Clinical Practice Guidelines

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EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update[☆]

European Association for the Study of the Liver[*]

Summary

Non-invasive tests are increasingly being used to improve the diagnosis and prognostication of chronic liver diseases across aetiologies. Herein, we provide the latest update to the EASL Clinical Practice Guidelines on the use of non-invasive tests for the evaluation of liver disease severity and prognosis, focusing on the topics for which relevant evidence has been published in the last 5 years.

Introduction

Liver fibrosis development marks a turning point in chronic liver disease and its presence and severity correlate with prognosis across aetiologies.[1–3] The presence of cirrhosis identifies patients who are at risk of developing clinical decompensation and liver-related mortality,[4] and who are at the highest risk of developing hepatocellular carcinoma, irrespective of the aetiology of chronic liver disease. Liver biopsy is still the reference standard for the assessment of liver fibrosis and allows for a detailed evaluation of the localisation and amount of fibrosis. The evidence supporting the use of liver biopsy has been reviewed in detail previously.[5] Although it provides extensive information and remains a key tool in hepatology, the liver biopsy specimen size has to be long enough and has to be interpreted by experts to provide reliable information.[6] In the field of non-alcoholic steatohepatitis (NASH), variability among pathologists exists.[7] In addition to these technical considerations, liver biopsy is invasive and can lead, even if rarely, to severe complications. This, added to its relatively high cost, make non-invasive, repeatable and ideally cheaper alternative tools for the assessment of fibrosis highly desirable. Importantly, diagnostic measures of fibrosis in chronic liver disease should have low inter- and intra-operator variance in order to allow a comparison over time, since fibrosis is a dynamic process,[8] which can regress. Non-invasive tests (NITs) should also provide prognostic information beyond fibrosis stage and allow for monitoring of liver fibrosis and its complications.

The available NITs for the diagnosis and staging of liver fibrosis have been reviewed extensively elsewhere and in the previous EASL-ALEH clinical practice guidelines (CPGs),[5] and a complete description is beyond the scope of the present update.

In brief, NITs for the assessment of chronic liver disease can be classified into:

a) blood-based tests (serum markers of fibrosis; laboratory variables);
b) methods assessing physical properties of the liver tissue (*e.g.* liver stiffness; attenuation; viscosity);
c) imaging methods assessing the anatomy of the liver and other abdominal organs. These approaches can be considered complementary in several clinical scenarios. It should be underlined that NITs, liver biopsy/invasive diagnostic methods, and clinical acumen have to be integrated to achieve correct diagnoses and risk stratification in chronic liver diseases.

Considerations on diagnostic accuracy, advantages and limitations of NITs for the assessment of chronic liver disease

It has to be underlined that the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of a test depend on the prevalence of the condition under evaluation in the referral population.[9] The accuracy of diagnostic tests for fibrosis and steatosis in chronic liver disease is usually evaluated by comparing their sensitivity and specificity and area under the receiver operator characteristic curve (AUROC) with liver biopsy as the reference standard. However, liver biopsy is not a perfect reference standard (see above), and it has been shown that an AUROC >0.90 is not achievable even for a perfect biomarker.[10]

A test should be able to correctly classify at least 80% of patients, and cut-offs with high sensitivity or high specificity should be chosen according to the clinical scenario (*e.g.* very sensitive cut-off avoiding false negatives if a given condition – *e.g.* cirrhosis – has to be ruled-out; Table 1). An AUROC below 0.80 is generally considered of too poor discriminatory accuracy to be of value in clinical practice. The calibration, or variance (goodness-of-fit, inter- or intra-operator variance) of a NIT is also important. Tests with poor reproducibility will result in imprecise measurements of little value for individual decision making. None of the existing NITs are ideal, and each of them has specific advantages and limitations.

There are several critical issues that should be considered when using NITs: availability, cost, and "context of use". For instance, non-patented serum biomarkers, which are based on simple, inexpensive and widely available parameters, are well suited for use by non-specialists for testing for liver fibrosis in

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Table 1. Common measures for evaluating the diagnostic accuracy of non-invasive fibrosis tests.

Measures	
Sensitivity	Probability that a patient with the condition (*e.g.* advanced fibrosis) tests positive
Specificity	Probability that a patient without the condition tests negative
Positive predictive value	Probability that a patient who tests positive has the condition
Negative predictive value	Probability that a patient who tests negative does not have the condition
Area under the receiver operating curve	The diagnostic ability of a binary classifier at a specific cut-off, *i.e.* the probability that this classifier will correctly rank a randomly chosen person with the disease higher than a randomly chosen person without the disease
Positive likelihood ratio	How many times more likely positive index test results are in the diseased group compared to the non-diseased group. Estimated as sensitivity/(1−specificity)
Negative likelihood ratio	How many times less likely negative index test results are in the diseased group compared to the non-diseased group. Estimated as (1−sensitivity)/specificity

large populations in primary healthcare settings or diabetes clinics. On the contrary, sophisticated techniques like magnetic resonance elastography (MRE), which are time consuming and costly with limited availability, are more suited for use by specialists in tertiary referral centres and for research purposes. In addition, when evaluating the performance of NITs, the context in which they have been validated and applicability, which is defined as the sum of reliability (the percentage of interpretable tests) plus failure rate (absence of test results), should be taken into account.

Generally, non-patented serum-based tests are highly applicable (>95%) and reproducible among different centres, but their results can be influenced by extrahepatic chronic diseases. Further, most NITs were developed and validated in secondary or tertiary settings, not tested for a context of use in primary care or the general population.

Liver stiffness measurement can be obtained by different methods (stand-alone bedside device: vibration controlled transient elastography [TE]; techniques integrated in ultrasound devices: point-shear wave elastography (pSWE), bidimensional shear wave elastography (2D-SWE); and MRE. TE is the most widely validated and available. TE using the appropriate probe and the other ultrasound-based measurements have an applicability of >95% (in patients who are not morbidly obese), provide results in real time and only take a few minutes to be performed. In addition, they require a relatively short training. However, liver stiffness is a physical property of the tissue, which depends not only on the amount of liver fibrosis but also on several other factors. Therefore, results of liver stiffness measurement (LSM) can overestimate fibrosis in case of inflammation, obstructive cholestasis, food ingestion, exercise, or venous congestion. These should be carefully excluded to avoid misdiagnosis. Meal ingestion increases liver stiffness values irrespective of the method used for its measurement. A minimum of 2 hours fasting was previously recommended.[5] However, several studies have since shown that return to normal values required at least 3 hours.[11–13] Therefore, a minimum of 3 hours fasting is required for a correct measurement and interpretation. Additional details and recommendations can be found in the previous version of the EASL CPGs on NITs for chronic liver disease.[5] They are provided in the supplementary information.

Imaging methods routinely used in chronic liver disease include ultrasound-based techniques, computerised tomography (CT)-based techniques and magnetic resonance (MR)-based techniques. They require specific devices and training and suffer from technique-specific limitations (in brief: ultrasound: operator-dependent; abdominal air and obesity limit exploration; CT scan: exposure to ionising radiation; MR: impossible in case of old metal prosthesis; cost still elevated, limited availability). Standard imaging methods did not prove accurate to diagnose initial stages of fibrosis.

General limitations of NITs include a suboptimal accuracy to diagnose mild and moderate fibrosis, and to adequately discriminate between adjacent stages of fibrosis;[5] further, we still lack NITs to diagnose subclinical hepatic inflammation and ballooning, and to mirror the exact severity of portal hypertension in compensated advanced chronic liver disease (cACLD) (Box 1). Specific advantages and limitations of the individual tests are described extensively elsewhere,[5] and are summarised in Table 2. Finally, the test-retest reliability of NITs and the potential impact of this reliability on their use remain incompletely studied and should be the object of future research.

Methodology used for the development of the present CPGs

Given the numerous recent publications reporting on the accuracy of existing and novel NITs to assess liver disease, the European Association for the study of Liver Disease (EASL) decided to update the previous CPGs.[5] The EASL Governing Board has involved a panel of experts in this field to elaborate on the present CPGs according to the new format recently adopted, based on PICO (**P** Patient, Population, or Problem; **I** Intervention, Prognostic Factor, or Exposure; **C** Comparison or Intervention (if appropriate), **O** Outcome) questions.[14] These CPGs are directed at consultant hepatologists, specialists in training, and general practitioners and refer specifically to adult patients. Their purpose is to provide guidance on the best available evidence on the use of NITs to assess chronic liver disease.

The panel has initially established the most relevant topics that needed to be addressed and updated taking into account the content of the previous EASL guidelines on this topic[5] and the

Box 1. Definition of compensated advanced chronic liver disease.

The term cACLD has been proposed as an alternative term for patients with chronic liver disease at risk of developing clinically significant portal hypertension, to better reflect that the spectrum of severe fibrosis and cirrhosis is a continuum in asymptomatic patients, and that distinguishing between the 2 is often not possible on clinical grounds. According to the Baveno VI consensus conference, LSM ≥10 kPa is suggestive of cACLD and ≥15 kPa is highly suggestive of cACLD.

cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement.

Table 2. Advantages and disadvantages of the main non-invasive tests used to diagnose and stage liver fibrosis.

	Serum markers		Transient elastography	pSWE	2D-SWE	MRE
Advantages	Non-patented • Good reproducibility • High applicability (95%) • No cost and wide availability • Well validated • Can be performed in the outpatient clinic • Prognostic value of some has been validated for some aetiologies of chronic liver disease on population level	Patented Good reproducibility • High applicability (95%) • Well validated • Can be performed in the outpatient clinic • Prognostic value of some has been validated for some aetiologies of chronic liver disease	• Most widely used and validated technique • Point-of-care (bedside; rapid, easy to learn) • Quality criteria well defined • Good reproducibility • High performance for cirrhosis (AUROC >0.9) • Prognostic value in compensated cirrhosis well validated	• Can be performed in combination with regular ultrasound if the device is provided with adequate software • ROI smaller than TE and location chosen by the operator • Higher applicability than TE (ascites and obesity) • Performance equivalent to that of TE for advancedfibrosis and cirrhosis • Prognostic value in cirrhosis • High applicability for spleen stiffness measurement	• Can be performed in combination with regular ultrasound if the device is provided with adequate software • Large ROI that can be adjusted in size and location chosen by the operator • Measures liver stiffness in real time • Good applicability • High performance for the diagnosis of significant fibrosis and cirrhosis • Prognostic value in compensated cirrhosis	• Can be implemented on a regular MRI machine • Examination of the whole liver • Higher applicability than TE (ascites and obesity) • High performance for the earlier fibrosis stage and for diagnosis of cirrhosis
Disadvantages	• Non-liver-specific • Performance not as good as TE and patented serum markers • False positive results with FIB-4 and NFS in case of age>65 yrs	• Cost • Non-liver-specific • Performance not as good as TE for cirrhosis • False positive results in case of extrahepatic inflammatory conditions, profibrotic, extrahepatic disease and other (*e.g.* haemolysis, Gilbert syndrome)	• Requires a dedicated device • ROI cannot be chosen • Applicability (>95%) lower than serum biomarker: (obesity, ascites, operator experience) • False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake and excessive alcohol intake	• False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake and excessive alcohol intake	• False positive in case of acute hepatitis, extrahepatic cholestasis, liver congestion, food intake and excessive alcohol intake	• Not applicable in case of iron overload • Requires a MRI facility • Time consuming • Costly • No clear data on prognostic value

2D-SWE, bidimensional shear wave elastography; FIB-4, fibrosis-4; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NFS, NAFLD fibrosis score; pSWE, point-shear wave elastography; ROI, region of interest; TE, transient elastography.

Table 3. This table shows that for the same value of specificity and sensitivity, the negative predictive value decreases and the positive predictive value increases with increasing prevalence of advanced fibrosis.

Prevalence of advanced fibrosis	Sensitivity	Specificity	Positive predictive value	Negative predictive value
10%	80%	80%	31%	97%
20%	80%	80%	50%	94%
30%	80%	80%	63%	90%
40%	80%	80%	73%	86%
50%	80%	80%	80%	80%

evidence that has been published since their publication (April 2015) until October 2020. The panel decided to structure the guidelines based on the aetiology of liver disease, since this allows for comparisons of homogeneous groups of patients. The complexity of cases of multifactorial disease was discussed, but the panel felt that evidence in this field is not strong enough to drive recommendations on NIT use in this scenario; the recommendations pertinent to the main aetiology responsible for liver disease should be applied, considering additional caution in the interpretation of the results. The main topics that the panel decided to address include the following, for which novel data are available:

a) identification of cases of advanced liver fibrosis in the general population, which requires special considerations given the low prevalence in this setting;
b) assessment of liver disease severity and prognosis in patients with excessive use of alcohol, since this is an increasing burden worldwide;[15]
c) assessment of liver disease severity and prognosis in patients with chronic hepatitis C after achieving sustained virological response, since guidance on this topic is an unmet need in hepatology;
d) assessment of liver disease severity and prognosis in patients with non-alcoholic fatty liver disease (NAFLD)/NASH, as well as monitoring liver lesions under treatment, since the incidence of NAFLD is massively increasing worldwide and novel therapies for NASH are being tested and will require the identification of the correct group of patients;[16]
e) assessment of liver disease severity and prognosis in patients with cholestatic and autoimmune liver disease (primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC], autoimmune hepatitis [AIH]), since these are emerging causes of liver disease[16] and were only partly addressed in the previous guidelines;
f) assessment of cACLD and portal hypertension, since the identification of this stage of the disease is key to improving patient outcomes.[17]

The Panel decided to develop PICO questions with a homogeneous format for each section. PICO questions were sent to the Delphi panel comprising 19 international experts in hepatology, pathology, radiology and primary care from Europe, Asia and America, and 1 patient, and were commented on and voted on using an online platform. The consensus of over 75% of voting members of the Delphi panel was needed to consider a question approved.

Based on the PICO questions, a literature search was performed using PubMed, and expanding to Embase, Google Scholar and Scopus when needed. References from papers were searched and identified further. The initial key words were: “Non-invasive test” OR “elastography” OR “imaging” OR “serum markers” OR “magnetic resonance” OR “computerized tomography” AND “liver cirrhosis” OR “chronic liver disease” OR “steatosis” OR “fibrosis”. Further, more specific key words were also utilised, such as: “NAFLD”, “NASH”, “SVR”, “PSC”, “PBC”, “autoimmune hepatitis”, “decompensation”, “portal hypertension”, “cACLD”, “CSPH”, “varices” for each specific topic of the guideline. The selection of references was based on appropriateness of study design, number of patients, and publication in peer review journals. Whenever available, meta-analyses were used; otherwise, original data were used. The resulting literature database was made available to all members of the panel.

The level of evidence (LoE) - based on the Oxford Centre for Evidence-Based Medicine (OCEBM) and the QUADAS-2 tool for accuracy of diagnostic studies – was used as a measure of the quality of the evidence.[18]

Each expert took responsibility and made proposals for statements for a specific section of the guideline and shared tables of evidence and text with the full panel.

The panel met on 2 occasions, once during an international meeting and once at the EASL premises in Geneva, as well as having 6 *ad hoc* teleconferences for discussion and voting.

All recommendations were discussed and approved by all participants. The strength of the recommendations in these guidelines has been graded according to the OCEBM.[19] The LoE classifications and recommendations are therefore based on 2 categories: strong or weak. The CPGs were reviewed and voted on by the Delphi panel. The results of voting were stratified as follows: less than 50% approval: re-write recommendation and resubmit to the Delphi panel; 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel; 75-90% approval: no need to re-write the recommendation but the document will take into account the comments; ≥ 90% approval: assumed as consensus, no change needed but small corrections possible.

The suggested changes were taken into account in a revised version, which was finally sent to the attention of the EASL Governing Board together with a response letter regarding each of the points raised by the Delphi panel members. The level of Delphi panel agreement on each of the statements and recommendations is shown in the Appendix.

The recommendations were subsequently approved by the EASL Governing Board. This document is intended to be valid until April 2025 unless the EASL Governing Board indicates the need for an earlier update.

General population

How accurate are non-invasive scores compared to liver biopsy in patients at risk of liver disease from low-prevalence populations?

The development, validation and widespread use of non-invasive fibrosis tests has changed clinical practice in

Recommendations

- Non-invasive fibrosis tests should be used for ruling out rather than diagnosing advanced fibrosis in low-prevalence populations **(LoE 1, Strong recommendation).**
- Non-invasive fibrosis tests should be preferentially used in patients at risk of advanced liver fibrosis (such as patients with metabolic risk factors and/or harmful use of alcohol) and not in unselected general populations **(LoE 2, Strong recommendation).**
- ALT, AST and platelet count should be part of the routine investigations in primary care in patients with suspected liver disease, so that simple non-invasive scores can be readily calculated **(LoE 2, Strong recommendation).**
- The automatic calculation and systematic reporting of simple non-invasive fibrosis tests such as FIB-4, in populations at risk of liver fibrosis (individuals with metabolic risk factors and/or harmful use of alcohol) in primary care, is recommended in order to improve risk stratification and linkage to care **(LoE 2, Strong recommendation).**

hepatology and has reduced the need for liver biopsies. Moreover, these tests are becoming increasingly available, while at the same time the epidemiology of chronic liver disease is changing, with NAFLD and alcohol-related liver disease (ALD) becoming the main cause of liver-related morbidity and mortality. As a consequence of the above, the context of use for non-invasive fibrosis tests is changing; they are increasingly used in populations at risk of liver disease to test for the presence of advanced fibrosis. The prevalence of advanced fibrosis in such settings is considerably lower compared to the prevalence seen in secondary/tertiary care, where these tests have been developed and validated. In a large meta-analysis of the diagnostic accuracy of NITs, which almost exclusively included studies performed in secondary care, the prevalence of advanced fibrosis was 37%, 29%, 19% and 51% in patients with chronic hepatitis B, chronic hepatitis C, NAFLD and ALD, respectively.[20] Particularly for NAFLD and ALD, the prevalence of advanced fibrosis in unselected populations at risk is <5%[21] and <10%,[22] respectively. The different context of use therefore raises the question of the diagnostic performance of these tests in populations with low prevalence of advanced fibrosis.

It is very likely that non-invasive fibrosis tests will have lower sensitivity and higher specificity when applied in populations with lower disease prevalence due to the well described spectrum effect,[9] as shown in a study in patients with ALD from a primary and secondary care setting.[22] Conversely, in secondary/tertiary care settings, where patients have more advanced disease, the PPV of NITs is expected to be higher (higher *a priori* probability of observing true positive cases) (see Table 3). Therefore, in populations of low prevalence, NITs are far better for ruling out rather than diagnosing the presence of advanced fibrosis. This indicates the need for at least 2 tiers of non-invasive fibrosis tests for selecting patients from low-prevalence populations for further investigations and follow-up in order to reduce false positive results. It also offers the possibility of using a simple non-invasive fibrosis test (such as fibrosis-4 [FIB-4]) in populations at risk of liver disease (such as patients with type 2 diabetes or potentially people living with HIV), to rule-out those with a low probability of having advanced fibrosis and prompt further testing for those with indeterminate and positive results. Automatic calculation of such tests when liver blood tests are requested can potentially improve risk stratification in patients at risk of advanced fibrosis. FIB-4 is simpler to calculate and performs better than other simple NITs in head-to-head comparisons, particularly in NAFLD. All simple NIT panels include aspartate aminotransferase (AST), therefore AST, together with alanine aminotransferase (ALT) and platelet count, should be routinely measured in primary care as part of the liver blood test panel.

Despite their potential to act as 'gate-keeping tests' in primary care liver fibrosis screening pathways, the simple fibrosis scores only include indirect markers of liver damage (AST, ALT), risk factors (age, BMI, diabetes) or liver function and portal hypertension (platelet count, cholesterol) and are not direct markers of liver fibrosis. Consequently, physicians should not blindly use FIB-4 or similar indirect NITs as singular decision tools;[23] due to their easy testing, repeated measurement can be performed, and this strategy is currently being evaluated.[24] If a suspicion of liver disease remains even after a normal NIT value, the patients should be referred for more accurate testing.

In order to minimise the spectrum effect, it is essential that NITs are applied to populations with risk factors for liver disease rather than unselected populations. This is because unselected populations have an increased range of potential differential diagnoses for positive results, which would normally be identified with closer patient evaluation and selection.[23] Moreover, it is essential that patients with abnormal liver blood tests are comprehensively investigated for the aetiology of the abnormality before or in parallel with non-invasive fibrosis assessment.[25]

Can non-invasive scores, serum markers, liver stiffness, and imaging methods improve identification of advanced fibrosis in patients at risk of liver disease from low-prevalence populations compared to clinical acumen?

Statement

- Non-invasive scores, serum markers, liver stiffness and imaging methods can identify advanced fibrosis in patients at risk from low-prevalence populations significantly better than clinical acumen alone **(LoE 1).**

Recommendations

- Individuals at risk of advanced fibrosis due to metabolic risk factors and/or harmful use of alcohol should be entered into appropriate risk stratification pathways using non-invasive fibrosis tests **(LoE 1, Strong recommendation).**
- The selection of NITs and the design of diagnostic pathways for testing low-prevalence populations for advanced fibrosis should be performed in consultation with a liver specialist **(LoE 3, Strong recommendation).**

There have been several studies of non-invasive fibrosis tests in populations with variable risk factors for liver disease, from unselected to patients with several predefined risk factors. In a systematic review that included 19 studies, in which 11 NITs were evaluated, the prevalence of advanced fibrosis depended on the risk factors of the included cohorts.[26] Two studies performed in the general population identified advanced fibrosis in 0.9% of participants using FibroTest™ (cut-off 0.59)[27] and 2% using FibroScan® (cut-off 9.6 kPa).[28] In studies targeting people at risk of NAFLD, the prevalence of advanced fibrosis ranged from 3.7% to 30%.[29] Significant fibrosis was present in 11-18% of people at risk of ALD.[30] A study performed in 4,021 young adults (mean age 24 years) using FibroScan®, revealed that 20% had suspected steatosis (controlled attenuation parameter [CAP] values ≥248 dB/m) and 2.7% suspicion of fibrosis (liver stiffness values ≥7.9 kPa).[31] The above estimates are based on NITs, therefore the true prevalence of advanced fibrosis in such populations is at least 50% lower, taking into account the low prevalence of the target condition which results in suboptimal PPVs of the NITs (Table 1).

Liver biopsy was performed in selected patients who had a positive NIT in some studies.[26,32–38] In contrast, no patients who tested negative were biopsied, making it impossible to calculate the specificity of NITs for advanced fibrosis in the context of low-prevalence populations. Conversely, not all patients with a positive test were biopsied and this could be due to a selection bias, leading to an overestimation of the sensitivity of non-invasive fibrosis tests in low-prevalence populations.

In a study that tested 128 patients from primary centres of municipal alcohol rehabilitation, liver biopsy was performed in all individuals and the prevalence of advanced fibrosis was 6%.[22] The specificities of enhanced liver fibrosis (ELF)™ (cut-off 10.5), FibroTest™ (cut-off 0.58), FibroScan® (cut-off 15 kPa) and 2D-SWE (cut-off 16.4 kPa) for advanced fibrosis were 97%, 93%, 97% and 97%, respectively, with sensitivities of 75%, 63%, 86% and 88%, respectively.

The implementation of pathways to test populations at risk of advanced fibrosis results in a significant increase in the detection of cases with advanced fibrosis/cirrhosis, compared to standard of care. In a study using FibroScan® in patients with hazardous alcohol intake or type 2 diabetes in 4 general practices, the number of patients with cirrhosis doubled compared to the period before study commencement.[38] In a community, pathways for patients with NAFLD using 2-tier non-invasive testing with FIB-4 followed by ELF™ in patients with indeterminate FIB-4 results, improved the detection of advanced fibrosis 4-fold and reduced unnecessary referrals by 88%.[37] Modelling suggests that only concordant NITs can produce diagnostic accuracy comparable to a liver biopsy and that currently single NITs do not have sufficient diagnostic accuracy, particularly for the diagnosis of cirrhosis.[39] Several cost-effectiveness analyses have shown that testing populations at risk for liver disease but with low prevalence of advanced fibrosis is cost-effective.[21,37,40–43,44]

The selection of a NIT in particular patients should be in accordance with the known indications and limitations of such tests (for instance avoid FibroTest™ in patients with Gilbert's or TE in patients with heart failure). It is therefore advisable that hepatologists are involved and consulted when NITs and pathways are designed and implemented in populations at risk outside secondary care. Fig. 1 summarises an algorithm that could be used for such a selection.

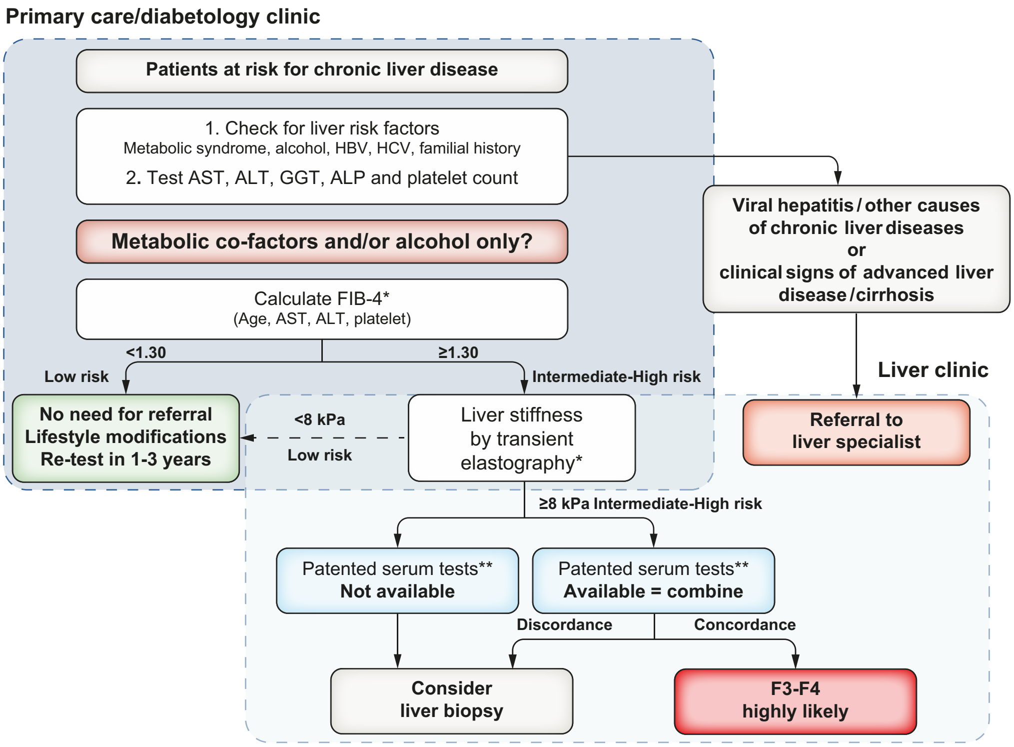

Fig. 1. Proposed use of NITs in patients observed in primary care or outside the liver clinic. As shown, FIB-4 can be used in patients with metabolic co-factors and/or alcoholic liver disease to identify patients requiring referral to the specialist liver clinic. *Transient elastography or FIB-4 may be performed before or after referral to liver specialist according to local availability and pathways. **Cut-offs to use: ELF™ 9.8 (NAFLD/ALD); FibroMeter 0.45 (NAFLD), Fibrotest 0.48 (NAFLD). ALD, alcohol-related liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; NAFLD, non-alcoholic fatty liver disease.

Alcohol-related liver disease

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for the diagnosis of ALD (liver fibrosis, alcoholic hepatitis and steatosis) in patients with chronic harmful alcohol use?

Recommendations

- In patients with ALD, LSM by TE <8 kPa is recommended to rule-out advanced fibrosis in clinical practice, with the following NITs as alternatives, if TE is not available **(LoE 3; strong recommendation).**
  - Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48
  - Non-patented tests: FIB-4 <1.3
- Upon referral of patients at risk of ALD, LSM by TE ≥12-15 kPa is recommended to rule-in advanced fibrosis, after considering causes of false positives **(LoE 2; strong recommendation).**
- In patients with elevated liver stiffness and biochemical evidence of hepatic inflammation (AST or GGT >2xULN), LSM by TE should be repeated after at least 1 week of alcohol abstinence or reduced drinking **(LoE 3; strong recommendation).**

Liver fibrosis

ALD is the dominant cause of liver-related mortality and morbidity worldwide.[45] Furthermore, patients with alcohol-related cirrhosis are diagnosed at later stages of disease, die at a younger age and are more likely to experience liver-related complications than patients with liver disease of any other aetiology.[46,47] Therefore, NITs for alcohol associated liver damage are appealing, as early disease detection could lead to reduced drinking, thereby interrupting disease progression.[48]

The most robust evidence involves TE for the diagnosis of advanced fibrosis in patients recruited from secondary and tertiary care centres. Since 2015, 6 single-aetiology studies,[49–52] 1 Cochrane meta-analysis,[53,54] and 2 individual patient data meta-analyses have assessed LSM by TE in ALD.[55] TE has excellent diagnostic accuracy for advanced fibrosis, with AUROCs above 0.90. For significant fibrosis, the diagnostic accuracy is good, with AUROCs around 0.85. Unfortunately, early diagnostic studies mostly assessed fibrosis using scoring systems developed for chronic viral hepatitis (METAVIR). These scores likely underestimate early stages of alcohol-related fibrosis, while for bridging fibrosis and cirrhosis, diagnostic estimates are probably reliable across histological fibrosis scoring systems. Therefore, our recommendations focus on advanced fibrosis.

The available evidence is mostly of moderate level, except 1 diagnostic test study at high level of evidence.[22] This study is also the only study to recruit patients from a primary care setting, which is why the main body of evidence concerns a population with a high prevalence of advanced fibrosis. A further concern of most early studies, is that most did not clearly exclude patients with obvious cirrhosis, thereby potentially overestimating diagnostic accuracies.

The Cochrane meta-analysis reported a 92% summary sensitivity for advanced fibrosis at a TE cut-off around 9.5 kPa (range 8.0 to 10.5 kPa)[53] while the most recent meta-analysis (n = 5,648 patients; ALD n = 946) found a sensitivity of 94% at an 8 kPa cut-off.[55] Therefore, we recommend ruling out advanced fibrosis in patients with TE below 8-10 kPa. The most recent individual patient data meta-analysis reported a specificity of 92% for advanced fibrosis at a cut-off of 15 kPa, and 89% for a 12 kPa cut-off, in line with the high-quality, single-centre study[22] which found a specificity of 95% for advanced fibrosis at 15 kPa, and a corresponding PPV of 84% (23% prevalence of advanced fibrosis). Consequently, advanced fibrosis may be suspected in patients with ALD and TE ≥12-15 kPa, but only after excluding causes of false positives.

Other technologies for LSM, pSWE and 2D-SWE, may perform similarly to TE, but only 1 centre has performed a head-to-head comparison between TE and 2D-SWE (Supersonic Aixplorer)[56] and only 2 recent studies have assessed pSWE using the Virtual Touch technique (Siemens Acuson 2000), with no comparator.[57,58]

It has been debated whether active use of alcohol may cause false positive LSMs. While abstinence reduces liver stiffness in detoxification studies, this reduction is paralleled by a reduction in biochemical markers of liver inflammation such as AST and gamma glutamyltransferase (GGT).[59–62] Consequently, it is the alcohol-related steatohepatitis rather than alcohol *per se*, which increases liver stiffness. In 1 study, a week of detoxification reduced TE by 22%, and TE correlated with AST and GGT both at baseline and after detoxification.[62] A second study reported a 16% decrease in TE after 5 days of hospitalisation for detoxification, in parallel with a 48% decrease in AST, from 77 to 40 U/L.[60] In outpatients, 4 weeks of detoxification led to a reduction in TE of 25%, together with a 29% reduction in AST, from 42 to 30 U/L, and a 58% reduction in GGT, from 153 to 64 U/L. In studies of diagnostic accuracy, the optimal cut-off values are 2-3 kPa higher in those with AST elevation 1-2x the upper limit of normal (ULN), and even more in patients with elevations >2x ULN.[49,52] In contrast, in an outpatient setting in patients with ALD and little biochemical evidence of hepatic inflammation, active drinking was not a predictor of false positive TE measurements. Consequently, AST of more than twice the ULN should raise caution for false positive LSMs. In patients with elevated liver stiffness *and* biochemical evidence of liver inflammation, we therefore suggest repeating the measurement after at least 1 week of abstinence or reduced drinking, in parallel with biochemical retesting.

Several serum markers have also been evaluated for diagnosing alcohol-related liver fibrosis, both patented such as FibroTest®, Hepascore, FibroMeter™ and ELF™ test; and non-commercial algorithms of routine biochemistry such as FIB-4 and Forns'. FIB-4 and Forns' have good diagnostic accuracies for advanced fibrosis. Their low cost and wide accessibility make them particularly suited to rule-out advanced fibrosis in low-prevalence populations. This is supported by a NPV of 95% for FIB-4 <3.25, and a NPV of 97% for Forns' index <6.8, in a study of 128 primary care patients with a 6% prevalence of advanced fibrosis.[22] The value for ruling out advanced fibrosis in primary care is however only evaluated by 1 study, so independent validation is required. Due to risk of misclassifications, the non-patented fibrosis scores cannot be recommended to rule-in advanced fibrosis.

Patented markers have higher diagnostic accuracies than non-patented markers, with AUROCs similar or close to LSM by

TE, but cut-offs vary substantially from study to study and would therefore need to be aligned and validated. There is a similar lack of studies investigating combination markers, either in parallel,[51] or sequential.[22] In cases of discrepancy between TE and patented serum markers, TE seems more reliable.[22,51]

Cost-benefit of using NITs for alcohol-related fibrosis

Of note, recent evidence suggests that TE and the ELF™ test are cost-beneficial in patients who consume excess alcohol.[41,63] The 2 studies both used 40-year-old males as exemplar, from Scandinavia and Spain, respectively. Both studies found cost-benefit of a sequential strategy using ELF™ followed by TE, if ELF™ is positive. The incremental cost-effectiveness ratios were €13,400 per quality-adjusted life year,[63] and $5,387-$8,430 per quality-adjusted life year.[41] However, single use of TE was the most cost-beneficial strategy in secondary care in 1 study,[41] while annual ELF™ alone was the optimal strategy for patients with ALD in another study.[63]

Alcoholic hepatitis

The existing evidence since 2015 on non-invasive markers for diagnosing alcoholic hepatitis consists of only 2 studies of moderate evidence on cytokeratin-18 (CK-18)-based markers of cell-death,[60,64] and 1 study on the AshTest.[65] The markers show moderate diagnostic accuracies (AUROCs of 0.84 and below), and the 3 studies are heterogeneous in their histological definition of alcoholic hepatitis, and in their patient cohorts. It is therefore not possible to recommend any NIT for use in patients with suspected alcoholic hepatitis.

In 1 study, both total (M65) and caspase-cleaved CK-18 (M30) correlated with histological ballooning, but they had inadequate diagnostic accuracy (AUROCs <0.80) for detecting patients with steatohepatitis, defined as a NAFLD activity score (NAS) ≥5.[60] Since NAS includes steatosis, in addition to ballooning and lobular inflammation, and since NAS has been designed for NAFLD which, although similar, is not histologically identical to ALD, the score is probably not a suitable outcome measure for alcohol-related hepatic inflammatory activity.

Another study[64] tested the CK-18 markers M65 and M30 to diagnose alcoholic hepatitis taking liver biopsy and the AHHS scoring system[66] as a reference standard. The cut-offs of M65 and M30 for ruling in alcoholic hepatitis were far higher than the cut-offs reported for diagnosing steatohepatitis, indicating a more severely ill patient population.

Steatosis

While steatosis remains a key feature of acute alcohol-related liver injury, it is not possible to recommend any NITs for diagnosing alcohol-related steatosis, as only 1 study exists.[22] They evaluated CAP using the FibroScan equipment. While CAP had superior diagnostic accuracy compared to bright liver echo pattern assessed by ultrasound, the diagnostic accuracies were modest.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy, HVPG, Child-Pugh or MELD score for the prediction of liver-related outcomes in patients with chronic harmful alcohol use?

Evidence from mixed-aetiology studies suggests that NITs are prognostic in patients with compensated cirrhosis/cACLD (more details on this definition are provided elsewhere in this guideline). This is very likely the case for alcohol-aetiology as well, although there is just 1 prognostic single-aetiology study.[67] However, this study only reported FibroTest, FibroMeter and Hepascore, assessed liver-related death as the only outcome, and included almost one-third with cirrhosis at baseline, not clearly excluding those with evidence of decompensated disease. The prognostic values (AUROC for 8-year survival or non-liver disease-related death) were 0.79 for FibroTest, 0.80 for Fibrometer, and 0.78 for Hepascore.

Since 2015, 12 studies have explored prognostic markers in cohorts of patients with alcohol-related cirrhosis, either decompensated or a combination of decompensated and compensated cirrhosis.[60,68–78] All studies are explorative, and most found that model for end-stage liver disease (MELD) scores performed similarly or better than the marker under investigation. MELD remains the recommended prognostic tool for prediction of short-term mortality and morbidity in decompensated cirrhosis.

Due to scarce evidence, we cannot at this point make any aetiology-specific recommendations regarding prognostic markers in alcohol-related, compensated liver disease.

HCV post-SVR/post-antiviral therapy

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for staging liver fibrosis in patients with HCV-related cACLD who achieved sustained virological response?

Statement

- Non-invasive scores and LSM by TE and other elastography methods are not accurate in detecting fibrosis regression after SVR in HCV patients diagnosed with cACLD prior to antiviral therapy **(LoE 3)**.

Recommendations

- The routine use of non-invasive scores and LSM by TE and other elastography methods is currently not recommended to detect fibrosis regression after SVR in HCV patients **(LoE 3; strong recommendation).**
- Cut-offs of LSM by TE used in patients with untreated HCV should not be used to stage liver fibrosis after SVR **(LoE 4; strong recommendation).**

Regression of fibrosis in HCV patients with cACLD has been described after sustained virological response (SVR) in patients treated with interferon-based therapies. A study in 38 HCV patients with cirrhosis with paired pre- and post-treatment liver biopsies (median interval 79 months) showed cirrhosis regression (decrease ≥1 METAVIR stage) in 61% of patients.[79] With the advent of direct-acting antivirals (DAAs) leading to SVR in most HCV patients with cirrhosis,[80] fibrosis regression will likely become even more common. However, post-SVR liver biopsies are not the standard of care. It is therefore a critical issue whether non-invasive methods can capture fibrosis regression and stage fibrosis after SVR in HCV patients with cACLD who still have residual risk of liver-related complications.

A recent meta-analysis including 24 studies (n = 2,934 HCV patients, SVR 75%, DAAs only n = 6) with paired LSM by TE, reported a median relative LSM decline from baseline of 28% (IQR 21.8–34.8), 6–12 months after the end-of-therapy in SVR patients, whereas no change was observed in non-SVR patients.[81] In the subgroup of 261 SVR patients classified as having advanced fibrosis or cirrhosis (LSM >9.5 kPa), 47% had post-treatment LSM <9.5 kPa.[81] However, most of the included studies in this meta-analysis were retrospective, interferon-based, with small sample sizes, and short follow-up after SVR. In addition, LSM confounders such as NAFLD, diabetes and alcohol were not taken into account. Most importantly, only 187 patients had biopsy-proven cirrhosis and none had paired liver biopsies. It is consequently impossible to conclude whether the observed LSM decrease is related to resolution of hepatic inflammation or to regression of liver fibrosis. As for DAAs, in a large real-life Italian cohort of 749 HCV patients with cACLD treated with DAAs (SVR 97%), a significant LSM decrease was observed between baseline and SVR12 (mean LSM 19.3 (±11.2) *vs.* 14.2 (±11.7) kPa, respectively) but with a short follow-up and no post-SVR liver biopsies.[82] Interestingly, in a study[83] with paired pre- and post-treatment LSM and liver biopsies (median interval 61 months) in 33 HCV patients with cirrhosis, the diagnostic accuracy of TE for diagnosing cirrhosis after SVR (cut-off 12 kPa) was suboptimal (95% specificity, but 61% sensitivity, meaning low value for ruling out cirrhosis). Another study in 112 patients with recurrent HCV infection after orthotopic liver transplantation (LT) and with paired liver biopsies 12 months after SVR (84 with paired LSM by TE; 34 with cirrhosis), showed that LSM decrease was significantly higher in patients with fibrosis regression compared to those without (47% *vs.* 30%, $p = 0.02$).[84] However, the percentage of LSM decrease did not accurately predict fibrosis regression (AUROC = 0.65).[84] The same study also demonstrated that LSM by TE 1 year after SVR can accurately predict the presence of advanced fibrosis with an AUROC of 0.90. The best LSM cut-offs to rule-out and rule-in advanced fibrosis were, respectively, 10.6 and 14 kPa.[84] Another issue is the significant variations in LSM using TE over time reported in untreated patients with chronic liver disease.[85]

Similarly, post-SVR LSM decrease has been reported using other devices such as pSWE (Virtual Touch)[86–88] and MRE.[89] Along this line, post-SVR decreases have been reported with non-invasive serum biomarkers like APRI, FIB-4 or ELF™.[84,86,88,90] These studies, despite contrasting results,[90] also showed a good diagnostic accuracy of LSM by pSWE (AUROC from 0.88 and 0.91)[87,88] and of APRI, FIB-4 and ELF™[84,86] for the diagnosis of advanced fibrosis after SVR, using liver biopsy as a reference. It should be kept in mind, however, that thresholds for LSM and NITs used in untreated viral hepatitis have proven inaccurate after SVR,[83,84,86,87] and it is necessary to validate the newer (lower) cut-offs in larger studies. Based on the high specificity, and awaiting further data, it seems reasonable to consider that patients with LSM >12 kPa after SVR have a high likelihood of persistent cACLD.

In summary, altogether these results question the accuracy of NITs to predict fibrosis regression and the presence of cACLD after SVR. Studies with larger sample sizes and longer follow-up are necessary to establish the role of non-invasive methods in the follow-up of HCV patients with cACLD after viral clearance.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy, HVPG, Child-Pugh or MELD score for the prediction of clinical outcomes (decompensation; HCC) in patients with HCV-related cACLD who achieved sustained virological response?

Statement

- In patients with cACLD previous to antiviral therapy for HCV, LSM post-SVR could be helpful to refine the stratification of residual risk of liver-related complications; yearly repetition of LSM can be carried out while we await confirmatory data **(LoE 3).**

Recommendations

- Patients with cACLD previous to antiviral therapy for HCV should continue to be monitored for HCC and portal hypertension irrespective of the results of NITs post-SVR **(LoE 3; strong recommendation).**

In patients with HCV-related cACLD, SVR reduces the risk of liver-related complications such as hepatic decompensation, hepatocellular carcinoma (HCC) as well as all-cause mortality.[91,92] However a residual risk of liver-related complications still persists after SVR, particularly HCC occurrence, and the role of non-invasive tools in stratifying this risk remains debated.[91,92]

The presence of clinically significant portal hypertension (CSPH, hepatic venous pressure gradient [HVPG] ≥10 mmHg), has been shown to be the strongest prognostic determinant in patients with cACLD.[93] It has been established that an HVPG reduction of 10% or more after therapy is associated with a decreased risk of first variceal haemorrhage.[17,94]

In a multicentre prospective study of 226 HCV patients with cirrhosis and CSPH, SVR after DAA therapy significantly reduced HVPG (>10% in 62% of patients) measured 24 weeks after therapy, compared to baseline.[95] However, CSPH persisted in most patients (78%) despite SVR, indicating persistent risk of decompensation. In another recent retrospective single-centre study in 90 HCV patients with portal hypertension (HVPG ≥6 mmHg), and SVR after DAA, a HVPG reduction ≥10% was reported in 67 patients with pre-treatment CSPH, which translated into a clinical benefit. In particular, patients who were compensated on inclusion and showed a HVPG decrease ≥10%, were completely protected from hepatic decompensation in the follow-up.[96] In the same cohort published earlier in 57 HCV patients with paired HVPG and TE, before and after SVR, the relative change in LSM was an independent predictor of a HVPG decrease >10% in the subgroup of patients (n = 40) with baseline CSPH.[97] However, the performance of TE for diagnosing an HVPG reduction ≥10% was inadequate (AUROC <0.8).[96] Similarly, in the Lens study,[95] LSM decreased markedly at SVR24 and SVR96,[98] but changes in LSM did not correlate with HVPG changes, nor with the risk of clinical decompensation. CSPH persisted in up to 53–65% of patients at SVR96.[98] Despite these negative data, LSM after SVR had a good accuracy for the diagnosis of post-treatment CSPH, with an AUROC ranging from 0.80[95] to 0.93.[96] Values of LSM by TE over

21–23 kPa were invariably associated with persistence of CSPH, while low LSM values did not rule-out CSPH (30% of patients with LSM <13.6 kPa still had CSPH).[95,96] Conversely, after orthotopic LT, 1 year post-SVR LSM had a high diagnostic accuracy to rule-out CSPH (AUROC = 0.88).[84] Consistent with these data, a cohort study on 230 HCV cirrhotic patients who achieved SVR on DAAs (151 of whom had follow-up LSM and upper endoscopy) suggested that LSM after SVR could predict varices progression after 36 months.[99]

In a large retrospective single-centre cohort of 505 HCV patients with cirrhosis treated with DAAs and followed for a median time of 25 months, baseline LSM using TE independently predicted the occurrence of HCC at 3 years (20% *vs.* 5% in patients with LSM >30 kPa *vs.* LSM ≤30 kPa, respectively).[100] When replacing LSM by FIB-4 in the model, FIB-4 ≥9 remained an independent predictor of HCC.[100] Another cohort study in 139 HCV patients with cirrhosis reported a lower LSM reduction, using TE, in patients developing HCC (median follow-up 15 months) with a difference in LSM from baseline to end-of-therapy lower than -30% being an independent predictor of HCC development.[101] Finally, a cohort study in 572 HCV patients with cACLD, with SVR after DAA treatment, showed that few patients (5.6%) developed liver decompensation – all of them with baseline LSM >20 kPa – and platelet count and LSM at 1 year of follow-up were independent predictors of HCC. Notably, the authors found that a follow-up LSM value <10 kPa, obtained in 40% of patients, identified a cohort at very low risk of HCC (<1/100 patient-years).[102]

Even if available evidence suggests that post-SVR LSM, using TE, can predict CSPH and HCC occurrence, given the significant LSM decrease observed after SVR, lower cut-offs should be defined and validated. Recent evidence suggests a decrease in liver-related events in patients with a decrease of LSM after SVR.[103] Further studies are needed to investigate the ability of post-SVR NITs to predict hepatic decompensation and death; we consider it reasonable to perform yearly repetition of LSM while we await further confirmatory data.

NAFLD/NASH

How accurate are non-invasive scores and imaging methods compared to liver biopsy for the diagnosis of steatosis in patients with metabolic risk factors and/or suspected NAFLD?

Statements

- CAP is a promising point-of-care technique for rapid and standardized detection of steatosis. However, given its limited availability and lack of head-to-head studies compared to ultrasound, CAP cannot yet be recommended as a first-line technique **(LoE 2).**
- Although there are no consensual cut-offs, values above 275 dB/m might be used to diagnose steatosis, since they showed over 90% sensitivity to detect steatosis **(LoE 2).**

Recommendations

- Non-invasive scores are not recommended for the diagnosis of steatosis in clinical practice **(LoE 2; strong recommendation).**
- Conventional ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice, despite its well-known limitations **(LoE 1; strong recommendation).**
- MRI-PDFF is the most accurate non-invasive method for detecting and quantifying steatosis. However, it is not recommended as a first-line tool given its cost and limited availability. Therefore, it is more suited to clinical trials **(LoE 2; strong recommendation).**

Several steatosis scores have been proposed for the detection of steatosis, including the SteatoTest^{TM}, the fatty liver index (FLI), the hepatic steatosis index (HSI), the lipid accumulation product, the index of NASH and the NAFLD liver fat score (NAFLD-LFS).[104] Although SteatoTest^{TM}, FLI, NAFLD-LFS, lipid accumulation product and HSI have been independently validated,[105–108] their diagnostic performances are difficult to compare. Indeed, they have been designed and validated against different standards: liver biopsy, ultrasound, or MR spectroscopy. Nevertheless, when FLI, NAFLD-LFS, and HSI were compared in a retrospective cohort of 324 patients with suspected NAFLD and liver biopsy, their diagnostic performances for detecting any steatosis (>5%) did not differ (AUROC 0.83, 0.80 and 0.81, respectively).[106] Further studies are needed, but it should be acknowledged that these scores do not add much to the information provided by clinical, laboratory and imaging examinations that are routinely performed in patients with suspected NAFLD.

Conventional ultrasound is the most commonly used imaging method for the diagnosis of steatosis, since it is widely available, innocuous, cheap and well established.[109] In a large meta-analysis[110] (n = 34 studies, 2,815 patients with suspected or known liver diseases), pooled sensitivities and specificities of ultrasound to detect steatosis (≥20–30%), taking liver biopsy as the reference, were 85% (80–89%) and 94% (87–97%), respectively. The main limitations of ultrasound are that it can only detect steatosis above 12.5–20%,[111] is prone to inter-operator variability and has reduced accuracy in patients with obesity.[112]

Magnetic resonance proton density fat fraction (MRI-PDFF) is an accurate, reproducible, quantitative imaging-based technique that has the ability to quantify liver fat in its entire dynamic range.[113] Quantification of steatosis using MRI-PDFF highly correlates with MR spectroscopy results.[114] In a recent meta-analysis (n = 6 studies in 635 patients with biopsy-proven NAFLD),[115] the summary AUROC values of MRI-PDFF for detecting steatosis ≥5%, and ≥33%, ≥66% were 0.98, 0.91, and 0.90, respectively. Pooled sensitivity and specificity were 93% and 94%, 74% and 90%, and 74% and 87%, respectively. Despite the high accuracy of MRI-PDFF for detecting and grading steatosis, cost and limited availability restrict its use in practice.

The ability to quantify steatosis by measuring ultrasonic attenuation of the echo wave, termed the CAP, has been implemented on the FibroScan device.[116] In the first individual data meta-analysis[117] published (n = 19 studies in 2,735 patients [537 with NAFLD; 19.6%] with liver biopsies), AUROCs of CAP for detecting steatosis ≥5–10%, ≥33% and ≥66% were 0.82, 0.86, and 0.88, respectively. Pooled sensitivities were 69%, 77%, and 88% and specificities 82%, 81% and 78%, respectively. Optimal cut-offs of 248 dB/m, 268 dB/m and 280 dB/m were proposed but notably several covariates, such as NAFLD, diabetes and BMI, influenced

CAP values. Nevertheless, the cut-off associated with significant steatosis (>33%) was almost always >250 dB/m. In addition, most included studies were conducted in small samples (<100 patients), heterogeneous populations (less than 20% with NAFLD) and were performed with the M probe. Two recent multicentre studies[118,119] addressed the accuracy of CAP in large cohorts (n = 393–450) of patients with NAFLD, using M and XL probes as recommended by the device's automatic probe selection tool. Failure rates using the XL probe were much lower (3–4%)[118,120] than those reported with the M probe (21%).[121] Accuracy for detecting steatosis ≥5% was good with AUROCs of 0.76–0.87. By contrast, accuracy was suboptimal for quantifying steatosis with AUROCs of 0.70–0.77 and 0.58–0.70 for steatosis ≥33% and ≥66%, respectively. Cut-off values of 263 dB/m[119] and 274 dB/m[118] had high sensitivities and PPVs (>90%) for detecting steatosis (≥5%). In a recent meta-analysis of individual data currently in press,[122] CAP measured by the XL probe in 930 patients with NAFLD and histologically proven steatosis accuracy was good for identifying any grade of steatosis *vs.* absence of steatosis (AUROC 0.819; 95% CI 0.769–0.869), but suboptimal to differentiate mild steatosis from higher grades (S0–S1 *vs.* S2–S2; AUROC 0.754; 95% CI 0.720–0.787). According to this meta-analysis, the optimal cut-off (according to Youden's index) to detect any steatosis in patients with NAFLD is 294 dB/m (sensitivity 0.790; specificity 0.740), but if a sensitivity of ≥0.90 was required, the cut-off dropped to 263 dB/m (95% CI 256–270).[122]

Quality criteria have been proposed (CAP IQR <30 or 40 dB/m)[123,124] but not externally validated.[118] When compared with MRI-PDFF for detecting and quantifying steatosis using liver biopsy as a reference, CAP was outperformed by MRI-PDFF.[125–127]

In summary, CAP is a promising point-of-care technique for rapid and standardized steatosis detection, with high applicability (>95%) when using the XL probe. Although there are no consensual cut-offs, values above 275 dB/m have high sensitivities and PPV (>90%) in NAFLD. However, CAP has suboptimal performance for quantifying steatosis and is outperformed by MRI-PDFF. CAP should be compared to ultrasound which, despite its limitations, remains the most widely used tool for first-line steatosis detection.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for the evaluation of NAFLD severity (presence of NASH and staging of liver fibrosis)

Statement

In patients with NAFLD:

Liver biopsy remains the reference standard for the diagnosis of NASH, because none of the available NITs has acceptable accuracy **(LoE 2)**.

Recommendations

In patients with NAFLD:

- The following NITs are recommended to rule-out advanced fibrosis in clinical practice **(LoE 1, strong recommendation):**
  - LSM by TE <8 kPa
  - Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48
  - Non-patented tests: FIB-4 <1.3 or NFS <-1.455
- Upon referral of a patient with FIB-4 over 1.3, the use of TE and/or patented serum tests should be used to rule-out/in advanced fibrosis (see Fig. 1) **(LoE 2, strong recommendation).**
- MRE is the most accurate non-invasive method for staging liver fibrosis. However, it is only marginally better than other NITs for F3–F4 fibrosis and it is not recommended as a first-line NIT given its cost and limited availability **(LoE 2; strong recommendation).** Therefore, it is more suited to clinical trials.

The diagnosis of NASH is clinically relevant because NASH is associated with faster liver fibrosis progression.[109,128] Several serum markers or scores such as CK-18 fragments, combinations of clinical variables, combination of clinical variables with the PNPLA3 I148M variant, metabolomics or lipidomic-based scores, as well as imaging techniques have been proposed for the non-invasive diagnosis of NASH. However, contrasting results from literature, lack of validation studies, and lack of availability of some of the variables included in many scores limit the recommendation of the proposed tools in clinical practice.[113,129] Thus, liver biopsy currently remains the reference standard for the diagnosis of NASH in patients with NAFLD.

Liver fibrosis is the main prognostic driver in patients with NAFLD, with advanced fibrosis being an independent risk factor for both hepatic and extrahepatic events and liver-related and global mortality.[130,131] Thus, advanced liver fibrosis has been used as the main endpoint in studies on NITs in patients with NAFLD. Proposed serum markers and scores for the assessment of fibrosis severity include NAFLD fibrosis score (NFS), FIB-4, BARD score, AST to platelet ratio (APRI), AST to ALT ratio (AAR), eLIFT, HEPAMET score, pro-C3, FibroMeter™, FibroTest® and ELF™. The most validated are NFS and FIB-4, which are non-patented tests. NFS is based on the combination of 6 variables (age, BMI, AST/ALT ratio, platelet count, hyperglycaemia and albumin) whereas FIB-4 is based only on the combination of age, AST, ALT and platelet count. These scores use 2 cut-offs to rule-out or rule-in advanced fibrosis: one with high sensitivity (1.3 for FIB-4, and -1.455 for NFS) and another with high specificity (3.25 for FIB-4 and 0.676 for NFS). Advantages of NFS and FIB-4 are the following: i) they are both based on simple variables widely available in clinical practice; ii) their results can be easily obtained at bedside on free online calculators; iii) their overall diagnostic accuracy for advanced fibrosis, as reported by a recent meta-analysis (n = 36 studies in 9,074 patients), is good with AUROCs of 0.80 for FIB-4 and 0.78 for NFS ([132]; iv) both can exclude the presence of advanced fibrosis with high NPV (>90%).[132] Disadvantages of NFS and FIB-4 are: i) their PPV for confirming advanced fibrosis is modest (<70%) with the risk of false positive results;[132] ii) about one-third of patients fall in-between the upper and lower cut-off values giving an undetermined result;[132] iii) older age has been suggested to affect their diagnostic accuracy.[133] Therefore higher cut-offs have been proposed for ruling out advanced fibrosis in patients older than 65 years (2.0 for FIB-4, and 0.12 for NFS) but they need to be externally validated;[133] iv) preliminary evidence suggests lower performance of NFS in obese patients[134,135] and in diabetic patients,[136,137] where FIB-4 could be preferred.[136,137] The 2 most validated patented serum fibrosis biomarkers are FibroMeter™ and ELF™. ELF™ has been evaluated in an independent meta-analysis (n = 11 studies in 4,452 patients) with an AUROC of 0.83 for detecting advanced fibrosis.[138] Overall, diagnostic accuracy of patented serum fibrosis tests for staging fibrosis is at least similar,[139] if not higher,[140] than that of FIB-4 and NFS, but their widespread application in clinical practice is limited by cost and availability.

TE is the most widely available device for LSM with the largest amount of data in the NAFLD setting. A large recent meta-analysis (M probe 17 studies; 2,642 patients; XL probe 3 studies 318 patients) reported a good diagnostic accuracy for advanced fibrosis (AUC 0.87 with M probe and 0.86 with XL probe) and cirrhosis (AUC 0.92 with M probe and 0.94 with XL probe).[132] The use of both M and XL probes reduces the failure rate to less than 5% of cases.[118,120] A recent study suggests using the same LSM cut-offs for M probe in non-obese and XL probe in obese patients.[141] TE has a high NPV (above 90%) to rule-out advanced fibrosis but a modest PPV in NAFLD compared to viral hepatitis; LSM more often leads to false positive results in NAFLD.[118,120] Contrasting results exist about the impact of ALT levels, BMI, skin-to-capsule distance and steatosis/CAP on LSM accuracy and risk of false positive results.[118,134,142–144] There is no agreement in clinical practice on LSM cut-offs for ruling out advanced fibrosis, even though 8 kPa is the most validated threshold, with an NPV above 90%.[113] According to the results of a recent meta-analysis[55] values of LSM by TE >12-15 kPa could be used to rule-in advanced fibrosis.

Regarding pSWE and 2D shear wave elastography (2D-SWE), 2 recent meta-analyses[145,146] suggest performance for detecting advanced fibrosis in keeping with those reported for FibroScan®.[147] However, they are less available in liver clinics and data in patients with NAFLD remain limited.

Finally, MRE can be considered the most accurate non-invasive method for detecting advanced fibrosis. In a recent individual patient data meta-analysis, based on 3 studies in 230 patients, comparing MRE to TE,[148] MRE outperformed TE for detecting advanced fibrosis (AUC 0.94 *vs.* 0.83, respectively, $p = 0.001$).[148] However, the amount of data in NAFLD remains limited. In addition, given its cost and limited availability, MRE cannot be recommended in clinical practice and is more suited to clinical trials.

Limitations of serum scores and TE together with the need to extend the search for NAFLD patients with fibrosis outside tertiary referral centres inspired clinical studies assessing whether combination strategies are better than the use of each method alone. A sequential combination of NFS or FIB-4 as first test – keeping patients at low risk in follow-up – followed by the use of TE in patients in the medium/high-risk area was better than each test alone, obtaining a diagnostic accuracy ranging from 75% to 80% and lowering the uncertainty area to <10%.[134,149] Similar results have been reported when combining eLIFT score with FibroMeter™[150] or FIB-4 with ELF™ score.[151]

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy, HVPG, Child-Pugh or MELD score for the prediction of liver-related outcomes in patients with NAFLD?

Recommendations

- Serum scores (APRI, FIB-4, NFS, ELF™) and LSM by TE should be used to stratify the risk of liver-related outcomes in NAFLD **(LoE 3; strong recommendation).**
- Repeated measurements of NITs can be used to refine stratification of risk of liver-related events in patients with NAFLD/NASH. Despite the lack of evidence regarding the optimal timeframe between subsequent LSM assessment, it seems reasonable to repeat NITs every 3 years in patients with early stage and every year in patients with advanced stage NAFLD (**LoE 3; weak recommendation**).

Available evidence suggests that non-invasive serum markers and elastography devices developed to predict the presence of liver fibrosis can also have a role in predicting the long-term prognosis of patients with NAFLD.

A recent retrospective longitudinal study evaluated the ability of non-invasive scores to detect fibrosis progression in 292 patients with NAFLD and paired liver biopsies (median time interval of 2.6 years).[152] Changes over time in APRI, FIB-4 and NFS were significantly associated with fibrosis progression (defined as 1 fibrosis stage) (cross-validated C-statistic for detecting progression to advanced fibrosis of 0.82 for APRI, 0.81 for FIB-4 and 0.80 for NFS). FIB-4 and NFS had high NPVs (around 90%), but suboptimal PPVs for predicting progression to advanced fibrosis.[152] Furthermore, data from the simtuzumab trials showed that an ELF™ value ≥9.76 (sensitivity 77%, specificity 66%) can predict progression to cirrhosis in patients with F3 fibrosis.[153]

In a retrospective cohort study of 320 patients with biopsy-proven NAFLD, NFS and FIB-4 accurately predicted the occurrence of liver events (AUROC 0.86 and 0.81, respectively), while having a lower accuracy for overall mortality (AUROC 0.70 and 0.67, respectively).[154] The authors reported a progressive impairment in clinical outcomes from patients at low to those at intermediate and further to those at high risk of advanced fibrosis, but they did not compare the accuracy of NITs with histology. Similarly, an APRI value >1.5 significantly predicted the occurrence of HCC in an Asian cohort (n = 6,508, median follow-up 5.6 years) of patients with ultrasonographic diagnosis of NAFLD.[155] Three other recent retrospective studies in patients with biopsy-proven NAFLD confirmed the good accuracy of both tests in predicting liver-related events and overall mortality.[156–158] One of these studies also showed that the severity of liver disease by histology was superior to NITs in predicting severe liver disease, but not in predicting overall mortality,[157] while another reported similar diagnostic accuracy for predicting liver-related events and overall mortality when considered together.[156]

The ability of FIB-4 to not only predict liver-related events and overall mortality, but also liver-related mortality, was reported by a French study in 360 patients with biopsy-proven NAFLD over a median follow-up of 6.4 years.[159] A large US cohort study in 11,154 individuals (NHANES cohort) of whom 34% had NAFLD on ultrasound reported that those diagnosed as having advanced fibrosis using NFS had higher overall, liver-related and cardiovascular mortality.[160] Finally, in 250 compensated cirrhotic patients enrolled in the simtuzumab trials (median follow-up 30.9 months), ELF™, at a cut-off of 11.27, could predict (C-statistic 0.68, sensitivity 51%, specificity 72%) the onset of clinical events with a similar accuracy to liver collagen content.[153]

As for LSM using TE, LSM and FibroMeter™ had good accuracy for predicting liver-related events, as well as liver-related and overall mortality, in the aforementioned study from France.[159] Similar results regarding the accuracy of LSM and FIB-4 for liver-related mortality were reported in another French study; the authors also observed a similar accuracy for FibroTest®.[161] In a large population of 2,251 patients with NAFLD (diagnosed by ultrasound and with a short follow-up [median of 27 months]), LSM performed well for predicting overall mortality and liver complications (higher rate of events in patients with LSM >12 kPa) but not for the prediction of cardiovascular events and extrahepatic cancers.[162] Consistently, baseline LSM independently predicted hepatic decompensation, HCC and liver-related death in 1,039 patients with NAFLD-related cACLD.[163] PNPLA3 I148M variants are associated with higher risk of developing cirrhosis and HCC, but genetic testing is not currently used in clinical practice.

Two recent retrospective studies investigated the impact of dynamic changes in FIB-4 and LSM on long-term outcomes. A population-based Swedish study on 40,729 individuals with availability of FIB-4 at 2 time points (baseline and within 5 years; mean time 2.4 years) showed that progression from a low- or intermediate-to a high-risk group was associated with an increased risk of severe liver disease (adjusted hazard ratio 7.99 and 8.64, respectively).[24] Similarly, a retrospective analysis of 533 patients with NAFLD-related cACLD and availability of LSM at baseline and within 1 year from the last follow-up (median time 37 months) showed that changes in LSM were independently associated with hepatic decompensation, HCC, overall mortality, and liver-related mortality (hazard ratio 1.96).[163] Further prospective studies are needed to assess the impact of dynamic changes in non-invasive scores and LSM on long-term outcomes. Even if there is lack of evidence and the optimal timeframe remains to be found, it seems reasonable to repeat NITs every 3 years in patients with early stage disease and every year in patients with advanced stage liver disease.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for patient selection and evaluation of treatment response in NAFLD therapeutic trials?

Recommendations

- Liver biopsy remains the reference for patient selection in phase IIb and phase III therapeutic trials and should be used for these purposes **(LoE 1; strong recommendation).**
- MRI-PDFF can be used to assess steatosis evolution under treatment **(LoE 2; weak recommendation).** However, the minimal decrease in MRI-PDFF that defines a clinically relevant change or treatment response needs to be better defined.
- Liver biopsy remains the reference to evaluate NASH resolution and liver fibrosis improvement and should be used for these purposes **(LoE 2; strong recommendation).**

New drugs for NASH need to follow a highly standardised process before getting approval for use in clinical practice.[164] After phase I, phase IIa trials demonstrate "on target effects" and provide pharmacokinetic and safety data. Then, phase IIb trials evaluate histological improvement in a significant subset of patients. Finally, phase III trials robustly confirm the histological improvement but also demonstrate the benefit regarding long-term clinical outcomes in large samples of patients. Study endpoints rely on NITs in phase IIa trials, whereas liver biopsy is used for phase IIb and III trials.[165] With the aim of selecting a subpopulation enriched in potential candidates, NITs are of interest to facilitate inclusions and reduce unnecessary screening liver biopsies in phase IIb and III therapeutic trials. Additionally, a non-invasive evaluation of treatment response instead of paired liver biopsies would increase the feasibility of clinical trials and likely improve patient retention. Ultimately, beyond therapeutic trials, NITs validated for the identification of patients who need to be treated and for treatment response evaluation will facilitate the practical management of patients once the new drugs become available on the market.

Patient selection for therapeutic trials

According to international guidelines, pharmacological therapy should be reserved for patients with NAFLD who have active disease and a significant amount of liver fibrosis.[30,109] Is has been recently shown that patients with NASH and a NAS ≥4 had a less-pronounced placebo response rate than those with a lower NAS.[166] Therefore, most of the phase IIb and phase III trials include patients with "fibrotic NASH" (NASH + NAS ≥4 + fibrosis stage F2-3). There is currently no validated test for the non-invasive diagnosis of NASH. The NITs able to accurately diagnose advanced F3/4 fibrosis are less accurate to identify earlier fibrosis stages and F2 patients.[167] Therefore, 3 tests have recently been developed specifically for the non-invasive diagnosis of fibrotic NASH: 2 blood tests, MACK-3 and NIS4, and the transient elastography-based FAST score.[168–170] The MACK-3 includes 4 serum markers (AST, glucose, insulin and CK18) as the NIS4 (miR-34 a-5p, alpha2-macroglobulin, YKL-40, HbA1c), while FAST combines, according to a non-patented formula, AST with LSM and CAP values. The studies carried out by the developers showed good accuracy with AUROCs for detecting fibrotic NASH between 0.80 and 0.85.[168–170] These tests require further external and independent validation in large cohorts.

Evaluation of treatment response in therapeutic trials

Weight loss is associated with a decrease in liver steatosis, and new potentially anti-steatotic drugs have been developed. In these contexts, a precise evaluation of steatosis evolution is of interest to evaluate the effectiveness of the intervention.

Cross-sectional studies have demonstrated that MRI-PDFF provides a non-invasive, accurate, precise, sensitive, and reproducible quantification of liver steatosis.[114] The ability of MRI-PDFF to track change in liver steatosis has been evaluated as a secondary endpoint in clinical trials with paired liver biopsies.[172–175] These preliminary studies have shown that changes in MRI-PDFF values correlate well with changes in steatosis on liver biopsy. In addition, it has been suggested that MRI-PDFF could be more sensitive than liver biopsy to detect small changes in liver steatosis.[176] Therefore, MRI-PDFF appears as a promising tool to monitor steatosis evolution and is used as a reference in phase IIa clinical trials evaluating drugs with an anti-steatotic mechanism of action. However, it should be acknowledged that currently available evidence comes from small series of patients, which used the rough histological grades to monitor steatosis evolution. Larger studies, using as reference, precise and sensitive tools able to track subtle changes of steatosis on liver biopsy such as morphometry, are therefore required to definitively validate MRI-PDFF as the reference for the non-invasive evaluation of steatosis evolution under treatment. Additionally, the minimum MRI-PDFF decrease corresponding to a clinically relevant change or to treatment response needs to be better defined. New methods of ultrasonography and elastography are in development for the quantification of liver steatosis, but there is currently no data about their ability to monitor the evolution of steatosis under treatment.

The FDA (US Food and Drug Administration) and the EMA (European Medicines Agency) recognise 2 endpoints for the conditional approval of drugs in pre-cirrhotic patients: i) resolution of NASH without worsening of liver fibrosis, and ii) at least 1 stage improvement in liver fibrosis without worsening of NASH.[165] There is currently no validated biomarker for liver inflammation and therefore no strong candidate for the non-invasive evaluation of NASH resolution. Ideally, the biomarker used to evaluate treatment response should be independent of the drug's mechanism of action. In 200 adults with NASH, a ≥17 IU/L decrease of ALT at week 24 was the strongest predictor (odd ratio >10) of histological response as defined by a ≥2-point improvement in NAS without worsening of fibrosis.[177] In a recent meta-analysis (n = 7 studies; 346 patients),[178] MRI-PDFF responders (defined as relative decline in liver fat ≥30%) were more likely to have NASH resolution (41% *vs.* 7%, *p* <0.001; odds ratio 5.45, 95% CI 1.53–19.46, *p* = 0.009) compared to MRI-PDFF non-responders. Such association between histological response and steatosis decrease was however not reproduced in another large study (n = 121 patients).[179] Thus, further studies are needed before any firm conclusions can be drawn. Moreover, as MRI-PDFF response has been evaluated in a short timeframe of months, it is unclear if the response is sustained in the long term and if it also translates to improvement in fibrosis.

Several NITs (serum markers and elastography) are accurate for the diagnosis of advanced fibrosis in NAFLD. Therapeutic trials represent a unique opportunity to evaluate their ability to monitor fibrosis evolution under treatment. Change over time of the blood test ELF^{TM} was independently associated with an increased risk of disease progression in 217 patients with NAFLD and advanced fibrosis from a phase IIb trial.[153] However, in another work including 54 F2-3 patients, the median relative change in liver stiffness by MRE was not significantly different between patients with fibrosis improvement (≥1 stage) and those without fibrosis improvement (-2.3% *vs.* 3.0%).[174] Very recent studies have suggested that ProC3, a blood marker that directly reflects collagen formation during fibrogenesis, may be useful to identify responders to pharmacological treatment in NASH,[171] but this requires confirmation in larger series.

Studies on the non-invasive evaluation of treatment response remain scarce in the literature, and the limited preliminary data available require confirmation in larger samples of patients. Consequently, liver biopsy currently remains the reference to evaluate NASH resolution and liver fibrosis improvement under therapy. The most relevant existing biomarkers and panels should be tested for this purpose, and extensive research should be conducted to find new candidate biomarkers. The many ongoing therapeutic trials in NASH include the evaluation of NITs as secondary endpoints; thus, evidence about their ability to monitor treatment response will accumulate.

Cholestatic and autoimmune liver disease (PBC, PSC, AIH)

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for the assessment of disease severity in patients with PBC and PSC?

Recommendations

- In patients with PBC, serum markers of fibrosis and non-invasive scores (combination of clinical and laboratory variables) are not recommended for fibrosis staging in clinical practice **(LoE 3; strong recommendation).**
- In patients with PBC, LSM by TE is the best surrogate marker for ruling in severe fibrosis/cACLD and should be used for this purpose using a cut-off of 10 kPa **(LoE 3; strong recommendation).**
- In patients with PSC, LSM by TE above 9.5 kPa can be used to support the diagnosis of advanced fibrosis in compensated patients with normal bilirubin and without high-grade stenosis **(LoE 3; weak recommendation).**

In general, studies on NITs in patients with PBC or PSC involve a small or very small number of patients.

In PBC, as in other chronic liver diseases, advanced histological stages are associated with poor prognosis;[180–185] fibrosis stage was recently demonstrated to be an independent predictor of outcome even in patients with biochemical treatment response.[186] However, liver biopsy is no longer indicated in the diagnostic work up of PBC, unless in specific situations (absence of PBC-specific antibodies, suspicion of coexistence of AIH or NASH or other co-morbidities) or in case of inadequate response to ursodeoxycholic acid (UDCA) therapy in order to characterise histological lesions that underlie the resistance to treatment.[187] Moreover, the course of the disease may be progressive, despite UDCA treatment, thus non-invasive assessment of fibrosis is crucial both at diagnosis and during follow-up of these patients.

Serum biomarkers of liver fibrosis including serum levels of hyaluronic acid, procollagen III aminoterminal propeptide, collagen IV and FibroTest® do not have adequate accuracy to differentiate between early and advanced fibrosis in PBC.[5] Similarly, non-invasive scores, namely APRI, FIB-4, AAR, red blood cell distribution width to platelet ratio, red blood cell distribution width to lymphocyte ratio and neutrophil to lymphocyte ratio, have a suboptimal diagnostic performance (AUROC <0.80) in predicting histological stage in PBC.[186,188–196] In 1 study, platelet count to spleen diameter ratio showed a good diagnostic performance in predicting advanced fibrosis stage.[197] LSM by TE was previously shown to correlate with liver fibrosis in PBC[184,198,199] and, based on prospective data,[198] a cut-off of 9 kPa was proposed to identify patients with *vs.* without significant fibrosis (10.7 kPa for advanced fibrosis[5]). A study including 44 patients with PBC confirmed the good accuracy of LSM by TE in predicting advanced fibrosis and cirrhosis (AUROCs

0.91 and 0.97, respectively), but reported higher optimal cut-offs for identification of advanced fibrosis and cirrhosis.[189] We suggest that an optimal cut-off of 10 kPa should be used to rule-in advanced fibrosis. One study including 41 patients with PBC assessed the diagnostic performance of pSWE and reported promising results in prediction of both significant and advanced fibrosis in this disease (AUROCs 0.81 and 0.91, respectively).[188] Finally, preliminary data on the use of MRE in PBC were reported but require further validation.[200]

In PSC, 2 studies published since the publication of the EASL-ALEH 2015 guidelines and including 62 and 39 patients with PSC confirmed the good accuracy of LSM by TE in predicting advanced fibrosis (AUROC 0.95, sensitivity 90%, specificity 91%) and cirrhosis (AUROCs 0.98 and 0.90, sensitivity 69% and 78%, specificity 98% and 90%, respectively) with similar optimal cut-offs for predicting cirrhosis (14.4 kPa, and 13.7 kPa, respectively).[201,202] Moreover, in the simtuzumab trial, the diagnostic performances of the optimal cut-offs for advanced fibrosis (≥9.6 kPa) and cirrhosis (≥14.4 kPa), reported by Corpechot *et al.*, were confirmed to have a good and excellent accuracy (AUROCs 0.80 and 0.95, sensitivity 74% and 100%, specificity 74% and 83%, respectively).[203] Liver stiffness by MRE was assessed in 20 patients with biopsy-proven PSC and the reported diagnostic accuracies for predicting fibrosis stage ≥F1, ≥F2, and F4 were excellent (AUROCs 0.97, 0.97 and 0.99, respectively), however these data need to be confirmed in larger independent cohorts.[204]

In patients with increased serum bilirubin due to the presence of a high-grade stenosis in the extrahepatic bile ducts, liver stiffness values need to be carefully interpreted due to the relevant risk of overestimation of the fibrosis stage.[204–206]

Preliminary data on spleen length measurement by ultrasound suggested a good diagnostic performance to identify cirrhosis (AUROC 0.85, sensitivity 73%, specificity 73%) when an optimal cut-off of 120 mm was applied.[207]

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy, HVPG, Child-Pugh or MELD scores for the prediction of liver-related outcomes in patients with PBC and PSC?

Recommendations

Primary biliary cholangitis

- In patients with PBC, non-invasive discrimination of early and advanced stage disease based on biochemical parameters (normal *vs.* abnormal albumin and bilirubin) and LSM by TE < or >10 kPa is recommended at baseline **(LoE 3, strong recommendation).**
- During treatment, risk stratification should be based on the assessment of response to therapy by using continuous (GLOBE and UK-PBC risk scores) and/or qualitative criteria (Paris II, Toronto, Rotterdam, Barcelona, Paris I) of response and LSM by TE **(LoE 3, strong recommendation).**

Primary sclerosing cholangitis

- In patients with PSC, both the ELF™ score and LSM by TE correlate with outcomes and they should be used for risk stratification both at baseline and during follow-up **(LoE 3, strong recommendation).**

Patients with PBC treated with UDCA demonstrate different disease courses depending on baseline (pre-treatment) features and biochemical response after 12 months of treatment; risk stratification is required.[187]

At baseline, the distinction of early from advanced disease stage is based on LSM by TE (LSM ≤10 kPa or LSM >10 kPa), serum levels of bilirubin and albumin (both parameters normal *vs.* at least 1 parameter abnormal) and, when available, histology (absent or mild fibrosis *vs.* bridging fibrosis or cirrhosis).[187]

On-treatment, the evalutation of prognosis is based on the assessment of biochemical response to UDCA by using qualitative criteria (Paris-I, Paris-II, Rotterdam, Toronto, Rochester, Ehime criteria) or by the recently proposed quantitative criteria (UK-PBC score and GLOBE score). The GLOBE score (which includes age, total bilirubin, alkaline phosphatase [ALP], albumin and platelet count), derived and validated in a multicentre international cohort of patients with PBC treated with UDCA was shown to accurately predict LT-free survival at 5 and 10 years (c-statistics 0.81 and 0.82 in derivation and validation cohort, respectively).[208] The UK-PBC score (including baseline albumin and platelet count, and bilirubin, AST or ALT and ALP 12 months after starting UDCA), derived and validated in a multicentre UK cohort of PBC patients treated with UDCA, accurately predict the risk of major outcomes (liver-related death, LT or bilirubin ≥100 μmol/L) at 5, 10, 15 years with reported AUROCs of 0.96, 0.95 and 0.94, respectively.[209] Both scores have been externally validated and were superior to qualitative criteria, and to MELD and Child-Pugh scores.[210–212,213] Further studies are needed to better define the applicability of the UK-PBC risk score in routine clinical practice.

Biochemical non-response, defined by the GLOBE score, and an APRI score >0.54 after 12 months of UDCA therapy, were recently shown to be independently associated with the risk of cirrhosis decompensation and their use in combination improve risk stratification in these patients.[214] Moreover, a recent study showed that a serum level of GGT >3.2-fold the ULN at 12 months after treatment identifies patients at increased risk of LT or liver-related death independently of ALP values.[215] Thus, in addition to biochemical response, APRI score and GGT can be used to refine risk stratification in these patients. Finally, ALP normalisation or serum bilirubin below 0.6x ULN after 12 months of treatment were recently associated with the lowest risk for LT or death in patients with PBC.[216] The ELF™ score has also been associated with clinical outcomes in PBC.[217]

In addition, on-treatment LSM by TE is indicated during follow-up, since worsening of LSM predicts patient outcomes.[5,187,198] An increase of 2.1 kPa/year in LSM by TE was associated with a 8.4-fold increase in the risk of adverse outcomes.[198] Despite the lack of evidence regarding the optimal timeframe between subsequent liver stiffness assessment, it seems reasonable to repeat LSM every 2 years in patients with early stage and every year in patients with advanced stage disease.

PSC is generally progressive and the natural history[218–220] is characterised by spontaneous fluctuation in bilirubin due to the occurrence of acute bacterial cholangitis, biliary stones or high-grade strictures. This explains the difficulty in accurately predicting prognosis by applying classical prognostic models (Child-Pugh score and MELD score). Histological stage assessed by liver biopsy is strongly associated with clinical outcomes[221] and is still considered a robust surrogate endpoint for clinical trials in PSC.[222]

The ELF^{TM} score demonstrated a good accuracy in predicting LT-free survival in several large independent cohorts of patients with PSC, with reported AUROCs ranging between 0.78 and 0.81 and optimal prognostic thresholds around 10.[223–227] Recently, the prognostic values of the serological markers of extracellular matrix remodelling, PRO-C3 and PRO-C5, showed comparable accuracy to ELF^{TM} in predicting LT-free survival (AUC 0.78, 0.74 *vs.* 0.81), moreover, PRO-C5 was able to predict LT-free survival independently from ELF^{TM} score.[226]

Four new composite scores including clinical, biochemical and radiological features were derived by using 3 large multicentre cohorts of patients with PSC. The Amsterdam-Oxford model (AOM, including PSC subtype, age at PSC diagnosis, albumin, platelets, AST, ALP and bilirubin) showed moderate accuracy in prediction of LT and PSC-related death (c-statistic 0.68) and calibration was satisfactory when applied both at diagnosis and during follow-up.[228] The AOM was then validated in an independent multicentre cohort showing increased accuracy that remains stable during follow-up (c-statistics at baseline, 1, 2, 3, 4 and at 5 years of follow-up: 0.67, 0.69, 0.72, 0.75, 0.75 and 0.75, respectively).[229] The Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTO, including bilirubin, albumin, serum ALP x the ULN, platelet count, AST, haemoglobin, sodium, patient age, and number of years since PSC diagnosis), derived with a machine learning technique, demonstrated a good accuracy (c-statistic 0.90) to predict hepatic decompensation and excellent to predict LT and PSC-related death, exceeding that of MELD and Mayo risk score (c-statistics 0.96 *vs.* 0.73 and 0.84).[230] Lastly, the Short-Term (RS_{ST}) and the Long-Term (RS_{LT}) UK-PSC risk score (including PSC type, age at diagnosis, haemoglobin at diagnosis, total bilirubin, albumin, platelet count, serum ALP at baseline and at year 2, and occurrence of variceal bleeding at year 2) showed good accuracy in predicting LT-free survival (c-statistics of both score $\geq$0.80) and the RS_{ST} outperformed the Mayo risk score, APRI and MELD.[231] Further data are needed to understand the practical application of these scores in the clinical setting.

Baseline LSM by TE and the increase of LSM over time were associated with prognosis[232] and thus recommended in the previous EASL-ALEH 2015 guidelines for prognostic purposes in PSC. Subsequent studies confirmed the association of LSM values with liver-related outcomes in patients with PSC[201,203] and histological stage.[203] Optimal thresholds of LSM for the prediction of prognosis differed between studies, depending on outcomes considered. A large multicentre prospective study is being performed by the International PSC Study group to assess the prognostic value of LSM by TE (FICUS study); an interim analysis confirmed the high predictive performance of LSM by TE (AUROC 0.88) with reported adjusted hazard ratios for adverse outcomes of 4.2 for baseline liver stiffness values between 9.6 and 14.3 kPa and of 16.3 for baseline LSM values above 14.3 kPa, both compared to baseline LSM <9.6 kPa. Despite the lack of evidence regarding the optimal timeframe, it seems reasonable to repeat LSM by TE and/or ELF^{TM} annually. LSM by MRE was also associated with the risk of cirrhosis decompensation.[204]

Spleen length at baseline and its changes during the follow-up were also associated with LT-free survival in patients with PSC[207,233] and the change of spleen volume seemed to predict liver-related outcomes better than the Mayo risk score and MELD.[234]

Finally, cholangiographic changes assessed by endoscopic retrograde cholangiopancreatography[235] and more recently, by MRI,[236] were used for prognostic purposes. Two risk scores (called the Anali score) that consider imaging features on MR (without or with gadolinium injection) were shown to be independently associated with survival without adverse outcomes, with reported c-statistics of 0.89 for the Anali without gadolinium and 0.76 for the Anali with gadolinium.[237] Moreover, a combination of Anali score without gadolinium and LSM by TE is able to better stratify patients according to the risk of development of major outcomes.[238] A study comparing cholangiographic findings obtained by ERCP and MRI reported a weak correlation between cholangiographic findings and major outcomes.[239] Finally, the relative enhancement of liver parenchyma (RLE) after hepatospecific contrast agent (Primovist®) injection was correlated with markers of disease severity (ALP, international normalised ratio), prognostic risk score and clinical outcomes.[240] In conclusion, in patients with PSC, recent evidence supports the use of MRI, alone or in combination with TE, for risk stratification, similarly a number of prognostic scores were proposed and this data needs to be further confirmed.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for assessing liver fibrosis and monitoring disease course in patients with AIH?

Recommendation

- LSM by TE can be used in patients with treated AIH to monitor the disease course together with transaminases and IgG, and to stage liver fibrosis after at least 6 months of immunosuppressive therapy **(LoE 3, weak recommendation).**

Several non-invasive methods used in viral and non-viral chronic liver disease to assess histological stage have been tested in AIH including non-invasive scores (APRI, FIB-4, AAR, NFS), LSM by TE, pSWE and 2D-SWE and imaging methods.

Non-invasive scores such as APRI, FIB-4 and AAR have a poor diagnostic accuracy in predicting liver fibrosis, especially in early fibrosis stages.[241–245] Indeed, the summary AUROCs of FIB-4, APRI and AAR for advanced fibrosis (F$\geq$3) were 0.76, 0.74 and 0.73, respectively. Similarly, the summary AUROCs of FIB-4 and APRI for cirrhosis were 0.66 and 0.75, respectively.[246] One study including 53 patients with AIH, suggested that the NFS has an adequate accuracy to predict cirrhosis (AUROC 0.91, sensitivity 0.90 and specificity 0.89).[241] However, this data needs to be further confirmed.

LSM by TE is positively correlated with histological fibrosis stage in AIH and is able to detect advanced fibrosis and cirrhosis with similar accuracy as in other chronic liver diseases. However, hepatic inflammation is a known confounding factor that can lead to overestimation of liver stiffness, independently from fibrosis stage.[5,247]

Monitoring fibrosis progression during immunosuppressive therapy is crucial, especially in patients with insufficient response, intolerance or non-adherence. A study collectively including 94 patients with biopsy-proven AIH showed that LSM assessed within the first 3 months from starting immunosuppressive treatment is more strongly correlated with histological disease activity and to a lesser degree with histological fibrosis stage. In particular, within the first 3 months (n = 34 patients), the diagnostic performance of LSM for predicting advanced fibrosis showed an optimal cut-off of 10.4 kPa with reported AUROC, sensitivity and specificity of 0.80, 60% and 88%, respectively. Within 6–12 months from treatment initiation (n = 25 patients) the same cut-off predict advanced fibrosis, with reported AUROC, sensitivity and specificity of 1.00, 100% and 100%, while after 4 years the reported AUROC, sensitivity and specificity were 0.96, 95% and 94%, respectively.[248] In another 3 studies, collectively including 261 patients with AIH, LSM values for predicting advanced fibrosis varied between 8.2 and 12.1 kPa depending on the percentage of treatment-naïve patients included, with reported AUROCs, sensitivity and specificity of 0.74–0.90, 59%–80% and 83%–85%, respectively.[241–243]

pSWE to detect histological fibrosis stage in 49 patients with AIH showed a moderate diagnostic accuracy to detect significant fibrosis, advanced fibrosis and cirrhosis (AUROCs 0.70, 0.76 and 0.75, respectively).[188] In 1 study, 2D-SWE showed promising results in predicting histological fibrosis stage in 103 patients affected by autoimmune liver diseases including 62 patients with AIH, 30 patients with PBC, 3 patients with PSC and 19 patients with PBC-AIH variant, but unfortunately data on the diagnostic performance of pSWE for each single disease was not provided.[249] Finally, liver stiffness measured by MRE showed a good diagnostic performance in predicting advanced fibrosis and cirrhosis in 36 patients with AIH.[250]

Platelet count to spleen diameter ratio, assessed in 76 patients with biopsy-proven AIH, showed a good diagnostic performance for predicting significant fibrosis, advanced fibrosis and cirrhosis (AUROC 0.84, 0.88, 0.97, respectively).[244]

To monitor disease course, complete biochemical remission, defined as normalisation of transaminases and immunoglobulin G, was able to predict low histological activity and was the only independent predictor of histological fibrosis regression over time. Decrease of LSM during disease course was strongly linked to complete biochemical remission in 1 study.[251]

Compensated advanced chronic liver disease and portal hypertension

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy for the diagnosis of cACLD?

Recommendations

- cACLD should be diagnosed using second line tests (patented serum tests or elastography) in a specialised setting **(LoE 2, strong recommendation)**.
- Fibrotest® or FibroMeter™ or ELF™ should be used to rule out cACLD if available **(LoE 3, strong recommendation)**.
- LSM by TE should be used to rule-out and diagnose cACLD using the following cut-offs: <8-10 kPa to rule-out; >12-15 kPa to rule-in. Intermediate values require further testing **(LoE 3 strong recommendation)**.
- pSWE and 2D-SWE should be used to rule-out and diagnose cACLD, with AUROCs >0.90 in the published meta-analyses **(LoE 2, strong recommendation)**.
- Inter-system variability should be taken into account when interpreting the results of different elastography techniques, since values, ranges and cut-offs are not comparable **(LoE 3, strong recommendation)**.

The discrimination between severe fibrosis and compensated cirrhosis is often unclear since fibrosis can be inhomogeneously distributed within the liver, particularly in some aetiologies (6), and since it is a dynamic process which can progress but also regress. Due to these considerations, and in order to better discriminate between patients at risk of developing portal hypertension and clinical decompensation, and patients in an earlier stage of chronic liver disease, it has been suggested to rename this clinical scenario including severe fibrosis and compensated cirrhosis as "compensated advanced chronic liver disease" (cACLD) (7).

Given its important prognostic implications, cACLD should be diagnosed using second-line tests (patented serum tests FibroTest®, FibroMeter™ and ELF™ or elastography) in a specialised setting. The performance of serum markers and liver stiffness to diagnose significant fibrosis, severe fibrosis and cirrhosis in compensated patients has been extensively reviewed in the previous EASL guidelines.[5]

Elastography updates are available in other recent guidelines from EFSUMB[247] and WFUMB.[252] Except for the novel data provided in the other specific sections of these guidelines, data on TE do not modify the previous recommendations and this method remains the best validated. Since 2015 there have been numerous publications and meta-analyses regarding the accuracy of pSWE and 2D-SWE for liver fibrosis staging in comparison to liver biopsy. In addition to the data already available for HCV and HBV, suggesting accuracies similar to TE, a meta-analysis on the performance of pSWE in 29 studies in patients with chronic liver disease due to non-viral aetiologies[253] showed an AUROC of 0.94 for advanced fibrosis and cirrhosis.

As for 2D-SWE, 2 meta-analyses, 1 including all aetiologies[145] and 1 in NAFLD,[132] showed that it had an accuracy similar to TE for advanced fibrosis detection. As for the diagnosis of cirrhosis, in the meta-analysis by Hermann *et al.*,[145] the AUROC of 2D-SWE was 0.92–0.95 (varying slightly among aetiologies), and was 0.003–0.034 (p = 0.022) larger than the AUROC of TE. This difference was strongest in patients with hepatitis B.

Inter-system variability should be taken into account, but as for cirrhosis, 1 study comparing 6 different systems showed a good to excellent agreement between measurements performed with different systems, with an interobserver agreement >0.90.[254] Nonetheless, knowledge of the specific cut-offs for each system must be applied since they do not completely overlap.

In summary, LSM by TE remains the most validated tool to diagnose and rule-out advanced fibrosis and cirrhosis in all the major aetiologies of chronic liver disease, holding a discriminating ability of >0.90. Published cut-offs to diagnose cirrhosis vary from 11 to 27 kPa according to the aetiology; however, cut-offs should be considered with caution owing to considerations regarding the prevalence of the fibrosis stage to be diagnosed in the target population. Rule-out and rule-in cut-offs can be used to minimise the risk of under- or overestimation. Furthermore, since it has been well demonstrated that the higher the liver stiffness, the higher the risk of advanced fibrosis and cirrhosis, approaches based on individualisation of risk based on nomograms can be useful in this setting.[50,255]

The definition of cACLD provided by the Baveno VI recommendations encompasses advanced fibrosis and compensated cirrhosis and is based on LSM by TE alone (2 measurements on different days showing ≥10 kPa suggestive of cACLD; ≥15 kPa highly suggestive of cACLD) and is aimed at providing a simple non-invasive tool to help identify asymptomatic patients at higher risk of developing clinical events in the absence of a confirmatory or contemporary liver biopsy, taking into account that fibrosis is a dynamic process that might regress from cirrhosis to a lesser degree of fibrosis.[8] These criteria have recently been refined in a validation study that included over 5,500 patients with chronic liver disease. The study showed that a cut-off of >12 kPa has >90% specificity for diagnosing cACLD, while a cut-off of <8 kPa (for NAFLD and ALD) or <7 kPa (for viral hepatitis) has >90% sensitivity for ruling out cACLD.[55] In 1 study including patients with chronic liver disease of different aetiologies, obesity and metabolic syndrome were associated with a high rate of false positive results when using the ≥10 kPa criteria.[256]

MRE using 2D gradient recalled echo holds a high accuracy for fibrosis staging in all the main aetiologies of liver disease[257] and is superior to TE in patients with NAFLD. However, its high cost and suboptimal availability limit its use in clinical practice.

As for conventional imaging methods, ultrasound, CT and MR are useful to identify signs of cirrhosis and portal hypertension (reviewed elsewhere),[258] but their accuracy to identify cirrhosis in compensated patients does not exceed an AUROC of 0.75–0.80 in the reported studies. Liver surface nodularity quantified by software analysis on CT scan images has been proposed and holds a high accuracy to detect cirrhosis (sensitivity 86%, specificity 92% using a cut-off of 2.75 in sections obtained in the portal venous phase).[259] However, its use in asymptomatic patients cannot be routinely recommended due to the risk of radiation exposure. On the other hand, quantification of this parameter in patients undergoing CT for any other cause seems reasonable and could improve the detection of new cases of cACLD/cirrhosis. Several innovative methods, mostly based on MR techniques have been proposed[260] and include diffusion-weighted imaging, hepatocellular contrast-enhanced (HCE) MRI, T1 relaxometry, T1ρ imaging, textural analysis, susceptibility-weighted imaging, and perfusion imaging. They are highly promising but need further evaluation and clinical validation and cannot yet be recommended for routine practice. Radiomics approaches are currently being developed to stage liver fibrosis based on US, CT and MR images, but are not ready for clinical implementation yet.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to HVPG measurement for diagnosing CSPH and monitoring portal hypertension?

Recommendations

- LSM by TE at a cut-off of >20-25 kPa should be used to diagnose CSPH in patients with cACLD **(LoE 1, strong recommendation).**
- Platelet count, spleen size and spleen stiffness should be used as additional NITs to further improve risk stratification for CSPH **(LoE 3, strong recommendation).**
- The presence of porto-systemic collaterals on ultrasound, CT or MRI is a sign of CSPH in patients with cACLD and should be routinely reported **(LoE 2, strong recommendation).**
- For an exact assessment of the severity of portal hypertension in cACLD beyond presence and absence of CSPH and for assessment of the haemodynamic response to treatment, HVPG remains the only validated tool and should not be substituted by NITs **(LoE 1, strong recommendation).**

Evidence regarding the use of serum markers of fibrosis to diagnose CSPH is scarce and data suggest an insufficient diagnostic accuracy, so their use is not recommended. In cACLD, a Child-Pugh score >5 points is associated with CSPH. Platelet count is inversely related to portal pressure, but its accuracy for CSPH does not exceed an AUROC of 0.75 in the literature.

Von Willebrand factor antigen (vWF-Ag) has been shown to correlate with HVPG in 2 independent studies,[261,262] and predicted CSPH independently of Child-Pugh score. A cut-off value of ≥241%, showed an AUROC of 0.85 to detect CSPH.[262] However, its use cannot be recommended yet because of the lack of further validation.

Among imaging parameters, liver surface nodularity score (LSNS), a measurement of liver surface nodularity on routine CT, correlates with HVPG ($r = 0.75$, $p < 0.001$) and predicts CSPH with good accuracy (AUROC 0.88; cut-off 2.8: PPV 88%).[263] In a pilot study including 30 patients, LSNS was measured on Gd-BOPTA-enhanced MRI and compared to CT, with similar results.[264] Several other parameters such as spleen size and portal vein diameter are associated with portal hypertension but show lower accuracy for the diagnosis of CSPH. On the other hand, the presence of porto-systemic collaterals on ultrasound, CT or MRI is a highly specific sign of CSPH in patients with cACLD and is associated with the presence of gastro-oesophageal varices and with worse prognosis (see below). As such, porto-systemic collaterals should be searched for and documented on routine imaging.

Multiparametric MRI showed promising results to predict CSPH in a small pilot study including 30 patients,[265] but this has not been validated yet.

LSM by TE (and more recently by pSWE and 2D-SWE) is the most validated quantitative individual NIT for portal hypertension in compensated patients. Its linear correlation with HVPG is good but not excellent (AUROC 0.67–0.86). However, using a cut-off of 20–25 kPa, LSM is able to identify CSPH with an AUROC of >0.90; in the meta-analysis by You *et al.*, the summary AUROC was 0.93 with a sensitivity of 87.5% (CI 75.8–93.9%) and a specificity of 85.3% (95% CI 76.9–90.9%).[266] As for aetiology-specific cut-offs, in the recent meta-analysis including 9 studies and 679 patients,[267] the summary sensitivity and specificity for CSPH in patients with ALD at a cut-off of 21.8 kPa was 89% and 71%; while for severe portal hypertension at a cut-off of 29.1 kPa, sensitivity and specificity were 88% and 74%, respectively. However, 7 of 9 included studies had average HVPG above 12 mmHg. Together with the relatively high sensitivities and low specificities, this indicates spectrum bias, with probable inclusion of many decompensated cirrhosis patients, which limits the clinical value of the analysis.

Table 4. Combination of tests used to assess the risk of CSPH and varices in cirrhosis.

Test	Formula	Suggested cut-off	Sensitivity and Specificity in cACLD
LSPS[268,269]	LS by TE × (spleen size in mm/platelet count in G/L)	1.08 to exclude CSPH 2.06 to diagnose CSPH 3.21 to rule-out/rule-in varices (any size)	Se 90%, Sp 91% Se 92%, Sp 90% Se 81%, Sp 86%
PH risk score[269]	5.953 + 0.188 × LS + 1.583 × sex (1: male; 0: female) + 26.705 × spleen diameter in mm/platelet count in G/L	0.06 to exclude CSPH 0.82 to diagnose CSPH	Se 90%, Sp 91% Se 93%, Sp 90%
Platelet to spleen ratio[279]	(platelet count in G/L)/(maximum spleen bipolar diameter in mm by ultrasound)	909 to rule-out/rule-in varices (any size)	Se 100%, Sp 71%

cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; LS, liver stiffness; LSPS, liver stiffness-spleen diameter to platelet ratio score; PH, portal hypertension.

The accuracy of LSM increases if this is combined with unrelated NITs, in particular platelet count and spleen size (liver stiffness-spleen diameter to platelet ratio score [LSPS];[268] PH risk score[269,270] (see Table 4 for the most used formulas).

Due to the small number of studies performed on heterogeneous populations, and the high variability of cut-offs,[271] pSWE cannot yet be recommended for the routine screening of CSPH in patients with cACLD. 2D-SWE has been tested in 9 studies against HVPG; on meta-analysis, the AUROC was 0.88 (95% CI, 0.85–0.91), with a summary sensitivity of 85% and summary specificity of 85%.[272] However, in the published studies, there is marked heterogeneity of cut-offs (16–38 kPa), and no recommendation can be given. A recent individual patient data meta-analysis suggested using 14 kPa as a cut-off of LSM by 2D-SWE to rule-out CSPH.[56]

Spleen stiffness measured by TE, pSWE or 2D-SWE has been tested in a limited number of studies *vs.* HVPG; while it is clear that this parameter correlates with portal pressure, it is unclear whether its performance is similar, inferior or superior to that of liver stiffness for the detection of CSPH. However, it seems reasonable to use spleen stiffness as a complementary NIT for CSPH, *e.g.* by applying both liver stiffness and spleen stiffness sequentially.[273,274] The cut-off value of 40 kPa is highly sensitive (98%) to rule-out CSPH, while values above 46–52 kPa are over 90% specific to rule it in in treatment-naïve patients with HCV-related cACLD.[275]

LSM, serum markers and imaging parameters do not reflect changes of HVPG on medical therapy with non-selective beta-blockers. Kim *et al.*[276] recently reported that changes in spleen stiffness measured by pSWE (Virtual Touch, Siemens, Germany) in 106 patients with cirrhosis and high-risk oesophageal varices before and on carvedilol for primary prophylaxis, predicted the HVPG changes with good performance (0.80 in the training set and 0.85 in the validation set). Marasco *et al.* suggested that spleen stiffness measurement (SSM) by TE could provide data on the haemodynamic response to non-selective beta-blockers as well.[277] Validation in independent cohorts is needed.

For an exact assessment of the severity of portal hypertension in cACLD beyond the presence and absence of CSPH, HVPG remains the only validated tool and cannot be substituted by NITs.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to endoscopy for diagnosing and excluding high-risk gastro-oesphageal varices?

Recommendations

- In patients with cACLD due to untreated viral hepatitis, HIV-HCV coinfection, alcohol, NAFLD, PBC and PSC, the finding of LSM by TE <20 kPa and platelet count >150 G/L (Baveno VI criteria) is a validated tool to rule-out high-risk varices and avoid endoscopic screening. These criteria should be used whenever TE is available **(LoE 1a; strong recommendation)**.
- Spleen stiffness can be used as an additional tool to refine the risk of high-risk varices in cACLD **(LoE 2; weak recommendation).**
- CT should not be used for primary screening for oesophageal and gastric varices, but when doing a routine CT, varices should be looked for and reported **(LoE 3, strong recommendation).**

Several NITs including laboratory tests (platelet count, individual components of the Child-Pugh score, MELD score); imaging signs (portal vein diameter and blood flow velocity, spleen size, nodularity of the liver surface, presence of porto-systemic collaterals), liver stiffness and spleen stiffness correlate with the presence and grade of gastro-oesophageal varices in patients with cACLD. None of them, taken individually, is sufficient to rule-in or rule-out varices and high-risk varices.[278] However, NITs used in combination achieve better results (*e.g.* platelet to spleen ratio[279]), and in particular the combination of liver stiffness and platelet count (and even more if spleen size is added, *e.g.* LSPS[268]) is markedly better at diagnosing varices and varices needing treatment than any of the individual NITs.[269] In a systematic review of the literature, LSM by TE <20 kPa combined to a platelet count >150 G/L invariably led to less than 5% of high-risk varices requiring treatment being missed.[17] This led to an expert recommendation to use these non-invasive criteria (defined "Baveno VI" criteria) to spare endoscopy in patients with cACLD. Since the publication of the criteria, several studies and 2 meta-analyses[280,281] confirmed the validity of this approach in all the major aetiologies of liver disease including HIV-HCV coinfection[282] and patients who achieved SVR after treatment of HCV,[283] showing rates of missed high-risk varices ranging from 0 to 2%; hence, these criteria can be considered validated. Since the Baveno VI criteria are conservative and enable no more than 10–25% of endoscopies to be spared, studies looking for expanded criteria have been published. On a recent meta-analysis, the standard criteria have been once more validated, but the number of missed varices appeared too high with the proposed "Expanded criteria".[284] Aetiology-specific cut-offs of liver stiffness[285] and the combination with spleen stiffness[286] might enable the number of unnecessary endoscopies to be further reduced without increasing the risk of missing high-risk varices above 5%, but further data are required. In addition, individualisation of risk/benefit assessment using nomograms derived from well calibrated models is a promising approach for the future.[255]

Spleen stiffness measured by TE or pSWE shows similar or even better accuracy (in some studies) *vs.* liver stiffness to identify patients at high risk or low risk of high-risk varices. The most commonly reported cut-off using TE is 46 kPa. However, the failure rate using the standard probe of TE is high. A dedicated probe (100 Hz instead of 50 Hz frequency) has recently been commercialised. In the only paper published to date,[287] 260 patients were prospectively included in 2 centres. The success rate for SSM was significantly higher with the dedicated probe (92.5% *vs.* 76.0% of standard probe, p <0.001) and accuracy to detect high-risk varices was superior and outperformed liver stiffness. The use of Baveno criteria alone, *vs.* combined to standard spleen stiffness *vs.* new probe spleen stiffness resulted in 8.1% *vs.* 26.5% *vs.* 38.9% spared endoscopies. The rate of missed high-risk varices was, respectively, 0% with Baveno criteria alone *vs.* 4.7% in combination with spleen stiffness (any of the probes).

In an open-label randomised controlled trial, a strategy based on liver and spleen stiffness measurement to prompt endoscopic screening was similar to "endoscopy in all" in terms of rate of index variceal bleeding observed in the follow-up.[288] A meta-analysis of data from 45 studies using liver and spleen stiffness measurement (by different methods – TE, pSWE and 2D-SWE) to diagnose high-risk varices reported an AUROC for spleen stiffness of 0.81 (slightly inferior to that of liver stiffness and LSPS), but with a high sensitivity (0.87 *vs.* 0.85 for liver stiffness).[289]

According to the available data, it seems reasonable to attempt to measure spleen stiffness in patients in whom liver stiffness cannot be measured, or in addition to liver stiffness to further refine risk stratification. Cut-offs should be chosen according to the technique used (pSWE, 2D-SWE or TE).

Liver and spleen stiffness measured by MRE have been tested in a limited number of studies to detect and exclude varices needing treatment. Studies include patients with compensated and decompensated cirrhosis; although they confirm that higher liver and spleen stiffness are observed in patients with high-risk varices, data is insufficient to warrant recommendations.

In patients with HCV-related cirrhosis within 1 year of starting antiviral therapy, the combination of platelet count (>120 G/L) and albumin (>2.6 g/dl) – the RESIST-HCV criteria[290] – might be sufficient to rule-out high-risk varices without measuring liver stiffness. These criteria yielded a NPV of 97–99% in a large training and validation multi-centric cohort leading to about 25% of endoscopies being spared, which was similar to the Baveno VI criteria. The combination of MELD score = 6 and platelet count >150 G/L could reduce endoscopies by 54% without missing high-risk varices in 1 study.[291] However, these data have not been validated yet.

Large varices can be diagnosed on multidetector contrast-enhanced CT (MDCT) images with good accuracy. In a meta-analysis of 11 studies[292] the AUROC for the detection of oesophageal and gastric varices was 0.86 and 0.91, respectively. However, the studies included both compensated and decompensated patients, and no definite conclusion regarding the use in cACLD can be taken. Since CT is often performed in patients with cirrhosis, we consider it reasonable to state that varices should be actively searched for and reported on MDCT imaging.

How accurate are non-invasive scores, serum markers, liver stiffness, and imaging methods compared to liver biopsy, HVPG, Child-Pugh or MELD score for the prediction of clinical decompensation, HCC and mortality in cACLD?

Recommendations

- In patients with cACLD, liver stiffness at diagnosis should be used in addition to liver function tests to stratify the risk of clinical decompensation and mortality **(LoE 1, strong recommendation).**
- Annual repeated measurements of liver stiffness can be used to refine risk stratification in patients with cACLD **(LoE 5, weak recommendation)**.
- Liver stiffness can be used in addition to clinical variables and accepted risk scores to stratify the risk of HCC in patients with cACLD due to HBV **(LoE 3, weak recommendation)**.

Liver-related mortality is almost invariably preceded by clinical decompensation. Therefore, clinical decompensation has to be considered the most relevant event to predict (together with the onset of HCC) in cACLD.

Several NITs hold prognostic value, but only few of them have been extensively validated in compensated patients.

Among serum markers and combination of blood tests, ELF™ and vWF[262] have been associated with the development of clinical decompensation and mortality in patients with cACLD. vWF had an accuracy similar to that of MELD score for mortality in 1 study (AUROC 0.71 for vWF-Ag *vs.* 0.65 for MELD; p = 0.2). Its prognostic value was independent of HVPG values and associated with markers of bacterial translocation and inflammation in another study.[293] Data do not seem sufficient to recommend the use of vWF in clinical practice.

Liver stiffness by TE (and to lesser extent by pSWE and 2D-SWE) is a strong and validated predictor of first clinical decompensation, risk of HCC and death in patients with compensated chronic liver disease.[294,295] Its accuracy was similar to that of HVPG for predicting decompensation in 2 studies.[296,297] Studies focusing on patients with cACLD confirmed the prognostic value of LSM by TE, which is maintained even above the threshold indicating CSPH, indicating a higher risk with higher values.[298,299]

In untreated HCV-related cirrhosis, both liver and spleen stiffness predicted clinical decompensation, the latter showing a stronger predictive value (independent of MELD score; cut-off for discrimination: 54 kPa).[297] However, data regarding spleen stiffness are still insufficient to recommend its use for prognostic assessment in cACLD.

Similarly, few papers regarding the prognostic value of liver and spleen stiffness by pSWE and 2D-SWE, and regarding changes of LSM in the follow-up are available. As expected, increased values correlate with worse prognosis.

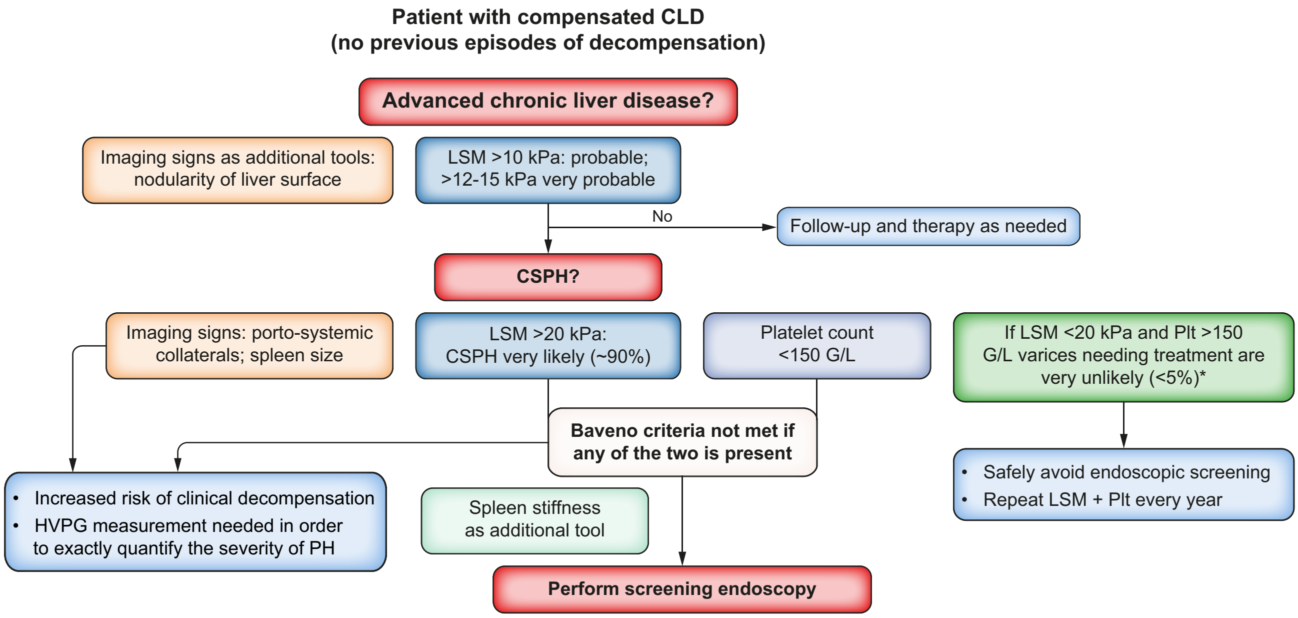

Fig. 2. Proposed use of NITs for risk stratification in patients with compensated chronic liver disease. CLD, chronic liver disease; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; PH, portal hypertension; Plt, platelet count.

Among imaging parameters, LSNS on routine CT remained associated with clinical decompensation and mortality independent of MELD score in patients with cirrhosis.[300] In addition, signs of portal hypertension and in particular the presence and area of porto-systemic collaterals are strongly associated with the development of clinical decompensation in patients with compensated cirrhosis, independent of liver function.[301,302] Fig. 2 shows how simple and readily available NITs can be applied to support clinical decisions in patients with cACLD.

Detailed information regarding HCC screening is provided in the EASL CPGs on HCC and in each of the EASL CPGs referring to specific diseases. Data regarding the prediction of HCC mostly come from cross-sectional and longitudinal studies in Asian cohorts of patients with untreated HBV.

Twelve risk scores have been developed based on clinical and laboratory characteristics (presence of cirrhosis, male gender, age, viral load) showing AUROCs 0.76–0.95 in the original cohorts.

The Page-B score and the modified PAGE-B scores have been externally validated and showed good results in Caucasian and Asian cohorts, with NPVs of 0.95–0.99 at 5 years.[303]

Liver stiffness is significantly associated with a higher risk of HCC, and changes in liver stiffness correlate with changes in the risk of HCC[304] in patients with cirrhosis due to HBV and HCV. A scoring system based on LSM, age, serum albumin and HBV DNA has been developed in patients with HBV[305] and ELF^{TM} score can further refine risk stratification in patients with intermediate risk according to liver stiffness-HCC risk index. Interestingly, the magnitude of the reduction of LSM on antiviral therapy (HBV)[306,307] or after achieving SVR (HCV)[101] is inversely associated with the risk of HCC in patients with cirrhosis due to these aetiologies. However, data is insufficient to indicate which patients can avoid HCC screening.

Appendix. Delphi round agreement on the statements and recommendations of the present CPGs

Statement/recommendation	Delphi Panel agreement
Non-invasive fibrosis tests should be used for ruling out rather than diagnosing advanced fibrosis in low-prevalence populations (LoE 1, Strong recommendation).	100%
Non-invasive fibrosis tests should be preferentially used in patients at risk of advanced liver fibrosis (such as patients with metabolic risk factors and/or harmful use of alcohol) and not in unselected general populations (LoE 2, Strong recommendation).	100%
ALT, AST and platelet count should be part of the routine investigations in primary care in patients with suspected liver disease, so that simple non-invasive scores can be readily calculated (LoE 2, Strong recommendation).	95%
The automatic calculation and systematic reporting of simple non-invasive fibrosis tests such as FIB-4, in populations at risk of liver fibrosis (individuals with metabolic risk factors and/or harmful use of alcohol) in primary care, is recommended in order to improve risk stratification and linkage to care (LoE 2, Strong recommendation).	100%

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Statement/recommendation	Delphi Panel agreement
Non-invasive scores, serum markers, liver stiffness and imaging methods can identify advanced fibrosis in patients at risk from low-prevalence populations significantly better than clinical acumen alone (LoE 1).	89%
Individuals at risk of advanced fibrosis due to metabolic risk factors and/or harmful use of alcohol should be entered into appropriate risk stratification pathways using non-invasive fibrosis tests (LoE 1, Strong recommendation).	100%
The selection of NITs and the design of diagnostic pathways for testing low-prevalence populations for advanced fibrosis should be performed in consultation with a liver specialist (LoE 3, Strong recommendation).	89%
In patients with ALD, LSM by TE <8 kPa is recommended to rule-out advanced fibrosis in clinical practice, with the following NITs as alternatives, if TE is not available (LoE 3; strong recommendation) - Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48 - Non-patented tests: FIB-4 <1.3	89%
Upon referral of patients at risk of ALD, LSM by TE ≥12-15 kPa is recommended to rule-in advanced fibrosis, after considering causes of false positives (LoE 2; strong recommendation).	89%
In patients with elevated liver stiffness and biochemical evidence of hepatic inflammation (AST or GGT >2x ULN), LSM by TE should be repeated after at least 1 week of alcohol abstinence or reduced drinking (LoE 3; strong recommendation).	95%
Non-invasive scores and LSM by TE and other elastography methods are not accurate in detecting fibrosis regression after SVR in HCV patients diagnosed with cACLD prior to antiviral therapy (LoE 3).	89%
The routine use of non-invasive scores and LSM by TE and other elastography methods is currently not recommended to detect fibrosis regression after SVR in HCV patients (LoE 3; strong recommendation).	89%
Cut-offs of LSM by TE used in patients with untreated HCV should not be used to stage liver fibrosis after SVR (LoE 4; strong recommendation).	95%
In patients with cACLD previous to antiviral therapy for HCV, LSM post-SVR could be helpful to refine the stratification of residual risk of liver-related complications; yearly repetition of LSM can be carried out while we await confirmatory data (LoE 3).	100%
Patients with cACLD previous to antiviral therapy for HCV should continue to be monitored for HCC and portal hypertension irrespective of the results of NITs post-SVR (LoE 3; strong recommendation).	79%
Non-invasive scores are not recommended for the diagnosis of steatosis in clinical practice (LoE 2; strong recommendation).	84%
Conventional ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice, despite its well-known limitations (LoE 1; strong recommendation).	100%
MRI-PDFF is the most accurate non-invasive method for detecting and quantifying steatosis. However, it is not recommended as a first-line tool given its cost and limited availability. Therefore, it is more suited to clinical trials (LoE 2; strong recommendation).	100%
CAP is a promising point-of-care technique for rapid and standardised detection of steatosis. However, given its limited availability and lack of head-to-head studies compared to ultrasound, CAP cannot yet be recommended as a first-line technique (LoE 2).	89%
Although there are no consensual cut-offs, values above 275 dB/m might be used to diagnose steatosis, since they showed over 90% sensitivity to detect steatosis (LoE 2).	79%
In patients with NAFLD: Liver biopsy remains the reference standard for the diagnosis of NASH, because none of the available NITs has acceptable accuracy (LoE 2).	89%
In patients with NAFLD: The following NITs are recommended to rule-out advanced fibrosis in clinical practice (LoE 1, strong): - LSM by TE <8 kPa - Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48 - Non-patented tests: FIB-4 <1.3 or NFS <-1.455	94%
Upon referral of a patient with FIB-4 over 1.3, the use of TE and/or patented serum tests should be used to rule-out/in advanced fibrosis (see Fig. 1) (LoE 2, strong recommendation).	94%
MRE is the most accurate non-invasive method for staging liver fibrosis. However, it is only marginally better than other NITs for F3–F4 fibrosis and it is not recommended as a first-line NIT given its cost and limited availability (LoE 2; strong recommendation). Therefore, it is more suited to clinical trials.	89%
Serum scores (APRI, FIB-4, NFS, ELF™) and LSM by TE should be used to stratify the risk of liver-related outcomes in NAFLD (LoE 3; strong recommendation).	89%
Repeated measurements of NITs can be used to refine stratification of risk of liver-related events in patients with NAFLD/NASH. Despite the lack of evidence regarding the optimal timeframe between subsequent LSM assessment, it seems reasonable to repeat NITs every 3 years in patients with early stage and every year in patients with advanced stage NAFLD (LoE 3; weak recommendation).	94%
Liver biopsy remains the reference for patient selection in phase IIb and phase III therapeutic trials and should be used for these purposes (LoE 1; strong recommendation).	95%
MRI-PDFF can be used to assess steatosis evolution under treatment (LoE 2; weak recommendation). However, the minimal decrease in MRI-PDFF that defines a clinically relevant change or treatment response needs to be better defined.	95%
Liver biopsy remains the reference to evaluate NASH resolution and liver fibrosis improvement and should be used for these purposes (LoE 2; strong recommendation).	84%
In patients with PBC, serum markers of fibrosis and non-invasive scores (combination of clinical and laboratory variables) are not recommended for fibrosis staging in clinical practice (LoE 3; strong recommendation).	79%
In patients with PBC, LSM by TE is the best surrogate marker for ruling in severe fibrosis/cACLD and should be used for this purpose using a cut-off of 10 kPa (LoE 3; strong recommendation).	89%
In patients with PSC, LSM by TE above 9.5 kPa can be used to support the diagnosis of advanced fibrosis in compensated patients with normal bilirubin and without high-grade stenosis (LoE 3; weak recommendation).	89%
In patients with PBC, non-invasive discrimination of early and advanced stage disease based on biochemical parameters (normal *vs.* abnormal albumin and bilirubin) and LSM by TE < or >10 kPa is recommended at baseline (LoE 3, strong recommendation).	94%

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Statement/recommendation	Delphi Panel agreement
During treatment, risk stratification should be based on the assessment of response to therapy by using continuous (GLOBE and UK-PBC risk scores) and/or qualitative criteria (Paris II, Toronto, Rotterdam, Barcelona, Paris I) of response and LSM by TE (LoE 3, strong recommendation).	89%
In patients with PSC, both the ELF^{TM} score and LSM by TE correlate with outcomes and they should be used for risk stratification both at baseline and during follow-up (LoE 3, strong recommendation).	89%
LSM by TE can be used in patients with treated AIH to monitor the disease course together with transaminases and IgG, and to stage liver fibrosis after at least 6 months of immunosuppressive therapy (LoE 3, weak recommendation).	84%
cACLD should be diagnosed using second-line tests (patented serum tests or elastography) in a specialised setting (LoE 2, strong recommendation).	100%
Fibrotest® or FibroMeter^{TM} or ELF^{TM} should be used to rule-out cACLD if available (LoE 3, strong recommendation).	83%
LSM by TE should be used to rule-out and diagnose cACLD using the following cut-offs: <8-10 kPa to rule-out; >12-15 kPa to rule-in. Intermediate values require further testing (LoE 3 strong recommendation).	89%
pSWE and 2D-SWE should be used to rule-out and diagnose cACLD, with AUROCs >0.90 in the published meta-analyses (LoE 2, strong recommendation).	100%
Inter-system variability should be taken into account when interpreting the results of different elastography techniques, since values, ranges and cut-offs are not comparable (LoE 3, strong recommendation).	89%
LSM by TE at a cut-off of >20-25 kPa should be used to diagnose CSPH in patients with cACLD (LoE 1, strong recommendation).	89%
Platelet count, spleen size and spleen stiffness should be used as additional NITs to further improve risk stratification for CSPH (LoE 3, strong recommendation).	89%
The presence of porto-systemic collaterals on ultrasound, CT or MRI is a sign of CSPH in patients with cACLD and should be routinely reported (LoE 2, strong recommendation).	100%
For an exact assessment of the severity of portal hypertension in cACLD beyond presence and absence of CSPH and for assessment of the haemodynamic response to treatment, HVPG remains the only validated tool and should not be substituted by NITs (LoE 1, strong recommendation).	84%
In patients with cACLD due to untreated viral hepatitis, HIV-HCV coinfection, alcohol, NAFLD, PBC and PSC, the finding of LSM by TE <20 kPa and platelet count >150 G/L (Baveno VI criteria) is a validated tool to rule-out high-risk varices and avoid endoscopic screening. These criteria should be used whenever TE is available (LoE 1a; strong recommendation).	100%
Spleen stiffness can be used as an additional tool to refine the risk of high-risk varices in cACLD (LoE 2; weak recommendation).	89%
CT should not be used for primary screening for oesophageal and gastric varices, but when doing a routine CT, varices should be looked for and reported (LoE 3, strong recommendation).	100%
In patients with cACLD, liver stiffness at diagnosis should be used in addition to liver function tests to stratify the risk of clinical decompensation and mortality (LoE 1, strong recommendation).	100%
Annual repeated measurements of liver stiffness can be used to refine risk stratification in patients with cACLD (LoE 5, weak recommendation).	89%
Liver stiffness can be used in addition to clinical variables and accepted risk scores to stratify the risk of HCC in patients with cACLD due to HBV (LoE 3, weak recommendation).	89%

Abbreviations

2D-SWE, bidirectional shear wave elastography; AAR, AST to ALT ratio; ALD, alcohol-related liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AOM, Amsterdam-Oxford model; AST, aspartate aminotransferase; AUROC, area under the receiver operator characteristic curve; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; CSPH, clinically significant portal hypertension; CT, computerised tomography; DAAs, direct-acting antivirals; EASL, European Association for the Study of the Liver; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; FLI, fatty liver index; GGT, gamma glutamyltransferase; HCC, hepatocellular carcinoma; HIS, hepatic steatosis index; HVPG, hepatic venous pressure gradient; LFS, liver fat score; LoE, level of evidence; LSM, liver stiffness measurement; LSNS, liver surface nodularity score; LSPS, liver stiffness-spleen diameter to platelet ratio score; LT, liver transplantation; MELD, model for end-stage liver disease; MR, magnetic resonance; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NFS, NAFLD fibrosis score; NIT(s), non-invasive tests; NPV, negative predictive value; OCEBM, Oxford Centre for Evidence-Based Medicine; PBC, primary biliary cholangitis; PPV, positive predictive value; PSC, primary sclerosing cholangitis; pSWE, point-shear wave elastography; SSM, spleen stiffness measurement; SVR, sustained virological response; TE, transient elastography; ULN, upper limit of normal; vWF, Von Willebrand factor; vWF-Ag, Von Willebrand factor antigen.

Conflict of interest

LC reports grant support from Gilead; consultant/advisory roles with Allergan, Alexion, Echosens, Gilead, Intercept, MSD, Novo Nordisk, Pfizer, and Servier; and sponsored lectures for Abbvie, Echosens, Gilead, Intercept, Novo Nordisk. SP reports consultant/advisory roles with AbbVie, Gilead, Intercept, Novordisk, and Pfizer; and sponsored lectures for Echosens, and Gilead. MT reports grant support from Novo Nordisk Foundation; sponsored lectures for Echosens, Siemens Healthcare, and Danish Agriculture & Food Council; and consulting fees from GE Healthcare. JB reports grants from Echosens, Intercept, and Inventiva; consulting fees from Echosens, Siemens, Diafir and Intercept; sponsored lectures for Echosens, Gilead, Intercept, Lilly and Siemens; consultant/advisory roles with BMS, Gilead, Intercept and Pfizer; and travel support from Gilead and Novartis. ET reports grant support from EU Horizon 2020 Grant for LiverScreen. AB, MF-R, and NC, report no conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data

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