensus

Children with NAFL/NASH should be vaccinated against hepatitis A and B.

Furthermore, the recommendations of the German vaccine commission of the Robert Koch Institute should be considered.

Recommendation, strong consensus

Commentary

With regard to lifestyle interventions and weight reduction, there is currently no systematic difference between children and adolescents with obesity and/or NAFLD The pillars of therapy include increasing exercise and modifying diet. The probability of weight loss and its maintenance increases with support from multidisciplinary teams [622, 623].

The multimodal lifestyle intervention is suitable for all children and adolescents for the primary treatment of NAFLD and has been shown to reduce the intrahepatic fat percentage [624, 625]. The combination of nutrition and exercise therapy is more effective than the respective individual intervention [626].

In a randomized intervention study with 40 children and adolescents with obesity and NAFLD, the dietary restriction of free sugars over 8 weeks led to a greater reduction in the hepatic fat content from 25 % to 17 % (measured by MR-PDFF) compared to the control group. In an 8-week randomized trial, the restriction of carbohydrates was superior to a low-fat diet when the daily caloric requirement was maintained, producing a significant reduction in hepatic fat content and an improvement in insulin resistance [627]. The prevention of metabolic syndrome in the sense of secondary prevention is achieved through early and long-term successful obesity therapy. Exercise is particularly effective in multimodal lifestyle therapy for improving insulin resistance [628]. Exercise therapy is probably also relevant for children of normal weight and NAFLD, as there is a connection between insulin resistance and skeletal muscle mass [629]. https://www.awmf.org/uploads/tx_szleitlinien/050-002l_S3_Therapie-Praevention-Adipositas-Kinder-%20Jugendliche_2019-11.pdf

Treatment: Bariatric procedure (surgery/endoscopy)

RECOMMENDATIONS

Bariatric procedures can be carried out in adolescents with extreme obesity (BMI > 99.5th percentile)

- can also lead to an improvement in NAFLD by reducing weight and improving the metabolic situation

- in exceptional cases, after all other therapy options have been exhausted and relevant psychiatric comorbidities have been excluded.
- should always be carried out at a specialized center to ensure structured, multi-professional pre- and aftercare, as well as long-term follow-up.

Strong recommendation, strong consensus

Commentary

Long-term therapeutic success in children/adolescents with extreme obesity and a metabolic syndrome with NAFLD is rarely achieved. For this reason, bariatric procedures as a way of treating NAFLD in children/adolescents have been discussed controversially for years [630]. The basic indication for bariatric measures takes into account the characteristics of these age groups. Particularly in the case of irreversible bariatric surgical procedures (stomach reduction; gastric bypass), the lifelong consequences must be taken into account [631, 632]. On the other hand, pediatric patients with extreme obesity can undergo bariatric procedures to improve their metabolic situation and thus improve their NAFLD [633]. The greatest evidence is available for the methods of gastric reduction and gastric bypass [634]. For small numbers of cases, surrogate markers of NAFLD (transaminases, sonography, elastography, scores) are usually described over the course of the disease [635], and in individual studies also for bariatric endoscopic procedures such as gastric banding [636]. These show in each case a significant improvement in the NAFLD (based on the different markers), but there is a lack of uniform criteria and long-term observations. Only one pediatric study evaluates liver biopsies before and 1 year after stomach reduction in 20 adolescent patients and found significant improvements in both histology and adipokines [637, 638]. In this context, the usefulness of a routine intraoperative liver biopsy in pediatric patients is also discussed [639]. The small number and heterogeneity of pediatric studies on the topic of "bariatric procedures and NAFLD" currently do not allow any clear recommendations on indications or contraindications. On the contrary, there is an urgent need for a structured documentation and follow-up in this particular patient group. Recommendations for endoscopic bariatric procedures such as a gastric balloon are given in the S3 guideline on Obesity Surgery (AWMF Register No. 088–001) under certain conditions for adulthood. Due to insufficient studies, no recommendation can be made for adolescents.

Management: Pharmacological Therapy (Vitamin E & N-3)

STATEMENT

There is currently insufficient data for a pharmacological therapy of NAFL or NASH in children and adolescents.

Strong consensus

Commentary

Although in the Treatment of NAFLD in Children (TONIC) Trial [640], a multicenter, placebo-controlled study, neither vitamin E (800 IE/d) nor metformin (500 mg twice daily) could achieve the primary endpoint of a substantial and persistent ALT reduction in children and adolescents, there was a significantly reduction in NASH (58 % vs 28 %, p = 0.006) and a significant decrease in the histological activity index (–1.8 vs –0.7) in the vitamin E group. There was less ballooning in the metformin group. In adults, there are considerable safety concerns about treatment with vitamin E (increased all-cause mortality, stroke and prostate carcinoma) [353]. The long-term safety of high-dose vitamin E treatment in children is unknown [641].

Studies on the effectiveness of omega-3 fatty acids have yielded conflicting results. While a combination of eicosapentaenoic acid and docosahexaenoic acid showed no significant therapeutic benefit in one study [642], the administration of docosahexaenoic acid (250 mg/day) for 6 months led to a significant improvement in liver fat content and cardiometabolic risk factors in another study [643]. It also reduced ALT levels at follow-up more than a year later [644]. The response to DHA seems to correlate with PNPLA3 polymorphisms (I148 M variant less responsive) [645]. Choline combined with DHA and vitamin E showed a significant reduction in ALT and steatosis [646]. Administration of cysteamine bitartrate (CBDR) for 1 year led to a significant reduction in ALT and inflammation but did not improve histological scores [647].

Although the relationship between altered gut microbiome and NAFLD have been well documented, randomized trials on factors influencing the gut microbiome in NAFLD are rare. A randomized trial with 8 weeks of *Lactobacillus rhamnosus* strain GG (12 billion CFU/day) led to significantly lower ALT regardless of changes in BMI [648]; another study showed a significant decrease in steatosis under VSL # 3 treatment *(Lactobacillus plantarum, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium infantis, Bifidobacterium breve, Bifidobacterium longum, Streptococcus salivarius* subsp. *thermophilus*) lasting 4 months [649]. In view of the low risk of undesirable effects, further studies on the long-term course and cost-benefit analyses are required. Individual substances are currently being tested in phase 2 studies on pediatric populations, including the dual PPARα/δ agonist elafibranor and the AT1 antagonist losartan. Losartan inhibits the production of plasminogen activator inhibitor 1 and blocks the renin angiotensin system, thereby exerting an anti-inflammatory and anti-fibrotic effect. However, data on effectiveness are still pending (STOP NAFLD trial, NCT03467217).

Monitoring: Clinical management/connection to obesity/hepatology centers

RECOMMENDATION

Children and adolescents with NASH should regularly be cared for at a specialized center linked to a child obesity center.

Recommendation, strong consensus

Commentary

The clinical management of pediatric NAFLD is a multidisciplinary challenge and includes care in a pediatric liver care center as well as a child obesity center. In addition to medical care, the integration of ecotrophology, physiotherapy and, if necessary, child and adolescent psychiatry as well as pediatric social care are decisive influencing factors for sustainable therapeutic success.

Monitoring: Non-invasive progress parameters (imaging/biomarkers)

RECOMMENDATIONS

In addition to anthropometric data, follow-up laboratory tests (transaminases, HOMA-IR, lipid profile) and sonographic evaluation of the liver should be carried out in children and adolescents with NAFLD to assess the clinical course.

Strong recommendation, strong consensus

In addition, the liver stiffness can be determined using ultrasound elastography.

Recommendation open, strong consensus

Commentary

Specific non-invasive biomarkers for assessing the progression of fibrosis are not sufficiently validated, but are urgently required for efficient risk stratification. The clinical assessment of the course of NAFLD in children and adolescents can relate in particular to the course of steatosis, the development of NASH and the quantification of fibrosis.

Anthropometric data (height, body weight, BMI, BMI percentile and SDS) including the physical status should always be collected. Any success of obesity therapy can also be documented within this context. As part of the laboratory workup, it is useful to regularly examine not only the liver parameters (ALT, AST, γ-GT) but also metabolic sequelae (fasting glucose, fasting insulin plasma levels, HOMA-IR, lipid profile).

An easy-to-use and inexpensive imaging technique is the ultrasound scan of the liver. However, the sensitivity is low and generally reliable proof of steatosis (device and operator-dependent) is only possible > 30 % fat accumulation in the liver [650]. Long-term monitoring can only provide a rough quantification of steatosis. The quality of the examination is further limited in extreme obesity. Detection of steatosis by MRI, e. g. using magnetic resonance proton density fat fraction MR-PDFF [651, 652] or measuring the hepatic fat fraction [653].

The prognosis of NAFLD in children is influenced by the development of NASH and progressive liver fibrosis. Non-invasive biomarkers (serum markers and imaging methods) for the detection of NASH and classification of the fibrosis degree were also increasingly being investigated in children and adolescents, but have not yet been adequately validated. Distinguished are clinical fibrosis scores (based on standard-of-care laboratory and clinical parameters), experimental serological biomarkers and imaging methods.

Clinical fibrosis scores were repeatedly examined in pediatric cohorts with histologically confirmed NAFLD. A South Korean study by Yang et al. [654] investigated 77 children and adolescents; it showed the highest test quality for the detection of moderate fibrosis (F ≥ 2) by determining the FIB-4 (AUROC 0.81). The validation of these data in a multicenter study conducted in the United States by Mansoor et al. [655] was unsuccessful and, with an AUROC of 0.69, markedly below the result described above. In fact, none of the examined fibrosis scores (AST/ALT ratio, FIB-4, NAFLD fibrosis score, APRI) showed sufficient test quality to detect any moderate or advanced fibrosis. A more recent study by Jackson et al. [656], who examined 146 children and adolescents with NAFLD, found AUROC values between 0.57 (NAFLD fibrosis score, PNFS [657]) and 0.67 (AST to platelet ratio index, APRI and pediatric NAFLD fibrosis index, PNFI) [658]. Interestingly, the determination of the ALT and the AST alone gave AUC-ROC values of 0.64 each. There is currently no superiority in the use of clinical fibrosis scores over measuring transaminase levels alone.

Another method for quantifying hepatic fibrosis is the determination of mechano-elastic tissue properties using elastography. For this purpose, both ultrasound-based modalities (transient elastography [659], Shear-Wave Elastography [660], Time-Harmonic Elastography [661]) and MR-based elastography [653, 662] are available. The diagnostic accuracy of these investigations is well above the results of clinical fibrosis scores (in particular AUROC > 0.87 for the detection of moderate fibrosis across all modalities), but further studies on independent cohorts are required to validate these methods. The diagnostic challenge lies particularly in patients with extreme obesity, since the penetration depth of the transient elastography is limited by the subcutaneous fatty tissue, and consequently leads to inaccurate measurements or are technically not feasible [663].

Interessenkonflikte

Potential conflicts of interest are listed in the Supplementary File.

References

[1] Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell 2021; 184: 2537–2564

[2] Morita Y, Ueno T, Sasaki N et al. Comparison of liver histology between patients with non-alcoholic steatohepatitis and patients with alcoholic steatohepatitis in Japan. Alcohol Clin Exp Res 2005; 29: 277S–281S

[3] Edmondson HA, Peters RL, Reynolds TB et al. SCLEROSING HYALINE NECROSIS OF THE LIVER IN THE CHRONIC ALCOHOLIC. A RECOGNIZABLE CLINICAL SYNDROME. Ann Intern Med 1963; 59: 646–673

[4] Ye Q, Zou B, Yeo YH et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020; 5: 739–752

[5] Young S, Tariq R, Provenza J et al. Prevalence and Profile of Nonalcoholic Fatty Liver Disease in Lean Adults: Systematic Review and Meta-Analysis. Hepatol Commun 2020; 4: 953–972

[6] Eslam M, Sanyal AJ, George J et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020; 158: 1999–2014.e1

[7] Fouad Y, Waked I, Bollipo S et al. What's in a name? Renaming "NAFLD" to "MAFLD". Liver Int 2020; 40: 1254–1261

[8] Roeb E. Excess Body Weight and Metabolic (Dysfunction)-Associated Fatty Liver Disease (MAFLD). Visc Med. 2021; 37 (4): 273–280. doi:10.1159/000515445

[9] Loomba R, Lim JK, Patton H et al. AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology 2020; 158: 1822–1830

[10] Petrick JL, Thistle JE, Zeleniuch-Jacquotte A et al. Body Mass Index, Diabetes and Intrahepatic Cholangiocarcinoma Risk: The Liver Cancer Pooling Project and Meta-analysis. Am J Gastroenterol 2018; 113: 1494–1505

[11] Sabrina V, Michael B, Jörg A et al. S3-Leitlinie: Diagnostik und Therapie des hepatozellulären Karzinoms. Z Gastroenterol 2022; 60: e56–e130

[12] Bitzer M, Voesch S, Albert J et al. S3-Leitlinie – Diagnostik und Therapie biliärer Karzinome. Z Gastroenterol 2022; 60: e186–e227

[13] Cairns SR, Peters TJ. Micromethods for quantitative lipid analysis of human liver needle biopsy specimens. Clin Chim Acta 1983; 127: 373–382

[14] Bedossa P, Poitou C, Veyrie N et al. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology 2012; 56: 1751–1759

[15] Kleiner DE, Brunt EM, Van Natta M et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005; 41: 1313–1321

[16] Flechtenmacher C, Schirmacher P, Schemmer P. Donor liver histology – a valuable tool in graft selection. Langenbecks Arch Surg 2015; 400: 551–557

[17] Xiao H, Shi M, Xie Y et al. Comparison of diagnostic accuracy of magnetic resonance elastography and Fibroscan for detecting liver fibrosis in chronic hepatitis B patients: A systematic review and meta-analysis. PLoS One 2017; 12: e0186660

[18] Dulai PS, Singh S, Patel J et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017; 65: 1557–1565

[19] Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology 2018; 155: 443–457.e17

[20] Xiao G, Zhu S, Xiao X et al. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology 2017; 66: 1486–1501

[21] Ooi GJ, Mgaieth S, Eslick GD et al. Systematic review and meta-analysis: non-invasive detection of non-alcoholic fatty liver disease related fibrosis in the obese. Obes Rev 2018; 19: 281–294

[22] Bedossa P, Consortium FP. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology 2014; 60: 565–575

[23] Lackner C. Hepatocellular ballooning in nonalcoholic steatohepatitis: the pathologist's perspective. Expert Rev Gastroenterol Hepatol 2011; 5: 223–231

[24] Davison BA, Harrison SA, Cotter G et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol 2020; 73: 1322–1332

[25] Longerich T, Schirmacher P. Determining the reliability of liver biopsies in NASH clinical studies. Nat Rev Gastroenterol Hepatol 2020; 17: 653–654

[26] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006; 23: 469–480

[27] Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. Lancet 2005; 366: 1059–1062

[28] Strobel D, Bernatik T, Blank W et al. Incidence of bleeding in 8172 percutaneous ultrasound-guided intraabdominal diagnostic and therapeutic interventions – results of the prospective multicenter DEGUM interventional ultrasound study (PIUS study). Ultraschall in Med 2015; 36: 122–131

[29] Crawford AR, Lin XZ, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. Hepatology 1998; 28: 323–331

[30] Colloredo G, Guido M, Sonzogni A et al. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol 2003; 39: 239–244

[31] Rockey DC, Caldwell SH, Goodman ZD et al. Liver biopsy. Hepatology 2009; 49: 1017–1044

[32] Chalasani N, Younossi Z, Lavine JE et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018; 67: 328–357

[33] Brunetti E, Silini E, Pistorio A et al. Coarse vs. fine needle aspiration biopsy for the assessment of diffuse liver disease from hepatitis C virus-related chronic hepatitis. J Hepatol 2004; 40: 501–506

[34] Palmer T, Georgiades I, Treanor D et al. Improved tissue sections for medical liver biopsies: a comparison of 16 vs 18g biopsy needles using digital pathology. J Clin Pathol 2014; 67: 415–419

[35] Aribaş BK, Arda K, Ciledağ N et al. Accuracy and safety of percutaneous US-guided needle biopsies in specific focal liver lesions: comparison of large and small needles in 1300 patients. Panminerva Med 2012; 54: 233–239

[36] Vijayaraghavan GR, Vedantham S, Rangan V et al. Effect of needle gauge and lobe laterality on parenchymal liver biopsy outcome: a retrospective analysis. Abdom Imaging 2015; 40: 1223–1229

[37] Hall TC, Deakin C, Atwal GS et al. Adequacy of percutaneous non-targeted liver biopsy under real-time ultrasound guidance when comparing the Biopince and Achieve biopsy needle. Br J Radiol 2017; 90: 20170397

[38] Forssell PL, Bonkowsky HL, Anderson PB et al. Intrahepatic hematoma after aspiration liver biopsy. A prospective randomized trial using two different needles. Dig Dis Sci 1981; 26: 631–635

[39] Tublin ME, Blair R, Martin J et al. Prospective Study of the Impact of Liver Biopsy Core Size on Specimen Adequacy and Procedural Complications. Am J Roentgenol 2018; 210: 183–188

[40] Kleiner DE, Bedossa P. Liver histology and clinical trials for nonalcoholic steatohepatitis-perspectives from 2 pathologists. Gastroenterology 2015; 149: 1305–1308

[41] Neuberger J, Patel J, Caldwell H et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut 2020; 69: 1382–1403

[42] Ratziu V, Charlotte F, Heurtier A et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005; 128: 1898–1906

[43] Merriman RB, Ferrell LD, Patti MG et al. Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. Hepatology 2006; 44: 874–880

[44] Larson SP, Bowers SP, Palekar NA et al. Histopathologic variability between the right and left lobes of the liver in morbidly obese patients undergoing Roux-en-Y bypass. Clin Gastroenterol Hepatol 2007; 5: 1329–1332

[45] Ooi GJ, Clouston A, Johari Y et al. Evaluation of the histological variability of core and wedge biopsies in nonalcoholic fatty liver disease in bariatric surgical patients. Surg Endosc 2021; 35: 1210–1218

[46] Vuppalanchi R, Unalp A, Van Natta ML et al. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic Fatty liver disease. Clin Gastroenterol Hepatol 2009; 7: 481–486

[47] Perrault J, McGill DB, Ott BJ et al. Liver biopsy: complications in 1000 inpatients and outpatients. Gastroenterology 1978; 74: 103–106

[48] Maharaj B, Bhoora IG. Complications associated with percutaneous needle biopsy of the liver when one, two or three specimens are taken. Postgrad Med J 1992; 68: 964–967

[49] Chi H, Hansen BE, Tang WY et al. Multiple biopsy passes and the risk of complications of percutaneous liver biopsy. Eur J Gastroenterol Hepatol 2017; 29: 36–41

[50] Schirmacher P, Fleig WE, Tannapfel A et al. [Bioptic diagnosis of chronic hepatitis. Results of an evidence-based consensus conference of the German Society of Pathology, of the German Society for Digestive and Metabolic Diseases and of Compensated Hepatitis (HepNet)]. Pathologe 2004; 25: 337–348

[51] Einaga N, Yoshida A, Noda H et al. Assessment of the quality of DNA from various formalin-fixed paraffin-embedded (FFPE) tissues and the use of this DNA for next-generation sequencing (NGS) with no artifactual mutation. PLoS One 2017; 12: e0176280

[52] Roeb E, Steffen HM, Bantel H et al. S2k-Leitlinie nicht alkoholische Fettlebererkrankungen. Z Gastroenterol 2015; 53: 668–723

[53] Wong VW, Chan WK, Chitturi S et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. J Gastroenterol Hepatol 2018; 33: 70–85

[54] Mueller J, Raisi H, Rausch V et al. Sensitive and non-invasive assessment of hepatocellular iron using a novel room-temperature susceptometer. J Hepatol 2017; 67: 535–542

[55] Mueller S, Nahon P, Rausch V et al. Caspase-cleaved keratin-18 fragments increase during alcohol withdrawal and predict liver-related death in patients with alcoholic liver disease. Hepatology 2017; 66: 96–107

[56] Kudaravalli P, John S. Nonalcoholic Fatty Liver. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC. 2021

[57] Larsson SC, Wallin A, Wolk A et al. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med 2016; 14: 178

[58] Stubbs MA, Morgan MY. Managing alcohol dependence and alcohol-related liver disease: a problem for the hepatologist, psychiatrist or economist? Clin Med (Lond) 2011; 11: 189–193

[59] Åberg F, Puukka P, Salomaa V et al. Risks of Light and Moderate Alcohol Use in Fatty Liver Disease: Follow-Up of Population Cohorts. Hepatology 2020; 71: 835–848

[60] Younossi ZM, Stepanova M, Ong J et al. Effects of Alcohol Consumption and Metabolic Syndrome on Mortality in Patients With Nonalcoholic and Alcohol-Related Fatty Liver Disease. Clin Gastroenterol Hepatol 2019; 17: 1625–1633.e1

[61] Li J, Zou B, Yeo YH et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019; 4: 389–398

[62] Younossi ZM, Koenig AB, Abdelatif D et al. Global epidemiology of non-alcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73–84

[63] Allen AM, Therneau TM, Larson JJ et al. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: A 20 year-community study. Hepatology 2018; 67: 1726–1736

[64] Estes C, Anstee QM, Arias-Loste MT et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol 2018; 69: 896–904

[65] Kabbany MN, Conjeevaram Selvakumar PK, Watt K et al. Prevalence of Nonalcoholic Steatohepatitis-Associated Cirrhosis in the United States: An Analysis of National Health and Nutrition Examination Survey Data. Am J Gastroenterol 2017; 112: 581–587

[66] Hofmann WP, Buggisch P, Schubert L et al. The Fatty Liver Assessment in Germany (FLAG) cohort study identifies large heterogeneity in NAFLD care. JHEP Rep 2020; 2: 100168

[67] Singh S, Allen AM, Wang Z et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015; 13: 643–654 e1-9; quiz e39-40.

[68] McPherson S, Hardy T, Henderson E et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015; 62: 1148–1155

[69] Hagström H, Nasr P, Ekstedt M et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017; 67: 1265–1273

[70] Sanyal AJ, Harrison SA, Ratziu V et al. The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials. Hepatology 2019; 70: 1913–1927

[71] Angulo P, Kleiner DE, Dam-Larsen S et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015; 149: 389–397.e10

[72] Bengtsson B, Stål P, Wahlin S et al. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. Liver Int 2019; 39: 1098–1108

[73] Bhala N, Angulo P, van der Poorten D et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology 2011; 54: 1208–1216

[74] Dyson J, Jaques B, Chattopadyhay D et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014; 60: 110–117

[75] Younossi ZM. Non-alcoholic fatty liver disease – A global public health perspective. J Hepatol 2019; 70: 531–544

[76] Kanwal F, Kramer JR, Mapakshi S et al. Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease. Gastroenterology 2018; 155: 1828–1837.e2

[77] Piscaglia F, Svegliati-Baroni G, Barchetti A et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. Hepatology 2016; 63: 827–838

[78] Cholankeril G, Wong RJ, Hu M et al. Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. Dig Dis Sci 2017; 62: 2915–2922

[79] Tacke F, Kroy DC, Barreiros AP et al. Liver transplantation in Germany. Liver Transpl 2016; 22: 1136–1142

[80] Kim D, Kim WR, Kim HJ et al. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 2013; 57: 1357–1365

[81] Nasr P, Ignatova S, Kechagias S et al. Natural history of nonalcoholic fatty liver disease: A prospective follow-up study with serial biopsies. Hepatol Commun 2018; 2: 199–210

[82] Ekstedt M, Hagström H, Nasr P et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015; 61: 1547–1554

[83] Shen H, Lipka S, Kumar A et al. Association between nonalcoholic fatty liver disease and colorectal adenoma: a systemic review and meta-analysis. J Gastrointest Oncol 2014; 5: 440–446

[84] Kim GA, Lee HC, Choe J et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol 2017. doi:10.1016/j.jhep.2017.09.012

[85] Bertot LC, Jeffrey GP, Wallace M et al. Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. Hepatol Commun 2017; 1: 53–60

[86] Iqbal U, Perumpail BJ, Akhtar D et al. The Epidemiology, Risk Profiling and Diagnostic Challenges of Nonalcoholic Fatty Liver Disease. Medicines (Basel) 2019: 6

[87] Younossi Z, Anstee QM, Marietti M et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11–20

[88] de Vries M, Westerink J, Kaasjager K et al. Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Patients With Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2020; 105: 3842–3853

[89] Jarvis H, Craig D, Barker R et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLoS Med 2020; 17: e1003100

[90] Sookoian S, Pirola CJ. Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. Aliment Pharmacol Ther 2017; 46: 85–95

[91] Hu XY, Li Y, Li LQ et al. Risk factors and biomarkers of non-alcoholic fatty liver disease: an observational cross-sectional population survey. BMJ Open 2018; 8: e019974

[92] Golabi P, Otgonsuren M, de Avila L et al. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). Medicine (Baltimore) 2018; 97: e0214

[93] Labenz C, Huber Y, Kalliga E et al. Predictors of advanced fibrosis in non-cirrhotic non-alcoholic fatty liver disease in Germany. Aliment Pharmacol Ther 2018; 48: 1109–1116

[94] Rinella ME. Screening for nonalcoholic fatty liver disease in patients with atherosclerotic coronary disease? – In principle yes, in practice not yet. Hepatology 2016; 63: 688–690

[95] Noureddin M, Jones C, Alkhouri N et al. Screening for Nonalcoholic Fatty Liver Disease in Persons with Type 2 Diabetes in the United States Is Cost-effective: A Comprehensive Cost-Utility Analysis. Gastroenterology 2020; 159: 1985–1987.e4

[96] Nones RB, Ivantes CP, Pedroso MLA. Can FIB4 and NAFLD fibrosis scores help endocrinologists refer patients with non-alcoholic fat liver disease to a hepatologist? Arch Endocrinol Metab 2017; 61: 276–281

[97] Ciardullo S, Muraca E, Perra S et al. Screening for non-alcoholic fatty liver disease in type 2 diabetes using non-invasive scores and association with diabetic complications. BMJ Open Diabetes Res Care 2020: 8

[98] Castera L. Non-invasive tests for liver fibrosis in NAFLD: Creating pathways between primary healthcare and liver clinics. Liver Int 2020; 40 (Suppl. 1): 77–81

[99] Pandyarajan V, Gish RG, Alkhouri N et al. Screening for Nonalcoholic Fatty Liver Disease in the Primary Care Clinic. Gastroenterol Hepatol (N Y) 2019; 15: 357–365

[100] EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia 2016; 59: 1121–1140

[101] Berzigotti A, Boursier J, Castera L et al. Easl Clinical Practice Guidelines (Cpgs) On Non-Invasive Tests For Evaluation Of Liver Disease Severity And Prognosis- 2020 Update. J Hepatol 2021; 75 (3): 659–689

[102] Younossi ZM, Corey KE, Alkhouri N et al. Clinical assessment for high-risk patients with non-alcoholic fatty liver disease in primary care and diabetology practices. Aliment Pharmacol Ther 2020; 52: 513–526

[103] Grecian SM, McLachlan S, Fallowfield JA et al. Non-invasive risk scores do not reliably identify future cirrhosis or hepatocellular carcinoma in Type 2 diabetes: The Edinburgh type 2 diabetes study. Liver Int 2020; 40: 2252–2262

[104] Mofrad P, Contos MJ, Haque M et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003; 37: 1286–1292

[105] Verma S, Jensen D, Hart J et al. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). Liver Int 2013; 33: 1398–1405

[106] Lee TY, Wu JC, Yu SH et al. The occurrence of hepatocellular carcinoma in different risk stratifications of clinically noncirrhotic nonalcoholic fatty liver disease. Int J Cancer 2017; 141: 1307–1314

[107] Fedchuk L, Nascimbeni F, Pais R et al. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2014; 40: 1209–1222

[108] Cheung CL, Lam KS, Wong IC et al. Non-invasive score identifies ultrasonography-diagnosed non-alcoholic fatty liver disease and predicts mortality in the USA. BMC Med 2014; 12: 154

[109] Lind L, Johansson L, Ahlström H et al. Comparison of four non-alcoholic fatty liver disease detection scores in a Caucasian population. World J Hepatol 2020; 12: 149–159

[110] Boursier J, Vergniol J, Guillet A et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016; 65: 570–578

[111] Demir M, Lang S, Nierhoff D et al. Stepwise combination of simple noninvasive fibrosis scoring systems increases diagnostic accuracy in nonalcoholic fatty liver disease. J Clin Gastroenterol 2013; 47: 719–726

[112] Lee J, Vali Y, Boursier J et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: A systematic review. Liver Int 2021; 41: 261–270

[113] Yoneda M, Imajo K, Eguchi Y et al. Noninvasive scoring systems in patients with nonalcoholic fatty liver disease with normal alanine aminotransferase levels. J Gastroenterol 2013; 48: 1051–1060

[114] Hagström H, Talbäck M, Andreasson A et al. Ability of Noninvasive Scoring Systems to Identify Individuals in the Population at Risk for Severe Liver Disease. Gastroenterology 2020; 158: 200–214

[115] McPherson S, Hardy T, Dufour JF et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. Am J Gastroenterol 2017; 112: 740–751

[116] EASL-Guideline. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388–1402

[117] Hernaez R, Lazo M, Bonekamp S et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011; 54: 1082–1090

[118] Bril F, Ortiz-Lopez C, Lomonaco R et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. Liver Int 2015; 35: 2139–2146

[119] Kromrey ML, Ittermann T, Berning M et al. Accuracy of ultrasonography in the assessment of liver fat compared with MRI. Clin Radiol 2019; 74: 539–546

[120] Iwasaki M, Takada Y, Hayashi M et al. Noninvasive evaluation of graft steatosis in living donor liver transplantation. Transplantation 2004; 78: 1501–1505

[121] Hyodo T, Yada N, Hori M et al. Multimaterial Decomposition Algorithm for the Quantification of Liver Fat Content by Using Fast-Kilovolt-Peak Switching Dual-Energy CT: Clinical Evaluation. Radiology 2017; 283: 108–118

[122] Tang A, Tan J, Sun M et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. Radiology 2013; 267: 422–431

[123] Tang A, Desai A, Hamilton G et al. Accuracy of MR imaging-estimated proton density fat fraction for classification of dichotomized histologic steatosis grades in nonalcoholic fatty liver disease. Radiology 2015; 274: 416–425

[124] Caussy C, Johansson L. Magnetic resonance-based biomarkers in non-alcoholic fatty liver disease and nonalcoholic steatohepatitis. Endocrinol Diabetes Metab 2020; 3: e00134

[125] Choi SJ, Kim SM, Kim YS et al. Magnetic Resonance-Based Assessments Better Capture Pathophysiologic Profiles and Progression in Nonalcoholic Fatty Liver Disease. Diabetes Metab J 2021; 45 (5): 739–752

[126] Yokoo T, Serai SD, Pirasteh A et al. Linearity, Bias, and Precision of Hepatic Proton Density Fat Fraction Measurements by Using MR Imaging: A Meta-Analysis. Radiology 2018; 286: 486–498

[127] Park CC, Nguyen P, Hernandez C et al. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease. Gastroenterology 2017; 152: 598–607.e2

[128] Bastati N, Feier D, Wibmer A et al. Noninvasive differentiation of simple steatosis and steatohepatitis by using gadoxetic acid-enhanced MR imaging in patients with nonalcoholic fatty liver disease: a proof-of-concept study. Radiology 2014; 271: 739–747

[129] Kim JW, Lee YS, Park YS et al. Multiparametric MR Index for the Diagnosis of Non-Alcoholic Steatohepatitis in Patients with Non-Alcoholic Fatty Liver Disease. Sci Rep 2020; 10: 2671

[130] Kaswala DH, Lai M, Afdhal NH. Fibrosis Assessment in Nonalcoholic Fatty Liver Disease (NAFLD) in 2016. Dig Dis Sci 2016; 61: 1356–1364

[131] Vali Y, Lee J, Boursier J et al. Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: A systematic review and meta-analysis. J Hepatol 2020; 73: 252–262

[132] Bedogni G, Bellentani S, Miglioli L et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006; 6: 33

[133] Koehler EM, Schouten JN, Hansen BE et al. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. Clin Gastroenterol Hepatol 2013; 11: 1201–1204

[134] Kwok R, Tse YK, Wong GL et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease–the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther 2014; 39: 254–269

[135] Krawczyk M, Liebe R, Lammert F. Toward Genetic Prediction of Nonalcoholic Fatty Liver Disease Trajectories: PNPLA3 and Beyond. Gastroenterology 2020; 158: 1865–1880.e1

[136] Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology 2011; 53: 1883–1894

[137] Trépo E, Valenti L. Update on NAFLD genetics: From new variants to the clinic. J Hepatol 2020; 72: 1196–1209

[138] Bianco C, Jamialahmadi O, Pelusi S et al. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. J Hepatol 2021; 74 (4): 775–782

[139] Chernbumroong S, Grove JI, Astbury S et al. Advanced machine learning techniques to identify a panel of biomarkers that identify nonalcoholic steatohepatitis. Hepatology (Baltimore, MD) 2017; 66: 53A–54A

[140] Zhu L, Baker SS, Gill C et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 2013; 57: 601–609

[141] Boursier J, Mueller O, Barret M et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatology 2016; 63: 764–775

[142] Lang S, Demir M, Martin A et al. Intestinal Virome Signature Associated With Severity of Nonalcoholic Fatty Liver Disease. Gastroenterology 2020; 159: 1839–1852

[143] Demir M, Lang S, Martin A et al. Phenotyping non-alcoholic fatty liver disease by the gut microbiota: Ready for prime time? J Gastroenterol Hepatol 2020; 35: 1969–1977

[144] Lang S, Farowski F, Martin A et al. Prediction of advanced fibrosis in non-alcoholic fatty liver disease using gut microbiota-based approaches compared with simple non-invasive tools. Sci Rep 2020; 10: 9385

[145] Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019; 156: 1264–1281.e4

[146] Ballestri S, Nascimbeni F, Lugari S et al. A critical appraisal of the use of ultrasound in hepatic steatosis. Expert Rev Gastroenterol Hepatol 2019; 13: 667–681

[147] Petzold G, Lasser J, Rühl J et al. Diagnostic accuracy of B-Mode ultrasound and Hepatorenal Index for graduation of hepatic steatosis in patients with chronic liver disease. PLoS One 2020; 15: e0231044

[148] Sasso M, Beaugrand M, de Ledinghen V et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010; 36: 1825–1835

[149] Karlas T, Petroff D, Sasso M et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017; 66: 1022–1030

[150] Eddowes PJ, Sasso M, Allison M et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019; 156: 1717–1730

[151] Petroff D, Blank V, Newsome PN et al. Assessment of hepatic steatosis by controlled attenuation parameter using the M and XL probes: an individual patient data meta-analysis. Lancet Gastroenterol Hepatol 2021; 6 (3): 185–198

[152] Semmler G, Wöran K, Scheiner B et al. Novel reliability criteria for controlled attenuation parameter assessments for non-invasive evaluation of hepatic steatosis. United European Gastroenterol J 2020; 8: 321–331

[153] Agarwal L, Aggarwal S, Shalimar S et al. Bariatric Surgery in Nonalcoholic Fatty Liver Disease (NAFLD): Impact Assessment Using Paired Liver Biopsy and Fibroscan. Obes Surg 2021; 31 (2): 617–626

[154] Wong VW. Predicting NASH response with liver fat: Are we back to square one? J Hepatol 2020; 72: 386–388

[155] Ferraioli G, Maiocchi L, Savietto G et al. Performance of the Attenuation Imaging Technology in the Detection of Liver Steatosis. J Ultrasound Med 2021; 40 (7): 1325–1332

[156] Jesper D, Klett D, Schellhaas B et al. Ultrasound-Based Attenuation Imaging for the Non-Invasive Quantification of Liver Fat – A Pilot Study on Feasibility and Inter-Observer Variability. IEEE J Transl Eng Health Med 2020; 8: 1800409

[157] Stern C, Castera L. Non-invasive diagnosis of hepatic steatosis. Hepatol Int 2017; 11: 70–78

[158] Caussy C, Reeder SB, Sirlin CB et al. Noninvasive, Quantitative Assessment of Liver Fat by MRI-PDFF as an Endpoint in NASH Trials. Hepatology 2018; 68: 763–772

[159] Caussy C, Alquiraish MH, Nguyen P et al. Optimal threshold of controlled attenuation parameter with MRI-PDFF as the gold standard for the detection of hepatic steatosis. Hepatology 2018; 67: 1348–1359

[160] Karlas T, Petroff D, Wiegand J. Collaboration, Not Competition: The Role of Magnetic Resonance, Transient Elastography, and Liver Biopsy in the Diagnosis of Nonalcoholic Fatty Liver Disease. Gastroenterology 2017; 152: 479–481

[161] Stine JG, Munaganuru N, Barnard A et al. Change in MRI-PDFF and Histologic Response in Patients with Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2020. doi:10.1016/j.cgh.2020.08.061

[162] Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007; 45: 846–854

[163] Shah AG, Lydecker A, Murray K et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009; 7: 1104–1112

[164] Wong VW, Vergniol J, Wong GL et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2012; 107: 1862–1871

[165] Wong VW, Vergniol J, Wong GL et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010; 51: 454–462

[166] Berger A, Shili S, Zuberbuhler F et al. Liver Stiffness Measurement With FibroScan: Use the Right Probe in the Right Conditions! Clin Transl Gastroenterol 2019; 10: e00023

[167] Pfeifer L, Goertz RS, Sturm J et al. Acoustic radiation force impulse (ARFI) and high-frequency ultrasound of the liver surface for the diagnosis of compensated liver cirrhosis. Ultraschall in Med 2014; 35: 44–50

[168] Dietrich CF, Bamber J, Berzigotti A et al. EFSUMB-Leitlinien und Empfehlungen zur klinischen Anwendung der Leberelastographie, Update 2017 (Langversion). Ultraschall in Med 2017; 38: e48

[169] EASL-Guideline. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63: 237–264

[170] Herrmann E, de Lédinghen V, Cassinotto C et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. Hepatology 2018; 67: 260–272

[171] Erman A, Sathya A, Nam A et al. Estimating chronic hepatitis C prognosis using transient elastography-based liver stiffness: A systematic review and meta-analysis. J Viral Hepat 2018; 25: 502–513

[172] Nierhoff J, Chávez Ortiz AA, Herrmann E et al. The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. Eur Radiol 2013; 23: 3040–3053

[173] Karlas T, Dietrich A, Peter V et al. Evaluation of Transient Elastography, Acoustic Radiation Force Impulse Imaging (ARFI), and Enhanced Liver Function (ELF) Score for Detection of Fibrosis in Morbidly Obese Patients. PLoS One 2015; 10: e0141649

[174] Siddiqui MS, Vuppalanchi R, Van Natta ML et al. Vibration-Controlled Transient Elastography to Assess Fibrosis and Steatosis in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2019; 17: 156–163.e2

[175] Jiang W, Huang S, Teng H et al. Diagnostic accuracy of point shear wave elastography and transient elastography for staging hepatic fibrosis in patients with non-alcoholic fatty liver disease: a meta-analysis. BMJ Open 2018; 8: e021787

[176] Hsu C, Caussy C, Imajo K et al. Magnetic Resonance vs Transient Elastography Analysis of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Pooled Analysis of Individual Participants. Clin Gastroenterol Hepatol 2019; 17: 630–637.e8

[177] Wan T, Köhn N, Kröll D et al. Applicability and Results of Liver Stiffness Measurement and Controlled Attenuation Parameter Using XL Probe for Metabolic-Associated Fatty Liver Disease in Candidates to Bariatric Surgery. A Single-Center Observational Study. Obes Surg 2021; 31 (2): 702–711

[178] Chuah KH, Lai LL, Vethakkan SR et al. Liver stiffness measurement in non-alcoholic fatty liver disease: Two is better than one. J Gastroenterol Hepatol 2020; 35: 1404–1411

[179] Ozturk A, Mohammadi R, Pierce TT et al. Diagnostic Accuracy of Shear Wave Elastography as a Non-invasive Biomarker of High-Risk Non-alcoholic Steatohepatitis in Patients with Non-alcoholic Fatty Liver Disease. Ultrasound Med Biol 2020; 46: 972–980

[180] Jamialahmadi T, Nematy M, Jangjoo A et al. Measurement of Liver Stiffness with 2D-Shear Wave Elastography (2D-SWE) in Bariatric Surgery Candidates Reveals Acceptable Diagnostic Yield Compared to Liver Biopsy. Obes Surg 2019; 29: 2585–2592

[181] Giuffrè M, Giuricin M, Bonazza D et al. Optimization of Point-Shear Wave Elastography by Skin-to-Liver Distance to Assess Liver Fibrosis in Patients Undergoing Bariatric Surgery. Diagnostics (Basel) 2020: 10

[182] Cassinotto C, Boursier J, Paisant A et al. Transient Versus 2-Dimensional Shear-Wave Elastography in a Multistep Strategy to Detect Advanced Fibrosis in NAFLD. Hepatology 2021; 73 (6): 2196–2205

[183] Furlan A, Tublin ME, Yu L et al. Comparison of 2D Shear Wave Elastography, Transient Elastography, and MR Elastography for the Diagnosis of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Am J Roentgenol 2020; 214: W20–W26

[184] Leong WL, Lai LL, Nik Mustapha NR et al. Comparing point shear wave elastography (ElastPQ) and transient elastography for diagnosis of fibrosis stage in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2020; 35: 135–141

[185] Ferraioli G, Barr RG. Ultrasound liver elastography beyond liver fibrosis assessment. World J Gastroenterol 2020; 26: 3413–3420

[186] Karlas T, Petroff D, Sasso M et al. Impact of controlled attenuation parameter on detecting fibrosis using liver stiffness measurement. Aliment Pharmacol Ther 2018; 47: 989–1000

[187] Ferraioli G. Review of Liver Elastography Guidelines. J Ultrasound Med 2019; 38: 9–14

[188] Barr RG, Wilson SR, Rubens D et al. Update to the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement. Radiology 2020; 296: 263–274

[189] Piscaglia F, Salvatore V, Mulazzani L et al. Ultrasound Shear Wave Elastography for Liver Disease. A Critical Appraisal of the Many Actors on the Stage. Ultraschall in Med 2016; 37: 1–5

[190] Jung J, Loomba RR, Imajo K et al. MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis. Gut 2021. doi:70 (10): 1946–1953

[191] Boursier J, Guillaume M, Leroy V et al. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. J Hepatol 2019; 71: 389–396

[192] Petta S, Wong VW, Cammà C et al. Serial combination of non-invasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. Aliment Pharmacol Ther 2017; 46: 617–627

[193] Ampuero J, Pais R, Aller R et al. Development and Validation of Hepamet Fibrosis Scoring System-A Simple, Noninvasive Test to Identify Patients With Nonalcoholic Fatty Liver Disease With Advanced Fibrosis. Clin Gastroenterol Hepatol 2020; 18: 216–225.e5

[194] Harrison SA, Ratziu V, Boursier J et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020; 5: 970–985

[195] Sugimoto K, Moriyasu F, Oshiro H et al. The Role of Multiparametric US of the Liver for the Evaluation of Nonalcoholic Steatohepatitis. Radiology 2020; 296: 532–540

[196] Lee DH, Cho EJ, Bae JS et al. Accuracy of Two-Dimensional Shear Wave Elastography and Attenuation Imaging for Evaluation of Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol 2021; 19 (4): 797–805

[197] Newsome PN, Sasso M, Deeks JJ et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020; 5: 362–373

[198] Puri P, Jain S, Fuchs M. Use of FibroScan-AST Score to Stratify High-Risk Nonalcoholic Steatohepatitis in US Veterans. Clin Gastroenterol Hepatol 2020; 18: 3060–3061

[199] McDonald N, Eddowes PJ, Hodson J et al. Multiparametric magnetic resonance imaging for quantitation of liver disease: a two-centre cross-sectional observational study. Sci Rep 2018; 8: 9189

[200] Dennis A, Mouchti S, Kelly M et al. A composite biomarker using multiparametric magnetic resonance imaging and blood analytes accurately identifies patients with non-alcoholic steatohepatitis and significant fibrosis. Sci Rep 2020; 10: 15308

[201] Feldstein AE, Wieckowska A, Lopez AR et al. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. Hepatology 2009; 50: 1072–1078

[202] Bantel H, Lugering A, Heidemann J et al. Detection of apoptotic caspase activation in sera from patients with chronic HCV infection is associated with fibrotic liver injury. Hepatology 2004; 40: 1078–1087

[203] Bechmann LP, Kocabayoglu P, Sowa JP et al. Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin counteracts bile acid-induced liver injury in superobese patients with nonalcoholic steatohepatitis. Hepatology 2013; 57: 1394–1406

[204] Bantel H, John K, Schulze-Osthoff K. Robust detection of liver steatosis and staging of NAFLD by an improved ELISA for serum cytokeratin-18 fragments. Am J Gastroenterol 2014; 109: 140–141

[205] Diab DL, Yerian L, Schauer P et al. Cytokeratin 18 fragment levels as a noninvasive biomarker for nonalcoholic steatohepatitis in bariatric surgery patients. Clin Gastroenterol Hepatol 2008; 6: 1249–1254

[206] Shen J, Chan HL, Wong GL et al. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. J Hepatol 2012; 56: 1363–1370

[207] Tamimi TI, Elgouhari HM, Alkhouri N et al. An apoptosis panel for non-alcoholic steatohepatitis diagnosis. J Hepatol 2011; 54: 1224–1229

[208] Musso G, Gambino R, Cassader M et al. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011; 43: 617–649

[209] Feldstein AE, Alkhouri N, De Vito R et al. Serum cytokeratin-18 fragment levels are useful biomarkers for nonalcoholic steatohepatitis in children. Am J Gastroenterol 2013; 108: 1526–1531

[210] Cusi K, Chang Z, Harrison S et al. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. J Hepatol 2014; 60: 167–174

[211] Liebig S, Stoeckmann N, Geier A et al. Multicenter Validation Study of a Diagnostic Algorithm to Detect NASH and Fibrosis in NAFLD Patients With Low NAFLD Fibrosis Score or Liver Stiffness. Clin Transl Gastroenterol 2019; 10: e00066

[212] Canbay A, Kälsch J, Neumann U et al. Non-invasive assessment of NAFLD as systemic disease-A machine learning perspective. PLoS One 2019; 14: e0214436

[213] Boursier J, Anty R, Vonghia L et al. Screening for therapeutic trials and treatment indication in clinical practice: MACK-3, a new blood test for the diagnosis of fibrotic NASH. Aliment Pharmacol Ther 2018; 47: 1387–1396

[214] Lonardo A, Bellentani S. Non-alcoholic Fatty Liver Disease Study G et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. Dig Liver Dis 2015; 47: 997–1006

[215] Miyake T, Kumagi T, Hirooka M et al. Body mass index is the most useful predictive factor for the onset of nonalcoholic fatty liver disease: a community-based retrospective longitudinal cohort study. J Gastroenterol 2013; 48: 413–422

[216] Subichin M, Clanton J, Makuszewski M et al. Liver disease in the morbidly obese: a review of 1000 consecutive patients undergoing weight loss surgery. Surg Obes Relat Dis 2015; 11: 137–141

[217] Younossi ZM, Golabi P, de Avila L et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019; 71: 793–801

[218] Aneni EC, Oni ET, Martin SS et al. Blood pressure is associated with the presence and severity of nonalcoholic fatty liver disease across the spectrum of cardiometabolic risk. J Hypertens 2015; 33: 1207–1214

[219] Wu KT, Kuo PL, Su SB et al. Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. J Clin Lipidol 2016; 10: 420–425.e1

[220] Koehler EM, Schouten JN, Hansen BE et al. Prevalence and risk factors of non-alcoholic fatty liver disease in the elderly: results from the Rotterdam study. J Hepatol 2012; 57: 1305–1311

[221] Caballería L, Pera G, Auladell MA et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. Eur J Gastroenterol Hepatol 2010; 22: 24–32

[222] Eguchi Y, Hyogo H, Ono M et al. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. J Gastroenterol 2012; 47: 586–595

[223] Summart U, Thinkhamrop B, Chamadol N et al. Gender differences in the prevalence of nonalcoholic fatty liver disease in the Northeast of Thailand: A population-based cross-sectional study. F1000Res 2017; 6: 1630

[224] Rich NE, Oji S, Mufti AR et al. Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018; 16: 198–210.e2

[225] Loomba R, Schork N, Chen CH et al. Heritability of Hepatic Fibrosis and Steatosis Based on a Prospective Twin Study. Gastroenterology 2015; 149: 1784–1793

[226] Schwimmer JB, Celedon MA, Lavine JE et al. Heritability of nonalcoholic fatty liver disease. Gastroenterology 2009; 136: 1585–1592

[227] Mantovani A, Zaza G, Byrne CD et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: A systematic review and meta-analysis. Metabolism 2018; 79: 64–76

[228] Mantovani A, Nascimbeni F, Lonardo A et al. Association Between Primary Hypothyroidism and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Thyroid 2018; 28: 1270–1284

[229] Musso G, Cassader M, Olivetti C et al. Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. Obes Rev 2013; 14: 417–431

[230] Candia R, Ruiz A, Torres-Robles R et al. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2015; 29: 656–662

[231] Ramezani-Binabaj M, Motalebi M, Karimi-Sari H et al. Are women with polycystic ovarian syndrome at a high risk of non-alcoholic Fatty liver disease; a meta-analysis. Hepat Mon 2014; 14: e23235

[232] Li M, Xu Y, Xu M et al. Association between nonalcoholic fatty liver disease (NAFLD) and osteoporotic fracture in middle-aged and elderly Chinese. J Clin Endocrinol Metab 2012; 97: 2033–2038

[233] Adams LA, Anstee QM, Tilg H et al. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017; 66: 1138–1153

[234] Adams LA, Waters OR, Knuiman MW et al. NAFLD as a risk factor for the development of diabetes and the metabolic syndrome: an eleven-year follow-up study. Am J Gastroenterol 2009; 104: 861–867

[235] Ampuero J, Aller R, Gallego-Durán R et al. Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH. J Hepatol 2020; 73: 17–25

[236] Leite NC, Salles GF, Araujo AL et al. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int 2009; 29: 113–119

[237] Park SK, Seo MH, Shin HC et al. Clinical availability of nonalcoholic fatty liver disease as an early predictor of type 2 diabetes mellitus in Korean

men: 5-year prospective cohort study. Hepatology 2013; 57: 1378–1383

[238] Portillo-Sanchez P, Bril F, Maximos M et al. High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. J Clin Endocrinol Metab 2015; 100: 2231–2238

[239] Targher G, Bertolini L, Padovani R et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007; 30: 1212–1218

[240] Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011; 34: 274–285

[241] Leung JC, Loong TC, Wei JL et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology 2017; 65: 54–64

[242] Vos B, Moreno C, Nagy N et al. Lean non-alcoholic fatty liver disease (Lean-NAFLD): a major cause of cryptogenic liver disease. Acta Gastroenterol Belg 2011; 74: 389–394

[243] Younossi ZM, Stepanova M, Negro F et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore) 2012; 91: 319–327

[244] Kim D, Kim W, Joo SK et al. Subclinical Hypothyroidism and Low-Normal Thyroid Function Are Associated With Nonalcoholic Steatohepatitis and Fibrosis. Clin Gastroenterol Hepatol 2018; 16: 123–131.e1

[245] Kim D, Vazquez-Montesino LM, Escober JA et al. Low Thyroid Function in Nonalcoholic Fatty Liver Disease Is an Independent Predictor of All-Cause and Cardiovascular Mortality. Am J Gastroenterol 2020; 115: 1496–1504

[246] Yan F, Wang Q, Lu M et al. Thyrotropin increases hepatic triglyceride content through upregulation of SREBP-1c activity. J Hepatol 2014; 61: 1358–1364

[247] Maratou E, Hadjidakis DJ, Kollias A et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009; 160: 785–790

[248] Tan S, Bechmann LP, Benson S et al. Apoptotic markers indicate nonalcoholic steatohepatitis in polycystic ovary syndrome. J Clin Endocrinol Metab 2010; 95: 343–348

[249] Liebe R, Esposito I, Bock HH et al. Diagnosis and management of secondary causes of steatohepatitis. J Hepatol 2021; 74: 1455–1471

[250] EASL-Guideline. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol 2018; 69: 154–181

[251] S3-Leitlinie-Alkoholkrankheiten. S3 Leitlinie Screening, Diagnose und Behandlung alkoholbezogener Störungen. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). 2020

[252] O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology 2010; 51: 307–328

[253] Farrell GC, Chitturi S, Lau GK et al. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J Gastroenterol Hepatol 2007; 22: 775–777

[254] Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009; 360: 2758–2769

[255] Mueller S, Englert S, Seitz HK et al. Inflammation-adapted liver stiffness values for improved fibrosis staging in patients with hepatitis C virus and alcoholic liver disease. Liver Int 2015; 35: 2514–2521

[256] Dunn W, Angulo P, Sanderson S et al. Utility of a new model to diagnose an alcohol basis for steatohepatitis. Gastroenterology 2006; 131: 1057–1063

[257] Wang RT, Koretz RL, Yee HF et al. Is weight reduction an effective therapy for nonalcoholic fatty liver? A systematic review. Am J Med 2003; 115: 554–559

[258] Plauth M, Bernal W, Dasarathy S et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr 2019; 38: 485–521

[259] Chalasani N, Younossi Z, Lavine JE et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012; 55: 2005–2023

[260] Burza MA, Romeo S, Kotronen A et al. Long-term effect of bariatric surgery on liver enzymes in the Swedish Obese Subjects (SOS) study. PLoS One 2013; 8: e60495

[261] Parry SA, Hodson L. Managing NAFLD in Type 2 Diabetes: The Effect of Lifestyle Interventions, a Narrative Review. Adv Ther 2020; 37: 1381–1406

[262] Koutoukidis DA, Koshiaris C, Henry JA et al. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: A systematic review and meta-analysis. Metabolism 2021; 115: 154455

[263] Harrison SA, Fincke C, Helinski D et al. A pilot study of orlistat treatment in obese, non-alcoholic steatohepatitis patients. Aliment Pharmacol Ther 2004; 20: 623–628

[264] Stratopoulos C, Papakonstantinou A, Terzis I et al. Changes in liver histology accompanying massive weight loss after gastroplasty for morbid obesity. Obes Surg 2005; 15: 1154–1160

[265] Barker KB, Palekar NA, Bowers SP et al. Non-alcoholic steatohepatitis: effect of Roux-en-Y gastric bypass surgery. Am J Gastroenterol 2006; 101: 368–373

[266] Dixon JB, Bhathal PS, O'Brien PE. Weight loss and non-alcoholic fatty liver disease: falls in gamma-glutamyl transferase concentrations are associated with histologic improvement. Obes Surg 2006; 16: 1278–1286

[267] Tendler D, Lin S, Yancy WS Jr et al. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. Dig Dis Sci 2007; 52: 589–593

[268] Harrison SA, Fecht W, Brunt EM et al. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Hepatology 2009; 49: 80–86

[269] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology 2015; 149: 367–378 e5; quiz e14-5.

[270] Lassailly G, Caiazzo R, Buob D et al. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. Gastroenterology 2015; 149: 379–388; quiz e15-6

[271] Lee Y, Doumouras AG, Yu J et al. Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2019; 17: 1040–1060.e11

[272] Katsagoni CN, Papatheodoridis GV, Ioannidou P et al. Improvements in clinical characteristics of patients with non-alcoholic fatty liver disease, after an intervention based on the Mediterranean lifestyle: a randomised controlled clinical trial. Br J Nutr 2018; 120: 164–175

[273] Fakhry TK, Mhaskar R, Schwitalla T et al. Bariatric surgery improves nonalcoholic fatty liver disease: a contemporary systematic review and meta-analysis. Surg Obes Relat Dis 2019; 15: 502–511

[274] Caiazzo R, Lassailly G, Leteurtre E et al. Roux-en-Y gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. Ann Surg 2014; 260: 893–898; discussion 898-9

[275] Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017; 67: 829–846

[276] Younossi ZM, Corey KE, Lim JK. AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology 2021; 160: 912–918

[277] Huang MA, Greenson JK, Chao C et al. One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. Am J Gastroenterol 2005; 100: 1072–1081

[278] Zelber-Sagi S, Kessler A, Brazowsky E et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006; 4: 639–644

[279] Promrat K, Kleiner DE, Niemeier HM et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010; 51: 121–129

[280] Haufe S, Engeli S, Kast P et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. Hepatology 2011; 53: 1504–1514

[281] Wong VW, Wong GL, Chan RS et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol 2018; 69: 1349–1356

[282] Berzigotti A, Albillos A, Villanueva C et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology 2017; 65: 1293–1305

[283] Mazzotti A, Caletti MT, Brodosi L et al. An internet-based approach for lifestyle changes in patients with NAFLD: Two-year effects on weight loss and surrogate markers. J Hepatol 2018; 69: 1155–1163

[284] Huber Y, Pfirrmann D, Gebhardt I et al. Improvement of non-invasive markers of NAFLD from an individualised, web-based exercise program. Aliment Pharmacol Ther 2019; 50: 930–939

[285] Axley P, Kodali S, Kuo YF et al. Text messaging approach improves weight loss in patients with nonalcoholic fatty liver disease: A randomized study. Liver Int 2018; 38: 924–931

[286] Sumida Y, Yoshikawa T, Tanaka S et al. The “donations for decreased ALT (D4D)” prosocial behavior incentive scheme for NAFLD patients. J Public Health (Oxf) 2014; 36: 629–634

[287] Johnson NA, Sachinwalla T, Walton DW et al. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology 2009; 50: 1105–1112

[288] Hallsworth K, Fattakhova G, Hollingsworth KG et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut 2011; 60: 1278–1283

[289] Sullivan S, Kirk EP, Mittendorfer B et al. Randomized trial of exercise effect on intrahepatic triglyceride content and lipid kinetics in nonalcoholic fatty liver disease. Hepatology 2012; 55: 1738–1745

[290] Houghton D, Thoma C, Hallsworth K et al. Exercise Reduces Liver Lipids and Visceral Adiposity in Patients With Nonalcoholic Steatohepatitis in a Randomized Controlled Trial. Clin Gastroenterol Hepatol 2017; 15: 96–102.e3

[291] Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol 2012; 56: 255–266

[292] Orci LA, Gariani K, Oldani G et al. Exercise-based Interventions for Nonalcoholic Fatty Liver Disease: A Meta-analysis and Meta-regression. Clin Gastroenterol Hepatol 2016; 14: 1398–1411

[293] Katsagoni CN, Georgoulis M, Papatheodoridis GV et al. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. Metabolism 2017; 68: 119–132

[294] Hashida R, Kawaguchi T, Bekki M et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. J Hepatol 2017; 66: 142–152

[295] Garvey WT, Mechanick JI, Brett EM et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. Endocr Pract 2016; 22 (Suppl. 3): 1–203

[296] Wirth A, Wabitsch M, Hauner H. The prevention and treatment of obesity. Dtsch Arztebl Int 2014; 111: 705–713

[297] Hickman IJ, Jonsson JR, Prins JB et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut 2004; 53: 413–419

[298] Thomas EL, Brynes AE, Hamilton G et al. Effect of nutritional counselling on hepatic, muscle and adipose tissue fat content and distribution in non-alcoholic fatty liver disease. World J Gastroenterol 2006; 12: 5813–5819

[299] Larson-Meyer DE, Newcomer BR, Heilbronn LK et al. Effect of 6-month calorie restriction and exercise on serum and liver lipids and markers of liver function. Obesity (Silver Spring) 2008; 16: 1355–1362

[300] Gerber L, Otgonsuren M, Mishra A et al. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. Aliment Pharmacol Ther 2012; 36: 772–781

[301] Stewart KE, Haller DL, Sargeant C et al. Readiness for behaviour change in non-alcoholic fatty liver disease: implications for multidisciplinary care models. Liver Int 2015; 35: 936–943

[302] Baldry EL, Aithal GP, Kaye P et al. Effects of short-term energy restriction on liver lipid content and inflammatory status in severely obese adults: Results of a randomized controlled trial using 2 dietary approaches. Diabetes Obes Metab 2017; 19: 1179–1183

[303] Deibert P, Lazaro A, Schaffner D et al. Comprehensive lifestyle intervention vs soy protein-based meal regimen in non-alcoholic steatohepatitis. World J Gastroenterol 2019; 25: 1116–1131

[304] Hohenester S, Christiansen S, Nagel J et al. Lifestyle intervention for morbid obesity: effects on liver steatosis, inflammation, and fibrosis. Am J Physiol Gastrointest Liver Physiol 2018; 315: G329–G338

[305] Markova M, Pivovarova O, Hornemann S et al. Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes. Gastroenterology 2017; 152: 571–585.e8

[306] Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr 2004; 79: 537–543

[307] Roeb E, Weiskirchen R. Fructose and Non-Alcoholic Steatohepatitis. Front Pharmacol 2021; 12: 634344

[308] Stanhope KL, Schwarz JM, Keim NL et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009; 119: 1322–1334

[309] Jensen T, Abdelmalek MF, Sullivan S et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. J Hepatol 2018; 68: 1063–1075

[310] Chung M, Ma J, Patel K et al. Fructose, high-fructose corn syrup, sucrose, and nonalcoholic fatty liver disease or indexes of liver health: a systematic review and meta-analysis. Am J Clin Nutr 2014; 100: 833–849

[311] Chiu S, Sievenpiper JL, de Souza RJ et al. Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of controlled feeding trials. Eur J Clin Nutr 2014; 68: 416–423

[312] Stricker S, Rudloff S, Geier A et al. Fructosekonsum ñ freie Zucker und ihr Einfluss auf die Gesundheit. Dtsch Arztebl International 2021; 118: 71–80

[313] Johnston RD, Stephenson MC, Crossland H et al. No difference between high-fructose and high-glucose diets on liver triacylglycerol or biochemistry in healthy overweight men. Gastroenterology 2013; 145: 1016–1025.e2

[314] Shai I, Schwarzfuchs D, Henkin Y et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008; 359: 229–241

[315] Pérez-Guisado J, Muñoz-Serrano A. The effect of the Spanish Ketogenic Mediterranean Diet on nonalcoholic fatty liver disease: a pilot study. J Med Food 2011; 14: 677–680

[316] Ryan MC, Itsiopoulos C, Thodis T et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013; 59: 138–143

[317] Trovato FM, Catalano D, Martines GF et al. Mediterranean diet and non-alcoholic fatty liver disease: the need of extended and comprehensive interventions. Clin Nutr 2015; 34: 86–88

[318] Misciagna G, Del Pilar Díaz M, Caramia DV et al. Effect of a Low Glycemic Index Mediterranean Diet on Non-Alcoholic Fatty Liver Disease. A Randomized Controlled Clinici Trial. J Nutr Health Aging 2017; 21: 404–412

[319] Gelli C, Tarocchi M, Abenavoli L et al. Effect of a counseling-supported treatment with the Mediterranean diet and physical activity on the severity of the non-alcoholic fatty liver disease. World J Gastroenterol 2017; 23: 3150–3162

[320] Tzima N, Pitsavos C, Panagiotakos DB et al. Adherence to the Mediterranean diet moderates the association of aminotransferases with the prevalence of the metabolic syndrome; the ATTICA study. Nutr Metab (Lond) 2009; 6: 30

[321] Kontogianni MD, Tileli N, Margariti A et al. Adherence to the Mediterranean diet is associated with the severity of non-alcoholic fatty liver disease. Clin Nutr 2014; 33: 678–683

[322] Aller R, Izaola O, de la Fuente B et al. MEDITERRANEAN DIET IS ASSOCIATED WITH LIVER HISTOLOGY IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE. Nutr Hosp 2015; 32: 2518–2524

[323] Trovato FM, Martines GF, Brischetto D et al. Fatty liver disease and lifestyle in youngsters: diet, food intake frequency, exercise, sleep shortage and fashion. Liver Int 2016; 36: 427–433

[324] Abenavoli L, Milic N, Peta V et al. Alimentary regimen in non-alcoholic fatty liver disease: Mediterranean diet. World J Gastroenterol 2014; 20: 16831–16840

[325] Suárez M, Boqué N, Del Bas JM et al. Mediterranean Diet and Multi-Ingredient-Based Interventions for the Management of Non-Alcoholic Fatty Liver Disease. Nutrients 2017: 9

[326] Velasco N, Contreras A, Grassi B. The Mediterranean diet, hepatic steatosis and nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care 2014; 17: 453–457

[327] Gepner Y, Shelef I, Schwarzfuchs D et al. Effect of Distinct Lifestyle Interventions on Mobilization of Fat Storage Pools: CENTRAL Magnetic Resonance Imaging Randomized Controlled Trial. Circulation 2018; 137: 1143–1157

[328] Stefan N, Häring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? Lancet Diabetes Endocrinol 2018; 6: 249–258

[329] Štefan L, Čule M, Milinović I et al. The Relationship between Lifestyle Factors and Body Compositionin Young Adults. Int J Environ Res Public Health 2017: 14

[330] Buzzetti E, Linden A, Best LM et al. Lifestyle modifications for nonalcohol-related fatty liver disease: a network meta-analysis. Cochrane Database Syst Rev 2021; 6: Cd013156

[331] Yaskolka Meir A, Rinott E, Tsaban G et al. Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. Gut 2021. doi:10.1136/gutjnl-2020-323106

[332] Zelber-Sagi S, Buch A, Yeshua H et al. Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial. World J Gastroenterol 2014; 20: 4382–4392

[333] Shojaee-Moradie F, Cuthbertson DJ, Barrett M et al. Exercise Training Reduces Liver Fat and Increases Rates of VLDL Clearance But Not VLDL Production in NAFLD. J Clin Endocrinol Metab 2016; 101: 4219–4228

[334] Cotrim HP, Freitas LA, Alves E et al. Effects of light-to-moderate alcohol consumption on steatosis and steatohepatitis in severely obese patients. Eur J Gastroenterol Hepatol 2009; 21: 969–972

[335] Hajifathalian K, Torabi Sagvand B, McCullough AJ. Effect of Alcohol Consumption on Survival in Nonalcoholic Fatty Liver Disease: A National Prospective Cohort Study. Hepatology 2019; 70: 511–521

[336] Mueller S, Seitz HK. Alkoholsucht und Leber: Wie wichtig ist ein Leberscreening auch für Suchttherapeuten? Suchtmedizin 2018; 20: 1–9

[337] Nascimento AF, Ip BC, Luvizotto RA et al. Aggravation of nonalcoholic steatohepatitis by moderate alcohol consumption is associated with decreased SIRT1 activity in rats. Hepatobiliary Surg Nutr 2013; 2: 252–259

[338] Seitz HK, Mueller S, Hellerbrand C et al. Effect of chronic alcohol consumption on the development and progression of non-alcoholic fatty liver disease (NAFLD). Hepatobiliary Surg Nutr 2015; 4: 147–151

[339] Wang Y, Seitz HK, Wang XD. Moderate alcohol consumption aggravates high-fat diet induced steatohepatitis in rats. Alcohol Clin Exp Res 2010; 34: 567–573

[340] Xu J, Lai KKY, Verlinsky A et al. Synergistic steatohepatitis by moderate obesity and alcohol in mice despite increased adiponectin and p-AMPK. J Hepatol 2011; 55: 673–682

[341] Ekstedt M, Franzén LE, Holmqvist M et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. Scand J Gastroenterol 2009; 44: 366–374

[342] Ascha MS, Hanouneh IA, Lopez R et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010; 51: 1972–1978

[343] Roerecke M, Vafaei A, Hasan OSM et al. Alcohol Consumption and Risk of Liver Cirrhosis: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2019; 114: 1574–1586

[344] Blomdahl J, Nasr P, Ekstedt M et al. Moderate alcohol consumption is associated with advanced fibrosis in non-alcoholic fatty liver disease and shows a synergistic effect with type 2 diabetes mellitus. Metabolism 2021; 115: 154439

[345] Bhurwal A, Rattan P, Yoshitake S et al. Inverse Association of Coffee with Liver Cancer Development: An Updated Systematic Review and Meta-analysis. J Gastrointestin Liver Dis 2020; 29: 421–428

[346] Zhao LG, Li ZY, Feng GS et al. Coffee drinking and cancer risk: an umbrella review of meta-analyses of observational studies. BMC Cancer 2020; 20: 101

[347] Godos J, Micek A, Marranzano M et al. Coffee Consumption and Risk of Biliary Tract Cancers and Liver Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies. Nutrients 2017: 9

[348] Poole R, Kennedy OJ, Roderick P et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017; 359: j5024

[349] Hayat U, Siddiqui AA, Okut H et al. The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies. Ann Hepatol 2021; 20: 100254

[350] Sanyal AJ, Chalasani N, Kowdley KV et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010; 362: 1675–1685

[351] Bjelakovic G, Nikolova D, Gluud LL et al. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev 2012: CD007176

[352] Miller ER 3rd, Pastor-Barriuso R et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005; 142: 37–46

[353] Klein EA, Thompson IM Jr, Tangen CM et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011; 306: 1549–1556

[354] Scorletti E, Bhatia L, McCormick KG et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the Welcome* study. Hepatology 2014; 60: 1211–1221

[355] Scorletti E, West AL, Bhatia L et al. Treating liver fat and serum triglyceride levels in NAFLD, effects of PNPLA3 and TM6SF2 genotypes: Results from the WELCOME trial. J Hepatol 2015; 63: 1476–1483

[356] Argo CK, Patrie JT, Lackner C et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. J Hepatol 2015; 62: 190–197

[357] Dasarathy S, Dasarathy J, Khiyami A et al. Double-blind randomized placebo-controlled clinical trial of omega 3 fatty acids for the treatment of diabetic patients with nonalcoholic steatohepatitis. J Clin Gastroenterol 2015; 49: 137–144

[358] Chen LH, Wang YF, Xu QH et al. Omega-3 fatty acids as a treatment for non-alcoholic fatty liver disease in children: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr 2018; 37: 516–521

[359] Yan JH, Guan BJ, Gao HY et al. Omega-3 polyunsaturated fatty acid supplementation and non-alcoholic fatty liver disease: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018; 97: e12271

[360] Parker HM, Cohn JS, O'Connor HT et al. Effect of Fish Oil Supplementation on Hepatic and Visceral Fat in Overweight Men: A Randomized Controlled Trial. Nutrients 2019: 11

[361] Reja M, Makar M, Visaria A et al. Increased serum selenium levels are associated with reduced risk of advanced liver fibrosis and all-cause mortality in NAFLD patients: National Health and Nutrition Examination Survey (NHANES) III. Ann Hepatol 2020; 19: 635–640

[362] Wong VW, Wong GL, Chan AW et al. Treatment of non-alcoholic steatohepatitis with Phyllanthus urinaria: a randomized trial. J Gastroenterol Hepatol 2013; 28: 57–62

[363] Navarro VJ, Belle SH, D'Amato M et al. Silymarin in non-cirrhotics with non-alcoholic steatohepatitis: A randomized, double-blind, placebo controlled trial. PLoS One 2019; 14: e0221683

[364] Geier A, Eichinger M, Stirnimann G et al. Treatment of non-alcoholic steatohepatitis patients with vitamin D: a double-blinded, randomized, placebo-controlled pilot study. Scand J Gastroenterol 2018; 53: 1114–1120

[365] Barchetta I, Del Ben M, Angelico F et al. No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. BMC Med 2016; 14: 92

[366] Behrouz V, Aryaeian N, Zahedi MJ et al. Effects of probiotic and prebiotic supplementation on metabolic parameters, liver aminotransferases, and systemic inflammation in nonalcoholic fatty liver disease: A randomized clinical trial. J Food Sci 2020; 85: 3611–3617

[367] Sepideh A, Karim P, Hossein A et al. Effects of Multistrain Probiotic Supplementation on Glycemic and Inflammatory Indices in Patients with Nonalcoholic Fatty Liver Disease: A Double-Blind Randomized Clinical Trial. J Am Coll Nutr 2016; 35: 500–505

[368] Scorletti E, Afolabi PR, Miles EA et al. Synbiotics Alter Fecal Microbiomes, But Not Liver Fat or Fibrosis, in a Randomized Trial of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2020; 158: 1597–1610.e7

[369] Mofidi F, Poustchi H, Yari Z et al. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. Br J Nutr 2017; 117: 662–668

[370] Sharpton SR, Maraj B, Harding-Theobald E et al. Gut microbiome-targeted therapies in nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. Am J Clin Nutr 2019; 110: 139–149

[371] Armstrong MJ, Gaunt P, Aithal GP et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016; 387: 679–690

[372] Newsome PN, Buchholtz K, Cusi K et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med 2021; 384 (12): 1113–1124

[373] Cusi K, Bril F, Barb D et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. Diabetes Obes Metab 2019; 21: 812–821

[374] Eriksson JW, Lundkvist P, Jansson PA et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia 2018; 61: 1923–1934

[375] Kahl S, Gancheva S, Straßburger K et al. Empagliflozin Effectively Lowers Liver Fat Content in Well-Controlled Type 2 Diabetes: A Randomized, Double-Blind, Phase 4, Placebo-Controlled Trial. Diabetes Care 2020; 43: 298–305

[376] Latva-Rasku A, Honka MJ, Kullberg J et al. The SGLT2 Inhibitor Dapagliflozin Reduces Liver Fat but Does Not Affect Tissue Insulin Sensitivity: A Randomized, Double-Blind, Placebo-Controlled Study With 8-Week Treatment in Type 2 Diabetes Patients. Diabetes Care 2019; 42: 931–937

[377] Belfort R, Harrison SA, Brown K et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006; 355: 2297–307

[378] Cusi K, Orsak B, Bril F et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med 2016; 165: 305–315

[379] Fujiwara N, Friedman SL, Goossens N et al. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018; 68: 526–549

[380] Kaplan DE, Serper M, John BV et al. Effects of Metformin Exposure on Survival in a Large National Cohort of Patients With Diabetes and Cirrhosis. Clin Gastroenterol Hepatol 2021; 19 (10): 2148–2160

[381] Bril F, Biernacki DM, Kalavalapalli S et al. Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial. Diabetes Care 2019; 42: 1481–1488

[382] Dormandy JA, Charbonnel B, Eckland DJ et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366: 1279–1289

[383] Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016; 375: 311–322

[384] Marso SP, Bain SC, Consoli A et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016; 375: 1834–1844

[385] Zinman B, Wanner C, Lachin JM et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373: 2117–2128

[386] Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380: 347–357

[387] Stefan N, Haring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019; 7: 313–324

[388] Dongiovanni P, Petta S, Mannisto V et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. J Hepatol 2015; 63: 705–712

[389] Kamal S, Khan MA, Seth A et al. Beneficial Effects of Statins on the Rates of Hepatic Fibrosis, Hepatic Decompensation, and Mortality in Chronic Liver Disease: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2017; 112: 1495–1505

[390] Lee JI, Lee HW, Lee KS et al. Effects of Statin Use on the Development and Progression of Nonalcoholic Fatty Liver Disease: A Nationwide Nested Case-Control Study. Am J Gastroenterol 2021; 116: 116–124

[391] Munoz AE, Pollarsky F, Marino M et al. Safety of Chronic Simvastatin Treatment in Patients with Decompensated Cirrhosis: Many Adverse Events but No Liver Injury. Dig Dis Sci 2021; 66 (9): 3199–3208

[392] Islam MM, Poly TN, Walther BA et al. Statin Use and the Risk of Hepatocellular Carcinoma: A Meta-Analysis of Observational Studies. Cancers (Basel) 2020: 12

[393] Bosch J, Gracia-Sancho J, Abraldes JG. Cirrhosis as new indication for statins. Gut 2020; 69: 953–962

[394] Mantovani A, Petracca G, Beatrice G et al. Glucagon-Like Peptide-1 Receptor Agonists for Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: An Updated Meta-Analysis of Randomized Controlled Trials. Metabolites 2021: 11

[395] Bajaj HS, Burrows M, Blavignac J et al. Extended-release naltrexone/bupropion and liver health: Pooled, post hoc analysis from four randomized controlled trials. Diabetes Obes Metab 2021; 23 (3): 861–865

[396] Pan CS, Stanley TL. Effect of Weight Loss Medications on Hepatic Steatosis and Steatohepatitis: A Systematic Review. Front Endocrinol (Lausanne) 2020; 11: 70

[397] Dietrich CG, Rau M, Jahn D et al. Changes in drug transport and metabolism and their clinical implications in non-alcoholic fatty liver disease. Expert Opin Drug Metab Toxicol 2017; 13: 625–640

[398] Vildhede A, Kimoto E, Pelis RM et al. Quantitative Proteomics and Mechanistic Modeling of Transporter-Mediated Disposition in Nonalcoholic Fatty Liver Disease. Clin Pharmacol Ther 2020; 107: 1128–1137

[399] Pierre V, Johnston CK, Ferslew BC et al. Population Pharmacokinetics of Morphine in Patients With Nonalcoholic Steatohepatitis (NASH) and Healthy Adults. CPT Pharmacometrics Syst Pharmacol 2017; 6: 331–339

[400] Sundelin EIO, Gormsen LC, Heeboll S et al. Hepatic exposure of metformin in patients with non-alcoholic fatty liver disease. Br J Clin Pharmacol 2019; 85: 1761–1770

[401] Tirona RG, Kassam Z, Strapp R et al. Apixaban and Rosuvastatin Pharmacokinetics in Nonalcoholic Fatty Liver Disease. Drug Metab Dispos 2018; 46: 485–492

[402] Rinella ME, Tacke F, Sanyal AJ et al. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. J Hepatol 2019; 71: 823–833

[403] Anania FA, Dimick-Santos L, Mehta R et al. Nonalcoholic Steatohepatitis: Current Thinking from the Division of Hepatology and Nutrition at the Food and Drug Administration. Hepatology 2021; 73 (5): 2023–2027

[404] Han MAT, Altayar O, Hamdeh S et al. Rates of and Factors Associated With Placebo Response in Trials of Pharmacotherapies for Nonalcoholic Steatohepatitis: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2019; 17: 616–629.e26

[405] Friedman SL, Neuschwander-Tetri BA, Rinella M et al. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018; 24: 908–922

[406] Konerman MA, Jones JC, Harrison SA. Pharmacotherapy for NASH: Current and emerging. J Hepatol 2018; 68: 362–375

[407] Lambrecht J, van Grunsven LA, Tacke F. Current and emerging pharmacotherapeutic interventions for the treatment of liver fibrosis. Expert Opin Pharmacother 2020; 21: 1637–1650

[408] Roeb E, Geier A. Nonalcoholic steatohepatitis (NASH) – current treatment recommendations and future developments. Z Gastroenterol 2019; 57: 508–517

[409] Younossi ZM, Ratziu V, Loomba R et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019; 394: 2184–2196

[410] Mullard A. FDA rejects NASH drug. Nat Rev Drug Discov 2020; 19: 501

[411] Taylor RS, Taylor RJ, Bayliss S et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology 2020; 158: 1611–1625.e12

[412] Acharya C, Bajaj JS. Chronic Liver Diseases and the Microbiome: Translating Our Knowledge of Gut Microbiota to Management of Chronic Liver Disease. Gastroenterology 2021; 160 (2): 556–572

[413] Lindén D, Ahnmark A, Pingitore P et al. Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice. Mol Metab 2019; 22: 49–61

[414] Schwartz BE, Rajagopal V, Smith C et al. Discovery and Targeting of the Signaling Controls of PNPLA3 to Effectively Reduce Transcription, Expression, and Function in Pre-Clinical NAFLD/NASH Settings. Cells 2020: 9

[415] DGAV D, DDG, DGEM, DGE-BV, DGPM, DGPRÄC, DKPM, VDBD, VDOE. S3-Leitlinie: Chirurgie der Adipositas und metabolischer Erkrankungen Version 2.3 (Februar 2018) AWMF-Register Nr. 088-001 ed: AWMF. 2018

[416] Lassailly G, Caiazzo R, Ntandja-Wandji LC et al. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. Gastroenterology 2020; 159 (4): 1290–1301

[417] Kwak M, Mehaffey JH, Hawkins RB et al. Bariatric surgery is associated with reduction in non-alcoholic steatohepatitis and hepatocellular carcinoma: A propensity matched analysis. Am J Surg 2020; 219 (3): 504–507

[418] Wirth KM, Sheka AC, Kizy S et al. Bariatric Surgery is Associated With Decreased Progression of Nonalcoholic Fatty Liver Disease to Cirrhosis: A Retrospective Cohort Analysis. Ann Surg 2020; 272 (1): 32–39

[419] Klebanoff MJ, Corey KE, Chhatwal J et al. Bariatric surgery for nonalcoholic steatohepatitis: A clinical and cost-effectiveness analysis. Hepatology 2017; 65: 1156–1164

[420] Alam S, Jahid Hasan M, Khan MAS et al. Effect of Weight Reduction on Histological Activity and Fibrosis of Lean Nonalcoholic Steatohepatitis Patient. J Transl Int Med 2019; 7: 106–114

[421] Panunzi S, Maltese S, Verrastro O et al. Pioglitazone and bariatric surgery are the most effective treatments for non-alcoholic steatohepatitis: A hierarchical network meta-analysis. Diabetes Obes Metab 2021; 23 (4): 980–990

[422] Mosko JD, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. Clin Gastroenterol Hepatol 2011; 9: 897–901

[423] Younus H, Sharma A, Miquel R et al. Bariatric Surgery in Cirrhotic Patients: Is It Safe? Obes Surg 2020; 30: 1241–1248

[424] Quezada N, Maturana G, Irarrazaval MJ et al. Bariatric Surgery in Cirrhotic Patients: a Matched Case-Control Study. Obes Surg 2020; 30: 4724–4731

[425] Vuppalanchi R, McCabe MEt, Tandra SR et al. Safety and Efficacy of Bariatric Surgery in Cirrhosis Patients With Extreme Obesity. Ann Surg 2022; 275 (1): e174–e180

[426] Goh GB, Schauer PR, McCullough AJ. Considerations for bariatric surgery in patients with cirrhosis. World J Gastroenterol 2018; 24: 3112–3119

[427] Hanipah ZN, Punchai S, McCullough A et al. Bariatric Surgery in Patients with Cirrhosis and Portal Hypertension. Obes Surg 2018; 28: 3431–3438

[428] Sharpton SR, Terrault NA, Posselt AM. Outcomes of Sleeve Gastrectomy in Obese Liver Transplant Candidates. Liver Transpl 2019; 25: 538–544

[429] Peterli R, Wolnerhanssen BK, Peters T et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. JAMA 2018; 319: 255–265

[430] Salminen P, Helmiö M, Ovaska J et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. Jama 2018; 319: 241–254

[431] Robert M, Espalieu P, Pelascini E et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. The Lancet 2019; 393: 1299–1309

[432] Colquitt JL, Pickett K, Loveman E et al. Surgery for weight loss in adults. Cochrane Database Syst Rev 2014; 8: CD003641

[433] Froylich D, Corcelles R, Daigle C et al. Effect of Roux-en-Y gastric bypass and sleeve gastrectomy on nonalcoholic fatty liver disease: a comparative study. Surg Obes Relat Dis 2016; 12 (1): 127–131

[434] von Schonfels W, Beckmann JH, Ahrens M et al. Histologic improvement of NAFLD in patients with obesity after bariatric surgery based on standardized NAS (NAFLD activity score). Surg Obes Relat Dis 2018; 14: 1607–1616

[435] Eilenberg M, Langer FB, Beer A et al. Significant Liver-Related Morbidity After Bariatric Surgery and Its Reversal-a Case Series. Obes Surg 2018; 28: 812–819

[436] Mahawar KK. Liver Dysfunction with Both Roux-en-Y and One-Anastomosis Gastric Bypass Is Almost Exclusively Seen with Longer Than Standard Limb Lengths. Obes Surg 2018; 28: 548–549

[437] Agarwal L, Sahu AK, Baksi A et al. Safety of metabolic and bariatric surgery in obese patients with liver cirrhosis: a systematic review and meta-analysis. Surg Obes Relat Dis 2021; 173 (3): 525–537

[438] Dietrich A, Aberle J, Wirth A et al. Adipositaschirurgie und Therapie metabolischer Erkrankungen. Dtsch Arztebl International 2018; 115: 705–711

[439] Kotinda A, de Moura DTH, Ribeiro IB et al. Efficacy of Intragastric Balloons for Weight Loss in Overweight and Obese Adults: a Systematic Review and Meta-analysis of Randomized Controlled Trials. Obes Surg 2020; 30: 2743–2753

[440] Imaz I, Martínez-Cervell C, García-Alvarez EE et al. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. Obes Surg 2008; 18: 841–846

[441] Lee Y, Dang JT, Switzer N et al. Bridging interventions before bariatric surgery in patients with BMI ≥ 50 kg/m(2): a systematic review and meta-analysis. Surg Endosc 2019; 33: 3578–3588

[442] Lee YM, Low HC, Lim LG et al. Intragastric balloon significantly improves nonalcoholic fatty liver disease activity score in obese patients with nonalcoholic steatohepatitis: a pilot study. Gastrointest Endosc 2012; 76: 756–760

[443] Bazerbachi F, Vargas EJ, Rizk M et al. Intragastric Balloon Placement Induces Significant Metabolic and Histologic Improvement in Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol 2021; 19: 146–154.e4

[444] Frutos MD, Morales MD, Luján J et al. Intragastric balloon reduces liver volume in super-obese patients, facilitating subsequent laparoscopic gastric bypass. Obes Surg 2007; 17: 150–154

[445] Forlano R, Ippolito AM, Iacobellis A et al. Effect of the BioEnterics intragastric balloon on weight, insulin resistance, and liver steatosis in obese patients. Gastrointest Endosc 2010; 71: 927–933

[446] Folini L, Veronelli A, Benetti A et al. Liver steatosis (LS) evaluated through chemical-shift magnetic resonance imaging liver enzymes in morbid obesity; effect of weight loss obtained with intragastric balloon gastric banding. Acta Diabetol 2014; 51: 361–368

[447] Due-Petersson R, Poulsen IM, Hedbäck N et al. Effect and safety of endoscopic sleeve gastroplasty for treating obesity – a systematic review. Dan Med J 2020: 67

[448] Sharaiha RZ, Kumta NA, Saumoy M et al. Endoscopic Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patients. Clin Gastroenterol Hepatol 2017; 15: 504–510

[449] Hajifathalian K, Mehta A, Ang B et al. Improvement in insulin resistance and estimated hepatic steatosis and fibrosis after endoscopic sleeve gastroplasty. Gastrointest Endosc 2021; 93 (5): 1110–1118

[450] Rohde U, Hedbäck N, Gluud LL et al. Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2016; 18: 300–305

[451] Gollisch KS, Lindhorst A, Raddatz D. EndoBarrier Gastrointestinal Liner in Type 2 Diabetic Patients Improves Liver Fibrosis as Assessed by Liver Elastography. Exp Clin Endocrinol Diabetes 2017; 125: 116–121

[452] van Baar ACG, Beuers U, Wong K et al. Endoscopic duodenal mucosal resurfacing improves glycaemic and hepatic indices in type 2 diabetes: 6-month multicentre results. JHEP Rep 2019; 1: 429–437

[453] van Baar ACG, Holleman F, Crenier L et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study. Gut 2020; 69: 295–303

[454] Machytka E, Bužga M, Zonca P et al. Partial jejunal diversion using an incisionless magnetic anastomosis system: 1-year interim results in patients with obesity and diabetes. Gastrointest Endosc 2017; 86: 904–912

[455] Samji NS, Heda R, Satapathy SK. Peri-transplant management of non-alcoholic fatty liver disease in liver transplant candidates . Transl Gastroenterol Hepatol 2020; 5: 10

[456] Thuluvath PJ, Hanish S, Savva Y. Liver Transplantation in Cryptogenic Cirrhosis: Outcome Comparisons Between NASH, Alcoholic, and AIH Cirrhosis. Transplantation 2018; 102: 656–663

[457] Haldar D, Kern B, Hodson J et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. J Hepatol 2019; 71: 313–322

[458] EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012; 57: 399–420

[459] Beckmann S, Drent G, Ruppar T et al. Body Weight Parameters are Related to Morbidity and Mortality After Liver Transplantation: A Systematic Review and Meta-analysis. Transplantation 2019; 103: 2287–2303

[460] Schlansky B, Naugler WE, Orloff SL et al. Higher Mortality and Survival Benefit in Obese Patients Awaiting Liver Transplantation. Transplantation 2016; 100: 2648–2655

[461] Leonard J, Heimbach JK, Malinchoc M et al. The impact of obesity on long-term outcomes in liver transplant recipients-results of the NIDDK liver transplant database. Am J Transplant 2008; 8: 667–672

[462] Sourianarayanane A, Arikapudi S, McCullough AJ et al. Nonalcoholic steatohepatitis recurrence and rate of fibrosis progression following liver transplantation. Eur J Gastroenterol Hepatol 2017; 29: 481–487

[463] Tokodai K, Karadagi A, Kjaernet F et al. Characteristics and risk factors for recurrence of nonalcoholic steatohepatitis following liver transplantation. Scand J Gastroenterol 2019; 54: 233–239

[464] Bhati C, Idowu MO, Sanyal AJ et al. Long-term Outcomes in Patients Undergoing Liver Transplantation for Nonalcoholic Steatohepatitis-Related Cirrhosis. Transplantation 2017; 101: 1867–1874

[465] Kakar S, Dugum M, Cabello R et al. Incidence of Recurrent NASH-Related Allograft Cirrhosis. Dig Dis Sci 2019; 64: 1356–1363

[466] van den Berg EH, Douwes RM, de Meijer VE et al. Liver transplantation for NASH cirrhosis is not performed at the expense of major post-operative morbidity. Dig Liver Dis 2018; 50: 68–75

[467] Kalaitzakis E, Björnsson E. Coronary artery disease in liver cirrhosis: does the aetiology of liver disease matter? J Hepatol 2009; 51: 962–963; author reply 963-4

[468] Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology 2002; 35: 105–109

[469] Nicolau-Raducu R, Gitman M, Ganier D et al. Adverse cardiac events after orthotopic liver transplantation: a cross-sectional study in 389 consecutive patients. Liver Transpl 2015; 21: 13–21

[470] Wang X, Li J, Riaz DR et al. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014; 12: 394–402.e1

[471] Vanwagner LB, Bhave M, Te HS et al. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. Hepatology 2012; 56: 1741–1750

[472] VanWagner LB, Serper M, Kang R et al. Factors Associated With Major Adverse Cardiovascular Events After Liver Transplantation Among a National Sample. Am J Transplant 2016; 16: 2684–2694

[473] Barone M, Viggiani MT, Losurdo G et al. Systematic review with meta-analysis: post-operative complications and mortality risk in liver transplant candidates with obesity. Aliment Pharmacol Ther 2017; 46: 236–245

[474] Hogan BJ, Gonsalkorala E, Heneghan MA. Evaluation of coronary artery disease in potential liver transplant recipients. Liver Transpl 2017; 23: 386–395

[475] Malik SM, deVera ME, Fontes P et al. Outcome after liver transplantation for NASH cirrhosis. Am J Transplant 2009; 9: 782–793

[476] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016; 64: 433–485

[477] Collins BH, Pirsch JD, Becker YT et al. Long-term results of liver transplantation in older patients 60 years of age and older. Transplantation 2000; 70: 780–783

[478] Kappus M, Abdelmalek M. De Novo and Recurrence of Nonalcoholic Steatohepatitis After Liver Transplantation. Clin Liver Dis 2017; 21: 321–335

[479] Finkenstedt A, Auer C, Glodny B et al. Patatin-like phospholipase domain-containing protein 3 rs738409-G in recipients of liver transplants is a risk factor for graft steatosis. Clin Gastroenterol Hepatol 2013; 11: 1667–1672

[480] Richards J, Gunson B, Johnson J et al. Weight gain and obesity after liver transplantation. Transpl Int 2005; 18: 461–466

[481] Germani G, Laryea M, Rubbia-Brandt L et al. Management of Recurrent and De Novo NAFLD/NASH After Liver Transplantation. Transplantation 2019; 103: 57–67

[482] Dick AA, Spitzer AL, Seifert CF et al. Liver transplantation at the extremes of the body mass index. Liver Transpl 2009; 15: 968–977

[483] Conzen KD, Vachharajani N, Collins KM et al. Morbid obesity in liver transplant recipients adversely affects longterm graft and patient survival in a single-institution analysis. HPB (Oxford) 2015; 17: 251–257

[484] Martin P, DiMartini A, Feng S et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014; 59: 1144–1165

[485] Hakeem AR, Cockbain AJ, Raza SS et al. Increased morbidity in overweight and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. Liver Transpl 2013; 19: 551–562

[486] Fujikawa T, Fujita S, Mizuno S et al. Clinical and financial impact of obesity on the outcome of liver transplantation. Transplant Proc 2006; 38: 3612–3614

[487] Pelletier SJ, Schaubel DE, Wei G et al. Effect of body mass index on the survival benefit of liver transplantation. Liver Transpl 2007; 13: 1678–1683

[488] Lai JC, Rahimi RS, Verna EC et al. Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multicenter Study. Gastroenterology 2019; 156: 1675–1682

[489] Czigany Z, Kramp W, Bednarsch J et al. Myosteatosis to predict inferior perioperative outcome in patients undergoing orthotopic liver transplantation. Am J Transplant 2020; 20: 493–503

[490] Ney M, Haykowsky MJ, Vandermeer B et al. Systematic review: pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates. Aliment Pharmacol Ther 2016; 44: 796–806

[491] Montano-Loza AJ, Angulo P, Meza-Junco J et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle 2016; 7: 126–135

[492] Carias S, Castellanos AL, Vilchez V et al. Nonalcoholic steatohepatitis is strongly associated with sarcopenic obesity in patients with cirrhosis undergoing liver transplant evaluation. J Gastroenterol Hepatol 2016; 31: 628–633

[493] van Vugt JLA, Alferink LJM, Buettner S et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: A competing risk analysis in a national cohort. J Hepatol 2018; 68: 707–714

[494] Vidot H, Kline K, Cheng R et al. The Relationship of Obesity, Nutritional Status and Muscle Wasting in Patients Assessed for Liver Transplantation. Nutrients 2019: 11

[495] Della Corte C, Mosca A, Vania A et al. Good adherence to the Mediterranean diet reduces the risk for NASH and diabetes in pediatric patients with obesity: The results of an Italian Study. Nutrition 2017; 39/40: 8–14

[496] Kawaguchi T, Izumi N, Charlton MR et al. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. Hepatology 2011; 54: 1063–1070

[497] Park JG, Tak WY, Park SY et al. Effects of Branched-Chain Amino Acid (BCAA) Supplementation on the Progression of Advanced Liver Disease: A Korean Nationwide, Multicenter, Prospective, Observational, Cohort Study. Nutrients 2020: 12

[498] Chen CJ, Wang LC, Kuo HT et al. Significant effects of late evening snack on liver functions in patients with liver cirrhosis: A meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2019; 34: 1143–1152

[499] Plank LD, Gane EJ, Peng S et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology 2008; 48: 557–566

[500] Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. J Gastroenterol Hepatol 2012; 27: 430–441

[501] easloffice@easloffice.eu EAftSotLEa, Liver EAftSot. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019; 70: 172–193

[502] Iwasa M, Iwata K, Hara N et al. Nutrition therapy using a multidisciplinary team improves survival rates in patients with liver cirrhosis. Nutrition 2013; 29: 1418–1421

[503] Yumuk V, Tsigos C, Fried M et al. European Guidelines for Obesity Management in Adults. Obes Facts 2015; 8: 402–424

[504] Durrer Schutz D, Busetto L, Dicker D et al. European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care. Obes Facts 2019; 12: 40–66

[505] Sutin AR, Stephan Y, Terracciano A. Weight Discrimination and Risk of Mortality. Psychol Sci 2015; 26: 1803–1811

[506] Wharton S, Lau DCW, Vallis M et al. Obesity in adults: a clinical practice guideline. CMAJ 2020; 192: E875–E891

[507] Debette-Gratien M, Tabouret T, Antonini MT et al. Personalized adapted physical activity before liver transplantation: acceptability and results. Transplantation 2015; 99: 145–150

[508] Zenith L, Meena N, Ramadi A et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014; 12: 1920–1926.e2

[509] Duarte-Rojo A, Ruiz-Margáin A, Montaño-Loza AJ et al. Exercise and physical activity for patients with end-stage liver disease: Improving functional status and sarcopenia while on the transplant waiting list. Liver Transpl 2018; 24: 122–139

[510] Brustia R, Savier E, Scatton O. Physical exercise in cirrhotic patients: Towards prehabilitation on waiting list for liver transplantation. A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2018; 42: 205–215

[511] Diwan TS, Lee TC, Nagai S et al. Obesity, transplantation, and bariatric surgery: An evolving solution for a growing epidemic. Am J Transplant 2020; 20: 2143–2155

[512] Kardashian AA, Dodge JL, Roberts J et al. Weighing the risks: Morbid obesity and diabetes are associated with increased risk of death on the liver transplant waiting list. Liver Int 2018; 38: 553–563

[513] Barone M, Viggiani MT, Avolio AW et al. Obesity as predictor of postoperative outcomes in liver transplant candidates: Review of the literature and future perspectives. Dig Liver Dis 2017; 49: 957–966

[514] Aller R, Fernandez-Rodriguez C, Lo Iacono O et al. Consensus document. Management of non-alcoholic fatty liver disease (NAFLD). Clinical practice guideline. . Gastroenterol Hepatol 2018; 41: 328–349

[515] Tsochatzis E, Coilly A, Nadalin S et al. International Liver Transplantation Consensus Statement on End-stage Liver Disease Due to Nonalcoholic Steatohepatitis and Liver Transplantation. Transplantation 2019; 103: 45–56

[516] Ratziu V, Ghabril M, Romero-Gomez M et al. Recommendations for Management and Treatment of Nonalcoholic Steatohepatitis. Transplantation 2019; 103: 28–38

[517] Idriss R, Hasse J, Wu T et al. Impact of Prior Bariatric Surgery on Perioperative Liver Transplant Outcomes. Liver Transpl 2019; 25: 217–227

[518] Nicoll A. Surgical risk in patients with cirrhosis. J Gastroenterol Hepatol 2012; 27: 1569–1575

[519] de Goede B, Klitsie PJ, Lange JF et al. Morbidity and mortality related to non-hepatic surgery in patients with liver cirrhosis: a systematic review. Best Pract Res Clin Gastroenterol 2012; 26: 47–59

[520] Newman KL, Johnson KM, Cornia PB et al. Perioperative Evaluation and Management of Patients With Cirrhosis: Risk Assessment, Surgical Outcomes, and Future Directions. Clin Gastroenterol Hepatol 2020; 18: 2398–2414.e3

[521] Schmitz A, Haste P, Johnson MS. Transjugular Intrahepatic Portosystemic Shunt (TIPS) Creation Prior to Abdominal Operation: a Retrospective Analysis. J Gastrointest Surg 2020; 24: 2228–2232

[522] Kim JJ, Dasika NL, Yu E et al. Cirrhotic patients with a transjugular intrahepatic portosystemic shunt undergoing major extrahepatic surgery. J Clin Gastroenterol 2009; 43: 574–579

[523] Heimbach JK, Watt KD, Poterucha JJ et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. Am J Transplant 2013; 13: 363–368

[524] Zamora-Valdes D, Watt KD, Kellogg TA et al. Long-term outcomes of patients undergoing simultaneous liver transplantation and sleeve gastrectomy. Hepatology 2018; 68: 485–495

[525] Merli M, Lattanzi B, Aprile F. Sarcopenic obesity in fatty liver. Curr Opin Clin Nutr Metab Care 2019; 22: 185–190

[526] Pais R, Barritt ASt, Calmus Y et al. NAFLD and liver transplantation: Current burden and expected challenges. J Hepatol 2016; 65: 1245–1257

[527] Osseis M, Lazzati A, Salloum C et al. Sleeve Gastrectomy After Liver Transplantation: Feasibility and Outcomes. Obes Surg 2018; 28: 242–248

[528] Tsamalaidze L, Stauffer JA, Arasi LC et al. Laparoscopic Sleeve Gastrectomy for Morbid Obesity in Patients After Orthotopic Liver Transplant: a Matched Case-Control Study. Obes Surg 2018; 28: 444–450

[529] Dziodzio T, Biebl M, Ollinger R et al. The Role of Bariatric Surgery in Abdominal Organ Transplantation-the Next Big Challenge? Obes Surg 2017; 27: 2696–2706

[530] Lazzati A, Iannelli A, Schneck AS et al. Bariatric surgery and liver transplantation: a systematic review a new frontier for bariatric surgery. Obes Surg 2015; 25: 134–42

[531] El Atrache MM, Abouljoud MS, Divine G et al. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. Clin Transplant 2012; 26: E505–E512

[532] Butte JM, Devaud N, Jarufe NP et al. Sleeve gastrectomy as treatment for severe obesity after orthotopic liver transplantation. Obes Surg 2007; 17: 1517–1519

[533] Choudhary NS, Puri R, Saraf N et al. Intragastric balloon as a novel modality for weight loss in patients with cirrhosis and morbid obesity awaiting liver transplantation. Indian J Gastroenterol 2016; 35: 113–116

[534] Baba HA, Theurer S, Canbay A et al. [Liver transplantation. Current aspects of pretransplantation diagnosis and rejection]. Pathologe 2020; 41: 505–514

[535] Chu MJ, Dare AJ, Phillips AR et al. Donor Hepatic Steatosis and Outcome After Liver Transplantation: a Systematic Review. J Gastrointest Surg 2015; 19: 1713–1724

[536] Dutkowski P, Schlegel A, Slankamenac K et al. The use of fatty liver grafts in modern allocation systems: risk assessment by the balance of risk (BAR) score. Ann Surg 2012; 256: 861–868; discussion 868-9

[537] Nasralla D, Coussios CC, Mergental H et al. A randomized trial of normothermic preservation in liver transplantation. Nature 2018; 557: 50–56

[538] Mergental H, Laing RW, Kirkham AJ et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nat Commun 2020; 11: 2939

[539] Jassem W, Xystrakis E, Ghnewa YG et al. Normothermic Machine Perfusion (NMP) Inhibits Proinflammatory Responses in the Liver and Promotes Regeneration. Hepatology 2019; 70: 682–695

[540] Lee SG. A complete treatment of adult living donor liver transplantation: a review of surgical technique and current challenges to expand indication of patients. Am J Transplant 2015; 15: 17–38

[541] Jin YJ, Kim KM, Hwang S et al. Exercise and diet modification in non-obese non-alcoholic fatty liver disease: analysis of biopsies of living liver donors. J Gastroenterol Hepatol 2012; 27: 1341–1347

[542] Rinella ME, Alonso E, Rao S et al. Body mass index as a predictor of hepatic steatosis in living liver donors. Liver Transpl 2001; 7: 409–414

[543] Younossi ZM, Tampi RP, Racila A et al. Economic and Clinical Burden of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes in the U. S. Diabetes Care 2020; 43: 283–289

[544] Schattenberg JM. [Non-alcoholic fatty liver disease (NAFLD)]. MMW Fortschr Med 2020; 162: 56–62

[545] Labenz C, Huber Y, Michel M et al. Impact of NAFLD on the Incidence of Cardiovascular Diseases in a Primary Care Population in Germany. Dig Dis Sci 2020; 65: 2112–2119

[546] Hagstrom H, Elfwen O, Hultcrantz R et al. Steatohepatitis Is Not Associated with an Increased Risk for Fibrosis Progression in Nonalcoholic Fatty Liver Disease. Gastroenterol Res Pract 2018; 2018: 1942648

[547] Vergniol J, Boursier J, Coutzac C et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology 2014; 60: 65–76

[548] Chalasani N, Abdelmalek MF, Loomba R et al. Relationship between three commonly used non-invasive fibrosis biomarkers and improvement in fibrosis stage in patients with non-alcoholic steatohepatitis. Liver Int 2019; 39: 924–932

[549] Hagstrom H, Talback M, Andreasson A et al. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. J Hepatol 2020; 73: 1023–1029

[550] Loomba R, Neuschwander-Tetri BA, Sanyal A et al. Multicenter Validation of Association Between Decline in MRI-PDFF and Histologic Response in NASH. Hepatology 2020; 72 (4): 1219–1229

[551] Allen AM, Hicks SB, Mara KC et al. The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity – A longitudinal cohort study. J Hepatol 2019; 71: 1229–1236

[552] Huber Y, Labenz C, Michel M et al. Tumor incidence in patients with non-alcoholic fatty liver disease. Deutsches Ärzteblatt 2020; 117: 719–724

[553] Ioannou GN, Green P, Kerr KF et al. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol 2019; 71: 523–533

[554] Kansagara D, Papak J, Pasha AS et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. Ann Intern Med 2014; 161: 261–269

[555] Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014; 11: e1001624

[556] Andersson KL, Salomon JA, Goldie SJ et al. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2008; 6: 1418–1424

[557] Colombo M. Screening and diagnosis of hepatocellular carcinoma. Liver Int 2009; 29 (Suppl. 1): 143–147

[558] Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. Am J Med 1996; 101: 422–434

[559] Moon AM, Weiss NS, Beste LA et al. No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis. Gastroenterology 2018; 155: 1128–1139.e6

[560] Nurnberg D, Jung A, Schmieder C et al. [What's the price of routine sonography – results of an analysis of costs and processes in a district hospital]. Ultraschall in Med 2008; 29: 405–417

[561] Schuler A, Reuss J, Delorme S et al. [Costs of clinical ultrasound examinations – an economical cost calculation and analysis]. Ultraschall in Med 2010; 31: 379–386

[562] Zoli M, Magalotti D, Bianchi G et al. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer 1996; 78: 977–985

[563] Kim SY, An J, Lim YS et al. MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma. JAMA Oncol 2017; 3: 456–463

[564] Shah TU, Semelka RC, Pamuklar E et al. The risk of hepatocellular carcinoma in cirrhotic patients with small liver nodules on MRI. Am J Gastroenterol 2006; 101: 533–540

[565] Tzartzeva K, Obi J, Rich NE et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology 2018; 154: 1706–1718.e1

[566] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Diagnostik und Therapie des hepatozellulären Karzinoms, Langversion1.0, AWMF Registrierungsnummer: 032-053OL. https://www.leitlinienprogramm-onkologie.de/Leitlinien.7.0.html

[567] Best J, Bechmann LP, Sowa JP et al. GALAD Score Detects Early Hepatocellular Carcinoma in an International Cohort of Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol 2020; 18: 728–735.e4

[568] Li T, Yin J, Yuan L et al. Downregulation of microRNA-139 is associated with hepatocellular carcinoma risk and short-term survival. Oncol Rep 2014; 31: 1699–1706

[569] Mourad L, El-Ahwany E, Zoheiry M et al. Expression analysis of liver-specific circulating microRNAs in HCV-induced hepatocellular Carcinoma in Egyptian patients. Cancer Biol Ther 2018; 19: 400–406

[570] Chen L, Chu F, Cao Y et al. Serum miR-182 and miR-331-3p as diagnostic and prognostic markers in patients with hepatocellular carcinoma. Tumour Biol 2015; 36: 7439–7447

[571] Shaheen NMH, Zayed N, Riad NM et al. Role of circulating miR-182 and miR-150 as biomarkers for cirrhosis and hepatocellular carcinoma post HCV infection in Egyptian patients. Virus Res 2018; 255: 77–84

[572] Loosen SH, Wirtz TH, Roy S et al. Circulating levels of microRNA193a-5p predict outcome in early stage hepatocellular carcinoma. PLoS One 2020; 15: e0239386

[573] Younossi ZM, Otgonsuren M, Henry L et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015; 62: 1723–1730

[574] Marrero JA, Kulik LM, Sirlin CB et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68: 723–750

[575] Ertle J, Dechene A, Sowa JP et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer 2011; 128: 2436–2443

[576] Grimaudo S, Pipitone RM, Pennisi G et al. Association Between PNPLA3 rs738409 C>G Variant and Liver-Related Outcomes in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2020; 18: 935–944.e3

[577] Liu YL, Patman GL, Leathart JB et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol 2014; 61: 75–81

[578] Kawamura Y, Arase Y, Ikeda K et al. Large-scale long-term follow-up study of Japanese patients with non-alcoholic Fatty liver disease for the onset of hepatocellular carcinoma. Am J Gastroenterol 2012; 107: 253–261

[579] Yang JD, Ahmed F, Mara KC et al. Diabetes Is Associated With Increased Risk of Hepatocellular Carcinoma in Patients With Cirrhosis From Nonalcoholic Fatty Liver Disease. Hepatology 2020; 71: 907–916

[580] Benhammou JN, Lin J, Hussain SK et al. Emerging risk factors for nonalcoholic fatty liver disease associated hepatocellular carcinoma. Hepatoma Res 2020: 6

[581] Kozlitina J, Smagris E, Stender S et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2014; 46: 352–356

[582] Mancina RM, Dongiovanni P, Petta S et al. The MBOAT7-TMC4 Variant rs641738 Increases Risk of Nonalcoholic Fatty Liver Disease in Individuals of European Descent. Gastroenterology 2016; 150: 1219–1230.e6

[583] Donati B, Dongiovanni P, Romeo S et al. MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals. Sci Rep 2017; 7: 4492

[584] Götz M, Anders M, Biecker E et al. [S2k Guideline Gastrointestinal Bleeding – Guideline of the German Society of Gastroenterology DGVS]. Z Gastroenterol 2017; 55: 883–936

[585] de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743–752

[586] Garcia-Tsao G, Abraldes JG, Berzigotti A et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017; 65: 310–335

[587] Zheng KI, Liu C, Li J et al. Validation of Baveno VI and expanded Baveno VI criteria to identify high-risk varices in patients with MAFLD-related compensated cirrhosis. J Hepatol 2020; 73: 1571–1573

[588] Rubino F, Puhl RM, Cummings DE et al. Joint international consensus statement for ending stigma of obesity. Nat Med 2020; 26: 485–497

[589] Hales CM, Carroll MD, Fryar CD et al. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. NCHS Data Brief 2017: 1–8

[590] Schienkiewitz A, Mensink GB, Scheidt-Nave C. Comorbidity of overweight and obesity in a nationally representative sample of German adults aged 18-79 years. BMC Public Health 2012; 12: 658

[591] Meixner L, Cohrdes C, Schienkiewitz A et al. Health-related quality of life in children and adolescents with overweight and obesity: results from the German KIGGS survey. BMC Public Health 2020; 20: 1722

[592] Kleiser C, Schienkiewitz A, Schaffrath Rosario A et al. Indicators of overweight and cardiovascular disease risk factors among 11- to 17-year-old boys and girls in Germany. Obes Facts 2011; 4: 379–385

[593] Wiegand S, Keller KM, Robl M et al. Obese boys at increased risk for nonalcoholic liver disease: evaluation of 16,390 overweight or obese children and adolescents. Int J Obes (Lond) 2010; 34: 1468–1474

[594] Schwimmer JB, Deutsch R, Kahen T et al. Prevalence of fatty liver in children and adolescents. Pediatrics 2006; 118: 1388–1393

[595] Mencin AA, Lavine JE. Advances in pediatric nonalcoholic fatty liver disease. Pediatr Clin North Am 2011; 58: 1375–1392

[596] Mencin AA, Lavine JE. Nonalcoholic fatty liver disease in children. Curr Opin Clin Nutr Metab Care 2011; 14: 151–157

[597] Newton KP, Hou J, Crimmins NA et al. Prevalence of Prediabetes and Type 2 Diabetes in Children With Nonalcoholic Fatty Liver Disease. JAMA Pediatr 2016; 170: e161971

[598] Kohli R, Boyd T, Lake K et al. Rapid progression of NASH in childhood. J Pediatr Gastroenterol Nutr 2010; 50: 453–456

[599] Mann JP, De Vito R, Mosca A et al. Portal inflammation is independently associated with fibrosis and metabolic syndrome in pediatric nonalcoholic fatty liver disease. Hepatology 2016; 63: 745–753

[600] Hagstrom H, Stal P, Hultcrantz R et al. Overweight in late adolescence predicts development of severe liver disease later in life: A 39years follow-up study. J Hepatol 2016; 65: 363–368

[601] Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S et al. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut 2009; 58: 1538–1544

[602] Nogrady B. Childhood obesity: A growing concern. Nature 2017; 551: S96

[603] Della Corte C, Mosca A, Majo F et al. Nonalcoholic fatty pancreas disease and Nonalcoholic fatty liver disease: more than ectopic fat. Clin Endocrinol (Oxf) 2015; 83: 656–662

[604] Dunn W, Sanyal AJ, Brunt EM et al. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). J Hepatol 2012; 57: 384–391

[605] Abeysekera KWM, Fernandes GS, Hammerton G et al. Prevalence of steatosis and fibrosis in young adults in the UK: a population-based study. Lancet Gastroenterol Hepatol 2020; 5: 295–305

[606] Bruce KD, Cagampang FR, Argenton M et al. Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression. Hepatology 2009; 50: 1796–1808

[607] Bugianesi E, Bizzarri C, Rosso C et al. Low Birthweight Increases the Likelihood of Severe Steatosis in Pediatric Non-Alcoholic Fatty Liver Disease. Am J Gastroenterol 2017; 112: 1277–1286

[608] Newton KP, Feldman HS, Chambers CD et al. Low and High Birth Weights Are Risk Factors for Nonalcoholic Fatty Liver Disease in Children. J Pediatr 2017; 187: 141–146.e1

[609] Liu CH, Ampuero J, Gil-Gomez A et al. miRNAs in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Hepatol 2018; 69: 1335–1348

[610] Nobili V, Donati B, Panera N et al. A 4-polymorphism risk score predicts steatohepatitis in children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr 2014; 58: 632–636

[611] Valenti L, Alisi A, Galmozzi E et al. I148M patatin-like phospholipase domain-containing 3 gene variant and severity of pediatric nonalcoholic fatty liver disease. Hepatology 2010; 52: 1274–1280

[612] Hudert CA, Selinski S, Rudolph B et al. Genetic determinants of steatosis and fibrosis progression in paediatric non-alcoholic fatty liver disease. Liver Int 2019; 39: 540–556

[613] Larrieta-Carrasco E, Acuna-Alonzo V, Velazquez-Cruz R et al. PNPLA3 I148M polymorphism is associated with elevated alanine transaminase levels in Mexican Indigenous and Mestizo populations. Mol Biol Rep 2014; 41: 4705–4711

[614] Teo K, Abeysekera KWM, Adams L et al. rs641738C>T near MBOAT7 is associated with liver fat, ALT and fibrosis in NAFLD: A meta-analysis. J Hepatol 2021; 74: 20–30

[615] Di Sessa A, Umano GR, Cirillo G et al. The rs72613567: TA Variant in the Hydroxysteroid 17-beta Dehydrogenase 13 Gene Reduces Liver Damage in Obese Children. J Pediatr Gastroenterol Nutr 2020; 70: 371–374

[616] Nobili V, Liccardo D, Bedogni G et al. Influence of dietary pattern, physical activity, and I148M PNPLA3 on steatosis severity in at-risk adolescents. Genes Nutr 2014; 9: 392

[617] Eng K, Lopez R, Liccardo D et al. A non-invasive prediction model for non-alcoholic steatohepatitis in paediatric patients with non-alcoholic fatty liver disease. Dig Liver Dis 2014; 46: 1008–1013

[618] Schwimmer JB, Dunn W, Norman GJ et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology 2010; 138: 1357–1364, 1364 e1-2

[619] Younossi ZM, Gramlich T, Liu YC et al. Nonalcoholic fatty liver disease: assessment of variability in pathologic interpretations. Mod Pathol 1998; 11: 560–565

[620] Schwimmer JB, Behling C, Newbury R et al. Histopathology of pediatric nonalcoholic fatty liver disease. Hepatology 2005; 42: 641–649

[621] Africa JA, Behling CA, Brunt EM et al. In Children With Nonalcoholic Fatty Liver Disease, Zone 1 Steatosis Is Associated With Advanced Fibrosis. Clin Gastroenterol Hepatol 2018; 16: 438–446.e1

[622] Mameli C, Zuccotti GV, Carnovale C et al. An update on the assessment and management of metabolic syndrome, a growing medical emergency in paediatric populations. Pharmacol Res 2017; 119: 99–117

[623] van der Heijden LB, Feskens EJM, Janse AJ. Maintenance interventions for overweight or obesity in children: a systematic review and meta-analysis. Obes Rev 2018; 19: 798–809

[624] Utz-Melere M, Targa-Ferreira C, Lessa-Horta B et al. Non-Alcoholic Fatty Liver Disease in Children and Adolescents: Lifestyle Change – a Systematic Review and Meta-Analysis. Ann Hepatol 2018; 17: 345–354

[625] Katsagoni CN, Papachristou E, Sidossis A et al. Effects of Dietary and Lifestyle Interventions on Liver, Clinical and Metabolic Parameters in Children and Adolescents with Non-Alcoholic Fatty Liver Disease: A Systematic Review. Nutrients 2020: 12

[626] Golabi P, Locklear CT, Austin P et al. Effectiveness of exercise in hepatic fat mobilization in non-alcoholic fatty liver disease: Systematic review. World J Gastroenterol 2016; 22: 6318–6327

[627] Goss AM, Dowla S, Pendergrass M et al. Effects of a carbohydrate-restricted diet on hepatic lipid content in adolescents with non-alcoholic fatty liver disease: A pilot, randomized trial. Pediatr Obes 2020; 15: e12630

[628] Africa JA, Newton KP, Schwimmer JB. Lifestyle Interventions Including Nutrition, Exercise, and Supplements for Nonalcoholic Fatty Liver Disease in Children. Dig Dis Sci 2016; 61: 1375–1386

[629] Kwon Y, Jeong SJ. Relative Skeletal Muscle Mass Is an Important Factor in Non-Alcoholic Fatty Liver Disease in Non-Obese Children and Adolescents. J Clin Med 2020: 9

[630] Dezsőfi A, Baumann U, Dhawan A et al. Liver biopsy in children: position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr 2015; 60: 408–420

[631] Pratt JSA, Browne A, Browne NT et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. Surg Obes Relat Dis 2018; 14: 882–901

[632] Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter B. Bariatrisch-chirurgische Maßnahmen bei Jugendlichen mit extremer Adipositas. Monatsschr Kinderheilkd 2012; 160: 1123–1128

[633] Weihe P, Weihrauch-Bluher S. Metabolic Syndrome in Children and Adolescents: Diagnostic Criteria, Therapeutic Options and Perspectives. Curr Obes Rep 2019; 8: 472–479

[634] Bolling CF, Armstrong SC, Reichard KW et al. Metabolic and Bariatric Surgery for Pediatric Patients With Severe Obesity. Pediatrics 2019: 144

[635] Corey KE, Stanley TL, Misdraji J et al. Prevalence and outcome of nonalcoholic fatty liver disease in adolescents and young adults undergoing weight loss surgery. Pediatr Obes 2014; 9: e91–e93

[636] Loy JJ, Youn HA, Schwack B et al. Improvement in nonalcoholic fatty liver disease and metabolic syndrome in adolescents undergoing bariatric surgery. Surg Obes Relat Dis 2015; 11: 442–449

[637] Nobili V, Carpino G, De Peppo F et al. Laparoscopic Sleeve Gastrectomy Improves Nonalcoholic Fatty Liver Disease-Related Liver Damage in Adolescents by Reshaping Cellular Interactions and Hepatic Adipocytokine Production. J Pediatr 2018; 194: 100–108.e3

[638] Franchitto A, Carpino G, Alisi A et al. The Contribution of the Adipose Tissue-Liver Axis in Pediatric Patients with Nonalcoholic Fatty Liver Disease after Laparoscopic Sleeve Gastrectomy. J Pediatr 2020; 216: 117–127.e2

[639] Jones RE, Yeh AM, Kambham N et al. Intraoperative Liver Biopsy During Adolescent Bariatric Surgery: Is It Really Necessary? Obes Surg 2020; 30: 69–76

[640] Lavine JE, Schwimmer JB, Van Natta ML et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011; 305: 1659–1668

[641] Nobili V, Alisi A, Valenti L et al. NAFLD in children: new genes, new diagnostic modalities and new drugs. Nat Rev Gastroenterol Hepatol 2019; 16: 517–530

[642] Janczyk W, Lebensztejn D, Wierzbicka-Rucinska A et al. Omega-3 Fatty acids therapy in children with nonalcoholic Fatty liver disease: a randomized controlled trial. J Pediatr 2015; 166: 1358–1363

[643] Pacifico L, Bonci E, Di Martino M et al. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2015; 25: 734–741

[644] Nobili V, Alisi A, Della Corte C et al. Docosahexaenoic acid for the treatment of fatty liver: randomised controlled trial in children. Nutr Metab Cardiovasc Dis 2013; 23: 1066–1070

[645] Nobili V, Bedogni G, Donati B et al. The I148M variant of PNPLA3 reduces the response to docosahexaenoic acid in children with non-alcoholic fatty liver disease. J Med Food 2013; 16: 957–960

[646] Zohrer E, Alisi A, Jahnel J et al. Efficacy of docosahexaenoic acid-choline-vitamin E in paediatric NASH: a randomized controlled clinical trial. Appl Physiol Nutr Metab 2017; 42: 948–954

[647] Schwimmer JB, Lavine JE, Wilson LA et al. In Children With Nonalcoholic Fatty Liver Disease, Cysteamine Bitartrate Delayed Release Improves Liver Enzymes but Does Not Reduce Disease Activity Scores. Gastroenterology 2016; 151: 1141–1154.e9

[648] Vajro P, Mandato C, Licenziati MR et al. Effects of Lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. J Pediatr Gastroenterol Nutr 2011; 52: 740–743

[649] Alisi A, Bedogni G, Baviera G et al. Randomised clinical trial: The beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2014; 39: 1276–1285

[650] Williams CD, Stengel J, Asike MI et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011; 140: 124–131

[651] Caussy C, Chen J, Alquiraish MH et al. Association Between Obesity and Discordance in Fibrosis Stage Determination by Magnetic Resonance vs Transient Elastography in Patients With Nonalcoholic Liver Disease. Clin Gastroenterol Hepatol 2018; 16: 1974–1982.e7

[652] Jayakumar S, Middleton MS, Lawitz EJ et al. Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib. J Hepatol 2019; 70: 133–141

[653] Hudert CA, Tzschatzsch H, Rudolph B et al. Tomoelastography for the Evaluation of Pediatric Nonalcoholic Fatty Liver Disease. Invest Radiol 2019; 54: 198–203

[654] Yang HR, Kim HR, Kim MJ et al. Noninvasive parameters and hepatic fibrosis scores in children with nonalcoholic fatty liver disease. World J Gastroenterol 2012; 18: 1525–1530

[655] Mansoor S, Yerian L, Kohli R et al. The evaluation of hepatic fibrosis scores in children with nonalcoholic fatty liver disease. Dig Dis Sci 2015; 60: 1440–1447

[656] Jackson JA, Konomi JV, Mendoza MV et al. Performance of fibrosis prediction scores in paediatric non-alcoholic fatty liver disease. J Paediatr Child Health 2018; 54: 172–176

[657] Alkhouri N, Mansoor S, Giammaria P et al. The development of the pediatric NAFLD fibrosis score (PNFS) to predict the presence of advanced fibrosis in children with nonalcoholic fatty liver disease. PLoS One 2014; 9: e104558

[658] Nobili V, Alisi A, Vania A et al. The pediatric NAFLD fibrosis index: a predictor of liver fibrosis in children with non-alcoholic fatty liver disease. BMC Med 2009; 7: 21

[659] Nobili V, Vizzutti F, Arena U et al. Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. Hepatology 2008; 48: 442–448

[660] Garcovich M, Veraldi S, Di Stasio E et al. Liver Stiffness in Pediatric Patients with Fatty Liver Disease: Diagnostic Accuracy and Reproducibility of Shear-Wave Elastography. Radiology 2017; 283: 820–827

[661] Hudert CA, Tzschatzsch H, Guo J et al. US Time-Harmonic Elastography: Detection of Liver Fibrosis in Adolescents with Extreme Obesity with Nonalcoholic Fatty Liver Disease. Radiology 2018; 288: 99–106

[662] Schwimmer JB, Behling C, Angeles JE et al. Magnetic resonance elastography measured shear stiffness as a biomarker of fibrosis in pediatric nonalcoholic fatty liver disease. Hepatology 2017; 66: 1474–1485

[663] Castera L, Foucher J, Bernard PH et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010; 51: 828–835

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