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# CLINICAL and MOLECULAR HEPATOLOGY

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## **KASL guidelines for NIT in CLD**

Optimal cut-offs of NIT for NAFLD

Diagnostic accuracy of FIB-4 in NAFLD patients with  
T2DM

Prediction of HCC recurrence using VCTE

HCC prediction using VCTE-determined LSM

# KASL clinical practice guidelines for noninvasive tests to assess liver fibrosis in chronic liver disease

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## INTRODUCTION

### Preamble

#### Purpose and scope

Liver fibrosis refers to scar-like changes that occur in the liver when inflammation persists over a long period of time. Assessing liver fibrosis is crucial for predicting the prognosis of chronic liver disease (CLD) and managing patients with these conditions. The standard test for evaluating liver fibrosis is liver biopsy, which is invasive. Therefore, there have been ongoing efforts to evaluate liver fibrosis noninvasively using imaging studies and serum biomarkers. However, clinical guidelines have yet to be established that will provide healthcare providers with practical information about noninvasive tests (NITs) for assessing liver fibrosis in patients with CLDs.

We have systematically reviewed Korean and international studies to prepare evidence-based guidelines that reflect domestic conditions. When related studies on clinically essential issues were sparse, we sought to present consensus opinions of experts. These guidelines have been developed through reviews of medical evidence by experts to provide a practical reference for NITs to assess liver fibrosis in CLD. They are not absolute standards for treatment, and the best choice of practice for individual patients could vary depending on the individual situation. These guidelines will need to be revised and updated as relevant evidence based on new research accumulates in the future. However, these guidelines should not be modified, transformed, or reproduced without permission.

#### Target population

The target population of these guidelines is adult and pediatric patients with CLD, including chronic hepatitis B (CHB), chronic hepatitis C (CHC), nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ALD), and other CLDs including primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and congestive hepatopathy.

#### Intended users

These guidelines aimed to provide clinical information useful for decision-making among healthcare providers treating patients with CLD, enabling effective evaluation of liver fibrosis through NITs. In addition, these guidelines present specific and practical information to resident physicians, practitioners, and trainers.

#### Guideline development group, process, and funding source

The Clinical Practice Guideline Committee for Noninvasive Tests to Assess Liver Fibrosis in Chronic Liver Disease (Committee) was organized in accordance with proposals by the approval of the Korean Association for the Study of the Liver (KASL) Board of Executives and consists of 17 gastroenterologists, one radiologist, one surgeon, one cardiovascular surgeon, and one pediatrician specializing in hepatology. All expenses were paid by KASL and the financial support did not influence the contents of the guidelines. Each member collected, analyzed relevant evidence, and wrote the manuscript in his or her field.

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### Abbreviations:

AAR, AST to ALT ratio; AARPRI, AAR-to-platelet ratio index; AGREE II, Appraisal of Guidelines for Research and Evaluation II; AIH, autoimmune hepatitis; ALD, Alcohol-related liver disease; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AsAGP, asialo  $\alpha$ 1-acid glycoprotein AARPRI; AST, aspartate aminotransferase; AUC, area under the curve; AVT, antiviral therapy; BMI, body mass index; CAP, controlled attenuation parameter; cACLD, compensated advanced chronic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CLD, chronic liver disease; CSPH, clinically significant PH; CT, computed tomography; DAA, direct-acting antiviral; DFS, disease-free survival; ELF, enhanced liver fibrosis test; FAST, FibroScan-AST; FIB-4, Fibrosis-4 index; FLI, fatty liver index; GGT, gamma-glutamyl transpeptidase; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HA, hyaluronic acid; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; HSI, hepatic steatosis index; HVP, hepatic venous pressure gradient; ICER, incremental cost-effectiveness ratio; IPD-MA, individual patient data meta-analysis; IQR, interquartile range; KASL, the Korea Association for the Study of the Liver; kPa, kilopascals; LS, liver stiffness; MELD, Model for End-Stage Liver Disease; MMP 2, matrix metalloproteinase 2; M2BPGi, Mac-2 binding protein glycosylation isomer; MRI, Magnetic resonance imaging; MRE, magnetic resonance elastography; MRS, MR spectroscopy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NLFS, NAFLD liver fat score; NIT, noninvasive test; NPV, negative predictive value; OS, overall survival; PBC, primary biliary cholangitis; PH, portal hypertension; PIIIICP, procollagen III C-terminal propeptide; PIIIINP, procollagen III N-terminal Propeptide; PPV, positive predictive value; PRO-C3, pro-collagen 3 neoepitope; PSC, primary sclerosing cholangitis; pSWE, point SWE; QALY, quality-adjusted life-year; RFA, radiofrequency ablation; ROI, region-of-interest; SS, spleen stiffness; SWE, Shear wave elastography; SVR, sustained virologic response; T2DM, type 2 diabetes mellitus; TDF, tenofovir disoproxil fumarate; TIMP-1, tissue inhibitor of metalloproteinase 1; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography; 2D-SWE, two-dimensional SWE

### Literature search for evidence collection

The committee collected and analyzed relevant Korean and international literature through PubMed, MEDLINE, and KoreaMed to establish guidelines based on the latest research and evidence. Only literature written in Korean and English was searched, and search terms included 'noninvasive', 'liver fibrosis', 'chronic liver disease', 'chronic hepatitis', 'hepatitis B', 'hepatitis C', 'viral hepatitis', 'nonalcoholic fatty liver', 'nonalcoholic steatohepatitis', 'alcoholic liver disease', 'primary biliary cholangitis', 'autoimmune hepatitis', 'primary sclerosing cholangitis', 'congestive hepatopathy', 'hepatectomy', and specific terms of the subject.

### Level of evidence and grade of recommendations

The literature collected for evidence was analyzed through systematic review, and the level of evidence was classified based on the revised Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) with modifications (Table 1). They were categorized based on the possibility of changes in the assessment through further research as follows: high (A), with lowest possibility; moderate (B), with certain possibility; and low (C), with highest possibility. Specifically, depending on the type of study, randomized controlled trials start at a high level of evidence (A) and observational studies start at a low level of evidence (C). Considering factors affecting the study's quality, the evidence level was raised or lowered further. The strength of recommendation was either strong (1) or weak (2) according to the GRADE system. This was determined considering the clinical effects of recommendation, patient receptivity, and socioeconomic aspects as well as

the level of evidence. A strong recommendation indicates, for example, that the interventions could be applied in most patients with a greater possibility of desirable effects, high-quality evidence, presumed patient-important outcomes, cost-effectiveness, preference, and compliance. A weak recommendation indicates a suggestion made with less certainty, which could be considered favorable for many patients. Alternative interventions could be chosen for "weak recommendations" according to the preferences of patients or medical practitioners.

### List of key questions

The committee selected the following key questions and presented relevant evidence and recommendations.

1. What are the types of NITs, the principles and methods of measurement for each test, their advantages and disadvantages, and considerations for interpretation?
2. What is the diagnostic performance of NITs for liver fibrosis in CHB?
3. What is the diagnostic performance of NITs for liver fibrosis in CHC?
4. What is the diagnostic performance of NITs for liver fibrosis in NAFLD?
5. What is the diagnostic performance of NITs for liver fibrosis in alcohol-related liver disease?
6. What is the diagnostic performance of NITs for liver fibrosis in other CLDs (PBC, autoimmune hepatitis, PSC, and congestive hepatopathy)?
7. What is the cost-effectiveness of NITs?
8. How effective are NITs in screening high-risk groups in CLDs?

**Table 1.** The grading of recommendation, assessment, development, and evaluation (GRADE) system

Criteria		
Quality of Evidence		
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	B
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	C
Strength of Recommendation		
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.	1
Weak	Variability in preference and values, or more uncertainty. A recommendation is made with less certainty, higher cost or resource consumption.	2

9. What is the diagnostic and prognostic performance of NITs for portal hypertension?
10. What is the performance of NITs for predicting hepatocellular carcinoma (HCC), hepatic decompensation, and death?
11. How useful are NITs for monitoring the progression of CLDs?
12. What is the usefulness of NITs for evaluating liver fibrosis in pediatric and adolescent patients?

#### Internal and external review and approval process

Manuscripts and recommendations prepared by each member were reviewed for content integrity and validity of evidence through several committee meetings, and the quality of the guidelines was evaluated according to the Appraisal of Guidelines for Research and Evaluation II (AGREE II) criteria. The recommendations were assessed and revised based on critical review by the Delphi Committee, which was composed of 11 experts in the field of hepatology belonging to the KASL. The guidelines were reviewed at a meeting of an external review board consisting of six specialists in the field of hepatology and at a symposium open to all KASL members and the public, and they were then further modified. The final manuscript was endorsed by the Board of Executives of the KASL.

#### Release of the guideline and plan for updates

The KASL Clinical Practice Guideline for Noninvasive Tests to Assess Liver Fibrosis in Chronic Liver Disease was released in Korean at the Liver Week 2024 event (June 27, 2024). The guideline in Korean is available on the KASL website (<https://www.kasl.org>). The KASL plans to update the guideline as novel evidence accumulates and revision of the guidelines is deemed necessary to improve the national health of Korea. Recently, there has been an effort to change the terminology from NAFLD to metabolic dysfunction-associated fatty liver disease or metabolic dysfunction-associated steatotic liver disease, and studies on noninvasive liver fibrosis assessment have been published in relation to this transition. As evidence accumulates, it is anticipated that future revisions will be necessary.

## TYPES OF NONINVASIVE TESTS

CLD is a major public health issue worldwide, with a considerable disease burden. The decision to initiate treatment for CLD and its prognosis are primarily determined by the degree of liver fibrosis and its progression, as well as the risk of developing cirrhosis. Thus far, liver biopsy has been the standard test for diagnosing intrahepatic inflammation, steatosis, and fibrosis. However, there are drawbacks such as high cost, invasiveness, risk of complications, potential for interpretation errors based on subjective judgment, and sample error due to small tissue samples.<sup>1,2</sup> Therefore, in real-world clinical practice, NITs based on imaging studies are commonly used, such as abdominal ultrasound and/or panels using serum markers.

### Serum markers

#### Principles and methods of measurement

Serum markers can be divided into indirect markers that reflect liver damage, intrahepatic inflammation, or changes in liver function and portal pressure, and direct markers that measure components released into the bloodstream during fibrogenesis or extracellular matrix remodeling processes.<sup>3</sup>

Indirect markers include aspartate aminotransferase (AST), alanine aminotransferase (ALT), apolipoprotein A1, platelet count, total bilirubin, prothrombin time, gamma-glutamyl transpeptidase (GGT), haptoglobin,  $\alpha$ 2-macroglobulin, cholesterol, and asialo  $\alpha$ 1-acid glycoprotein (AsAGP).<sup>4-6</sup> As liver fibrosis progresses, serum ALT generally decreases, while AST tends to remain stable or increase. As a result, the AST-to-ALT ratio (AAR) increases, allowing for the prediction of the progression of liver fibrosis. Other indirect markers may provide some insight into the degree of liver fibrosis; however, generally, their diagnostic performance is not high.<sup>7</sup> Therefore, rather than using indirect markers alone, it is more common to combine various markers to create formulas or algorithms for diagnosis, such as AAR, AST-to-platelet ratio index (APRI), BARD score, Fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), and Forns index (Table 2).<sup>8-18</sup>

In some studies of patients with CHC, an AAR >1 was suggested as a diagnostic basis for cirrhosis; however, in other studies for patients with CHC and NAFLD, this mark-

er showed relatively low diagnostic performance.<sup>14,15</sup> APRI had been also studied among patients with CHC and NAFLD.<sup>14,16-18</sup> BARD score is a combination of AAR, body mass index (BMI), and type 2 diabetes mellitus (T2DM), and was developed using patients with biopsy-proven NAFLD.<sup>10,14</sup> FIB-4<sup>11</sup> and NFS<sup>12</sup>, both of which produce two cutoff values, have shown better positive and negative predictive values (PPVs and NPVs) than other indirect markers. In other words, using a cutoff value demonstrating high PPV (or specificity), advanced fibrosis ( $\geq$ F3) can be diagnosed, while using a cutoff value showing high NPV (or sensitivity), it can be excluded. For intermediate values (the so-called “gray zone”), liver biopsy should be considered.

FIB-4<sup>11,14</sup> was developed from patients co-infected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV); an algorithm has been proposed that sequentially applies other NITs, such as vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE), after excluding patients with a low likelihood of liver fibrosis using FIB-4’s high-sensitivity cutoff.<sup>19-21</sup> NFS, a model developed from patients with biopsy-proven NAFLD, is composed of age, T2DM, BMI, AAR, serum albumin, and platelet counts.<sup>17,22,23</sup>

Direct markers include procollagen III C-terminal propeptide (PIIICP), procollagen III N-terminal propeptide (PIIINP), matrix metalloproteinase 2 (MMP 2), hyaluronic acid (HA),

**Table 2.** Predictive models for liver fibrosis based on serum markers

Type	Equations	Primary study population
Based on indirect markers		
AAR <sup>14,15</sup>	AST [IU/L]/ALT [IU/L]	Chronic hepatitis C Nonalcoholic fatty liver disease
APRI <sup>16,18</sup>	(AST [IU/L]/(AST ULN [IU/L])/Platelet count [10 <sup>9</sup> /L]×100	Chronic hepatitis C Nonalcoholic fatty liver disease
BARD score <sub>10</sub>	AST/ALT ratio $\geq$ 0.8=2 points, weighted sum of BMI $\geq$ 28 [kg/m <sup>2</sup> ]=1 point, T2DM=1 point	Nonalcoholic fatty liver disease
FIB-4 <sup>11</sup>	Age [years]×AST [IU/L]/(Platelet count [10 <sup>9</sup> /L]× $\sqrt$ ALT [IU/L])	Coinfection with hepatitis C virus and human immunodeficiency virus
NFS <sup>12</sup>	-1.675+0.037×age [years]+0.094×BMI [kg/m <sup>2</sup> ]+1.13×IFG or T2DM (yes=1, no=0)+0.99×AST/ALT ratio-0.013×Platelet count [10 <sup>9</sup> /L]-0.66×serum albumin [g/dL]	Nonalcoholic fatty liver disease
Forns index <sup>13</sup>	7.811-3.131×ln(Platelet count [10 <sup>9</sup> /L])+0.781×ln(GGT[IU/L])+3.467×ln(age [years])-0.014×cholesterol [mg/dL]	Chronic hepatitis C
Based upon direct markers		
ELF <sup>3</sup>	-7.412+0.681×ln(HA)+0.775×ln(PIIINP)+0.494×ln(TIMP1)	Chronic hepatitis C
FibroTest <sup>30,32</sup>	Patented algorithm combining total bilirubin, GGT, $\alpha$ 2-macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and sex	Chronic hepatitis C
ADAPT <sup>27</sup>	exp (log <sub>10</sub> ((age [years]×PRO-C3 [ng/mL])/ $\sqrt$ platelet count [10 <sup>9</sup> /L]))+T2DM (yes=1, no=0)	Nonalcoholic fatty liver disease
FIBC3 <sup>28</sup>	-5.939+0.053×age [years]+0.076×BMI [kg/m <sup>2</sup> ]+1.614×T2DM (yes=1, no=0) -0.009×Platelet count [10 <sup>9</sup> /L]+0.071×PRO-C3 [ng/mL]	Nonalcoholic fatty liver disease
NIS4 <sup>24</sup>	e <sup>y</sup> /(1+e <sup>y</sup> ), where y= $\beta_0$ + $\beta_1$ ×log <sub>10</sub> (miR-34a-5p [Fold])+ $\beta_2$ × $\alpha$ 2-macroglobulin [g/L]+ $\beta_3$ ×(YKL-40 [ng/mL])+ $\beta_4$ ×(HbA1c [%])	Nonalcoholic fatty liver disease
NIS2+ <sup>31</sup>	e <sup>y</sup> /(1+e <sup>y</sup> ), where y= $\beta_0$ + $\beta_1$ ×log <sub>10</sub> (miR-34a-5p [Fold])+ $\beta_2$ ×log <sub>10</sub> (YKL-40 [ng/mL])+ $\beta_3$ ×sex (female=0, male=1)+ $\beta_4$ ×log <sub>10</sub> (miR-34a-5p [Fold])×sex (female=0, male=1)	Nonalcoholic fatty liver disease

AAR, AST/ALT ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; ULN, upper limit of normal; BMI, body mass index; T2DM, type 2 diabetes mellitus; NFS, nonalcoholic fatty liver disease fibrosis score; IFG, impaired fasting glucose; GGT, gamma-glutamyl transpeptidase; ELF, enhanced liver fibrosis; HA, hyaluronic acid; PIIINP, N-terminal peptide of pro-collagen III; TIMP1, tissue inhibitor of metalloproteinase 1; PRO-C3, pro-collagen 3 neopeptide; HbA1c, glycated hemoglobin. Beta coefficients of NIS2+ and NIS4 are not the same.

tissue inhibitor of metalloproteinase 1 (TIMP-1), YKL-40, and Mac-2 binding protein glycosylation isomer (M2BPGi).<sup>3,24-26</sup> In real-world practice, the use of equations which combine such direct markers is common; enhanced liver fibrosis test (ELF), FibroTest, ADAPT, FIB3, NIS4, and NIS2+ (Table 2).<sup>3,24,27-32</sup>

ELF, based upon direct markers, i.e., HA, PIIINP, and TIMP-1, showed acceptable diagnostic performance among patients with CHC and NAFLD.<sup>3</sup> FibroTest, which is primarily based on direct markers, also showed acceptable diagnostic performance among patients with CHC and NAFLD.<sup>30,32</sup> Furthermore, FIB3<sup>28</sup> and ADAPT<sup>27</sup>, which are based on pro-collagen 3 neopeptide (PRO-C3) as a direct marker as well as age, T2DM, platelet counts, and BMI, were also suggested. There have also been some studies reporting the usefulness of M2BPGi.<sup>26</sup>

#### Advantages, disadvantages, and considerations for interpretation

Serum biomarkers are generally easy to prescribe and utilize in a clinical setting, and unlike abdominal ultrasound, subjective judgments by physicians can be excluded. However, although they generally have high NPV, PPVs might vary according to the prevalence of liver fibrosis, so careful interpretation might be required.<sup>33</sup>

In terms of cost, predictive models based on indirect markers typically incur minimal additional expense since they rely on blood tests commonly conducted in clinics. In contrast, tests based on direct markers may require specialized equipment or reagents, which could limit their availability, depending on the scale or characteristics of specific healthcare facilities. Additionally, some markers are commercially patented, potentially resulting in relatively high costs. Nevertheless, direct markers generally exhibit higher diagnostic performance than indirect markers.

Serum markers are primarily collected from blood; hence, they can be influenced by various systemic conditions such as inflammation or infections within and outside the liver, abnormalities in other organs, or other acute illnesses. Therefore, interpretation should be done with caution depending on the patient's condition.<sup>34</sup> For example, in predictive models for liver fibrosis, ALT is often utilized as a key factor. However, ALT tends to decrease somewhat with age, so an increase in AAR can overestimate liver fibrosis in older populations.<sup>35</sup> Furthermore, conditions such as liv-

er congestion, acute hepatitis, or cholangitis, which can non-specifically cause a rapid increase in ALT, can distort the results of several serum markers based upon ALT, regardless of liver fibrosis.<sup>35</sup>

#### [Recommendations]

1. Liver fibrosis can be assessed noninvasively and conveniently using serum markers. (B1)

### Vibration-controlled transient elastography

VCTE, first introduced in 2003, has been reported to assess the degree of liver fibrosis noninvasively and accurately, and is currently widely used for the assessment of liver fibrosis.<sup>36-38</sup>

#### Principles and methods of measurement

##### *Principles of measurement*

VCTE is a diagnostic method that assesses the degree of liver fibrosis by measuring liver stiffness (LS) values.<sup>39</sup> Low-frequency elastic waves generated by the probe pass through the skin, between the ribs, propagate to the liver, and the movement speed of the ultrasound emitted and returned through the transducer is measured (Fig. 1). The measured propagation speed of the elastic wave is converted to LS according to the elastic modulus based on Hooke's law, and is expressed in kilopascals (kPa).<sup>37,40</sup> The stiffness of the tissue is proportional to the square of the propagation speed of the shear wave, so the faster the movement speed, the harder the liver, suggesting that liver fibrosis has relatively progressed.<sup>37</sup> LS values on VCTE ranges from 1.5–75 kPa, and the upper limit of normal (ULN) LS is approximately 5–5.5 kPa.<sup>41</sup>

The controlled attenuation parameter (CAP), which is measured alongside LS during VCTE, applies the signals obtained from VCTE to the diagnosis of liver steatosis, allowing for the assessment of the degree of fat deposition.<sup>42</sup>

##### *Methods of measurement*

In a supine position with the right arm raised as much as possible above the head, the probe is positioned perpendicularly on the skin surface between the right ribs at the location of the liver. The operator presses the button on the probe while avoiding the blood vessels within the liver.

Measurements are repeated more than 10 times, and the automatically calculated median value and error are recorded.<sup>43</sup> After consuming food, the amount of liver blood flow can increase, which may lead to a higher LS value; hence, fasting for at least 4 hours is recommended.<sup>44</sup>

### Advantages and disadvantages

The advantages of VCTE include being painless and noninvasive, the ability to conduct easy and quick examinations in an outpatient setting, and the capacity to obtain immediate results. Additionally, the results are highly reproducible, it directly measures LS, and the amount of liver parenchyma examined is more than 100 times that of liver biopsy.<sup>39,45</sup> The technique is also not difficult, so there is not a substantial learning curve for practitioners,<sup>46</sup> and it has excellent diagnostic performance for liver fibrosis in CLDs of various causes.<sup>47-49</sup>

However, results of VCTE can be difficult to obtain from patients with ascites or narrow intercostal space.<sup>39</sup> In cases of ascites, the elastic waves may not reach the liver parenchyma, and when the intercostal space is narrow, it becomes difficult to position the probe correctly. In addition, results of VCTE may be unreliable in individuals with a high BMI (>28 kg/m<sup>2</sup>). The risk of obtaining unreliable results of VCTE was relatively lower in studies conducted on Asians (1.1–3.5%) compared to those on populations in Western countries (4.3–7.0%), which can be attributed to the relatively lower BMI of Asians.<sup>50</sup> In addition, during pregnancy, VCTE examination is not recommended due to changes in the position of the liver.

### Considerations for interpretation

Some studies have suggested that the interquartile range (IQR) divided by the median value of valid tests (IQR/M) should be less than 0.3 to ensure the reliability of LS.<sup>51,52</sup> In addition, the risk of overestimating LS has been reported with elevated ALT, independently of liver fibrosis.<sup>53-55</sup> Therefore, patients with a high ALT level may not be good candidates for VCTE examination, or clinicians may need to apply different cutoff values for assessing liver fibrosis depending on the degree of ALT elevation.<sup>56</sup> In addition, other confounding factors including extra-hepatic cholestasis,<sup>57</sup> liver congestion due to heart failure,<sup>58</sup> and excessive alcohol consumption<sup>59-61</sup> also influence LS on VCTE.

LS measurement using VCTE demonstrated high diagnostic performance for liver fibrosis; however, considering the various clinical situations that may affect LS, the results should be interpreted by experts.

### [Recommendations]

1. VCTE can evaluate the degree of liver fibrosis noninvasively, rapidly, and conveniently. (A1)

### Shear wave elastography

Shear wave elastography (SWE) assesses the degree of liver fibrosis by measuring the speed of shear waves along with image information during abdominal ultrasound examination,<sup>37,40,62,63</sup> and techniques include both point SWE (pSWE) and two-dimensional SWE (2D-SWE).

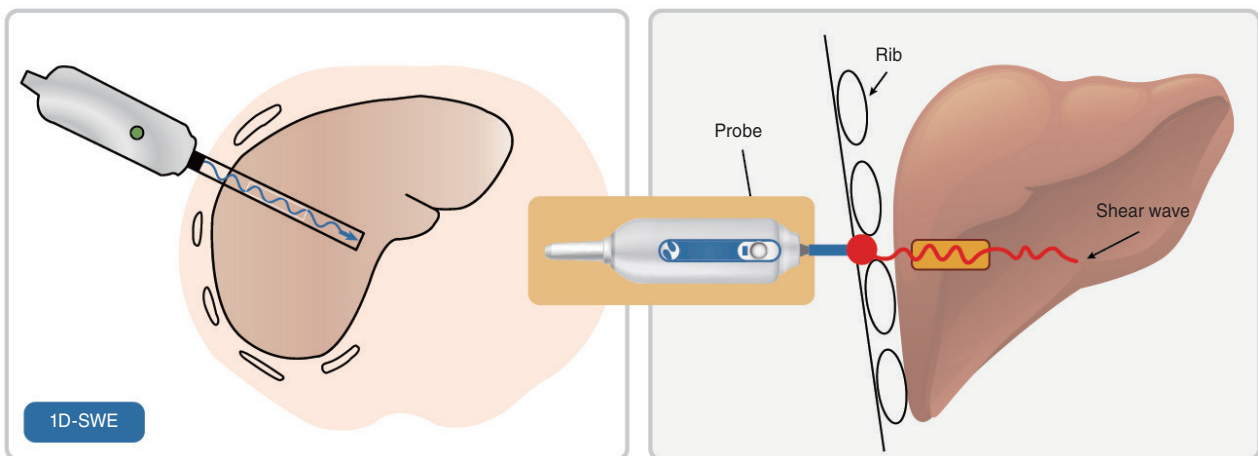


Figure 1. Principles of vibration-controlled transient elastography.<sup>43</sup>



### Principles of measurement

SWE imaging technique was designed in 1988 by Sarvazyan et al.<sup>64</sup> The basic principle is to measure the shear strain of different materials against externally applied force using SWE values that vary depending on the tissue medium.<sup>65,66</sup> To assess the degree of liver fibrosis, the transverse wave elasticity value is quantitatively calculated by measuring the propagation speed of the transverse shear wave generated in the region of interest (ROI) using acoustic radiation force impulse (ARFI) transmitted vertically from the transducer (Figs. 2 and 3).<sup>65,66</sup>

### Methods of measurement

For SWE, the probe is placed on the right upper abdomen, where the liver is anatomically located. Then, shear

strain is applied, the deformation of the medium measured, and Young's modulus presented as a quantitative value. The examination is usually performed on the right lobe of the liver through the intercostal space, and the ROI is selected in an area free of blood vessels and bile ducts. While the patient briefly holds their breath, the elastic modulus value is measured. If it is measured at a shallow depth of less than 1 cm below the liver capsule, the reproducibility and diagnostic ability of the test may be reduced due to reverberation artifacts, so the measurement is performed at a depth of 1.5–2 cm (Figs. 2 and 3). Because results may vary depending on measurement depth, a consistent depth is recommended for all follow-up tests on the same patient. Measurements can be made up to 7–8 cm from the probe, but to ensure the reproducibility of the test and

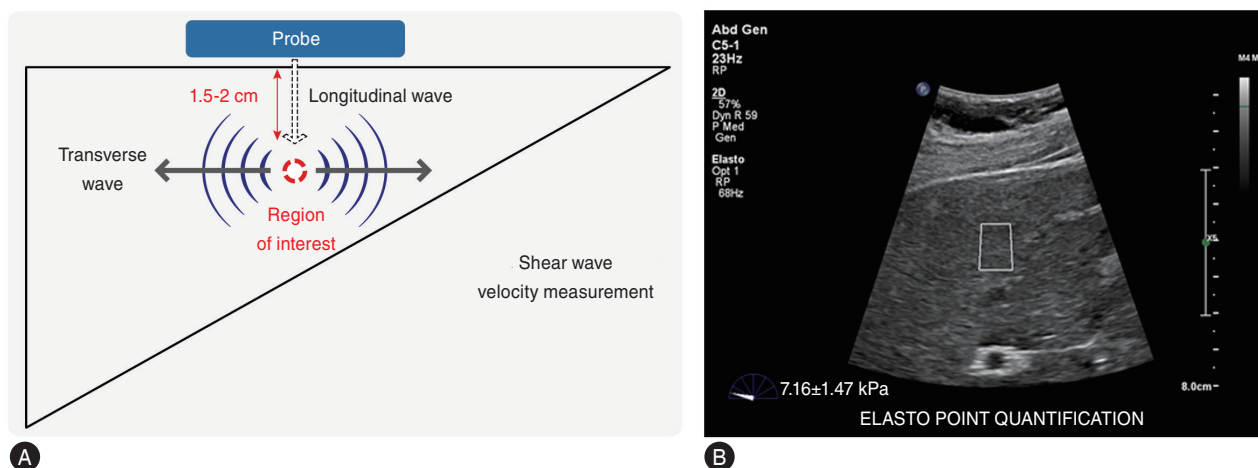


Figure 2. Principles of point shear wave elastography (A) and actual images (B).

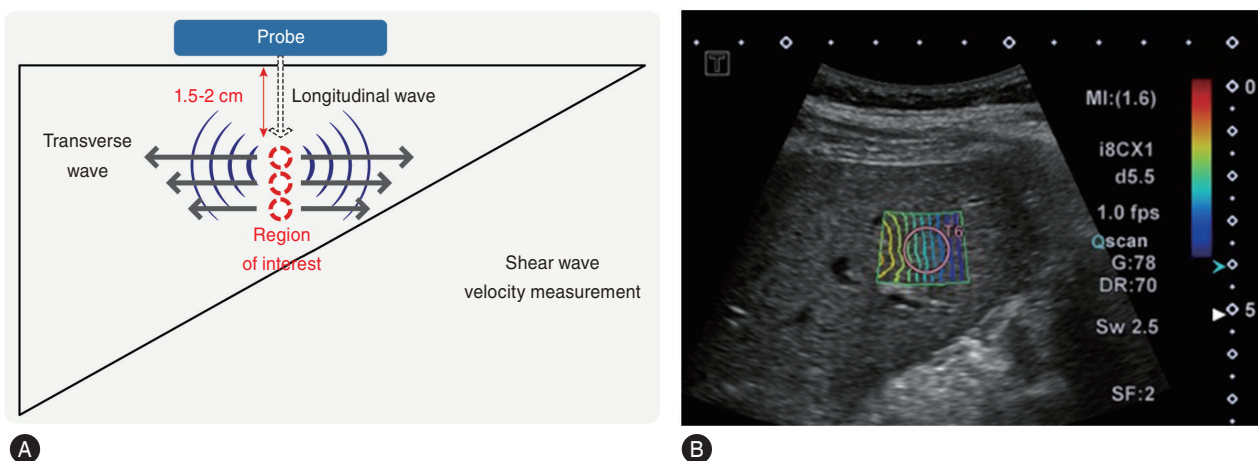


Figure 3. Principles of two-dimensional shear wave elastography (A) and actual images (B).

appropriate diagnostic ability for liver fibrosis, a distance of 4 to 4.5 cm should be maintained. After food intake, elasticity may increase due to increased hepatic blood flow, so fasting is required at least 4 hours before the test.<sup>38,67-69</sup> To increase the reliability of the test, the standard deviation of the elastic modulus values measured in more than 60% of repeat tests should be less than 30% of the median value.<sup>38,67-69</sup>

#### *Point shear wave elastography*

pSWE is a method of calculating the speed of shear waves obtained through focal tissue displacement using ARFI.<sup>37,40</sup> A shear wave is generated from the probe using a longitudinal wave with a frequency of 2.67 MHz in the ROI. At this time, detection pulses from multiple channels of ultrasound calculate the speed of the shear wave at a specific location and then present the elasticity of the tissue in m/s (measurement range: 0.5–4.4 m/s) (Fig. 2).<sup>40,43</sup> The test is repeated approximately 10 times and then the median of the effective elastic modulus value expressed in m/s or kPa is obtained.<sup>43,67,69</sup>

#### *Two-dimensional shear wave elastography*

2D-SWE is an elasticity test that uses ARFI, like pSWE, and generates a focal wave using a B-mode ultrasonic transducer. However, unlike pSWE, which focuses ultrasonic waves on one specific area and then generates shear waves at one frequency, 2D-SWE continuously generates sound waves targeting multiple focal zones in the longitudinal direction of ultrasonic waves. It generates a high-frequency range (60–600 Hz) shear wave amplified into a cone shape by focusing it (Fig. 3). Due to these differences, it has been reported that the diagnostic ability of 2D-SWE is higher than that of pSWE.<sup>67-72</sup> Afterwards, the progress of the shear wave is captured in real-time through ultrafast imaging using a plane wave that can obtain images at up to 20,000 frames per second, and the quantitative elastic modulus value is displayed in m/s or kPa on the ultrasound screen.<sup>43</sup> 2D-SWE can obtain an elastic image of a SWETM box in a wider range than pSWE and can measure elasticity by having one or more circular ROIs whose sizes can be adjusted.<sup>37,40,67,73-75</sup> The results are obtained after repeating the test 5 to 10 times and then obtaining the median of all valid measurements.<sup>69</sup>

#### **Advantages**

SWE is an objective and reproducible test and has the advantage of being able to obtain quantitative measurements without manual pressure while directly evaluating tissue elasticity. In addition, not only can elastography be determined in real time but the degree of liver fibrosis is provided in quantified values. Unlike VCTE, it can be examined while confirming the anatomical structure of the liver.<sup>76,77</sup>

#### **Considerations for interpretation**

The values of SWE for each disease vary from study to study, and the optimal cutoff values for diagnosing the stage of liver fibrosis have not been determined.<sup>70</sup> In addition, the range of shear wave elasticity measurements for diagnosing each stage of liver fibrosis is relatively wide, and the difference in cutoff values for distinguishing successive stages of liver fibrosis is also small.<sup>68,70,78</sup> For SWE to be a reliable staging criterion, the IQR/M should be less than 30% and less than 15% when reported in kPa and m/s, respectively.<sup>68,69,79,80</sup> Also, as with VCTE, the test results may be overestimated in cases of intrahepatic inflammation, cholestasis, right heart failure leading to liver congestion, amyloidosis, or food intake, so caution is required in the interpretation of the results.<sup>63,67-69,73,74,81</sup>

#### **[Recommendations]**

1. SWE can noninvasively assess the degree of liver fibrosis while observing the anatomical structure of the liver. (B1)

#### **Magnetic resonance elastography**

MRE leverages a technique based on phase-contrast magnetic resonance imaging to quantitatively assess the degree of liver fibrosis.

#### **Principles and methods of measurement**

MRE employs an active driver to produce shear waves, which are transmitted to liver tissue through a passive driver attached to the patient's body via a plastic tube (Fig. 4).

The passive driver is usually positioned on the right lobe of the liver, typically at the intersection of the right midclavicular line and the xiphoid process, due to the left lobe's

sensitivity to heart movement. The shear wave frequency should be fixed at 60 Hz, as it influences wave propagation speed. The amplitude is usually set at 50% as a default, but can be adjusted according to abdominal wall thickness to ensure optimal wave transmission and image quality. It is recommended the patient fast for at least four hours before the test to avoid falsely increased LS measurements due to postprandial blood flow. Magnitude and phase images are acquired at the end-expiratory phase across four axial levels. These images are processed with a multimodel direct inversion algorithm to produce grayscale and color elastogram images, as well as wave images depicting shear-wave propagation through the abdomen (Fig. 5).

LS value is quantified on MRE by drawing ROIs on grayscale elastogram images and calculating the weighted arithmetic mean of these measurements.

$$\text{Weighted arithmetic mean} = (m_1w_1 + m_2w_2 + m_3w_3 + m_4w_4) \div (w_1 + w_2 + w_3 + w_4),$$

where  $m_1$ - $m_4$  represent the average liver stiffness values from each slice, and  $w_1$ - $w_4$  are the corresponding area sizes.

When drawing ROIs, areas covered by a 95% confidence grid and those prone to measurement errors should be

carefully avoided. These include areas within 1 cm of the liver capsule, the gallbladder fossa, around major intrahepatic vessels, and 'hot spots', which refer to focal areas of higher stiffness than the surrounding liver, often found near the liver dome or directly beneath the passive driver. Automated software now exists that measures LS on MRE. It segments the liver in the magnitude image, automatically draws ROIs to avoid major intrahepatic vessels, and then transfers these regions to the grayscale elastogram image.<sup>82,83</sup>

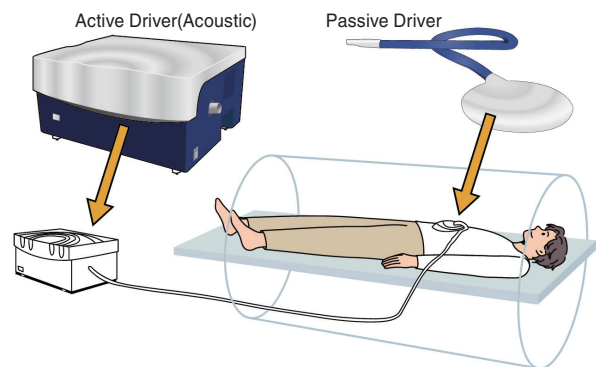


Figure 4. Principles of magnetic resonance elastography.

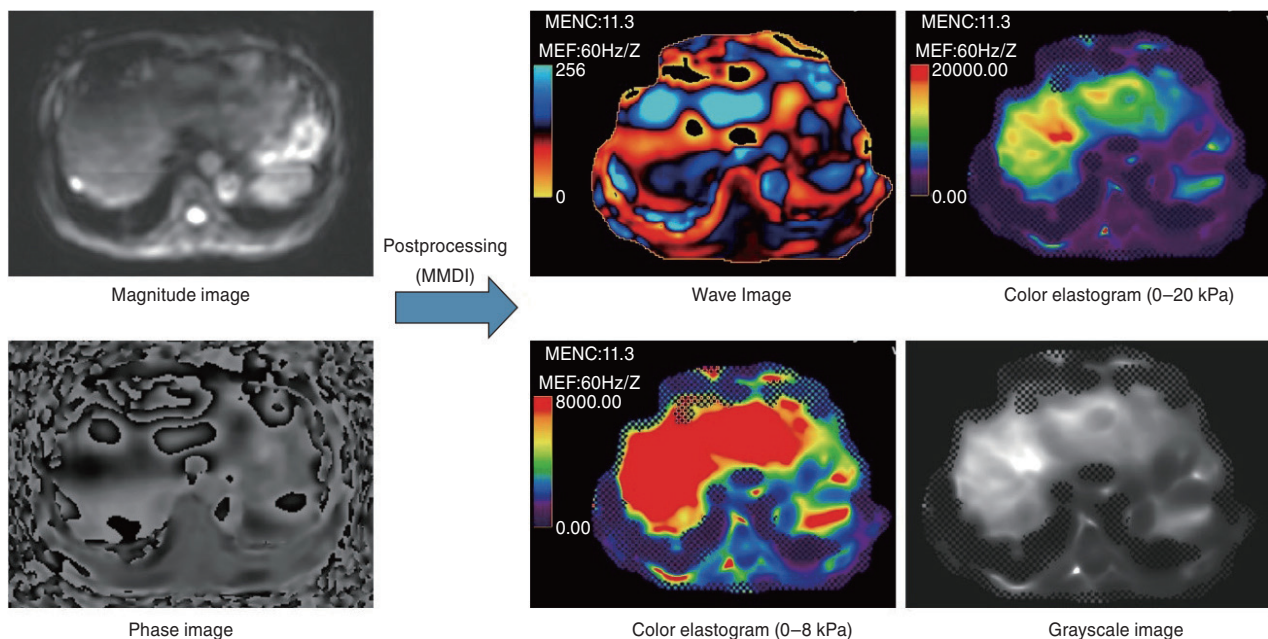


Figure 5. Examples of actual magnetic resonance elastography images. MMDI, multimodel direct inversion algorithm.

### Advantages and disadvantages

MRE shows the highest diagnostic performance among various NITs for assessing the degree of liver fibrosis.<sup>84</sup> Its repeatability has been validated in multiple studies, and a repeatability coefficient of 19% (indicating that changes in measurements above 19% are significant at a 95% confidence level) has been provided by the Quantitative Imaging Biomarker Alliance group under the Radiological Society of North America.<sup>85</sup> The reproducibility of the test has also been validated, demonstrating little variation in measurements across different MRI manufacturers, main magnetic field strengths (e.g., 1.5 Tesla vs. 3.0 Tesla), or imaging sequences (e.g., 2D gradient recalled echo vs. 2D spin echo-echo planar imaging [SE-EPI]).<sup>86,87</sup> The measurement success rate has been reported to be high, between 95% and 100%.<sup>88</sup>

For the few instances where MRE might fail, alternative strategies based on the specific cause of failure can be considered. If MRE fails due to excessive hepatic iron deposition, using a 1.5 Tesla machine or trying a 2D SE-EPI sequence may help. Situations where the bowel interferes between the liver and the passive driver, or where liver anatomy has been altered by surgical procedures or conditions like situs inversus, suggest relocating the passive driver to the liver's left lobe as a viable alternative. While MRE can still proceed in the presence of ascites, excessive fluid may necessitate conducting paracentesis prior to repeat testing.<sup>89</sup>

Constraints on MRE that have yet to be addressed include patient conditions such as claustrophobia, body size exceeding the scanner's capacity, or the presence of metallic implants (e.g., biliary stents, transjugular intrahepatic portosystemic shunt stents, or vascular embolization coils), which interfere with magnetic resonance imaging itself. The technique's main drawbacks are its high cost and limited accessibility.

### Considerations when interpreting MRE

Similar to other tissues, viscosity—as well as elasticity—can influence the speed of shear-wave propagation in MRE.<sup>90</sup> Since LS measurements using MRE may be falsely elevated by intrahepatic inflammation or bile stasis, it is advisable to conduct the examination after these clinical conditions have been addressed.<sup>91-93</sup> In contrast, liver steatosis does not affect LS.<sup>94,95</sup> Recent efforts have included distin-

guishing between intrahepatic inflammation and fibrosis using 3-dimensional<sup>96</sup> or multifrequency<sup>97</sup> MRE sequences.<sup>98,99</sup>

### [Recommendations]

1. MRE can assess the degree of liver fibrosis accurately and noninvasively. (A1)

## DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS

### Chronic hepatitis B

Assessment of liver fibrosis in patients with CHB is crucial for determining treatment timing and prognosis. Liver biopsy can reveal the extent of inflammation and fibrosis, which can help inform treatment decisions.<sup>1</sup> Antiviral therapy (AVT) is initiated when liver biopsy reveals moderate inflammation ( $\geq$ A2) or significant fibrosis ( $\geq$ F2).<sup>100,101</sup> However, due to the invasive nature of liver biopsy, alternate NITs such as serum markers, VCTE, SWE, and MRE have been employed.

#### Serum markers

Serum markers are easy to use and highly reproducible in clinical practice. While serum markers cannot easily distinguish between different stages of liver fibrosis, they have high specificity for diagnosing significant fibrosis or cirrhosis (F4) and are often used to rule out these stages. APRI, FIB-4, and FibroTest are the most extensively studied in research comparing liver biopsy and serum markers for assessing the degree of liver fibrosis in patients with CHB.

Although sensitivity and specificity vary across studies due to different cutoff values, the specificity of APRI and FIB-4 for diagnosing significant fibrosis is 83–90% and 84–95% and that for diagnosing cirrhosis is 69–93% and 75%, respectively, in patients with CHB (Table 3).<sup>102-104</sup> A meta-analysis of nine studies including 1,798 patients with CHB revealed that the area under the curve (AUC) for APRI to diagnose significant fibrosis and cirrhosis was 0.79 and 0.75, respectively.<sup>105</sup>

Unlike APRI and FIB-4, FibroTest comprises substances that are directly related to the turnover of extracellular ma-

trix and liver fibrosis, thus exhibiting better performance to diagnose significant fibrosis and cirrhosis (Table 3).<sup>103,106,107</sup> A study of 194 patients with CHB in Korea found that FibroTest had an AUC, sensitivity, and specificity of 0.90, 79%, and 93% for diagnosing significant fibrosis and 0.87, 80%, and 84% for diagnosing cirrhosis, respectively.<sup>106</sup> A meta-analysis of 16 studies including 2,494 patients with CHB found that the sensitivity and specificity of FibroTest for diagnosing significant fibrosis were 61% and 79%, respectively, whereas another meta-analysis of 13 studies including 1,754 patients with CHB found that these values were 62% and 91%, respectively, for diagnosing cirrhosis.<sup>107</sup> A study of 284 patients with CHB in France found that the AUCs of FibroTest and APRI were 0.78 and 0.72, respectively, for diagnosing significant fibrosis and 0.82 and 0.77, respectively, for diagnosing cirrhosis, with no significant difference in diagnostic performance.<sup>108</sup> However, another meta-analysis of 28 studies directly compared the diagnostic performance of serum markers using Bayesian inference in patients with CHB and found lower performance for APRI than for FIB-4 and FibroTest in terms of diagnosing cirrhosis.<sup>109</sup>

M2BPGi has recently been proposed as a marker for assessing the degree of liver fibrosis in patients with CLD, including viral hepatitis.<sup>110,111</sup> A meta-analysis of nine studies including 1,499 patients with CHB found that M2BPGi had a diagnostic AUC, cutoff value, sensitivity, and specificity of 0.72, 0.97, 67%, and 68%, respectively, for significant fibrosis and 0.81, 1.43, 67%, and 82%, respectively, for cirrhosis.<sup>112</sup>

Among serum markers, APRI and FIB-4 measure liver enzyme levels, which might generate false-positive results in patients with acute hepatitis, independent of the degree of liver fibrosis. Because FibroTest analyzes haptoglobin, FibroTest can generate false-negative results such as an increase due to acute inflammation and false-positive results due to hemolysis. Moreover, confirming the results of FibroTest can be time-consuming due to the need for various indicators, and its high cost limits widespread use of the test.<sup>113</sup>

In summary, despite the limitations of relatively small, cross-sectional studies, serum markers exhibit high specificity in diagnosing significant fibrosis and cirrhosis, proving valuable in ruling out these conditions.

### Vibration-controlled transient elastography

The diagnostic performance of VCTE for assessing the degree of liver fibrosis in patients with CHB has been widely studied based on liver histology. In several studies, LS values in patients with CHB during the immune inactive phase were 4.8–5.0 kPa, similar to values observed in normal healthy adults. However, in patients with hepatitis B e antigen (HBeAg)-negative CHB during the immune active phase, LS values were higher at 2.5–14.5 kPa.<sup>114,115</sup>

Table 4 shows that the AUC, cutoff value, sensitivity, and specificity for diagnosing significant fibrosis using VCTE were 0.66–0.97, 5.2–8.8 kPa, 59–93%, and 38–92%, respectively, and for diagnosing cirrhosis using VCTE were 0.85–0.98, 9.4–14.1 kPa, 52–100%, and 83–99%, respectively.<sup>41,47,49,104,106,108,116–123</sup> The diagnostic performance of VCTE for cirrhosis in patients with CHB was better overall than that for significant fibrosis.

In a meta-analysis of 18 studies including 2,772 patients with CHB, the AUC, cutoff value, sensitivity, and specificity were 0.86, 7.9 kPa, 74%, and 78% for diagnosing significant fibrosis and 0.93, 11.7 kPa, 85%, and 82%, respectively, for diagnosing cirrhosis.<sup>120</sup> Another meta-analysis of 27 studies including 4,386 patients with CHB found that the AUC, cutoff value, sensitivity, and specificity were 0.81, 7.2 kPa, 81%, and 82% for diagnosing significant fibrosis and 0.93, 12.2 kPa, 86%, and 88%, respectively, for diagnosing cirrhosis.<sup>121</sup> Furthermore, a meta-analysis of 28 studies including 4,540 patients with CHB found that the AUC, cutoff value, sensitivity, and specificity were 0.84, 6.0–8.8 kPa, 76%, and 79% for diagnosing significant fibrosis and 0.90, 8.0–14.1 kPa, 84%, and 84%, respectively, for diagnosing cirrhosis.<sup>123</sup>

However, it was unclear whether patients with acute liver disease, congestive hepatopathy, infiltrative liver disease, or obstructive cholestasis were excluded in the meta-analyses described above, and the reliability of VCTE results (whether fasting or not, with IQR/M  $\leq$ 0.3) was not clearly presented. The type of probe used to measure LS was also not clearly stated.

Furthermore, in a meta-analysis comparing the diagnostic performance of VCTE for significant fibrosis and cirrhosis among patients with CHB in Europe and Asia, ethnic disparities were observed.<sup>124</sup> The AUC, sensitivity, and specificity for diagnosing significant fibrosis in patients with CHB were 0.80, 73% and 66% in Europe and 0.87, 73%

**Table 3.** Diagnostic performance of serum markers for liver fibrosis in patients with CHB

Cross-sectional study																	
Serum marker	Reference	No. of patients	Nation	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)							
				No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%		
FIB-4	Zhu et al. <sup>104</sup> (2011)	175	China	79 (45.1)	0.86 (0.80–0.91)	1.7	74.0/84.0	-	-	-	-	1.0	0.77 (0.68–0.85)	29 (16.6)	0.77 (0.68–0.85)	1.0	69.0/75.0
APRI	Sebastiani et al. <sup>105</sup> (2011)	253	Italy	146 (57.7)	0.69 (0.63–0.76)	1.5	37.0/98.0	-	-	-	-	2.0	0.66 (0.60–0.71)	45 (17.8)	0.66 (0.60–0.71)	2.0	20.6/83.6
	Zhu et al. <sup>104</sup> (2011)	175	China	79 (45.1)	0.81 (0.74–0.87)	0.5	82.0/83.0	-	-	-	-	1.0	0.83 (0.77–0.90)	29 (16.6)	0.83 (0.77–0.90)	1.0	76.0/69.0
Fibro-Test	Sebastiani et al. <sup>105</sup> (2011)	253	Italy	146 (57.7)	0.69 (0.63–0.75)	0.48	54.0/83.0	-	-	-	-	0.75	0.93 (0.82–0.98)	45 (17.8)	0.93 (0.82–0.98)	0.75	42.0/91.0
	Kim et al. <sup>106</sup> (2012)	194	Korea	164 (84.5)	0.90 (0.84–0.97)	0.32	79.0/83.0	114 (58.8)	0.91 (0.86–0.95)	0.52	86.0/90.0	0.68	0.87 (0.82–0.92)	75 (38.7)	0.87 (0.82–0.92)	0.68	80.0/84.0
Meta-analysis																	
Serum marker	Reference	No. of patients	No. of studies	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)							
				No. of studies (patients)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%		
FIB-4	Xiao et al. <sup>102</sup> (2015)	6,513	23	22 (6,455)	0.76 (0.69–0.87)	3.25	16.2/95.2	22 (6,338)	0.80 (0.74–0.91)	3.25	17.0/98.0	1.63–2.65	0.78 (0.71–0.93)	19 (6,068)	0.78 (0.71–0.93)	1.63–2.65	64.3/85.5
APRI	Xiao et al. <sup>102</sup> (2015)	9,080	37	34 (8,855)	0.72 (0.61–0.88)	1.5	34.1/89.5	33 (8,254)	0.76 (0.68–0.87)	1.5	33.0/91.0	1.5	0.72 (0.50–0.85)	34 (8,773)	0.72 (0.50–0.85)	1.5	36.9/92.5
Fibro-Test	Salkic et al. <sup>107</sup> (2014)	4,248	16	16 (2,494)	0.78	0.48	62.0/79.0	-	-	-	-	0.74	0.87 (1,754)	13	0.87	0.74	62.0/91.0

CHB, chronic hepatitis B; FIB-4, fibrosis-4 index; APRI, aspartate aminotransferase-to-platelet ratio index; AUC, area under the curve; CI, confidence interval.

**Table 4.** Diagnostic performance of VCTE for liver fibrosis in patients with CHB

Cross-sectional study													
Reference	No. of patients	Nation	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)				
			No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)
Oliveri et al. <sup>41</sup> (2008)	268	Italy	115 (42.9)	0.97 (0.94–0.99)	7.5	93.0/88.0	-	-	-	0.97 (0.95–0.99)	11.8	93.0/88.0	
Chan et al. <sup>49</sup> (2009)	161	China	-	-	-	-	78 (48.4)	0.87 (0.82–0.93)	8.4	84.0/76.0	13.4	79.0/92.0	
Marcellin et al. <sup>47</sup> (2009)	173	France	87 (50.3)	0.81 (0.73–0.86)	7.2	70.0/83.0	43 (24.9)	0.93 (0.88–0.96)	8.1	86.0/85.0	11.0	70.0/83.0	
Degos et al. <sup>108</sup> (2010)	284	France	118 (41.5)	0.78 (0.72–0.83)	5.2	89.0/88.0	-	-	-	0.85 (0.78–0.93)	12.9	52.0/93.0	
Sporea et al. <sup>116</sup> (2010)	140	Romania	107 (76.4)	0.66	7.0	59.0/70.0	40 (28.6)	0.75	8.8	53.0/85.0	13.6	86.0/99.0	
Viganò et al. <sup>117</sup> (2011)	217	Italy	128 (59.0)	0.85 (0.77–0.91)	8.7	64.0/92.0	-	-	-	0.94 (0.90–0.98)	9.4	100/82.0	
Zhu et al. <sup>104</sup> (2011)	175	China	79 (45.1)	0.95 (0.91–0.98)	7.9	88.0/91.0	-	-	-	0.98 (0.96–0.99)	13.8	93.0/91.0	
Cardoso et al. <sup>119</sup> (2012)	202	France	85 (42.0)	0.82	7.2	74.0/88.0	34 (17.0)	0.82	8.1	88.0/81.0	11.0	75.0/90.0	
Kim et al. <sup>106</sup> (2012)	194	Korea	164 (84.5)	0.87 (0.80–0.94)	8.8	78.0/87.0	114 (58.8)	0.90 (0.85–0.95)	10.2	86.3/90.4	14.1	84.0/85.0	
Verveer et al. <sup>118</sup> (2012)	125	Netherlands	75 (60.0)	0.85	6.0	-	39 (31.2)	0.91	9.0	-	13.0	-	
Meta-analysis													
Reference	No. of patients	No. of studies	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)				
			No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)
Chon et al. <sup>120</sup> (2012)	2,772	18	10 (1,625)	0.859 (0.857–0.860)	7.9	74.3/78.3	4 (960)	0.887 (0.886–0.887)	8.8	74.0/63.8	11.7	84.6/81.5	
Li et al. <sup>21</sup> (2016)	4,386	27	19	0.88 (0.85–0.81)	7.2	81.0/82.0	19	0.91 (0.88–0.93)	9.1	82.0/87.0	12.2	86.0/88.0	
Qi et al. <sup>122</sup> (2018)	7,798	45	35 (6,202)	0.86 (0.83–0.89)	7.3	78.0/81.0	-	-	-	0.92 (0.90–0.94)	12.4	84.0/87.0	
Mingkai et al. <sup>123</sup> (2022)	4,540	28	23 (3,879)	0.84 (0.81–0.87)	6.0–8.8	76.0/79.0	-	-	-	0.90 (0.88–0.93)	8.0–14.1	84.0/84.0	

VCTE, vibration-controlled transient elastography; CHB, chronic hepatitis B; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

and 82%, respectively, in Asia, indicating superior performance in Asia. In diagnosing cirrhosis among patients with CHB, studies from Europe reported an AUC of 0.91 with a sensitivity of 67% and a specificity of 92%, whereas studies in Asia demonstrated the same AUC but with a higher sensitivity of 81% and a specificity of 86%. These ethnic differences might have been due to regional differences or variations in obesity and BMI across studies, which could have affected VCTE results and require further investigation.<sup>81</sup>

The diagnostic performance for significant fibrosis and cirrhosis varied across studies due to the nature of the selected study population and differences in cutoff values, but the diagnostic performance in most studies was relatively high at >0.80. An algorithm with cutoff values of 9.4 and 13.1 kPa has been proposed in Europe, which increased the sensitivity and specificity of diagnosing cirrhosis to >90%.<sup>117</sup>

In addition, given the high specificity of serum markers in diagnosing significant fibrosis and cirrhosis in patients with CHB, sequential VCTE can improve the diagnostic performance if serum markers fail to rule out these conditions.<sup>106,125</sup> In a study involving 194 patients with CHB, the AUCs for diagnosing significant fibrosis and cirrhosis increased from 0.89 to 0.94 and from 0.92 to 0.93, respectively, with FibroTest plus VCTE compared with that for FibroTest alone.<sup>106</sup> Another study with 222 patients with CHB in Korea demonstrated that sequentially performing sequential VCTE and ELF for diagnosing cirrhosis allowed 61–65% of all patients to avoid liver biopsy.<sup>126</sup>

In patients with CHB, intrahepatic inflammation may influence the results of VCTE, leading to overestimation of liver fibrosis.<sup>118,127</sup> Because elevated ALT levels in CHB might increase LS measurements independently of the degree of liver fibrosis, results of VCTE should be interpreted with caution.<sup>81</sup> Additionally, because AVT might reduce LS due to improvements in intrahepatic inflammation, cutoff values established in studies involving patients not receiving AVT might not be applicable to those on AVT. Furthermore, VCTE might be challenging to conduct in patients with right hepatectomy, ascites, severe obesity, or during pregnancy, and results could be aberrant due to postprandial measurement, liver masses, liver congestion, cholestasis, or infiltrative liver disease.<sup>41</sup>

## Shear wave elastography

### *Point shear wave elastography*

Table 5 summarizes the findings of liver fibrosis assessment in patients with CHB using pSWE.<sup>128–133</sup> The AUC, cutoff value, sensitivity, and specificity for diagnosing significant fibrosis and cirrhosis were 0.76–0.86, 1.23–1.59 m/s, 59–90%, and 63–88% and 0.72–0.97, 1.75–1.98 m/s, 67–85%, and 73–92%, respectively.

In a meta-analysis of eight studies including 518 patients with CHB, the AUC for diagnosing significant fibrosis and cirrhosis was 0.79 and 0.90, respectively, with cutoff values of 1.34 and 1.80 m/s, respectively.<sup>128</sup> Among 126 patients with CHB who underwent liver resection, pSWE demonstrated AUCs of 0.86 and 0.95 for significant fibrosis and cirrhosis, respectively, outperforming APRI and FIB-4, which had AUCs of 0.75–0.77 and 0.75–0.78, respectively.<sup>133</sup> The AUC for diagnosing significant fibrosis and cirrhosis in 180 patients with CHB was 0.76 and 0.83 for pSWE and 0.81 and 0.80 for VCTE, respectively, suggesting similar diagnostic performance. Similar to VCTE, pSWE was influenced by ALT level, with higher cutoff values for diagnosing significant fibrosis and cirrhosis observed in patients with elevated ALT levels compared to in patients without elevated ALT levels.<sup>130</sup> A study in China involving 81 patients with CHB assessed liver fibrosis by liver biopsy and found AUCs of 0.76 and 0.72 for diagnosing significant fibrosis and 0.75 and 0.87 for diagnosing cirrhosis with pSWE and VCTE, respectively, suggesting similar diagnostic performance between pSWE and VCTE.<sup>131</sup>

### *Two-dimensional shear wave elastography*

Numerous studies have highlighted the excellent diagnostic performance of 2D-SWE in the assessment of liver fibrosis in patients with CHB (Table 6).<sup>134–143</sup> The AUC, cutoff value, sensitivity, and specificity using 2D-SWE were 0.88–0.97, 6.9–8.2 kPa, 77–94%, and 74–92% for diagnosing significant fibrosis and 0.83–0.98, 8.0–21.4 kPa, 80–97%, and 73–95%, respectively, for diagnosing cirrhosis.

A meta-analysis of data from 13 studies of 400 patients with CHB found that the AUC, cutoff value, sensitivity, and specificity were 0.91, 7.1 kPa, 88%, and 74% for diagnosing significant fibrosis and 0.91, 11.5 kPa, 80%, and 93%, respectively, for diagnosing cirrhosis.<sup>144</sup> A meta-analysis of 11 studies including 2,623 patients with CHB found that the AUC and cutoff value were 0.92 and 7.9 kPa, respectively,



**Table 5.** Diagnostic performance of pSWE for liver fibrosis in patients with CHB

Cross-sectional study														
Reference	No. of patients	Nation	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)					
			No. of patients (%)	AUC (95% CI)	Cutoff value (m/s)	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value (m/s)	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value (m/s)	Sensitivity%/specificity%
Friedrich-Rust et al. <sup>129</sup> (2013)	114	Germany	32 (28.1)	0.79 (0.67–0.91)	1.23	-	13 (11.4)	0.94 (0.88–0.99)	1.60	-	5 (4.4)	0.97 (0.93–1.00)	1.75	-
Dong et al. <sup>131</sup> (2015)	81	China	49 (60.5)	0.76 (0.63–0.90)	1.30	82.9/65.0	24 (29.6)	0.88 (0.80–0.97)	1.54	76.2/90.0	8 (9.9)	0.72 (0.50–0.94)	1.84	66.7/85.5
Zhang et al. <sup>130</sup> (2015)	180	China	129 (71.7)	0.76 (0.70–0.83)	1.46	59.0/88.0	69 (38.3)	0.85 (0.79–0.91)	1.59	71.0/86.0	33 (18.3)	0.83 (0.75–0.90)	1.75	73.0/84.0
Park et al. <sup>132</sup> (2016)	105	Korea	78 (74.3)	0.81 (0.73–0.90)	1.31	89.7/63.0	51 (48.6)	0.85 (0.77–0.92)	1.81	78.4/78.8	30 (28.6)	0.75 (0.66–0.85)	1.98	66.7/73.3
Li et al. <sup>133</sup> (2017)	126	China	76 (60.3)	0.86 (0.79–0.92)	1.59	67.6/88.5	34 (27.0)	0.94 (0.88–0.98)	1.74	87.5/85.1	20 (15.9)	0.95 (0.89–0.98)	1.92	85.0/92.5
Meta-analysis														
Reference	No. of patients	No. of studies	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)					
			No. of studies (patients)	AUC (95% CI)	Cutoff value (m/s)	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value (m/s)	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value (m/s)	Sensitivity%/specificity%
Friedrich-Rust et al. <sup>129</sup> (2012)	518	8	8 (518)	0.79 (0.63–0.96)	1.34	79.0/85.0	8 (518)	0.83 (0.70–0.96)	1.55	86.0/86.0	8 (518)	0.90 (0.79–1.00)	1.80	92.0/86.0

pSWE, point shear wave elastography; CHB, chronic hepatitis B; AUC, area under the curve; CI, confidence interval.

**Table 6.** Diagnostic performance of 2D-SWE for liver fibrosis in patients with CHB

Cross-sectional study														
Reference	No. of patients	Nation	Significant fibrosis (≥F2)				Advanced fibrosis (≥F3)				Cirrhosis (F4)			
			No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)
Leung et al. <sup>134</sup> (2013)	226	China	136 (60.2)	0.88 (0.82–0.94)	7.1	84.7/92.1	80 (35.4)	0.93 (0.88–0.97)	7.9	89.8/90.3	35 (15.5)	0.98 (0.95–0.99)	10.1	97.4/93.0
Zeng et al. <sup>135</sup> (2014)	206	China	112 (54.4)	0.92 (0.88–0.96)	7.2	86.4/87.0	64 (31.1)	0.95 (0.92–0.97)	9.1	91.9/85.7	39 (18.9)	0.95 (0.91–0.98)	11.7	91.9/85.7
Zheng et al. <sup>136</sup> (2015)	167	China	98 (58.7)	0.86 (0.80–0.91)	8.0	85.7/73.9	58 (34.7)	-	-	-	34 (20.4)	0.93 (0.88–0.96)	21.4	91.2/79.7
Wu et al. <sup>137</sup> (2016)	437	China	206 (47.1)	0.90 (0.87–0.93)	8.2	78.2/85.3	123 (28.1)	-	-	-	61 (14.0)	0.93 (0.90–0.95)	11.3	91.8/84.3
Zhuang et al. <sup>138</sup> (2017)	304	China	264 (86.8)	0.97 (0.95–0.99)	7.6	92.0/90.0	214 (70.4)	0.96 (0.94–0.99)	9.2	91.6/96.7	167 (54.9)	0.98 (0.97–1.00)	10.4	94.6/94.9
Zeng et al. <sup>139</sup> (2017)	257	China	119 (46.3)	0.88 (0.83–0.92)	7.1	88.9/76.4	64 (24.9)	0.92 (0.87–0.95)	8.3	89.7/76.8	34 (13.2)	0.93 (0.89–0.96)	11.3	93.6/87.3
Xie et al. <sup>140</sup> (2021)	161	China	130 (80.7)	0.92 (0.87–0.96)	7.3	83.1/87.1	84 (52.2)	0.92 (0.86–0.95)	8.0	94.1/77.9	64 (39.8)	0.94 (0.89–0.97)	10.0	90.6/89.7
Song et al. <sup>141</sup> (2023)	420	China	306 (72.9)	0.89 (0.85–0.92)	6.9	77.0/86.0	227 (54.0)	0.91 (0.88–0.94)	7.4	80.0/86.0	134 (31.9)	0.83 (0.79–0.87)	8.0	81.0/73.0
Meta-analysis														
Reference	No. of patients	No. of studies	Significant fibrosis (≥F2)				Advanced fibrosis (≥F3)				Cirrhosis (F4)			
			No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)
Herrmann et al. <sup>144</sup> (2018)	400	4	4 (400)	0.91 (0.89–0.94)	7.1	87.6/73.6	4 (400)	0.93 (0.91–0.95)	8.1	94.9/73.1	4 (400)	0.96 (0.92–0.96)	11.5	79.9/93.3
Wei et al. <sup>142</sup> (2020)	2,623	11	-	0.92 (0.89–0.94)	7.9	88.0/83.0	-	-	-	-	-	-	-	-
Dong et al. <sup>145</sup> (2021)	3,085	13	13 (1,716)	0.89 (0.86–0.92)	7.6	80.9/79.3	8 (1,020)	0.95 (0.91–0.95)	9.1	89.1/84.7	12 (782)	0.94 (0.92–0.96)	10.9	87.3/86.1

CHB, chronic hepatitis B; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

for diagnosing significant fibrosis.<sup>142</sup> The mean cutoff for diagnosing significant fibrosis in studies excluding patients previously treated with AVT was 7.2 kPa, lower than the mean of 8.9 kPa in studies that included patients treated with AVT.<sup>142</sup> Further studies are needed to establish cutoff values based on AVT, which is a potential confounder.

In a comparative study of serum markers in 304 patients with CHB in China, the AUCs for diagnosing significant fibrosis were 0.97 for 2D-SWE, 0.73–0.79 for APRI, and 0.98 for FIB-4 and those for diagnosing cirrhosis were 0.97 for 2D-SWE, 0.73–0.79 for APRI, and 0.98 for FIB-4.<sup>138</sup> A meta-analysis found that 2D-SWE showed significantly better performance for diagnosing significant fibrosis and cirrhosis than VCTE, by 11.2% and 6.5%, respectively.<sup>144</sup> However, a study of 106 patients with CHB in Greece found a slightly higher measurement success rate for VCTE than for 2D-SWE among patients with obesity (92% vs. 86%).<sup>145</sup>

ALT levels can affect the results of SWE, and a study of 515 patients with CHB showed that having two cutoff values based on ALT improved the performance of 2D-SWE for diagnosing significant fibrosis and cirrhosis.<sup>146</sup> Cutoff values of 5.4 and 9.0 kPa were applied for ALT  $\leq 2$  times the ULN, while 7.1 and 11.2 kPa were used for ALT levels  $>2$  times the ULN to diagnose significant fibrosis. In addition, cirrhosis has been diagnosed using cutoff values of 8.1 and 12.3 kPa for ALT levels  $\leq 2$  times the ULN and 11.9 and 24.7 kPa for ALT levels  $>2$  times the ULN.<sup>147</sup>

Moreover, in a cohort of 266 patients with CHB, the application of deep learning radiomics alongside SWE demonstrated enhanced diagnostic performance for significant fibrosis and cirrhosis compared to using 2D-SWE alone.<sup>148</sup>

### Magnetic resonance elastography

Numerous studies have demonstrated the high accuracy of MRE in diagnosing liver fibrosis in patients with CHB, consistently showing a diagnostic AUC of  $>0.90$  (Table 7).<sup>143,149-153</sup> The AUC, cutoff value, sensitivity, and specificity of MRE were 0.91–0.99, 2.5–3.2 kPa, 82–97%, and 95–100% for diagnosing significant fibrosis and 0.89–0.99, 3.5–4.3 kPa, 84–100%, and 91–98%, respectively, for diagnosing cirrhosis in patients with CHB. A study of 170 patients with CHB in Korea found that MRE had AUC and cutoff values of 0.97 and 2.7 kPa for diagnosing significant fibrosis and of 0.92 and 3.7 kPa for diagnosing cirrhosis.<sup>149</sup> Unlike VCTE, MRE did not correlate with inflammatory sta-

tus in the liver, and the measurement success rate was 93%.<sup>149</sup>

A study of 63 patients with CHB in Singapore found that MRE had a higher diagnostic performance than the serum markers of APRI, AAR, and prothrombin index for diagnosing significant fibrosis and cirrhosis.<sup>150</sup> In a meta-analysis of 24 studies including 5,111 patients with CHB, the cutoff values for diagnosing significant fibrosis and cirrhosis were 3.0 and 4.6 kPa, respectively, and diagnostic performance was better for MRE than for VCTE.<sup>153</sup> In a meta-analysis of 15 studies including 2,128 patients, the AUC was 0.94–0.97 for MRE and 0.82–0.85 for pSWE for diagnosing significant fibrosis, with MRE having significantly better diagnostic performance.<sup>154</sup> A meta-analysis of 72 studies involving 20,356 patients with CHB found that the AUCs of MRE, 2D-SWE, pSWE, and FIB-4 were 0.97, 0.89, 0.76, and 0.75 and 0.97, 0.94, 0.77, and 0.82, respectively, for diagnosing significant fibrosis and cirrhosis.<sup>143</sup>

The AUC for stratifying liver fibrosis by MRE was similarly high at 0.97 and 0.98 among 281 patients with and without CHB, respectively, but the cutoff values for diagnosing cirrhosis in patients with CHB and other causes of CLD were 3.67 and 4.65 kPa, respectively.<sup>151</sup> These differences in cutoff values based on the cause of liver disease are similar to previous findings with VCTE and might be due to histological differences between hepatitis due to other causes such as CHC.<sup>50,155</sup> CHB tends to result in a macronodular and heterogeneous liver morphology, and total fibrosis might be lower in CHB than in CHC.<sup>50,116,155</sup>

A Korean study of 63 AVT naïve patients with CHB, high viral titers, and normal or mildly elevated ALT levels found AUCs for MRE, 2D-SWE, FIB-4, and APRI of 0.91, 0.84, 0.70, and 0.72, respectively, for diagnosing significant fibrosis. This indicated significantly better diagnostic performance for MRE than for FIB-4 and APRI, but the AUC of 2D-SWE did not significantly differ from that of FIB-4 or APRI.<sup>152</sup> These results suggest that MRE is a more accurate noninvasive method for diagnosing significant fibrosis and determining AVT in treatment-naïve patients with CHB compared with 2D-SWE.

**Table 7.** Diagnostic performance of MRE for liver fibrosis in patients with CHB

Cross-sectional study														
Reference	No. of patients	Nation	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)					
			No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%
Lee et al. <sup>149</sup> (2014)	170	Korea	151 (88.8)	0.99 (0.97–0.99)	2.7	95.4/95.6	125 (73.5)	0.99 (0.97–0.99)	3.0	95.2/93.8	81 (47.6)	0.99 (0.97–0.99)	3.9	95.1/94.5
Venkatesh et al. <sup>150</sup> (2014)	63	Singapore	39 (61.9)	0.99 (0.94–1.00)	3.2	97.4/100	29 (46.0)	0.99 (0.93–1.00)	3.7	100/94.1	21 (33.3)	0.98 (0.92–1.00)	4.3	100/95.2
Chang et al. <sup>151</sup> (2016)	281	Korea	257 (91.5)	0.97 (0.95–0.99)	2.6	90.7/96.0	213 (75.8)	0.95 (0.92–0.97)	2.9	89.2/88.2	139 (49.5)	0.92 (0.89–0.95)	3.7	83.5/90.7
Park et al. <sup>152</sup> (2019)	63	Korea	44 (69.8)	0.91 (0.81–0.97)	2.5	81.8/94.7	30 (47.6)	-	-	-	16 (25.4)	0.89 (0.79–0.96)	3.5	88.9/97.8
Meta-analysis														
Reference	No. of patients	No. of studies	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)					
			No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%	No. of studies (patients)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%
Xiao et al. <sup>153</sup> (2017)	1,470	9	9 (1,470)	0.98 (0.95–0.98)	3.0	92.8/93.7	9 (1,470)	0.97 (0.96–0.99)	3.6	89.6/93.2	9 (1,470)	0.97 (0.97–0.98)	4.6	89.5/92.0
Dong et al. <sup>143</sup> (2021)	1,134	9	9 (716)	0.97 (0.95–0.98)	3.1	89.3/91.7	8 (493)	0.97 (0.96–0.99)	4.0	88.6/91.1	8 (274)	0.97 (0.97–0.98)	4.7	91.4/92.4

MRE, magnetic resonance elastography; CHB, chronic hepatitis B; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

### [Recommendations]

1. APRI, FIB-4, and FibroTest have low sensitivity and high specificity, making them suitable for excluding significant fibrosis and cirrhosis in patients with CHB. (B1)
2. VCTE can diagnose significant fibrosis and cirrhosis with high sensitivity and specificity in patients with CHB. (A1)
3. SWE and MRE demonstrate excellent diagnostic performance for significant fibrosis and cirrhosis in patients with CHB. (B1)
4. Sequential or simultaneous testing of serum markers and VCTE will likely improve the diagnostic performance of significant fibrosis and cirrhosis in patients with CHB. (B2)

## Chronic hepatitis C

Assessment of fibrotic burden in patients with CHC is crucial as it is a major factor determining prognosis, including HCC development, occurrence of liver-related complications, and mortality.<sup>156</sup> Various serum markers, including FIB-4 and APRI, have been developed in CHC cohorts, and imaging studies such as VCTE and SWE are also utilized in the diagnosis of liver fibrosis in patients with CHC.

### Serum markers

Various serum markers have been evaluated in patient cohorts undergoing liver biopsy in order to improve noninvasive diagnosis of liver fibrosis in patients with CHC, including several with sufficient validation through multiple studies (Table 8).<sup>3,9,13,157-166</sup>

FIB-4 was developed in a cohort of 832 patients with concurrent CHC and HIV infection.<sup>11</sup> In a study involving 847 patients with CHC, the AUC for diagnosing advanced fibrosis was 0.85, and that of diagnosing cirrhosis was 0.91. A FIB-4 value  $<1.45$  demonstrated a high NPV of 94.7%, while a FIB-4 value  $>3.25$  showed a high PPV of 82.1%, making it useful for excluding or diagnosing advanced fibrosis.<sup>157</sup> The diagnostic performance of FIB-4 was assessed in 101 patients with CHC in Korea, and the AUC for diagnosing significant fibrosis was 0.87, with a cutoff value of 1.935, sensitivity of 97.1%, and specificity of 69.7%. The AUC for diagnosing advanced fibrosis was 0.86, with a cut-

off value of 3.81, sensitivity of 76.9%, and specificity of 85.5%. For diagnosing cirrhosis, the AUC was 0.83, with a cutoff value of 3.84, sensitivity of 85.0%, and specificity of 75.3%.<sup>167</sup> In Western studies, the AUCs for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis ranged from 0.76 to 0.85, 0.83 to 0.88, and 0.83 to 0.93, respectively.<sup>158-160</sup> However, in a Taiwanese study involving 1,716 patients with CHC, the AUC for diagnosing significant fibrosis with FIB-4 was 0.7, and that for advanced fibrosis and cirrhosis was 0.73, showing lower diagnostic accuracy compared to those reported in Western studies.<sup>161</sup> This may be influenced by the substantial presence of patients with either no or mild fibrosis and those with elevated ALT levels in the Taiwanese study compared to Western studies.

In a meta-analysis encompassing 37 studies, the median AUC for diagnosing significant fibrosis with FIB-4 ranged from 0.66 to 0.70, while the median AUC for diagnosing cirrhosis was in the range of 0.75 to 0.82.<sup>109</sup> In a meta-analysis involving 11 studies, FIB-4 showed a sensitivity of 89% and specificity of 42% at low cutoff values ranging from 0.60 to 1.45 for significant fibrosis (Table 9).<sup>168</sup> At higher cutoff values ranging from 1.0 to 3.25, FIB-4 exhibited a sensitivity of 59% and specificity of 74% for significant fibrosis. For cirrhosis, at a low cutoff value of 1.45, FIB-4 had a sensitivity of 87% and specificity of 61%, while at higher cutoff values ranging from 3.25 to 4.44, the sensitivity was 51%, and the specificity was 86%.

APRI was developed in a cohort of 270 patients with CHC, and it demonstrated an AUC of 0.80 for significant fibrosis and 0.89 for diagnosing cirrhosis.<sup>9</sup> An APRI value  $\leq 0.5$  demonstrated a sensitivity of 91% and specificity of 47% for excluding significant fibrosis, while an APRI value  $>1.5$  showed a sensitivity of 41% and specificity of 95% for diagnosing significant fibrosis. An APRI value  $\leq 1.0$  had a sensitivity of 89% and specificity of 75% for excluding cirrhosis, while an APRI value  $>2.0$  showed a sensitivity of 57% and specificity of 93% for diagnosing cirrhosis.

In a multicenter prospective study involving 430 patients with CHC, an APRI value  $\leq 1.0$  showed a sensitivity of 70% and specificity of 79% for excluding advanced fibrosis, while an APRI value  $>2.0$  demonstrated a sensitivity of 36% and specificity of 92% for diagnosing advanced fibrosis.<sup>163</sup> However, in the aforementioned Korean study, the AUC for diagnosing advanced fibrosis and cirrhosis with

**Table 8.** The diagnostic performance of serum markers for liver fibrosis in patients with CHC

Serum marker	Reference	No. of patients	Nation	Significant fibrosis (≥F2)				Advanced fibrosis (≥F3)				Cirrhosis (F4)				
				No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	
FIB-4	Vallet-Richard et al. <sup>157</sup> (2007)	847	France	-	-	-	-	146 (17.2)	0.85 (0.82-0.89)	<1.45	74.0/80.0	61 (7.2)	0.91 (0.86-0.95)	-	-	
				229 (67.3)	0.85 (0.81-0.89)	-	-	155 (45.5)	0.87 (0.83-0.91)	<1.45	92.0/64.0	124 (36.4)	0.89 (0.85-0.92)	-	-	
				200 (45.9)	0.76 (0.71-0.80)	-	-	132 (30.3)	-	-	54.0/91.0	61 (14.0)	0.83 (0.76-0.89)	-	-	
				-	-	-	-	610 (39.9)	0.83 (0.81-0.85)	-	-	-	348 (23.0)	0.87 (0.85-0.88)	-	-
				908 (52.9)	0.70 (0.68-0.72)	2.9	62.7/78.0	745 (43.4)	0.73 (0.71-0.75)	2.9	69.1/76.1	436 (25.4)	0.73 (0.70-0.75)	3.1	72.0/73.4	
				312 (62.9)	0.80 (0.74-0.86)	-	-	168 (33.9)	0.88 (0.84-0.93)	≤1.45	82.0/58.0	74 (14.9)	0.93 (0.89-0.97)	-	-	
				270 (47.0)	0.80 (0.74-0.87)	≤0.5	91.0/47.0	-	-	-	-	28 (15.0)	0.89 (0.84-0.94)	≤1.0	89.0/75.0	
				430 (2008)	-	-	41.0/95.0	160 (37.0)	-	≤1	70.0/79.0	85 (20.0)	-	≥2.0	57.0/93.0	
				340 (67.3)	0.83 (0.79-0.88)	≤0.5	91.0/51.0	155 (45.5)	0.86 (0.82-0.90)	-	-	124 (36.4)	0.86 (0.82-0.90)	≤1	82.0/74.0	
				436 (45.9)	0.76 (0.72-0.81)	0.5	33.1/96.6	-	-	-	-	61 (14.0)	0.86 (0.81-0.91)	2.0	71/99.7	
APRI	Li et al. <sup>160</sup> (2014)	1,529	US	-	-	-	-	610 (39.9)	0.81 (0.78-0.83)	-	-	348 (23.0)	0.81 (0.78-0.83)	-	-	
				908 (52.9)	0.68 (0.66-0.70)	1.4	72.4/63.2	745 (43.4)	0.68 (0.66-0.70)	1.6	67.1/68.8	436 (25.4)	0.70 (0.68-0.73)	2.2	64.9/75.4	
				312 (62.9)	0.48 (0.39-0.58)	-	-	168 (33.9)	0.52 (0.42-0.62)	≥1.0	36.0/73.0	74 (14.9)	0.53 (0.42-0.64)	-	-	
				476 (24.8)	0.86 (0.78-0.87)	<4.2	94.0/51.0	-	-	-	-	-	-	-	-	
				340 (67.3)	0.83 (0.78-0.87)	>6.9	30.0/95.0	155 (45.5)	0.85 (0.81-0.89)	-	-	124 (36.4)	0.87 (0.83-0.91)	-	-	
				496 (2020)	0.75 (0.71-0.80)	<4.2	89.0/58.0	-	-	-	-	-	-	-	-	
				476 (24.8)	0.86 (0.78-0.87)	<6.9	44.0/93.0	-	-	-	-	-	-	-	-	
				340 (67.3)	0.83 (0.78-0.87)	<4.2	89.0/58.0	155 (45.5)	0.85 (0.81-0.89)	-	-	124 (36.4)	0.87 (0.83-0.91)	-	-	
				436 (2012)	0.75 (0.71-0.80)	<4.2	94.0/51.0	-	-	-	-	-	-	-	-	
				436 (2012)	0.75 (0.71-0.80)	<4.2	94.0/51.0	-	-	-	-	-	-	-	-	
Forns Index	Forns et al. <sup>13</sup> (2002)	476	Spain	118 (24.8)	0.86 (0.78-0.87)	<4.2	94.0/51.0	-	-	-	-	-	-	-		
				340 (67.3)	0.83 (0.78-0.87)	<4.2	89.0/58.0	155 (45.5)	0.85 (0.81-0.89)	-	-	124 (36.4)	0.87 (0.83-0.91)	-	-	

**Table 8.** Continued

Serum marker	Reference	No. of patients	Nation	Significant fibrosis (≥F2)				Advanced fibrosis (≥F3)				Cirrhosis (F4)				
				No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/specificity%	
ELF*	Rosen-berg et al. <sup>3</sup> (2004)	496	UK	-	0.77 (0.69–0.84)	0.063	95.0/29.0	-	-	-	-	-	-	-	-	-
ELF†	Martinez et al. <sup>158</sup> (2011)	340	Spain	229 (67.3)	0.81 (0.76–0.86)	≤0.45	90.0/52.0	155 (45.5)	0.83 (0.79–0.87)	-	-	124 (36.4)	0.82 (0.78–0.87)	≤0.06	90.0/53.0	52.0/90.0
ELF*	Zarski et al. <sup>159</sup> (2012)	436	France	200 (45.9)	0.78 (0.74–0.83)	-	-	-	-	-	-	61 (14.0)	0.88 (0.83–0.92)	-	-	-
ELF†	Lichting-hagen et al. <sup>164</sup> (2013)	79	Germany	68 (86.1)	0.9	7.7	100.0/12.5	-	-	-	-	-	-	-	-	-
FibroTest	Imbert-Bismut et al. <sup>166</sup> (2001)	339	France	78 (80.0)	0.87	0.48	75.0/85.0	-	-	-	-	-	-	-	-	-
	Poynard et al. <sup>165</sup> (2012)	1,289	France	788 (61.0)	0.75 (0.72–0.77)	0.48	66.0/85.0	-	-	-	-	199 (15.0)	0.85 (0.82–0.88)	0.74	68.0/89.0	-
	Zarski et al. <sup>159</sup> (2012)	436	France	200 (45.9)	0.80 (0.75–0.84)	0.48	75.8/66.2	-	-	-	-	61 (14.0)	0.86 (0.83–0.90)	0.74	71.4/81.0	-
Fibro-Meter	Zarski et al. <sup>159</sup> (2012)	436	France	200 (45.9)	0.82 (0.78–0.86)	0.411	87.6/56.4	-	-	-	-	61 (14.0)	0.89 (0.86–0.93)	0.88	69.6/88.7	-
Hepascore	Zarski et al. <sup>159</sup> (2012)	436	France	200 (45.9)	0.82 (0.78–0.85)	0.5	74.7/72.5	-	-	-	-	61 (14.0)	0.89 (0.86–0.93)	0.84	76.8/81.3	-

CHC, chronic hepatitis C; FIB-4, fibrosis-4; APRI, aspartate aminotransferase-to-platelet ratio index; ELF, enhanced liver fibrosis; AUC, area under the curve; CI, confidence interval.

\* $-6.38 - (\ln(\text{age}) \times 0.14) + (\ln(\text{HA}) \times 0.616) + (\ln(\text{P3NP}) \times 0.586) + (\ln(\text{TIMP1}) \times 0.472)$ .

† $-7.412 + (\ln(\text{HA}) \times 0.681) + (\ln(\text{P3NP}) \times 0.775) + (\ln(\text{TIMP1}) \times 0.494)$ .

‡ $2.494 + 0.846 \times \ln(\text{HA}) + 0.735 \times \ln(\text{P3NP}) + 0.391 \times \ln(\text{TIMP1})$ .

**Table 9.** Meta-analysis on the diagnostic performance of noninvasive tests for liver fibrosis in patients with CHC<sup>68</sup>

Noninvasive test	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)			
	No. of studies	Cutoff value	Sensitivity% (95% CI)	No. of studies	Cutoff value	Sensitivity% (95% CI)	No. of studies	Cutoff value	Sensitivity% (95% CI)	Specificity% (95% CI)
FIB-4	11	0.6–1.45 (low)	89.0 (79.0–95.0)	11	1.45 (low)	80.0 (72.0–86.0)	2	1.45 (low)	87.0 (74.0–94.0)	61.0 (53.0–69.0)
	9	1–3.25 (high)	59.0 (43.0–73.0)	11	3.25 (high)	37.0 (28.0–46.0)	3	3.25–4.44 (high)	51.0 (39.0–63.0)	86.0 (81.0–90.0)
APRI	47	0.4–0.7 (low)	82.0 (77.0–86.0)	18	0.5–1.0 (low)	84.0 (82.0–86.0)	24	0.75–1.0 (low)	77.0 (73.0–81.0)	78.0 (74.0–81.0)
	36	1.5 (high)	39.0 (32.0–47.0)	15	1.5–2.0 (high)	53.0 (43.0–62.0)	19	2 (high)	48.0 (41.0–56.0)	94.0 (91.0–95.0)
FibroTest	7	0.1–0.3 (low)	91.0 (86.0–94.0)	9	0.32–0.67	73.0 (56.0–85.0)	8	0.56–0.74	60.0 (43.0–76.0)	86.0 (81.0–91.0)
	10	0.6–0.7 (high)	57.0 (46.0–67.0)	-	-	-	-	-	-	-
VCTE	37	5.2–10.1 kPa	79.0 (74.0–84.0)	19	8.6–15.4 kPa	88.0 (82.0–92.0)	36	9.2–17.3 kPa	89.0 (84.0–92.0)	91.0 (89.0–93.0)
pSWE	3	1.21–1.34 m/s	79.0 (75.0–83.0)	4	1.49–2.11	85.0 (69.0–94.0)	4	1.6–2.3 m/s	84.0 (72.0–91.0)	77.0 (50.0–92.0)

CHC, chronic hepatitis C; FIB-4, fibrosis-4 index; APRI, aspartate aminotransferase-to-platelet ratio index; VCTE, vibration-controlled transient elastography; pSWE, point shear wave elastography, CI, confidence interval; kPa, kilopascal.



APRI was 0.76.<sup>167</sup> In the Taiwanese study, the AUCs for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis were 0.68, 0.68, and 0.70, respectively.<sup>161</sup> This may be attributed to differences in age, ALT levels, and the extent of liver fibrosis among patients included in each study.

In a meta-analysis encompassing 33 studies and 6,259 patients with CHC, the AUC for diagnosing significant fibrosis with APRI was 0.77, and that for diagnosing cirrhosis was 0.83.<sup>169</sup> In another meta-analysis involving 47 studies, APRI demonstrated a sensitivity of 82% and specificity of 57% for diagnosing significant fibrosis at low cutoff values ranging from 0.4 to 0.7.<sup>168</sup> In the analysis of 36 studies, using a high cutoff value of 1.5, APRI showed a sensitivity of 39% and specificity of 92% for diagnosing significant fibrosis. Furthermore, for diagnosing cirrhosis, APRI demonstrated a sensitivity of 77% and specificity of 78% at low cutoff values ranging from 0.75 to 1.0. At a high cutoff value of 2.0, the sensitivity was 48%, and the specificity was 94%.

In various studies on CHC, comparisons of the diagnostic performance of APRI and FIB-4 for liver fibrosis have shown conflicting results.<sup>158,159,161,162,167</sup> In a meta-analysis, the diagnostic performance of APRI and FIB-4 for significant fibrosis were found to be similar. However, for diagnosing cirrhosis, FIB-4 exhibited superior diagnostic performance compared to APRI.<sup>162</sup> Caution is needed when interpreting the results from APRI, as it relies on AST alone, and those from FIB-4, as it incorporates AST, ALT, and age in its predictive model. These models may lead to overestimation in patients with intrahepatic inflammation or in elderly individuals.

The Forns index was developed in a cohort of 476 patients with CHC, and the AUC for diagnosing significant fibrosis was 0.86. The cutoff value of <4.5 was suggested, showing a NPV of 96%.<sup>13</sup> In a Korean study, the AUC for diagnosing advanced fibrosis with the Forns index was 0.806, and that for cirrhosis was 0.822, demonstrating similarity to FIB-4 and APRI.<sup>167</sup> In a study involving 340 patients with CHC, the AUC for diagnosing significant fibrosis with the Forns index was 0.83. When applying a cutoff value of >6.9, it showed a sensitivity of 44% and specificity of 93%. These results were similar to APRI's AUC of 0.83, FIB-4's AUC of 0.83, and ELF's AUC of 0.85.<sup>158</sup> Additionally, the AUC for diagnosing advanced fibrosis using the Forns index was 0.85, and for diagnosing cirrhosis, it was 0.87. In a

meta-analysis, the Forns index showed high diagnostic performance for diagnosing significant fibrosis across 18 studies, with a low cutoff value ranging from 4.2 to 4.5, demonstrating a sensitivity of 88% and specificity of 40%.<sup>168</sup>

ELF was developed through a multi-center cohort study involving 1,021 patients with CLDs, including 496 individuals with CHC.<sup>3</sup> In the CHC patient group, the AUC for diagnosing significant fibrosis was 0.77, with a cutoff value of 0.063. It demonstrated a sensitivity of 95%, specificity of 29%, PPV of 27.7%, and NPV of 94.9%. In a prospective study involving 79 patients with CHC, the ELF test showed the AUC of 0.90 for diagnosing significant fibrosis.<sup>164</sup> At a cutoff value of 7.7, it demonstrated a sensitivity of 100% and specificity of 12.5%. At a cutoff value of 9.8, the sensitivity was 84.6%, and the specificity was 75.0%. At a cutoff value of 11.3, it had a sensitivity of 64.1% and specificity of 97.5%. In a meta-analysis encompassing 11 studies, the ELF test showed an AUC for diagnosing advanced fibrosis ranging from 0.77 to 0.98.<sup>170</sup> The cutoff values varied from 9.30 to 10.59, with sensitivity ranging from 65% to 100% and specificity ranging from 29% to 99%. Caution is needed when interpreting or comparing cutoff values for ELF as it has undergone multiple modifications for simplification. In a meta-analysis encompassing 37 studies directly comparing diagnostic performance among different NITs for liver fibrosis patients with CHC, the diagnostic performance for significant fibrosis was similar for the Forns index, APRI, FIB-4, and ELF. However, for diagnosing cirrhosis, FIB-4, which had an AUC of 0.89, outperformed APRI's AUC of 0.83 and ELF's AUC of 0.82.<sup>158</sup>

FibroTest was developed in a cohort of 339 patients with CHC, and it demonstrated an AUC of 0.87 for diagnosing significant fibrosis with a cutoff value of 0.48. It showed a sensitivity of 75% and specificity of 85%.<sup>109,166</sup> In a meta-analysis involving seven studies, FibroTest showed a sensitivity of 91% and specificity of 41% for diagnosing significant fibrosis at low cutoff values ranging from 0.1 to 0.3.<sup>168</sup> In a meta-analysis involving 10 studies, using high cutoff values ranging from 0.6 to 0.7, FibroTest exhibited a sensitivity of 57% and specificity of 85% for diagnosing significant fibrosis. In a meta-analysis encompassing 37 studies, FibroTest demonstrated AUCs for diagnosing significant fibrosis and cirrhosis in the ranges of 0.72–0.83 and 0.81–0.92, respectively.<sup>109</sup> When comparing diagnostic perfor-

mance, FibroTest outperformed FIB-4 and APRI in the diagnosis of significant fibrosis and cirrhosis.

Additionally, Hepascore,<sup>171</sup> FibroMeter,<sup>172</sup> PIIINP and MMP 1,<sup>173</sup> fibrosis probability index,<sup>174</sup> BARD score,<sup>10</sup> and others have been reported as serum markers for liver fibrosis in patients with CHC.

Generally, serum markers exhibit superior diagnostic performance for cirrhosis rather than significant fibrosis, and direct markers provide more accurate diagnosis of significant fibrosis compared to indirect markers.<sup>168</sup> However, Korean studies on serum markers for diagnosing liver fibrosis in patients with CHC have been limited, and further validation with large cohorts of Korean patients is necessary. Additionally, more research is needed to assess the utility of serum markers for assessing liver fibrosis with those measured after sustained virologic response (SVR) in patients with CHC.

#### **Vibration-controlled transient elastography**

The usefulness of VCTE in patients with CHC has been demonstrated through numerous studies. Sensitivity for diagnosing significant fibrosis in patients with CHC varies between 48–96%, with specificity ranging from 32–93%, depending on characteristics and cutoff values in different studies. Sensitivity for diagnosing cirrhosis was 65–100%, and specificity was 85–96% (Table 10).<sup>108,119,127,159,165,175-180</sup>

The diagnostic performance of VCTE in patients with CHC was first evaluated through a multicenter prospective study in France in 2005.<sup>176</sup> For 327 patients with CHC, the AUC of VCTE for diagnosing significant fibrosis was 0.79, with a cutoff value of 8.7 kPa, sensitivity of 56%, and specificity of 91%. The AUC for diagnosing advanced fibrosis was 0.91; cutoff value, 9.6 kPa; sensitivity, 86%; and specificity, 85%. The AUC for diagnosing cirrhosis was 0.97; cutoff value, 14.5 kPa; sensitivity, 86%; and specificity, 96%. The largest-scale study conducted to date included 1,289 patients with CHC enrolled in three cohorts.<sup>165</sup> The AUC for diagnosing significant fibrosis was 0.76, with a cutoff value of 8.8 kPa, sensitivity of 48%, and specificity of 93%. The AUC for diagnosing cirrhosis was 0.90, with a cutoff value of 14.5 kPa, showing similar results with a sensitivity of 65% and specificity of 95%.

In a multicenter study involving 349 patients with CHC in Korea, the AUC of VCTE for diagnosing significant fibrosis was 0.82, with a cutoff value of 6.8 kPa, and sensitivity and

specificity of 67.0% and 86.4%, respectively.<sup>180</sup> The proposed cutoff values for significant or advanced fibrosis in this study were slightly lower compared to previous research because the study only included patients with ALT levels below five times the upper normal limit to compensate for higher LS values in patients with elevated ALT. Furthermore, the AUC for diagnosing cirrhosis was 0.91, with a cutoff value of 14.5 kPa, showing sensitivity and specificity of 81.8% and 89.0%, respectively, similar to studies conducted in Western populations.

In a meta-analysis of 37 studies involving CHC, the cutoff value of VCTE for significant fibrosis ranged from 5.2 to 10.1 kPa, with a sensitivity of 79% and specificity of 83%. The cutoff value for cirrhosis ranged from 9.2 to 17.3 kPa, with a sensitivity of 89% and specificity of 91% (Table 9).<sup>168</sup> In a meta-analysis of 17 studies presented at the American Gastroenterological Association, involving 5,812 patients with CHC, the cutoff value for VCTE was 12.5 kPa, with a sensitivity of 86% and specificity of 90%.<sup>181</sup> Additionally, in groups with a cirrhosis prevalence of less than 5%, a cutoff value of 12.5 kPa resulted in a false-negative rate of 0.7% and a false-positive rate of 8.6%. In high-risk groups with a cirrhosis prevalence of 30%, the false-negative rate was only 4.2% and the false-positive rate was 6.3%.

The ANRS HCEP-23, a prospective study conducted in 19 institutions in France, compared the diagnostic performance of nine serum markers and VCTE in patients with CHC infection.<sup>159</sup> In 382 patients evaluated with both serum markers and VCTE, the diagnostic performance for significant fibrosis was (in descending order): VCTE (AUC 0.83), FibroMeter (AUC 0.83), Hepascore (AUC 0.82), and FibroTest (AUC 0.81). For diagnosing cirrhosis, the highest diagnostic performance (in descending order) was: VCTE (AUC 0.93), FibroMeter (AUC 0.90), FibroTest (AUC 0.87), APRI (AUC 0.87), ELF (AUC 0.87), Hepascore (AUC 0.89), and FIB-4 (AUC 0.84).

In a meta-analysis comparing the diagnostic performance of serum markers and VCTE, including 37 studies, both FIB-4 and APRI showed similar diagnostic performance to VCTE for significant fibrosis.<sup>109</sup> For cirrhosis, FIB-4 showed similar diagnostic performance to VCTE, while the diagnostic performance of APRI was significantly lower than VCTE. In another meta-analysis comparing the diagnostic performance of APRI and VCTE using a low cutoff value of 0.75–1.0 for diagnosing cirrhosis, VCTE accurately

**Table 10.** The diagnostic performance of VCTE for liver fibrosis in patients with CHC

Reference	No. of patients	Nation	Significant fibrosis (≥F2)				Advanced fibrosis (≥F3)				Cirrhosis (F4)			
			No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)
Castéra et al. <sup>175</sup> (2005)	183	France	136 (74.3)	0.83 (0.76–0.88)	7.1	67.0/89.0	83 (45.3)	0.90 (0.85–0.94)	9.5	73.0/91.0	46 (25.1)	0.95 (0.91–0.98)	12.5	87.0/91.0
Zioli et al. <sup>176</sup> (2005)	327	France	163 (65.0)	0.79 (0.73–0.84)	8.7	56.0/91.0	76 (30.3)	0.91 (0.87–0.96)	9.6	86.0/85.0	49 (19.5)	0.97 (0.93–1.00)	14.5	86.0/96.0
Ganne-Carrié et al. <sup>177</sup> (2006)	298	France	-	-	-	-	-	-	-	-	30 (10.0)	-	10.4	88.0/85.0
Castéra et al. <sup>178</sup> (2009)	298	France	-	-	-	-	-	-	-	-	70 (23.5)	0.96 (0.93–0.98)	12.6	83.0/95.0
Degos et al. <sup>108</sup> (2010)	913	France	562 (61.6)	0.75 (0.71–0.78)	5.2	89.7/92.2	285 (31.2)	-	-	-	126 (13.8)	0.90 (0.86–0.93)	12.9	72.2/89.3
Fraquelli et al. <sup>127</sup> (2011)	453	Italy	197 (44.0)	-	8.8	81.0/77.0	88 (20.0)	-	-	-	44 (10.0)	-	14.6	100.0/88.0
Cardoso et al. <sup>119</sup> (2012)	363	France	197 (54.0)	0.86	7.1	68.0/89.0	87 (24.0)	-	9.5	68.0/92.0	31 (9.0)	0.94	12.5	84.0/94.0
Poynard et al. <sup>165</sup> (2012)	1,289	France	788 (61.0)	0.76 (0.73–0.79)	8.8	48.0/93.0	-	-	-	-	199 (15.0)	0.90 (0.87–0.92)	14.5	65.0/95.0
Zarski <sup>155</sup> (2012)	382	France	200 (45.9)	0.82 (0.78–0.86)	5.2	96.6/84.8	132 (30.3)	-	-	-	61 (14.0)	0.93 (0.89–0.96)	12.9	76.8/89.6
Schwabi et al. <sup>179</sup> (2015)	226	Austria	210 (92.9)	0.85	7.2	-	159 (70.3)	-	-	-	124 (54.8)	0.85	14.5	-
Seo et al. <sup>180</sup> (2015)	349	Korea	303 (86.8)	0.82 (0.77–0.86)	6.8	67.0/86.4	118 (33.8)	0.86 (0.82–0.90)	8.6	79.8/83.1	22 (6.3)	0.91 (0.86–0.95)	14.5	81.8/89.0

CHC, chronic hepatitis C; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

classified the presence or absence of cirrhosis in more patients compared to APRI in both low-prevalence and high-prevalence groups.<sup>168</sup> Additionally, VCTE had lower false-positive and false-negative rates. Furthermore, when comparing VCTE with FIB-4 using a low cutoff value of 0.6–1.45, the diagnostic performance of VCTE was similar to FIB-4, but the false-positive rate was significantly lower. FibroTest demonstrated similar diagnostic performance to VCTE for diagnosing significant fibrosis and cirrhosis.

Studies have been conducted to enhance the diagnostic performance for significant fibrosis and cirrhosis in patients with CHC by combining serum marker and VCTE.<sup>182,183</sup> In a study involving 729 patients with CHC, the AUC for diagnosing significant fibrosis and cirrhosis with VCTE was 0.79 and 0.91, respectively.<sup>182</sup> When combining the serum marker FibroMeter with VCTE, the diagnostic AUC improved to 0.85 for significant fibrosis and 0.922 for cirrhosis. In a study involving 3,754 patients with chronic hepatitis, of whom 45.5% had CHC, a sequential approach using a scoring system including age, AST, GGT, platelet count, and prothrombin time for initial assessment of liver fibrosis followed by FibroMeter and VCTE resulted in a sensitivity of 76.1% for diagnosing advanced fibrosis and 92.1% for cirrhosis.<sup>183</sup>

Study on the diagnostic performance of VCTE for liver fibrosis in patients with CHC infection after AVT and achieving SVR is limited. In a study involving patients with a LS value of 10 kPa or more before treatment and who subsequently achieved SVR after AVT, despite a reduction in LS after achieving SVR, more than half of the patients had evidence of cirrhosis on histologic examination three years later.<sup>184</sup> Furthermore, the AUC for diagnosing cirrhosis using VCTE after achieving SVR was only 0.75, and LS values before treatment was the factor most strongly associated with cirrhosis. Serum markers such as APRI and FIB-4 showed similar results.

Thus, VCTE demonstrates high diagnostic performance with AUC above 0.8 for diagnosing fibrosis in most studies involving CHC. However, limitations of previous study include unclear exclusion criteria for comorbid conditions that could affect the results of VCTE, as well as the inclusion of patients with significant intrahepatic inflammation, which may lead to overestimation of test values.<sup>118,127</sup>

### Shear wave elastography

The diagnostic performance of pSWE and 2D-SWE for liver fibrosis has been evaluated in several studies involving patients with CHC. In a study involving 61 patients with CHC, the AUC of pSWE for diagnosing significant fibrosis was 0.79, with a cutoff value of 1.33 m/s.<sup>185</sup> The AUC for diagnosing advanced fibrosis was 0.83, with a cutoff value of 1.43 m/s, and for diagnosing cirrhosis, the AUC was 0.84, with a cutoff value of 1.55 m/s. In a study involving 101 patients with CHC in Korea, the AUC of pSWE for diagnosing significant fibrosis was 0.85, with a cutoff value of 1.335 m/s, yielding a sensitivity of 84% and specificity of 76%. The AUC for diagnosing advanced fibrosis was 0.84, with a cutoff value of 1.645 m/s, resulting in a sensitivity of 80% and specificity of 76%.<sup>167</sup> For diagnosing cirrhosis, the AUC was 0.83, with a cutoff value of 1.665 m/s, and a sensitivity of 85% and specificity of 69%. The diagnostic performance of pSWE was similar to FIB-4, APRI, and the Forns index for both advanced fibrosis and cirrhosis. In a meta-analysis including three studies, the cutoff value for diagnosing significant fibrosis using pSWE was 1.21–1.34 m/s, with a sensitivity of 79% and specificity of 89%. For diagnosing cirrhosis, based on analysis of four studies, the cutoff value was 1.6–2.3 m/s, with a sensitivity of 84% and specificity of 77%.<sup>168</sup>

In a multicenter prospective study in Europe involving 241 patients with CHC, the diagnostic performance of pSWE and VCTE was compared.<sup>186</sup> The AUCs of pSWE and VCTE for diagnosing significant fibrosis were 0.81 and 0.85, respectively, while the AUCs for diagnosing advanced fibrosis were 0.88 and 0.92, and for diagnosing cirrhosis were 0.89 and 0.94, indicating similar diagnostic performance. However, the measurement failure rate of VCTE was 10%, significantly higher than the 5.3% observed with pSWE. pSWE showed diagnostic performance similar to ELF and FibroTest for diagnosing all stages of liver fibrosis.

In a study involving 211 patients with CHC, 2D-SWE demonstrated an AUC for diagnosing significant fibrosis of 0.83, with a cutoff value of 6.16 kPa.<sup>187</sup> The AUC for diagnosing advanced fibrosis was 0.95, with a cutoff value of 6.8 kPa, yielding a sensitivity of 97% and specificity of 90%. However, the diagnostic performance was lower in cases where BMI was >30 kg/m<sup>2</sup>. In a prospective study in Japan involving 233 patients with CHC, 2D-SWE was feasible in 98.7% of patients.<sup>188</sup> The AUC for diagnosing signif-

icant fibrosis was 0.92, with a cutoff value of 1.56 m/s, yielding a sensitivity of 85% and specificity of 86%. The AUC for diagnosing advanced fibrosis was 0.94, with a cutoff value of 1.72 m/s, resulting in a sensitivity of 89% and specificity of 84%. For diagnosing cirrhosis, the AUC was 0.949, with a cutoff value of 1.93 m/s, and a sensitivity of 91.4% and specificity of 90.8%.

In a study comparing the diagnostic performance of 2D-SWE with serum markers, 2D-SWE showed significantly superior performance to serum markers including HA, type IV collagen 7S, M2BPGi, APRI, and FIB-4 in the diagnosis of all stages of fibrosis.<sup>188</sup> In a study comparing the diagnostic performance of 2D-SWE, APRI, and FIB-4 in 79 patients with CHC, the AUCs for diagnosing significant fibrosis were as follows: 2D-SWE, 0.75; VCTE, 0.95; FIB-4, 0.81; and APRI, 0.77; with 2D-SWE having the lowest AUC.<sup>189</sup> For diagnosing cirrhosis, the AUCs were: 2D-SWE, 0.83; VCTE, 0.99; FIB-4, 0.81; and APRI, 0.77; with 2D-SWE demonstrating lower AUC compared to VCTE.

The diagnostic performance of SWE in patients with CHC has not been extensively validated compared to other NITs, and caution should be exercised in interpreting results due to the diversity of the equipment used. While the measurement success rate, including among obese patients, may be higher than that of VCTE, results may be overestimated in cases of severe intrahepatic inflammation. Furthermore, comparative studies with other NITs are limited, and conflicting results have been reported. However, overall, studies have reported high diagnostic accuracy and similar performance to VCTE, suggesting that SWE may be useful for evaluating liver fibrosis in patients with CHC.

### Magnetic resonance elastography

Research on the utility of MRE for assessing the degree of liver fibrosis in patients with CHC is limited. The first study involving 114 patients with CHC was conducted in Japan, revealing an AUC for diagnosing significant fibrosis of 0.99, with a cutoff value of 3.2 kPa, and sensitivity and specificity of 89% and 100%, respectively.<sup>190</sup> For diagnosing advanced fibrosis, the AUC was 0.97, with a cutoff value of 4.0 kPa, and sensitivity and specificity of 87% and 100%, respectively. For diagnosing cirrhosis, the AUC was 0.98, with a cutoff value of 4.6 kPa, and sensitivity and specificity of 100% and 85%, respectively. When compared to serum markers such as AAR, APRI, and FIB-4, MRE

demonstrated significantly higher diagnostic performance for liver fibrosis at all stages.

In a study conducted in Japan involving 141 patients, MRE demonstrated the AUC for diagnosing the significant fibrosis of 0.88, with a cutoff value of 3.4 kPa, and sensitivity and specificity of 78% and 86%, respectively.<sup>191</sup> For diagnosing advanced fibrosis, the AUC was 0.93, with a cutoff value of 3.61 kPa, and sensitivity and specificity of 96% and 75%, respectively. For diagnosing cirrhosis, the AUC was 0.97, with a cutoff value of 5.03 kPa, and sensitivity and specificity of 87% and 87%, respectively. Furthermore, MRE exhibited higher diagnostic performance for significant fibrosis and advanced fibrosis with AUCs of 0.86 and 0.92 respectively, compared to 2D-SWE (AUCs of 0.81 and 0.87), FIB-4 (AUCs of 0.81 and 0.87), and M2BPGi (AUCs of 0.79 and 0.86). MRE demonstrated significantly higher diagnostic performance for diagnosing cirrhosis compared to 2D-SWE (AUC, 0.91), FIB-4 (AUC, 0.84), and M2BPGi (AUC, 0.85).

In a meta-analysis including 12 studies and 697 patients with CHC, MRE demonstrated the AUC of 0.88 for diagnosing significant fibrosis, with sensitivity of 77% and specificity of 83%.<sup>192</sup> The AUC for diagnosing advanced fibrosis was 0.94, with sensitivity of 84% and specificity of 89%. For diagnosing cirrhosis, the AUC was 0.92, with sensitivity of 94% and specificity of 81%.

Although the usefulness of MRE in CHC warrants further validation, it demonstrated a higher measurement success rate compared to other NITs and exhibited high diagnostic performance regardless of intrahepatic inflammation.<sup>192,193</sup> Therefore, it is deemed useful for patients with CHC.

### [Recommendations]

1. In patients with CHC, liver fibrosis can be assessed using serum markers (B1), VCTE (A1), 2D-SWE (B1), and MRE (B1).

## Nonalcoholic fatty liver disease

The prognosis of NAFLD varies based on histological findings. This makes it important to diagnose liver steatosis and liver fibrosis, and to monitor changes. In particular, liver fibrosis is the most important factor for determining the long-term prognosis in NAFLD, including HCC develop-

ment and liver-related death.<sup>194</sup> In patients with NAFLD, although liver biopsy is the standard for diagnosing intrahepatic inflammation, liver steatosis, and liver fibrosis, it has limitations including high cost, the risk of complications such as bleeding or infection, differences in interpretation between investigators or depending on timing, and sampling errors based on the amount of tissue collected.<sup>1,2</sup> In clinical practice, NITs are used first to evaluate liver steatosis and liver fibrosis such as serum markers and imaging tests, including VCTE, SWE, and MRE.<sup>195-197</sup> When NAFLD is accompanied by obesity or elevated ALT, increasing severity of liver steatosis has been reported to be associated with decreased diagnostic performance of serum markers such as FIB-4 and NFS and VCTE,<sup>198,199</sup> meaning that caution is required when interpreting these test results.

### Serum markers

There have been studies diagnosing liver fibrosis noninvasively using various serum markers, and some of the most thoroughly validated methods include FIB-4, NFS, and ELF (Table 11).<sup>29,200-202</sup>

FIB-4 was proposed in a cohort of 832 patients with CHC/HIV coinfection,<sup>11</sup> and its diagnostic performance for liver fibrosis has been studied in patients with NAFLD.<sup>203</sup> In a Japanese study of patients with NAFLD diagnosed by liver biopsy, NFS and FIB-4 showed higher diagnostic performance for advanced fibrosis compared to other NITs, and this diagnostic performance was similar to MRE.<sup>203</sup> In a recent meta-analysis of 32 studies including 13,764 patients, FIB-4 showed an AUC of 0.76, sensitivity of 42%, and specificity of 93% for diagnosing advanced fibrosis.<sup>200</sup> In another individual patient data meta-analysis (IPD-MA) of 36 studies including 5,735 patients, FIB-4 showed an AUC of 0.76 for diagnosing advanced fibrosis, which was higher than that of NFS, at 0.73; on this basis, the authors proposed an algorithm combining FIB-4 with VCTE.<sup>204</sup> Specifi-

cally, advanced fibrosis can be excluded in patients with FIB-4 <1.3 and VCTE <8 kPa, while cirrhosis can be diagnosed in patients with FIB-4 ≥3.48 and VCTE ≥20 kPa, allowing unnecessary liver biopsy to be avoided. Patient age also needs to be considered when interpreting FIB-4 values. In patients with NAFLD under 35 years old, the diagnostic value of serum markers such as FIB-4 and NFS decreases, and other NITs should be considered.<sup>35</sup> While a standard upper cutoff value can be set at 2.67, an age-adjusted lower cutoff value of 1.30 has been recommended for 35–64-year-olds and 2.0 for elderly patients aged ≥65 years old.<sup>35</sup>

NFS was validated in 733 patients with biopsy-proven NAFLD in the US; the AUC of NFS for diagnosing advanced fibrosis was 0.82–0.88, and two cutoff values were suggested (<–1.455 [low probability, NPV 88–93%], >0.676 [high probability, PPV 82–90%]).<sup>12</sup> In a meta-analysis of 3,064 patients across 13 studies, the AUC of NFS for diagnosing advanced fibrosis was 0.85, the cutoff value to exclude advanced fibrosis was <–1.455, with a sensitivity of 90% and specificity of 60%, and the cutoff value to diagnose advanced fibrosis was >0.676, with a sensitivity of 67% and specificity of 97%.<sup>10,12,17,22,23,29,205-210</sup> Recently, there has been a report that the age-adjusted lower cutoff value for elderly patients aged ≥65 years old should be set to 0.12.<sup>35</sup> In a Korean study of 412 patients with biopsy-proven NAFLD, an NFS cutoff value of <–1.455 could be used to exclude advanced fibrosis with a high NPV of 86.6%, and an NFS cutoff value of >0.676 could be used to diagnose advanced fibrosis with a PPV of 50%.<sup>211</sup> In another Korean study of 315 patients with biopsy-proven NAFLD, when NFS cutoff values of <–1.455 and >0.676 were used, the AUC for diagnosing advanced fibrosis was 0.843, and the NPV was 89.3–95.7%.<sup>198</sup> In a recent meta-analysis of 33 studies, the AUC of NFS for diagnosing advanced fibrosis was 0.74, the sensitivity was 38%, and the specificity was

**Table 11.** Meta-analysis on the diagnostic performance of serum markers for liver fibrosis in patients with NAFLD

Serum marker	No. of studies	No. of patients	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Cirrhosis (F4)	
			AUC	Cutoff value	AUC	Cutoff value	AUC	Cutoff value
FIB-4 <sup>200,201</sup>	32	13,764	0.74	>1.3–1.9	0.74–0.76	>2.67–3.25	0.86–0.88	>3.50–4.12
NFS <sup>200</sup>	33	13,337	0.66	<–1.455	0.74–0.85	>0.676	-	-
ELF <sup>29,202</sup>	16	5,002	0.82	>–0.1068	0.9	>0.3576	-	-

NAFLD, nonalcoholic fatty liver disease; FIB-4, fibrosis-4 index; NFS, NAFLD fibrosis score; ELF, enhanced liver fibrosis; AUC, area under the curve.

94% (Table 11).<sup>200</sup>

ELF is a panel that was proposed based on three matrix proteins (HA, TIMP-1, and PIIINP) tested in 192 patients with biopsy-proven NAFLD in the UK. ELF is mostly used for diagnosing liver fibrosis in Europe, but can be used at some institutions in Korea as well. The AUC of ELF for diagnosing advanced fibrosis was 0.90, and with a cutoff value of 0.3576, the sensitivity was 80%, the specificity was 90%, the PPV was 71%, and the NPV was 94% (Table 11).<sup>29,205</sup>

Recently, there have been new attempts to screen patients with NAFLD at high risk of liver fibrosis by constructing a random forest model using machine learning based on existing NITs, such as VCTE, FIB-4, and NFS.<sup>212,213</sup> Other serum markers have also been reported for diagnosis of liver fibrosis, including M2BPGi, AsAGP,<sup>214-217</sup> growth differentiation factor 15 (GDF15),<sup>218</sup> pro-collagen 3 neoepitope (PRO-C3),<sup>27,28</sup> and A disintegrin and metalloproteinase with thrombospondin motifs like 2 (ADAMTSL2)<sup>219</sup> but further validation is required.

The NIS4 algorithm, which consists of four serum markers, including microRNA-34a, alpha-2 macroglobulin, YKL-40, and glycated hemoglobin, was proposed based on an international, multicenter cohort study.<sup>24</sup> When screening a high-risk group with an NAFLD activity score (NAS)  $\geq 4$  and significant fibrosis, the NIS4 algorithm showed an AUC of 0.80 and was not significantly affected by sex or levels of BMI, AST, and ALT. An optimized NIS2+™ algorithm has also been published, using only the microRNA-34a and YKL-40 components of the NIS4 algorithm. When screening high-risk groups, the NIS2+ showed higher diagnostic power than the NIS4 algorithm, with AUCs of 0.813 and 0.792, respectively.<sup>31</sup> The NASH-PT scoring system was proposed to identify NAFLD patients at risk for nonalcoholic steatohepatitis (NASH) based on a single-center cohort in Korea.<sup>220</sup> The NASH-PT scoring system includes *PNPLA3* and *TM6SF2* genotypes, T2DM, insulin resistance, AST, and high-sensitivity C-reactive protein. When used to differentiate NAFLD and NASH with a cutoff value of 0.785, the AUC was 0.787. Meanwhile, the test was also validated in a recent Chinese cohort of 276 patients, where the AUC was 0.80 when using a cutoff value of -0.11.<sup>221</sup> Gut microbes and their metabolites have also been proposed as a marker for diagnosing significant fibrosis in patients with non-obese NAFLD.<sup>222</sup>

### Vibration-controlled transient elastography

There have been many studies published on the diagnostic value of VCTE in patients with NAFLD (Table 12),<sup>19,199,208,223-237</sup> and it has shown high sensitivity and specificity in meta-analyses.<sup>203,205,238</sup> VCTE shows an AUC of 0.65–0.98 for diagnosing advanced fibrosis, with cutoff values of 6.6–10.4 kPa, and an AUC of 0.94–0.97 for diagnosing cirrhosis, with cutoff values of 10.3–17 kPa, demonstrating high diagnostic value in both cases. This meta-analysis encompassed 63 studies involving 19,199 patients. However, in patients with abdominal obesity, the accuracy of VCTE decreases, and around 5–20% of patients are unable to undergo the test at all using a regular M probe.<sup>205,239</sup> In these cases, an XL probe can be used to greatly reduce the failure rate.<sup>240,241</sup> In a study of severely obese subjects who underwent bariatric surgery with a mean BMI of 42.3 kg/m<sup>2</sup>, VCTE showed an AUC of 0.85 and a cutoff value of 7.6 kPa for diagnosing advanced fibrosis.<sup>228</sup> In this study, an XL probe was used for 96 out of 100 patients based on a skin-to-liver capsule distance criterion of  $\geq 2.5$  cm. In a multicenter study in Hong Kong and France, patients with a BMI  $< 30$  kg/m<sup>2</sup> or  $\geq 30$  kg/m<sup>2</sup> underwent VCTE with an M or XL probe, respectively, and showed almost identical median LS value by VCTE and similar diagnostic performance with an M or XL probe.<sup>242</sup> On the other hand, one study in Japan reported that different cutoff values have to be used for advanced fibrosis when using an XL probe versus an M probe (XL probe, 8.2 kPa vs. M probe, 10.8 kPa), but further studies are needed to validate the results.<sup>236</sup> According to one single-center study, in obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>) or patients with ALT  $\geq 100$  IU/L, the accuracy of VCTE decreased,<sup>199</sup> and higher CAP scores were associated with an increased false positive rate for VCTE.<sup>243,244</sup> The authors proposed that NFS or liver biopsy should be used simultaneously to evaluate liver fibrosis in patients with a CAP score  $> 300$  dB/m and VCTE value of 10.1–12.5 kPa. Caution is required when interpreting the results of VCTE, since they are affected by fasting duration, abdominal obesity,<sup>245</sup> cholestasis, elevated AST and ALT, and liver steatosis.

In one recent international, multi-center cohort study, the FibroScan-AST (FAST) score was proposed, reflecting the results of VCTE, CAP score, and AST ( $e^{-1.65 + 1.07 \times \ln(\text{liver stiffness measurement [LSM] + 2.66 \times 10^{-8} \times \text{CAP}^3 - 63.3 \times \text{AST}^{-1})} / [1 + e^{-1.65 + 1.07 \times \ln(\text{LSM} + 2.66 \times 10^{-8} \times \text{CAP}^3 - 63.3 \times \text{AST}^{-1})}]$ ).<sup>246</sup> As a scoring system to screen for

**Table 12.** Diagnostic performance of VCTE for liver fibrosis in patients with NAFLD

Author (year)	No. of patients	Nation	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)					
			No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity/specificity (%)
Lupsor et al. <sup>223</sup> (2010)	72	Romania	18 (25.0)	0.79 (0.67–0.88)	6.8	66.7/84.3	5 (6.9)	0.98 (0.74–1.22)	10.4	100/97.0	-	-	-	-
Wong et al. <sup>208</sup> (2010)	246	Hong Kong, France	101 (41.1)	0.84 (0.79–0.90)	5.8	91.1/50.3	56 (22.8)	0.93 (0.89–0.97)	7.9	91.0/75.0	25 (10.2)	0.95 (0.94–0.96)	10.3	92.0/88.0
Gaia et al. <sup>224</sup> (2011)	72	Italy	33 (45.8)	0.80 (0.70–0.91)	7	76.0/80.0	17 (23.6)	0.76 (0.71–0.8)	8.0	65.0/80.0	9 (12.5)	0.94 (0.84–1.05)	10.5	78.0/95.0
Petta et al. <sup>225</sup> (2011)	146	Italy	68 (47.0)	0.79	7.25	69.0/70.0	33 (23.0)	0.87	8.75	76.0/78.0	11 (8.0)	-	-	-
Kumar et al. <sup>226</sup> (2013)	205	India	129 (62.9)	0.85 (0.78–0.92)	7.0	77.0/78.0	102 (49.8)	0.94 (0.89–0.98)	9.0	96.0/78.0	85 (41.5)	0.96 (0.92–1.00)	11.8	100/82.0
Mahadeva et al. <sup>227</sup> (2013)	131	Malaysia	75 (57.3)	0.67 (0.57–0.77)	6.8	66.2/59.6	29 (22.1)	0.77 (0.66–0.87)	7.1	70.4/66.6	8 (6.1)	0.95 (0.85–1.05)	11.3	87.5/89.3
Naveau et al. <sup>228</sup> (2014)	100	France	22 (22.0)	0.81 (0.76–0.86)	7.6	73.0/78.0	9 (9.0)	0.85 (0.81–0.89)	7.6	100/74.0	-	-	-	-
Chan et al. <sup>229</sup> (2015)	147	Malaysia	43 (30.2)	-	6.7	100.0/44.7	31 (21.0)	-	8.0	95.0/66.0	3 (2.0)	-	17.0	100/94.0
Boursier et al. <sup>230</sup> (2016)	452	France	290 (64.1)	0.84 (0.82–0.86)	6.1	-	172 (38.0)	0.83 (0.81–0.85)	8.7	88.4/62.9	58 (12.8)	0.86 (0.84–0.89)	18.0	-
Rosso et al. <sup>231</sup> (2016)	105	Italy	62 (59.1)	0.80	6.8	71.0/81.0	38 (36.2)	0.80	6.6	84.0/64.0	8 (7.6)	-	-	-
Lee et al. <sup>232</sup> (2017)	94	Korea	46 (47.9)	0.76 (0.65–0.87)	7.4	62.5/91.7	27 (27.7)	0.87 (0.77–0.97)	8.0	82.6/84.9	14 (14.9)	0.88 (0.74–0.93)	10.8	91.7/81.2
Park et al. <sup>233</sup> (2017)	104	USA	32 (31.1)	0.86 (0.77–0.95)	6.9	79.3/84.6	21 (20.4)	0.8 (0.64–0.93)	7.3	78.0/78.0	8 (7.8)	0.69 (0.45–0.94)	6.9	62.5/66.3
Garg et al. <sup>234</sup> (2018)	76	India	28 (36.8)	0.65 (0.52–0.77)	7.3	70.0/58.7	9 (11.8)	0.83 (0.72–0.94)	12.5	63.6/87.7	-	-	-	-
Anstee et al. <sup>19</sup> (2019)	3,202	Multi-nation	2,680 (83.2)	-	-	-	2,262 (70.1)	0.80 (0.79–0.80)	9.9	83.0/61.0	1,283 (40.0)	-	-	-
Petta et al. <sup>199</sup> (2019)	968	Hong Kong, France, Italy	-	-	-	-	276 (28.5)	0.86 (0.84–0.89)	9.6	72.5/81.8	-	-	-	-
Furlan et al. <sup>23</sup> (2020)	62	USA	43 (71.0)	0.77 (0.64–0.89)	8.8	51.2/94.4	23 (38.7)	0.86 (0.77–0.95)	6.7	56.4/70.3	9 (14.5)	-	-	-
Oeda et al. <sup>236</sup> (2020)	96	Japan	50 (52.1)	0.78	7.0	90.0/54.0	29 (30.2)	0.84	10.8	76.0/79.0	5 (5.2)	0.97	16.8	100/90.0
Lee et al. <sup>237</sup> (2022)	539	Korea	173 (32.1)	0.82 (0.78–0.85)	6.7	71.0/81.0	74 (13.7)	0.92 (0.89–0.94)	8.3	86.0/86.0	46 (8.5)	0.95 (0.93–0.97)	9.8	96.0/87.0

NAFLD, nonalcoholic fatty liver disease; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.



patients with NASH, with a NAS  $\geq 4$  and significant fibrosis, the cutoff value was 0.35, the PPV was 83%, and the NPV was 85%. In addition, the c-index was 0.85 in an external validation cohort, demonstrating high diagnostic performance.

In another recent international cohort across seven centers, the AGILE score based on VCTE was reported to have a significantly higher PPV for diagnosing advanced fibrosis or cirrhosis compared to FIB-4 or VCTE alone.<sup>247</sup> AGILE 3+, which is calculated based on age, sex, AST/ALT ratio, platelet count, T2DM, and VCTE, at a lower cutoff value of 0.451 and upper cutoff value of 0.679, showed an AUC of 0.76 and a PPV of 0.72 for diagnosing advanced fibrosis. Meanwhile, for cirrhosis, when AGILE 4 was used with a lower cutoff value of 0.251 and an upper cutoff value of 0.565, the AUC was 0.93 and the PPV was 0.73. Given that FIB4, NFS, and ELF showed lower PPVs, the AGILE score showed superior diagnostic performance.

VCTE also showed good diagnostic performance in patients with NAFLD and T2DM. In a recent meta-analysis of 1,780 patients with NAFLD and T2DM, in patients with FIB-4  $\geq 1.3$  or NFS  $\geq 1.455$ , VCTE ( $\geq 8$  kPa) or AGILE 3+

( $\geq 0.45$ )<sup>247</sup> could be used either individually or sequentially to diagnose advanced fibrosis with high accuracy.<sup>248</sup>

### Shear wave elastography

When pSWE is used to diagnose significant fibrosis in patients with NAFLD, the AUC is  $\geq 0.8$ .<sup>249,250</sup> pSWE shows particularly high diagnostic performance for advanced fibrosis, with a sensitivity of 100% and specificity of 91%.<sup>251</sup> In a single-center cohort study in Korea, when used to diagnose advanced fibrosis, pSWE showed an AUC of 0.861 and a cutoff value of 1.395, but in patients with liver steatosis, the AUC decreased with increasing severity to 0.911, 0.847, and 0.686, respectively, in patients with mild, moderate, and severe steatosis.<sup>198</sup> In several meta-analyses, pSWE showed similar diagnostic performance to VCTE (Table 13).<sup>252,253</sup>

In a prospective study, the AUC of 2D-SWE for diagnosing advanced fibrosis was 0.920, showing similar diagnostic performance to MRE (AUC 0.929) and VCTE (AUC 0.915).<sup>254</sup> In a recent meta-analysis of 47,609 patients with NAFLD across 82 studies, the AUC of 2D SWE for diagnosing advanced fibrosis was 0.72, showing a slightly lower

**Table 13.** Meta-analysis of the diagnostic performance of VCTE, pSWE, 2D-SWE, and MRE for liver fibrosis in patients with NAFLD<sup>253</sup>

Method	No. of studies	No. of patients	AUC (95% CI)	Cutoff value	Sensitivity % (95% CI)	Specificity % (95% CI)
<b>VCTE</b>						
Significant fibrosis ( $\geq F2$ )	37	2,763	0.83 (0.80–0.87)	3.8–10.2 kPa	80.0 (76.0–83.0)	73.0 (68.0–77.0)
Advanced fibrosis ( $\geq F3$ )	44	4,219	0.85 (0.83–0.87)	6.8–12.9 kPa	80.0 (77.0–83.0)	77.0 (74.0–80.0)
Cirrhosis (F4)	22	337	0.89 (0.84–0.93)	6.9–19.4 kPa	76.0 (70.0–82.0)	88.0 (85.0–91.0)
<b>pSWE</b>						
Significant fibrosis ( $\geq F2$ )	9	805	0.86 (0.78–0.90)	1.18–1.81 m/s	69.0 (59.0–77.0)	85.0 (80.0–88.0)
Advanced fibrosis ( $\geq F3$ )	11	1,209	0.89 (0.83–0.95)	1.34–4.21 m/s	80.0 (70.0–88.0)	86.0 (82.0–92.0)
Cirrhosis (F4)	8	759	0.90 (0.82–0.95)	1.36–2.54 m/s	76.0 (59.0–87.0)	88.0 (82.0–92.0)
<b>2D-SWE</b>						
Significant fibrosis ( $\geq F2$ )	4	488	0.75 (0.58–0.87)	8.3–11.6 kPa	71.0 (56.0–83.0)	67.0 (43.0–84.0)
Advanced fibrosis ( $\geq F3$ )	4	488	0.72 (0.60–0.84)	9.3–13.1 kPa	72.0 (65.0–78.0)	72.0 (52.0–86.0)
Cirrhosis (F4)	3	372	0.88 (0.81–0.91)	14.4–15.7 kPa	78.0 (50.0–93.0)	84.0 (74.0–90)
<b>MRE</b>						
Significant fibrosis ( $\geq F2$ )	6	209	0.91 (0.80–0.97)	2.86–4.14 kPa	78.0 (67.0–85.0)	89.0 (83.0–94.0)
Advanced fibrosis ( $\geq F3$ )	10	214	0.92 (0.88–0.95)	2.99–4.8 kPa	83.0 (77.0–88.0)	89.0 (86.0–92.0)
Cirrhosis (F4)	5	41	0.90 (0.81–0.95)	3.35–6.7 kPa	81.0 (66.0–90.0)	90.0 (85.0–94.0)

VCTE, vibration-controlled transient elastography; pSWE, point shear wave elastography; 2D-SWE, two-dimensional shear wave elastography; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

diagnostic value than pSWE (AUC 0.89) and VCTE (AUC 0.92), suggesting that further research is needed.<sup>253</sup>

Caution is required when interpreting the results of SWE, since they are affected by fasting duration, abdominal obesity, liver disease accompanied by cholestasis, AST, ALT, and liver steatosis. Notably, 2D-SWE has been reported to be easier to perform than VCTE in obese patients, because the measurement location can be adjusted in real-time.<sup>255</sup>

### Magnetic resonance elastography

MRE shows excellent diagnostic performance for liver fibrosis in patients with NAFLD,<sup>256-258</sup> can be used to measure the whole liver (unlike VCTE), is not dependent on the examiner, and is not restricted by obesity.<sup>258</sup> MRE is the most accurate NIT for liver fibrosis, and its diagnostic performance is better than VCTE.<sup>203,233,259</sup> In several meta-analyses, MRE showed a high diagnostic performance for each stage of liver fibrosis, with an AUC of 0.84–0.93, and the measurement failure rate was <5%, which was lower than VCTE (Table 13).<sup>192,253,260,261</sup> In another recent IPD-MA involving international cohorts, for significant fibrosis the AUC was 0.92 and the cutoff value was 3.14 kPa, for advanced fibrosis the AUC was 0.92 and the cutoff value was 3.53 kPa, and for cirrhosis the AUC was 0.94 and the cutoff value was 4.45 kPa, demonstrating excellent diagnostic performance.<sup>262</sup> MRE is not significantly affected by equipment from different manufacturers or the strength of the magnetic field,<sup>86</sup> and is highly reproducible.<sup>263</sup> However, it is difficult to use universally across all healthcare institutions due to high cost and low accessibility. In addition, iron deposition can make it difficult to measure signal intensity.<sup>264</sup> Another drawback is that MRE results are affected by infiltrative liver disease, severe liver steatosis, liver congestion, and acute inflammation.<sup>265</sup>

Recently, a score based on MRI-PDFF and MRE ( $-12.17+7.07\times\log_{10}\text{MRE}+0.037\times\text{PDFF}+3.55\times\log_{10}\text{AST}$ ) has been proposed based on a US cohort study.<sup>266</sup> When diagnosing NASH patients with NAS  $\geq 4$  and significant fibrosis, the AUC was 0.929 and the cutoff value was 0.165, showing better diagnostic performance than FIB-4 (AUC, 0.711), NFS (AUC, 0.689), or FAST score (AUC, 0.868).

Another recent multicenter study in the US and Japan compared the MEFIB index,<sup>20</sup> which combines MRE and FIB-4 (MRE  $\geq 3.3$  kPa+FIB-4  $\geq 1.6$ ), with FAST score<sup>246</sup> for diagnosing significant fibrosis. In the US cohort, the AUCs of the MEFIB index and FAST score were 0.86 and 0.757, respectively, and in the Japanese cohort they were 0.899 and 0.724, with the MEFIB index showing significantly better diagnostic performance.<sup>267</sup>

Although MRE can be affected by fasting duration, abdominal obesity, cholestasis, AST or ALT values, and liver steatosis, it has been reported to show a higher measurement success rate than VCTE in severely obese patients because it is less affected by the thickness of subcutaneous fat.<sup>245</sup>

### Noninvasive tests for liver steatosis

#### Serum panel

Liver steatosis can be diagnosed by several noninvasive serum panels using clinical information, such as age or sex, and the results of blood tests. Examples include the fatty liver index (FLI), NAFLD liver fat score (NLFS), and hepatic steatosis index (HSI) (Table 14).<sup>268-270</sup>

Liver steatosis can be excluded if the FLI is <30, and can be diagnosed if the FLI is >60 with an AUC of 0.84, PPV of 99%, and NPV of 15%.<sup>268</sup> The FLI also showed adequate diagnostic performance in Korean patients,<sup>271,272</sup> but it was reported that the cutoff value should be 29.<sup>273</sup> One Chinese

**Table 14.** Serum markers for diagnosing liver steatosis in patients with NAFLD

Panel	Calculation Method	Cutoff value	AUC
FLI <sup>268</sup>	$(e^{0.953 \times \log_e(\text{triglycerides [mg/dL]} + 0.139 \times \text{BMI [kg/m}^2\text{]} + 0.718 \times \log_e(\text{GGT [IU/L]} + 0.053 \times \text{waist circumference [cm]} - 15.745)) / (1 + e^{0.953 \times \log_e(\text{triglyceride s[mg/dL]} + 0.139 \times \text{BMI [kg/m}^2\text{]} + 0.718 \times \log_e(\text{GGT[IU/L]} + 0.053 \times \text{waist circumference [cm]} - 15.745))}) \times 100$	$\geq 60$ (diagnosis), $< 30$ (exclusion)	0.85
NLFS <sup>269</sup>	$-2.89+1.18\times\text{metabolic syndrome (yes=1, no=0)}+0.45\times\text{T2DM (yes=2, no=0)}+0.15\times(\text{fasting insulin } [\mu\text{U/L}])+0.04\times\text{AST [IU/L]}+0.94\times\text{AST/ALT}$	$> -0.64$	0.86–0.87
HSI <sup>270</sup>	$8\times\text{ALT/AST+BMI [kg/m}^2\text{]}$ (T2DM +2; female +2)	$\geq 36$ (diagnosis), $< 30$ (exclusion)	0.81

NAFLD, nonalcoholic fatty liver disease; FLI, fatty liver index; NLFS, nonalcoholic fatty liver disease liver fat score; HSI, hepatic steatosis index; BMI, body mass index; GGT, gamma-glutamyl transferase; T2DM, type 2 diabetes mellitus; AST, aspartate aminotransferase; ALT, alanine transaminase; AUC, area under the curve.

study suggested that the cutoff value for the FLI in Asian patients should be 30,<sup>274</sup> while another study from Taiwan reported that a cutoff value of 35 was suitable for male patients and 20 for female patients.<sup>275</sup>

The NLFS was proposed using a Finnish cohort of 470 patients, with a cutoff value of -0.640, sensitivity of 86%, specificity of 71%, and AUC of 0.86–0.87,<sup>269</sup> and also showed suitable diagnostic performance in Korean patients.<sup>276</sup>

The HSI was developed based on a Korean cohort of 5,462 patients with ultrasound-defined NAFLD,<sup>270</sup> in patients with HSI <30, liver steatosis could be excluded with a sensitivity of 93.1%, whereas in patients with HSI >36, liver steatosis could be diagnosed with a specificity of 92.4% (AUC 0.812). The HSI has also demonstrated effective diagnostic performance in Western patients as well as Asian patients.<sup>277,278</sup>

#### *Controlled attenuated parameter*

CAP is a method of quantifying ultrasound attenuation due to liver steatosis, which is included in VCTE devices, and can be used to accurately determine the amount of intrahepatic fat.<sup>42,279</sup> In a Korean study of patients with CLD, including NAFLD, the AUCs of CAP for diagnosing mild, moderate, and severe steatosis were 0.885, 0.894, and 0.800, respectively, and the cutoff values were 250 dB/m, 299 dB/m, and 327 dB/m.<sup>280</sup> The diagnostic performance of CAP was recently validated in a single-center Korean study of 539 patients with biopsy-proven NAFLD. The AUCs for diagnosing mild, moderate, and severe steatosis were 0.80, 0.73, and 0.70, and the cutoff values were 271 dB/m, 287 dB/m, and 290 dB/m.<sup>237</sup> In a multicenter study of 450 patients with NAFLD in the UK, the AUCs of CAP for diagnosing mild, moderate, and severe steatosis were 0.87, 0.77, and 0.70, respectively, and the cutoff values were 302 dB/m, 331 dB/m, and 337 dB/m, which were higher cutoff values than in East Asian patients.<sup>281</sup> In a meta-analysis of 1,297 patients with biopsy-proven NAFLD across nine studies, the AUCs of CAP for diagnosing mild, moderate, and severe steatosis were 0.96, 0.82, and 0.70, and CAP values were reported to vary depending on ethnicity, age, and BMI.<sup>282</sup> In another recently published IPD-MA including 13 studies, the AUCs of CAP for diagnosing mild, moderate, and severe steatosis were 0.819, 0.754, and 0.717.<sup>283</sup> Standards for the diagnostic performance of CAP for liver

steatosis, based on the M probe, were recently validated in three multicenter studies, including Europe and Hong Kong, and the accuracy of CAP was reported to decrease when IQR was >40 dB/m.<sup>284</sup>

#### *Quantitative ultrasound assessment of liver steatosis*

Methods of quantifying liver steatosis using ultrasound include tissue attenuation imaging and tissue scatter-distribution imaging.<sup>285</sup> Tissue attenuation imaging in the liver quantifies steatosis in real-time by measuring the weakening of the ultrasound signal due to fat in hepatocytes, while tissue scatter-distribution imaging quantifies steatosis by measuring the extent of scattering of the ultrasound signal due to fat in hepatocytes.<sup>286,287</sup> In one recent Korean study, the extent of liver steatosis measured by tissue attenuation imaging and tissue scatter-distribution imaging were found to be significantly correlated with the extent of liver steatosis measured by MRI-PDFF, and the AUCs for diagnosing the presence or absence of liver steatosis (>5%) were 0.861 and 0.964, respectively.<sup>288</sup> In a Taiwanese cohort of patients with CLD, the AUCs of tissue attenuation imaging for diagnosing mild, moderate, and severe steatosis were 0.97, 0.99, and 0.97, respectively, demonstrating high diagnostic performance.<sup>289</sup> The efficacy of tissue attenuation imaging and CAP for diagnosing liver steatosis was compared in a prospective cohort study in China; the AUCs for diagnosing moderate steatosis were 0.751 and 0.572, respectively, and the cutoff values were 0.793 dB/cm/MHz and 328 dB/m, and the sensitivities were similar at 87.5% and 82.14%.<sup>290</sup>

#### *Magnetic resonance imaging*

Magnetic resonance imaging (MRI) is better than abdominal ultrasound for diagnosing small amounts of liver steatosis, and is the most precise imaging technique for diagnosing NAFLD. In addition to qualitative contrast-enhanced imaging of steatosis using the Dixon technique, quantitative MRI techniques can be divided into MR spectroscopy (MRS) and MRI-PDFF.<sup>291</sup> MRS can directly measure the proton signal from the acryl groups on triglycerides, and shows a very strong correlation with histological findings and very high sensitivity.<sup>241,292</sup> MRI-PDFF uses the difference in the precession of protons in water and fat within a magnetic field. MRI-PDFF allows fat deposits to be mapped across the whole liver, meaning that the extent of

liver steatosis accumulation can be diagnosed in a given part of the liver.

MRI-PDFF has shown very high concordance with histological findings in studies using diverse equipment, and demonstrates the AUC of 0.95 for diagnosing severe steatosis ( $\geq 67\%$ ).<sup>293,294</sup> In one meta-analysis, the AUC was 0.98 for diagnosing mild or worse steatosis, 0.91 for moderate or worse steatosis, and 0.90 for severe or worse steatosis.<sup>295</sup> A prospective study and meta-analysis comparing MRI-PDFF with CAP also reported that MRI-PDFF had superior diagnostic performance for liver steatosis (Table 15).<sup>233,296</sup>

MRS and MRI-PDFF allow for accurate diagnosis of liver steatosis because the effects of iron deposition and fibrosis can be excluded.<sup>297</sup> However, in order for MRI to be widely used for diagnosing liver steatosis, the problems of high cost and low accessibility will need to be overcome.

**[Recommendations]**

1. Serum markers can be used to exclude advanced fibrosis among patients with NAFLD. (B1)
2. In patients with NAFLD, liver fibrosis can be assessed using VCTE, SWE, or MRE. (A1)

**Alcohol-related liver disease**

ALD is the principal cause of liver-related morbidity and mortality worldwide.<sup>298</sup> The spectrum of ALD is diverse, including asymptomatic early stages to decompensated states. Continued alcohol intake during the early stages of asymptomatic alcohol-related liver disease can lead to the development of alcoholic hepatitis, acute-on-chronic liver failure, or decompensated liver disease.<sup>299</sup> Unfortunately, most patients with alcohol-related liver disease are diagnosed after reaching the decompensated stages; therefore, mortality remains high despite post-diagnosis alcohol abstinence.<sup>300</sup> It is expected that NITs will be useful in the early detection of asymptomatic ALD.

**Serum markers**

Various serum markers have been proposed to diagnose alcohol-related liver fibrosis. The diagnostic performances of ELF and FibroTest were high among various serum markers in ALD (Table 16).<sup>301-307</sup>

The diagnostic performance of ELF was excellent, with an AUC of 0.90–0.92 for diagnosing advanced fibrosis and 0.90–0.94 for diagnosing cirrhosis.<sup>303,306,307</sup> In a study including 289 patients with ALD, the sensitivity and specificity

**Table 15.** The diagnostic performance of MRI-PDFF and CAP for liver steatosis in patients with NAFLD<sup>296</sup>

Method	No. of studies	No. of patients	AUC	Cutoff value	Sensitivity% (95% CI)	Specificity% (95% CI)	PLR% (95% CI)	NLR% (95% CI)
Mild steatosis ( $\geq S1$ )								
MRI-PDFF	6	667	0.97	5.36	92.0 (87.0–95.0)	93.0 (90.0–96.0)	14.16 (8.97–22.35)	0.08 (0.05–0.14)
CAP	11	1,893	0.85	273.58	82.0 (79.0–84.0)	83.0 (80.0–86.0)	4.41 (2.84–6.86)	0.28 (0.21–0.37)
M-probe	5	548	0.96	254.4	88.0 (83.0–92.0)	92.0 (88.0–95.0)	7.32 (3.54–15.15)	0.14 (0.10–0.21)
XL-probe	4	450	0.8	300	69.0 (57.0–78.0)	82.0 (68.0–91.0)	3.61 (1.86–7.03)	0.38 (0.27–0.54)
Moderate steatosis ( $\geq S2$ )								
MRI-PDFF	9	969	0.91	15.36	79.0 (72.0–85.0)	88.0 (84.0–91.0)	6.54 (4.88–8.76)	0.25 (0.18–0.33)
CAP	18	3,295	0.83	288.5	81.0 (79.0–83.0)	63.0 (61.0–65.0)	2.40 (1.96–2.93)	0.29 (0.25–0.34)
M-probe	11	1,433	0.84	283.21	82.0 (77.0–86.0)	66.0 (55.0–76.0)	2.66 (1.90–3.71)	0.28 (0.22–0.34)
XL-probe	6	730	0.84	297.43	94.0 (84.0–98.0)	57.0 (40.0–72.0)	2.08 (1.45–2.98)	0.25 (0.15–0.40)
Severe steatosis ( $\geq S3$ )								
MRI-PDFF	8	804	0.90	20.35	71.0 (62.0–79.0)	89.0 (86.0–92.0)	6.35 (4.76–8.48)	0.33 (0.25–0.45)
CAP	17	2,835	0.79	309.09	79.0 (77.0–81.0)	56.0 (53.0–58.0)	2.12 (1.75–2.58)	0.36 (0.31–0.43)
M-probe	10	1,336	0.75	299.77	85.0 (75.0–92.0)	57.0 (47.0–66.0)	1.85 (1.56–2.20)	0.32 (0.23–0.45)
XL-probe	6	730	0.80	325.71	79.0 (72.0–84.0)	62.0 (47.0–75.0)	2.36 (1.74–3.20)	0.33 (0.26–0.42)

MRI-PDFF, MRI-proton density fat fraction; CAP, controlled attenuation parameter; NAFLD, nonalcoholic fatty liver disease; AUC, area under the curve; CI, confidence interval; PNR, positive likelihood ratio; NLR, negative likelihood ratio.

ty of ELF were 89% and 78%, respectively, at a cutoff value of 9.8, and 79% and 91%, respectively, at a cutoff value of 10.5 in diagnosing advanced fibrosis.<sup>303</sup> In a study of 266 patients with alcohol use disorder, the sensitivity and specificity of ELF were 77% and 90% at a cutoff value of 10.5 in diagnosing advanced fibrosis, and 93% and 80% at a cutoff value of 10.1 in diagnosing cirrhosis.<sup>307</sup>

In a study involving 289 patients with ALD, FibroTest exhibited an AUC of 0.90, sensitivity of 67%, and specificity of 89% at a cutoff value of 0.58 for diagnosing advanced fibrosis. Additionally, the AUCs for diagnosing significant fibrosis and cirrhosis were 0.86 and 0.89, respectively.<sup>303</sup> The diagnostic performance of FibroTest was comparable to ELF in diagnosing advanced fibrosis, and exhibited no significant difference from VCTE in intention-to-diagnose analysis.<sup>303</sup>

The diagnostic performance of FIB-4 and Forns index has primarily been reported in studies comparing them with other serum markers or VCTE.<sup>301-303</sup> FIB-4 showed an AUC of 0.85, sensitivity of 58%, specificity of 91%, and NPV of 88% at a cutoff value of 3.25 for diagnosing advanced fibrosis. Forns index exhibited an AUC of 0.86, sensitivity of 71%, specificity of 89%, and NPV of 91% at a cutoff value of 6.8 for diagnosing advanced fibrosis.<sup>303</sup> In a subgroup analysis of 128 patients from a primary clinic with a prevalence of 6% advanced fibrosis, the NPVs of ELF <10.5, FibroTest <0.58, FIB-4 <3.25, and Forns index <6.8 were 98%, 94%, 95%, and 97%, respectively, in diagnosing advanced fibrosis. This result suggests that serum markers can be used to exclude advanced fibrosis in primary care. However, the cutoff values varied among studies, and an independent validity study is needed in other research endeavors.

A recent study including 459 individuals with ALD and 137 controls reported the diagnostic performance of proteomics biomarker panels using a machine learning model for diagnosing liver fibrosis.<sup>308</sup> The AUC of proteomics biomarker panels in diagnosing significant fibrosis was 0.92, comparable to VCTE, SWE, ELF, and FibroTest. The AUC of proteomics biomarker panels in diagnosing advanced fibrosis was 0.97, also comparable VCTE, SWE, or ELF. The diagnostic performance of the proteomics biomarker panels for liver fibrosis was high, but further validation in a large patient population is needed to apply these results in clinical settings.

### Vibration-controlled transient elastography

VCTE is the most extensively studied NIT in ALD (Table 17).<sup>60,301,302,304,307,309-313</sup> In a Cochrane meta-analysis involving 14 studies and 834 patients with ALD, the summary sensitivity and specificity for diagnosing advanced fibrosis were 92% and 70%, respectively, at a cutoff value of 9.5 kPa (ranges, 8–11 kPa).<sup>314</sup> In a Korean study including 45 patients with ALD, VCTE demonstrated an AUC of 0.98 for diagnosing advanced fibrosis and 0.97 for diagnosing cirrhosis. The cutoff value of 25.8 kPa yielded a sensitivity of 90% and a specificity of 87% for diagnosing cirrhosis.<sup>310</sup>

In an IPD-MA involving 10 studies and 1,026 patients with ALD, the AUC for diagnosing significant fibrosis using VCTE was 0.86, with a sensitivity of 78% and specificity of 77% at a cutoff value of 9.0 kPa. The AUC for diagnosing advanced fibrosis was 0.90, with a sensitivity of 81% and specificity of 83% at a cutoff value of 12.1 kPa. Additionally, the AUC for diagnosing cirrhosis was 0.91, with a sensitivity of 84% and specificity of 85% at a cutoff value of 18.6 kPa.<sup>315</sup> The cutoff value for diagnosing liver fibrosis in patients with ALD is higher compared to other CLDs, and LS measures increased significantly with rising serum AST or total bilirubin levels in patients with ALD. The study suggested an increase in cutoff values for diagnosing each stage of liver fibrosis as serum AST or total bilirubin levels increase. In a study involving 452 patients with ALD and 1,391 patients with CHC, AST and LS values were proportional. Additionally, LS measurements increased exponentially with rising AST within the same stage of liver fibrosis. This study suggested that ALD mainly causes damage to the liver lobules unlike CHC, which primarily involve damage to portal tracts. Consequently, there is a considerable impact of AST on LS values in patients with ALD. This study indicated that adjusting cutoff values based on AST levels can improve the diagnostic performance of VCTE for liver fibrosis.<sup>316</sup>

Baveno VI introduced the concept of compensated advanced chronic liver disease (cACLD) and proposed that cACLD can be ruled out at LS values less than 10 kPa, while the likelihood of cACLD is high when LS values exceed 15 kPa.<sup>317</sup> In a subgroup analysis of ALD (n=946) from a study including 5,648 patients from 10 countries in Europe, the AUC for diagnosing cirrhosis was 0.97, with a sensitivity of 90% and specificity of 87% at a cutoff value of 25.8 kPa. The diagnostic performance for advanced fibro-

**Table 16.** Diagnostic performance of serum markers for liver fibrosis in patients with ALD

Serum markers	Reference	No. of patients	Nation	Significant fibrosis ( $\geq F2$ )				Advanced fibrosis ( $\geq F3$ )				Cirrhosis (F4)					
				No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)		
FIB-4	Fernandez et al. <sup>301</sup> (2015)	135	Belgium	98 (72.6)	-	-	-	65 (48.1)	0.70	(0.60-0.80)	-	-	41 (30.4)	0.73	(0.63-0.82)	-	-
	Voican et al. <sup>302</sup> (2017)	193	France	117 (60.6)	-	-	-	78 (40.4)	0.63	(0.54-0.70)	-	-	29 (15.0)	0.80	(0.71-0.87)	-	-
	Thiele et al. <sup>303</sup> (2018)	289	Denmark	146 (50.5)	0.77	(0.71-0.83)	-	66 (23.0)	0.85	(0.80-0.90)	3.25	58.0/91.0	49 (17.0)	0.89	(0.86-0.93)	-	-
	Nguyen-Khiac et al. <sup>304</sup> (2008)	103	France	77 (74.8)	0.54	(0.40-0.68)	-	53 (51.4)	0.43	(0.30-0.56)	-	-	33 (32.0)	0.56	(0.38-0.73)	-	-
APRI	Zhang et al. <sup>305</sup> (2014)	99	China	60 (60.6)	0.76	(0.67-0.86)	0.59	25 (25.2)	0.69	(0.56-0.82)	0.95	40.0/97.0	9 (9.10)	0.65	(0.43-0.87)	1.1	44.0/94.0
	Fernandez et al. <sup>301</sup> (2015)	135	Belgium	98 (72.6)	-	-	-	65 (48.1)	0.65	(0.54-0.75)	-	-	41 (30.4)	0.75	(0.65-0.84)	-	-
	Voican et al. <sup>302</sup> (2017)	193	France	117 (60.6)	-	-	-	78 (40.4)	0.59	(0.50-0.67)	-	-	29 (15.0)	0.63	(0.47-0.75)	-	-
	Thiele et al. <sup>303</sup> (2018)	289	Denmark	146 (50.5)	0.75	(0.69-0.81)	-	66 (23.0)	0.80	(0.74-0.86)	1	38.0/90.0	49 (17.0)	0.85	(0.81-0.90)	-	-
	Connoley et al. <sup>306</sup> (2021)	81	UK	63* (77.8)	-	-	$\leq 0.5$	59 <sup>†</sup> (72.8)	-	-	-	-	54 <sup>‡</sup> (66.7)	-	-	$\leq 1$	59.0/80.0
	Fernandez et al. <sup>301</sup> (2015)	135	Belgium	98 (72.6)	-	-	-	65 (48.1)	0.64	(0.53-0.74)	-	-	41 (30.4)	0.78	(0.68-0.88)	-	-
	Voican et al. <sup>302</sup> (2016)	193	France	117 (60.6)	-	-	-	78 (40.4)	0.64	(0.55-0.71)	-	-	29 (15.0)	0.80	(0.67-0.87)	-	-
	Thiele et al. <sup>303</sup> (2018)	289	Denmark	146 (50.5)	0.80	(0.74-0.85)	-	66 (23.0)	0.86	(0.81-0.91)	6.8	71.0/89.0	49 (17.0)	0.89	(0.84-0.94)	-	-
ELF	Thiele et al. <sup>303</sup> (2018)	289	Denmark	146 (50.5)	0.84	(0.80-0.89)	7.7	66 (23.0)	0.92	(0.89-0.96)	10.5	79.0/91.0	49 (17.0)	0.94	(0.91-0.97)	-	-
	Madsen et al. <sup>307</sup> (2020)	266	Denmark	141 (53.0)	-	-	-	62 (23.3)	0.92	(0.88-0.96)	10.5	77.0/90.0	45 (16.9)	0.93	(0.90-0.97)	10.1	93.0/80.0
	Connoley et al. <sup>306</sup> (2021)	81	UK	63* (77.8)	0.92	(0.87-0.98)	8.3	59 <sup>†</sup> (72.8)	0.90	(0.83-0.97)	-	-	54 <sup>‡</sup> (66.7)	0.90	(0.82-0.97)	9.8	91.0/63.0
	Nguyen-Khiac et al. <sup>304</sup> (2008)	103	France	77 (74.8)	0.79	(0.69-0.90)	-	53 (51.4)	0.80	(0.70-0.91)	-	-	33 (32.0)	0.84	(0.72-0.97)	-	-
FibroTest	Fernandez et al. <sup>301</sup> (2015)	135	Belgium	98 (72.6)	-	-	-	65 (48.1)	0.81	(0.73-0.89)	-	-	41 (30.4)	0.88	(0.81-0.94)	-	-

**Table 16.** Continued

Serum markers	Reference	No. of patients	Nation	Significant fibrosis (≥ F2)				Advanced fibrosis (≥ F3)				Cirrhosis (F4)			
				No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/ specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/ specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity%/ specificity%
	Voican et al. <sup>302</sup> (2017)	193	France	117 (60.6)	-	-	-	78 (40.4)	0.85 (0.79–0.90)	0.49	69.7/83.7	29 (15.0)	0.88 (0.79–0.93)	0.75	64.3/84.9
	Thiele et al. <sup>303</sup> (2018)	289	Denmark	146 (50.5)	0.86 (0.81–0.90)	-	-	66 (23.0)	0.90 (0.86–0.94)	0.58	67.0/89.0	49 (17.0)	0.89 (0.85–0.92)	-	-
FibroMeter	Nguyen-Khac et al. <sup>304</sup> (2008)	103	France	77 (74.8)	0.82 (0.72–0.93)	-	-	53 (51.4)	0.88 (0.80–0.95)	-	-	33 (32.0)	0.85 (0.74–0.96)	-	-
Hepascore	Nguyen-Khac et al. <sup>304</sup> (2008)	103	France	77 (74.8)	0.76 (0.64–0.88)	-	-	53 (51.4)	0.88 (0.74–0.93)	-	-	33 (32.0)	0.76 (0.63–0.90)	-	-

ALD, Alcohol-related liver disease; FIB-4, fibrosis-4 index; APRI, aspartate aminotransferase-to-platelet ratio index; ELF, enhanced liver fibrosis; AUC, area under the curve; CI, confidence interval.

\*Ishak ≥3.

†Ishak ≥4.

‡Ishak ≥5.

sis showed that the sensitivity was 94% at a cutoff value of 8 kPa and the specificity was 89% at a cutoff value of 12 kPa. Therefore, this study suggested a dual cutoff value of <8 kPa for excluding and >12 kPa for diagnosing cACLD in ALD.<sup>313</sup> A single-center prospective study in Denmark showed a sensitivity of 91%, specificity of 95%, PPV of 84%, and NPV of 98% for diagnosing advanced fibrosis at a cutoff value of 15 kPa.<sup>303</sup> Therefore, advanced fibrosis can be excluded at LS values <8–10 kPa in patients with ALD. In addition, it can be suspected after excluding false-positive causes at LS values ≥12–15 kPa.

Although there has been debate regarding whether current alcohol intake can lead to false-positive results in VCTE examination, it should be considered that alcohol intake can influence LS measurements, potentially causing false positives. In a study that involved 50 patients with ALD admitted for alcohol abstinence with a mean duration of 5.3 days, LS decreased in nearly all patients. The decline was proportional to the decrease in AST level.<sup>60</sup> In another study, LS values significantly decreased by a mean of 21.7% in 56.5% of the patients studied after one week of abstinence from admission. The decrease in LS values was proportional to the reduction in biochemical markers of intrahepatic inflammation, AST and GGT.<sup>318</sup> Therefore, the increase in LS measurements after alcohol use is due to the alcohol-induced intrahepatic inflammation rather than alcohol itself.

In a study involving 50 patients with ALD admitted for alcohol abstinence, the AUC for diagnosing cirrhosis increased from 0.92 to 0.95 after excluding patients with AST levels above 100 IU/L. Moreover, the specificity increased from 80% to 90%, with only a slight change in sensitivity from 96% to 95%.<sup>60</sup> Therefore, VCTE should be repeated after at least one week of alcohol abstinence. Alternatively, cutoff values may be adjusted according to serum AST levels in patients with ALD and elevated biochemical markers due to intrahepatic inflammation.

In a comparison of the diagnostic performance for liver fibrosis between VCTE and serum markers, the diagnostic performance of VCTE was relatively superior to that of non-patented serum markers or FibroTest.<sup>301-303</sup> The diagnostic performance of ELF was comparable to that of VCTE in intention-to-diagnose analysis. However, in per-protocol analysis, VCTE demonstrated superior diagnostic performance compared to ELF (AUC of 0.97 vs. 0.92).<sup>303</sup> The ac-

**Table 17.** Diagnostic performance of VCTE for liver fibrosis in patients with ALD

Reference	No. of patients	Nation	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)			
			No. of patients (%)	AUC (95% CI)	Cutoff Value (kPa)	Sensitivity/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff Value (kPa)	Sensitivity/specificity%	No. of patients (%)	AUC (95% CI)
Nguyen-Khac et al. <sup>304</sup> (2008)	103	France	77 (74.8)	0.91 (0.85–0.98)	7.8	80.0/90.5 (51.4)	0.90 (0.82–0.97)	11	86.7/80.5 (32.0)	0.92 (0.87–0.98)	19.5	85.7/84.2
Nahon et al. <sup>305</sup> (2008)	147	France	134 (91.1)	-	-	110 (74.8)	0.94 (0.90–0.97)	12.9	81.0/89.0 (53.7)	0.87 (0.81–0.93)	22.6	84.0/80.0
Kim et al. <sup>310</sup> (2009)	45	Korea	40 (88.9)	-	-	36 (80.0)	0.98 (0.94–1.02)	-	-	0.97 (0.93–1.01)	25.8	90.0/87.0
Janssens et al. <sup>311</sup> (2010)	49	Belgium	41 (83.7)	-	-	32 (65.3)	0.74	17	72.0/76.5 (40.8)	0.86	21.1	75.0/80.0
Mueller et al. <sup>60</sup> (2010)	101	German	-	-	-	-	0.91	8	91.0/75.0	0.92 (0.87–0.97)	11.5	100/77.0
Fernandez et al. <sup>301</sup> (2015)	135	Belgium	98 (72.6)	-	-	65 (48.1)	0.89 (0.83–0.95)	10.3	91.0/67.0 (30.4)	0.93 (0.90–0.97)	18	90.0/86.0
Thiele et al. <sup>312</sup> (2016)	199	France	84* (42.2)	0.95 (0.91–0.98)	9.6	-	-	-	36† (18.1)	0.96 (0.93–0.98)	19.7	97.0/90.0
Voican et al. <sup>302</sup> (2017)	193	Denmark	117 (60.6)	-	-	78 (40.4)	0.90 (0.83–0.93)	12	75.6/92.2 (15.0)	0.93 (0.88–0.97)	15	93.1/85.4
Thiele et al. <sup>303</sup> (2018)	289	Denmark	146 (50.5)	0.88 (0.84–0.92)	-	66 (23.0)	0.97 (0.95–0.99)	15	91.0/95.0 (17.0)	0.97 (0.95–0.99)	-	-
Madsen et al. <sup>307</sup> (2020)	266	Denmark	141 (53.0)	-	-	62 (23.3)	0.96 (0.94–0.99)	15.5	91.0/84.0 (16.9)	0.96 (0.94–0.98)	19.7	90.0/91.0
Papatheodoridi et al. <sup>313</sup> (2021)	946	Europe	-	-	-	360 (38.0)	-	10	86.9/80.7	-	-	-
								15	72.1/92.1			

ALD, Alcohol-related liver disease; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

\*Ishak ≥3.

†Ishak ≥5.



curacy of VCTE was more superior to that of ELF in cases where there is a disagreement between the two methods.<sup>303</sup> Therefore, if VCTE can be performed accurately, excluding false positives, it has higher diagnostic performance than serum markers. However, in primary or secondary healthcare settings where VCTE cannot be routinely conducted, it can be replaced with serum markers such as ELF.

### Shear wave elastography

In a prospective study conducted in Europe, which included 199 patients with alcohol use disorder, the diagnostic performance of 2D-SWE and VCTE was comparable (Table 18).<sup>312</sup> Another study demonstrated that the diagnostic performance of 2D-SWE (AUC of 0.97) was superior to serum markers (AUC of APRI: 0.80, FIB-4: 0.85, Forns index: 0.86) (Table 18).<sup>303</sup> The diagnostic performance of 2D-SWE was also comparable to that of ELF (AUC, 0.92) and FibroTest (AUC, 0.90) in intention-to-diagnose analysis and superior in per protocol analysis.

In three studies, pSWE demonstrated superior diagnostic performance compared to serum markers (Table 18).<sup>305,319,320</sup> Among these studies, a Korean study found an AUC of pSWE for diagnosing advanced fibrosis was 0.90, with a sensitivity of 90.9% and specificity of 76.3% at a cutoff value of 1.47 m/s. Additionally, the AUC for diagnosing cirrhosis was 0.91, with a sensitivity of 97.2% and the specificity of 74.8% at a cutoff value of 1.66 m/s.<sup>320</sup> The diagnostic performance of pSWE was superior to serum markers including APRI, FIB-4, and Forns index.

### Magnetic resonance elastography

In a study including 90 patients with ALD, diagnostic performance of MRE and FibroMeter was compared; however, the diagnostic performance of MRE was likely inaccurate due to the liver fibrosis stage being determined based on VCTE rather than on liver biopsy.<sup>321</sup>

#### [Recommendations]

1. VCTE can be used to screen or exclude advanced fibrosis in patients with ALD. (B1)
2. ELF, FibroTest, FIB-4, and SWE can be used to assess liver fibrosis in patients with ALD. (B2)

**Table 18.** Diagnostic performance of shear wave elastography for liver fibrosis in patients with ALD

Reference	No. of patients	Nation	Test	Significant fibrosis (≥F2)			Advanced fibrosis (≥F3)			Cirrhosis (F4)					
				No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)	No. of patients (%)	AUC (95% CI)	Cutoff value	Sensitivity/specificity (%)
Zhang et al. <sup>305</sup> (2015)	99	China	pSWE	60 (60.6)	0.85 (0.77-0.92)	1.27 m/s	77.0/85.0	25 (25.2)	0.88 (0.79-0.96)	1.4	84.0/82.0	9 (9.1)	0.89 (0.82-0.96)	1.65 m/s	89.0/84.0
Kiani et al. <sup>319</sup> (2016)	82	France	pSWE	34 (41.5)	0.87	1.63 m/s	82.4/83.3	17 (20.7)	0.86	1.84	82.4/78.5	13 (15.9)	0.89	1.94 m/s	92.3/81.6
Cho et al. <sup>320</sup> (2020)	251	Korea	pSWE	204 (81.3)	0.93 (0.89-0.97)	1.46 m/s	84.8/89.4	175 (69.7)	0.90 (0.86-0.95)	1.47	90.9/76.3	144 (57.3)	0.91 (0.87-0.95)	1.66 m/s	97.2/74.8
Thiele et al. <sup>312</sup> (2016)	199	Denmark	2D-SWE	84* (42.2)	0.94 (0.91-0.97)	10.2 kPa	82.0/93.0	-	-	-	-	36† (18.1)	0.95 (0.92-0.98)	16.4 kPa	94.0/91.0
Thiele et al. <sup>303</sup> (2018)	289	Denmark	2D-SWE	146 (50.5)	0.88 (0.84-0.92)	-	-	66 (23.0)	0.97 (0.94-0.99)	16.4	90.0/96.0	49 (17.0)	0.97 (0.94-0.99)	-	-

ALD, Alcohol-related liver disease; pSWE, point shear wave elastography; 2D-SWE, 2D shear wave elastography. AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

\*Ishak ≥3.

†Ishak ≥5.

## Other chronic liver diseases

Other CLDs include autoimmune liver diseases such as PBC, AIH, and PSC, as well as congestive hepatopathy.

In autoimmune liver diseases, advanced histological stages are associated with poor prognosis; thus, accurate assessment is crucial.<sup>322-325</sup> Treatment monitoring after diagnosis requires regular evaluation of changes in liver fibrosis, with a preference for noninvasive methods. Among NITs, VCTE is the most commonly used.

Congestive hepatopathy arises from chronic elevation of hepatic venous pressure due to various causes of heart failure and may progress to liver fibrosis and cirrhosis over time.<sup>326</sup> Principal causes include Fontan operation performed for congenital heart disease, rheumatic heart disease, or constrictive pericarditis, with a recent increase in cases due to ischemic cardiomyopathy. In congestive hepatopathy, the degree of hepatic congestion and changes in cardiac function can significantly alter LS measurements, thereby reducing the reliability of NITs.<sup>58,327</sup>

### Primary biliary cholangitis

Serum markers such as APRI and FIB-4 have suboptimal diagnostic performance in assessing histological stage in PBC. A study involving 1,828 North American and European patients with PBC revealed an APRI AUC of 0.64 for diagnosing significant fibrosis, 0.68 for advanced fibrosis, and 0.69 for cirrhosis, while the AUCs for FIB-4 were 0.64, 0.69, and 0.73, respectively, all below the threshold of 0.80.<sup>322</sup> In two retrospective studies conducted in Western countries, the AUC for diagnosing advanced fibrosis with APRI ranged from 0.67 to 0.77, and that for FIB-4 ranged from 0.35 to 0.70.<sup>328,329</sup>

LS on VCTE was previously shown to correlate with liver fibrosis in PBC (Table 19).<sup>330-333</sup> In a prospective French study of 146 patients who underwent VCTE, the AUC for diagnosing significant fibrosis was 0.91, with a cutoff value of 8.8 kPa, a sensitivity of 67%, and a specificity of 100%.<sup>331</sup> The AUC for diagnosing advanced fibrosis was 0.95, cutoff value 10.7 kPa, sensitivity 90%, and specificity 93%. The AUC for diagnosing cirrhosis reached 0.99, with a cutoff of 16.9 kPa, sensitivity 93%, and specificity 99%. When comparing the diagnostic performance of VCTE, APRI, and FIB-4 for advanced fibrosis, their respective AUCs were 0.95, 0.86, and 0.83, indicating superior perfor-

mance by VCTE.<sup>331</sup> A prospective study including 44 Japanese patients with PBC confirmed the high performance of VCTE for diagnosing advanced fibrosis and cirrhosis, with AUCs of 0.91 and 0.97, respectively.<sup>332</sup> However, higher cutoff values were used than in other studies, at 17.9 kPa and 25.1 kPa, respectively.

In a recent multicenter prospective study, which evaluated 167 Italian patients in a PBC registry, the diagnostic performance of VCTE were assessed before treatment initiation.<sup>334</sup> The study introduced a dual cutoff approach where a cutoff value of 6.5 kPa or lower could exclude advanced fibrosis, while values exceeding 11.0 kPa could diagnose it. This dual cutoff approach demonstrated an NPV of 94%, a PPV of 89%, and an error rate of 5.6%.

In terms of pSWE, the AUC for diagnosing significant fibrosis was 0.81 with a cutoff value of 5.56 kPa, sensitivity of 81.8%, and specificity of 73.3% in a study involving 41 Korean patients with PBC.<sup>335</sup> For diagnosing advanced fibrosis, the AUC increased to 0.91, with a cutoff value of 6.04 kPa, sensitivity of 100%, and specificity of 81.6%. A retrospective study from Greece involving 53 patients with PBC evaluated the diagnostic performance of 2D-SWE.<sup>336</sup> The AUC for diagnosing significant fibrosis was 0.874, with a cutoff value of 7.8 kPa, sensitivity of 84.4%, and specificity of 87.0%. The AUC for diagnosing advanced fibrosis was 0.853, cutoff value 10.0 kPa, sensitivity of 80.8%, and specificity of 81.0%. The AUC for diagnosing cirrhosis was 0.903, with a cutoff value of 11.9 kPa, sensitivity of 90.0%, and specificity of 82.6%.

Recent research in the US involving 98 patients with PBC has explored the performance of MRE in diagnosing liver fibrosis.<sup>337</sup> The AUC for diagnosing significant fibrosis was relatively low at 0.60, with a cutoff value of 3.8 kPa, sensitivity of 51%, and specificity of 90%. The AUC for diagnosing advanced fibrosis was 0.71, with a cutoff value of 3.7 kPa, sensitivity of 75%, and specificity of 76%. Diagnosis of cirrhosis yielded a higher AUC of 0.82, with a cutoff value of 4.6 kPa, sensitivity of 80%, and specificity of 83%. The diagnostic performance of MRE was notably lower in differentiating mild stages of liver fibrosis. Furthermore, the performance of MRE was further diminished in patients exhibiting stage 3-4 inflammation in liver biopsy, those with ALT levels more than twice the UNL, or when AIH overlapped with PBC.

In summary, VCTE demonstrates excellent accuracy for

**Table 19.** Diagnostic performance of VCTE in autoimmune liver disease

Disease	Reference	No. of patients	Nation	Significant fibrosis (≥F2)				Advanced fibrosis (≥F3)				Cirrhosis (F4)			
				No. of patients (%)	AUC (95% CI)	Cutoff Value (kPa)	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%	No. of patients (%)	AUC (95% CI)	Cutoff value (kPa)	Sensitivity%/specificity%
PBC	Gómez-Domínguez et al. <sup>330</sup> (2008)	55	Spain	-	-	-	-	16 (29.1)	0.86 (0.72–0.94)	14.7	56.0/100.0	2 (3.6)	0.96 (0.87–0.99)	15.6	88.0/98.0
	Floreani et al. <sup>333</sup> (2011)	120	Italia	88 (80.0)	0.89 (0.81–0.97)	5.9	82.0/92.0	50 (50.0)	0.92 (0.85–0.99)	7.6	90.0/92.0	17 (15.0)	0.99 (0.94–1.00)	11.4	99.0/94.0
	Corpechot et al. <sup>331</sup> (2012)	103	France	52 (50.0)	0.91 (0.86–0.96)	8.8	67.0/100.0	30 (29.0)	0.95 (0.92–0.99)	10.7	90.0/93.0	15 (14.5)	0.99 (0.97–1.00)	16.9	93.0/99.0
	Koizumi et al. <sup>332</sup> (2017)	44	Japan	17 (38.6)	0.92 (0.80–0.97)	16.0	94.1/80.8	13 (29.5)	0.91 (0.79–0.97)	17.9	92.3/76.7	6 (13.6)	0.91 (0.69–0.98)	25.1	83.3/70.7
	Hartl et al. <sup>343</sup> (2016)	94	Germany	56 (59.6)	0.87 (0.79–0.97)	5.8	90.0/72.0	33 (35.1)	0.93 (0.82–0.95)	10.4	83.0/98.0	20 (13.8)	0.96 (0.85–0.98)	16.0	88.0/100.0
AIH	Anastasiou et al. <sup>341</sup> (2016)	53	Germany	44 (83.0)	0.78 (0.79–0.97)	10.05	61.4/88.9	29 (54.7)	0.74 (0.84–0.96)	12.1	83.3/80.9	15 (28.3)	0.842 (0.77–0.98)	19.0	81.8/92.9
	Xu et al. <sup>339</sup> (2017)	100	China	84 (84.0)	0.88 (0.82–0.95)	6.45	82.1/87.5	50 (50.0)	0.88 (0.84–0.96)	8.75	80.0/84.0	23 (23.0)	0.91 (0.85–0.98)	12.5	87.0/89.6
	Guo et al. <sup>344</sup> (2017)	108	China	78 (72.2)	0.89 (0.81–1.00)	6.27	84.6/76.7	54 (54.5)	0.90 (0.89–1.00)	8.18	79.6/85.2	24 (22.2)	0.88 (0.76–1.00)	12.67	87.5/88.1
	Paranaguá-Vezozzo et al. <sup>345</sup> (2023)	33	Brazil	26 (78.8)	0.91 (0.81–1.00)	6.3	76.9/100.0	18 (54.5)	0.83 (0.69–0.91)	8.7	72.2/80.0	8 (24.2)	0.88 (0.88–1.00)	12.3	87.5/88.0
	Corpechot et al. <sup>348</sup> (2014)	66	France	32 (48.5)	0.84 (0.82–0.99)	7.4	60.0/86.0	15 (22.7)	0.93 (0.89–1.00)	9.6	93.3/83.0	9 (13.6)	0.95 (0.93–1.00)	14.4	100.0/88.0
PSC	Ehiken et al. <sup>346</sup> (2016)	62	Germany	27 (43.5)	0.91 (0.82–0.99)	8.8	81.5/88.6	20 (32.3)	0.95 (0.89–1.00)	9.6	90.0/90.5	16 (25.8)	0.98 (0.93–1.00)	14.4	68.8/97.8
	Muir et al. <sup>365</sup> (2019)	58	US	-	-	-	-	-	0.80 (0.68–0.91)	9.6	67.0/74.0	-	0.95 (0.88–1.00)	14.4	100.0/83.0

VCTE, vibration-controlled transient elastography; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; AUC, area under the curve; CI, confidence interval; kPa, kilopascal.

assessing liver fibrosis in patients with PBC. However, evidence regarding the cutoff values and practical application of VCTE after achieving a biochemical response to ursodeoxycholic acid treatment remains insufficient. Additionally, research on the effectiveness of SWE and MRE in this patient population is still limited.

### Autoimmune hepatitis

In patients with AIH, serum markers such as APRI and FIB-4 exhibit low diagnostic performance for liver fibrosis.<sup>338-341</sup> According to a meta-analysis that included 16 studies evaluating the diagnostic performance of NITs in AIH, the AUC with APRI ranged from 0.60 to 0.64 for diagnosing significant fibrosis and was 0.74 for advanced fibrosis.<sup>342</sup> The AUC for diagnosing cirrhosis was 0.75, with cutoff values ranging from 1.50 to 2.00, and both sensitivity and specificity were 70%. Similarly, the AUCs with FIB-4 for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis were 0.66, 0.76, and 0.66, respectively.

LS measurements on VCTE have been shown to accurately reflect the histological extent of liver fibrosis in AIH (Table 19).<sup>339,341,343-345</sup> Retrospective studies report that for patients with AIH, the AUC with VCTE for diagnosing advanced fibrosis ranges from 0.74 to 0.90, with cutoff values between 8.2 and 12.1 kPa, sensitivity from 59% to 80%, and specificity from 83% to 85%.<sup>339,341,344,345</sup> Additionally, a meta-analysis comparing VCTE, APRI, and FIB-4 using the diagnostic odds ratio also demonstrated that VCTE is superior in diagnosing advanced fibrosis (31.6 vs. 4.60 vs. 4.70) and cirrhosis (80.5 vs. 12.9 vs. 5.5).<sup>342</sup>

In a German prospective study involving 94 patients with biopsy-proven AIH, the AUC for diagnosing significant fibrosis using VCTE was 0.87, with a cutoff value of 5.8 kPa.<sup>343</sup> The AUC for diagnosing advanced fibrosis was 0.93 with a cutoff value of 10.4 kPa, and the AUC for diagnosing cirrhosis was 0.96 with a cutoff value of 16.0 kPa, a sensitivity of 99%, and a specificity of 100%. However, when distinguishing patient groups based on the duration of immunosuppressive treatment, those assessed with VCTE between 6 to 12 months after starting treatment showed superior diagnostic performance in all stages of liver fibrosis, with AUCs ranging from 0.97 to 1.0, compared to those assessed within 3 months of treatment initiation, who had AUCs ranging from 0.68 to 0.80. These results suggest that liver inflammation may influence LS values. This indi-

cates that in patients with AIH, VCTE results obtained after six months of immunosuppressive therapy—when liver inflammation has subsided—can more accurately differentiate between significant and advanced fibrosis.

In a Korean study involving 49 patients with AIH, pSWE demonstrated the following diagnostic performance: The AUC for diagnosing significant fibrosis was 0.70, with a cutoff value of 4.47 kPa, sensitivity of 93.6%, and specificity of 44.4%.<sup>335</sup> The AUC for diagnosing advanced fibrosis was 0.76, with a cutoff value of 7.11 kPa, sensitivity of 66.7%, and specificity of 78.6%. The AUC for diagnosing cirrhosis was 0.75, with a cutoff value of 9.28 kPa, sensitivity of 63.6%, and specificity of 86.8%. These results were superior to those obtained using APRI and FIB-4. A retrospective study of 20 patients with AIH using 2D-SWE found the AUC of 0.78 for diagnosing significant fibrosis, with a cutoff value of 7.29 kPa, sensitivity of 85.7%, and specificity of 38.5%.<sup>346</sup>

Research on MRE in patients with AIH is limited. However, a retrospective study involving 36 patients with AIH demonstrated promising results.<sup>347</sup> The AUC for diagnosing advanced fibrosis was 0.97, with a cutoff value of 4.1 kPa, sensitivity of 89.5%, and specificity of 100%. The AUC for diagnosing cirrhosis was 0.98, with a cutoff value of 4.5 kPa, sensitivity of 92.3%, and specificity of 96%. Although no studies have yet directly compared MRE with VCTE, its diagnostic performance exceeds that of APRI and FIB-4, suggesting potential reliability in assessing liver fibrosis in patients with AIH.

In summary, VCTE shows excellent diagnostic performance for liver fibrosis in patients with AIH. However, caution is needed in interpreting these results, as LS may be overestimated in the presence of liver inflammation, independent of actual liver fibrosis.

### Primary sclerosing cholangitis

The diagnostic performance of VCTE for liver fibrosis in patients with PSC has primarily been evaluated in Europe, as indicated in Table 19.<sup>325,348,349</sup> A prospective study in France involving 66 patients with PSC showed the following results: the AUC for diagnosing significant fibrosis was 0.84 with a cutoff value of 8.6 kPa, sensitivity of 72%, and specificity of 89%. The AUC for diagnosing advanced fibrosis was 0.93 with a cutoff value of 9.6 kPa, sensitivity of 93%, and specificity of 83%.<sup>348</sup> The AUC for diagnosing cir-

rhosis was 0.95 with a cutoff value of 14.4 kPa, sensitivity of 100%, and specificity of 88%. Furthermore, VCTE showed superior diagnostic performance for significant and advanced fibrosis compared to APRI and FIB-4. In a phase 2 study assessing the efficacy of simtuzumab in patients with PSC, VCTE demonstrated the AUC of 0.80 for diagnosing advanced fibrosis and 0.95 for cirrhosis, with cutoff values of 9.6 kPa and 14.4 kPa, respectively, which were the same as those used in the French prospective study.<sup>325</sup> A retrospective study in Germany involving 62 patients with PSC found an AUC of 0.91 for diagnosing significant fibrosis with a cutoff value of 8.8 kPa, an AUC of 0.95 for diagnosing advanced fibrosis with a cutoff value of 9.6 kPa, and an AUC of 0.978 for diagnosing cirrhosis at a cutoff value of 14.4 kPa.<sup>349</sup>

In a retrospective study conducted in the US involving 20 patients with PSC, MRE demonstrated excellent diagnostic performance.<sup>350</sup> The AUC for diagnosing significant fibrosis was 0.97, with a cutoff value of 3.26 kPa, sensitivity of 85%, and specificity of 100%. The AUC for diagnosing cirrhosis was 0.99, with a cutoff value of 4.93 kPa, sensitivity of 100%, and specificity of 94%. However, validation in a larger patient cohort is necessary, and further research is needed, with particular attention to the diagnostic performance for advanced fibrosis. Research on serum markers and SWE in patients with PSC remains limited.

Indeed, VCTE has shown excellent diagnostic performance for liver fibrosis in patients with PSC, particularly in studies conducted in Europe. This suggests that the appropriate cutoff values for diagnosing advanced fibrosis and cirrhosis in patients with PSC are 9.6 kPa and 14.4 kPa, respectively. However, there is a lack of literature involving Korean and Asian patients. Caution is needed when interpreting these results, as elevated total bilirubin due to extrahepatic bile duct strictures can lead to an overestimation of fibrosis stages.<sup>57</sup>

### Congestive hepatopathy

In patients with congestive hepatopathy, the diagnostic performance of serum markers for liver fibrosis is low.<sup>351</sup> A study involving 27 patients post-Fontan surgery used the FibroSure test, which includes serum markers such as  $\alpha$ 2-macroglobulin, total bilirubin, GGT, apolipoprotein A1, and haptoglobin, and compared the results with liver biopsy outcomes.<sup>352</sup> The PPV was only 33%, and the NPV was

53%. This low diagnostic performance is likely due to the distinct pathophysiology of congestive hepatopathy compared to other liver diseases. Serum markers such as AST and ALT, which are part of some fibrosis marker panels and are useful indicators of inflammation within the liver, have limited utility in diagnosing fibrosis in congestive hepatopathy, which is not primarily an inflammatory disease.<sup>351</sup>

In patients with congestive hepatopathy, LS values on VCTE are generally elevated, primarily due to increased hepatic blood flow.<sup>353-355</sup> A Korean study involving 45 patients with at least 10 years of Fontan duration showed that the LS values were consistently high across various stages of liver fibrosis: 26.1 kPa for significant fibrosis, 22.1 kPa for advanced fibrosis, and 24.2 kPa for cirrhosis, indicating LS elevation irrespective of the histological stage of fibrosis.<sup>354</sup> In contrast, a study involving 32 patients with congestive hepatopathy due to cardiac valve disease demonstrated that the average LS measurement before valve surgery was 7.9 kPa, which significantly decreased to 6.0 kPa post-surgery as hepatic congestion improved.<sup>356</sup>

Conflicting results have been reported regarding the utility of MRE in patients with congestive hepatopathy. In a US study involving 29 patients who underwent Fontan surgery, LS on MRE showed a significant correlation ( $R=0.62$ ) with the histological degree of liver fibrosis.<sup>357</sup> However, another study involving 34 patients who underwent Fontan surgery reported that the average LS on MRE for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis was 4.36 kPa, 4.02 kPa, and 3.33 kPa, respectively, showing no significant differences across histological stages of liver fibrosis.<sup>358</sup>

In summary, in patients with congestive hepatopathy, LS measurements on VCTE are influenced not only by histological liver fibrosis but also by hepatic congestion and cardiac function, limiting the utility of this approach. Similarly, the role of MRE is currently based on retrospective studies involving a small number of patients, which have yielded conflicting results. This underscores the need for further validation in future research.

### [Recommendations]

1. VCTE can be used to assess liver fibrosis in patients with PBC, AIH, and PSC. (B1)

## Cost-effectiveness

Studies on the cost-effectiveness of NITs for liver fibrosis have predominantly been based on VCTE. According to a prospective cohort study involving 6,295 individuals across six countries in Europe and Asia, using VCTE as a screening method was found to be cost-effective compared to liver function tests.<sup>359</sup> The incremental cost-effectiveness ratio (ICER) was reported to be €6,217 per quality-adjusted life-year (QALY) in the general population. Notably, for populations over the age of 45 at high-risk for ALD, the ICER for VCTE screening was exceptionally favorable, calculated at €2,570 per QALY.

In a Canadian study targeting populations at high-risk for liver fibrosis, such as patients with T2DM or obesity, a sequential testing strategy using the NFS, followed by VCTE and confirmation with MRE, was found to be cost-effective. The ICER per QALY was calculated to be \$7,991 Canadian dollars for patients with T2DM and \$9,051 Canadian dollars for patients with obesity.<sup>360</sup> However, several considerations need to be kept in mind: (1) Serum markers like NFS and FIB-4 have limited diagnostic performance in diagnosing significant or lesser liver fibrosis in patients with T2DM.<sup>361,362</sup> (2) Interventions such as aggressive lifestyle modifications are recommended before the advanced stages of liver fibrosis in high-risk groups such as those with T2DM.<sup>363</sup> Given these considerations, some studies suggest that directly implementing VCTE in patients with NAFLD and T2DM could be cost-effective by facilitating timely treatment. However, further validation through large-scale data is necessary to substantiate these findings.<sup>364</sup>

Cost-effectiveness studies of NITs for liver fibrosis in patients with NAFLD have predominantly been conducted in the US, Canada, and western Europe (Table 20). One US study analyzed the cost-effectiveness of four approaches: 1) NFS alone, 2) VCTE, 3) a combined strategy of NFS and VCTE, and 4) liver biopsy.<sup>365</sup> Both the NFS alone and the combined NFS and VCTE strategies proved cost-effective compared to liver biopsy, with ICERs per QALY of \$5,795 and \$5,768, respectively. Another US study assessed the use of FIB-4, VCTE, and MRE, either alone or in combination, for diagnosing cirrhosis in patients with NAFLD.<sup>366</sup> The sequential use of FIB-4 followed by VCTE was found to be the most cost-effective, particularly across a range of cirrhosis prevalence from 0.27% in the general population to

4% in tertiary care settings. In two UK studies, a strategy of using FIB-4 followed by VCTE or the ELF test in primary care settings, and then referring to specialized care based on the results, proved effective in reducing healthcare costs.<sup>367,368</sup> In a Canadian study, a strategy of performing SWE after FIB-4 was cost-effective for diagnosing significant fibrosis at a cost of \$148.85 per diagnosis, accurately diagnosing 84% of the patients, and was also 92% accurate for advanced fibrosis, proving to be the most cost-effective.<sup>369</sup> A recent US study compared the cost-effectiveness of MRE and VCTE following a high FIB-4 score ( $\geq 2.67$ ) in patients with NAFLD suspected of having advanced fibrosis.<sup>370</sup> Although MRE was more expensive at \$392,945 compared to \$384,557 for VCTE, it offered superior QALY (51.13 vs. 49.94), resulting in an ICER of \$7,048 per QALY, suggesting cost-effectiveness. Collectively, these findings indicate that in primary care settings, sequential testing using serum markers such as FIB-4 followed by imaging tests like VCTE or SWE may be the most cost-effective approach for assessing liver fibrosis in patients with NAFLD. However, due to differences in healthcare systems and costs among countries, further validation in local contexts, including Korea, is necessary.

Recent research on the cost-effectiveness of NITs for liver fibrosis in patients with alcohol use disorder has compared four distinct strategies: 1) routine clinical care including liver function tests and abdominal ultrasound, 2) conducting the ELF test followed by VCTE, 3) performing both the ELF test and VCTE if the Forns index is  $\geq 6.8$ , and 4) directly performing VCTE.<sup>371</sup> These findings indicate that in primary care settings, where the prevalence of liver fibrosis is relatively low, the strategy of conducting an ELF test followed by VCTE is the most cost-effective. This approach costs \$194 per patient, with an accuracy of 96%, and an ICER ranging from \$5,387 to \$8,430 per QALY. Conversely, in secondary care settings where liver fibrosis is more common, directly performing VCTE is more cost-effective, costing \$297 per patient with an accuracy of 93% and an ICER ranging from \$490 to \$1,037 per QALY.

A systematic review of cost-effectiveness studies on the use of VCTE in patients with various CLD analyzed four cost-effectiveness studies and four cost-utility studies published between 2009 and 2015.<sup>372</sup> The review found that while VCTE is less expensive than liver biopsy, it generally offers lower diagnostic performance. However, its cost-ef-

**Table 20.** Cost-effectiveness analysis of noninvasive tests for liver fibrosis in patients with NAFLD

Reference	Location	Cost year (currency)	Modelling method	Sample size	Interventions	Incremental cost-effectiveness results
Tapper et al. <sup>365</sup> (2015)	US	2014 (US dollar)	Probabilistic decision analytical microsimulation state-transition	Hypothetical cohort of 10,000 50-year-old Americans with NAFLD	- VCTE - NFS - NFS + VCTE - Liver biopsy	Liver biopsy: \$6,484/QALY VCTE: \$6,334/QALY NFS: \$5,795/QALY NFS+VCTE: \$5,768/QALY
Vilar-Gomez et al. <sup>366</sup> (2020)	US	2017 (US dollar)	Decision tree	Hypothetical cohort of middle-aged patients with NAFLD (0.27–4% prevalence of LC)	- VCTE - MRE - FIB-4 - FIB-4 + VCTE - FIB-4 + MRE - FIB-4 + liver biopsy	FIB-4 + VCTE: least costly FIB-4 + MRE: \$2,918/QALY FIB-4 + liver biopsy: \$5,156/QALY
Congly et al. <sup>369</sup> (2021)	Canada	2019 (Canadian dollar)	Decision tree	1,958 patients evaluated within the Calgary NAFLD pathway	- SWE - VCTE - FIB-4 - NFS - FIB-4 + SWE - NFS + SWE - FIB-4 + VCTE - NFS + VCTE - Liver biopsy	NFS+SWE: \$566.35/correct diagnosis SWE: \$2557.68/correct diagnosis Liver biopsy: \$2411.81/correct diagnosis
Sangha et al. <sup>370</sup> (2023)	US	2020 (US dollar)	Decision tree and Markov state-transition	Hypothetical cohort of 10,000 50-year-old patients with FIB-4 score of $\geq 2.67$ and suspected advanced fibrosis	- VCTE - MRE	VCTE: \$7,700/QALY MRE: \$7,048/QALY

NAFLD, nonalcoholic fatty liver disease; VCTE, vibration-controlled transient elastography; NFS, nonalcoholic fatty liver disease fibrosis score; QALY, quality-adjusted life year; NAFLD, nonalcoholic fatty liver disease. LC, liver cirrhosis; MRE, magnetic resonance elastography; FIB-4, fibrosis-4 index; SWE, shear wave elastography.

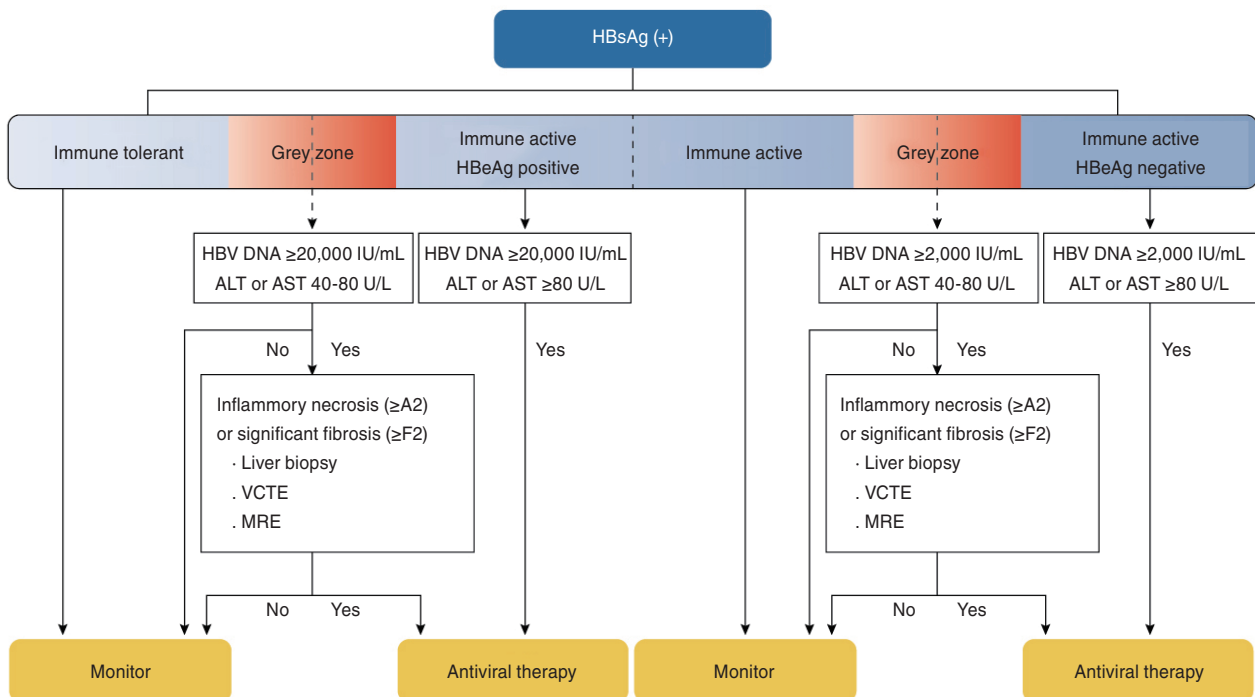
fectiveness improves as the severity of liver fibrosis increases. Notably, VCTE showed excellent cost-effectiveness in patients with CHC, where the ICER per QALY compared to liver biopsy ranged from \$9,000 to \$14,000.

Cost-effectiveness analyses heavily depend on the prevalence of the condition within a target population, necessitating tailored strategies based on specific group characteristics. In primary care settings, where the prevalence of advanced fibrosis and cirrhosis is relatively low, a strategy of initially using serum markers followed by sequential imaging tests such as VCTE has proven to be most cost-effective for assessing liver fibrosis in patients with both NAFLD and ALD. Thus, employing such strategies in primary care to screen high-risk groups is advisable, though there is a lack of Korean data to fully support this. Recent clinical utility has been demonstrated for combined approaches using serum markers and imaging tests, such as the AGILE score and the MEFIB index, in patients with NAFLD.<sup>247,261</sup> These approaches have shown promise; however, further research is needed to assess their cost-effectiveness. Additionally, as effective pharmacological treatments for NAFLD/NASH are developed, the cost-

effectiveness of NITs for liver fibrosis is likely to improve further.

**[Summary]**

In cost-effectiveness analyses, the prevalence of a condition within a target population heavily influences the need for tailored strategies. For patients with NAFLD or alcohol use disorder, the approach to assessing liver fibrosis can vary significantly based on the clinical setting. In environments where the prevalence of cirrhosis is low, it is cost-effective to first use serum markers followed by imaging tests such as VCTE or SWE. Conversely, in settings with a high prevalence of cirrhosis, directly initiating imaging tests like VCTE or SWE can be more cost-effective. However, there is a notable lack of domestic literature in this area, underscoring the need for further research to validate these strategies within local contexts and ensure the most efficient use of resources in diagnosing liver fibrosis.



**Figure 6.** Antiviral therapy algorithm for chronic hepatitis B patients in the gray zone. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography.



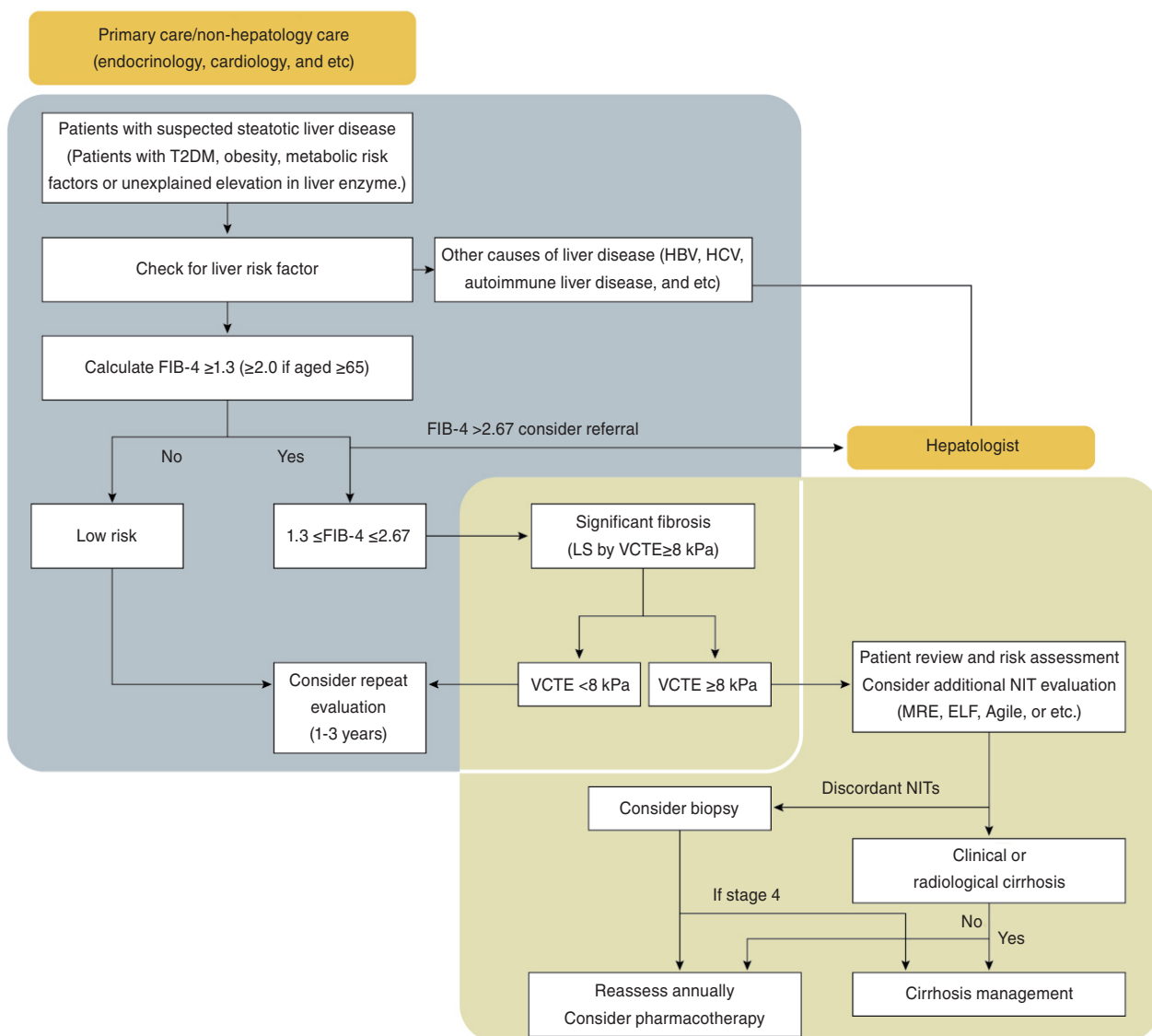
## SCREENING HIGH-RISK GROUPS

### Chronic hepatitis B

Patients with CHB are considered a high-risk group requiring continuous monitoring and management. However, the risk of HCC and the effectiveness of AVT vary depending on the natural immunological course of the virus.<sup>373,374</sup>

Approximately 30% of patients with CHB fall into a gray zone.<sup>375,376</sup> In these patients, serum hepatitis B virus (HBV) DNA and ALT levels do not match a specific phase of the

natural course. Periodic and meticulous monitoring is essential to identify gray zone status in patients with CHB, which can be achieved using liver biopsy or NITs for liver fibrosis. The risk of HCC in patients in the gray zone has been reported to be higher than that during the immune-tolerant and immune-inactive phases. However, these patients have often been excluded from AVT as the serum ALT, an indicator of liver damage, is not significantly elevated.<sup>375-377</sup> According to a recent multinational study, AVT in patients with CHB in the gray zone may reduce the risk of HCC by up to 70% compared to no treatment. The cumula-



**Figure 7.** Algorithm for screening high-risk groups of patients with nonalcoholic fatty liver disease. T2DM, type 2 diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; FIB-4, fibrosis-4 index; VCTE, vibration-controlled transient elastography; LS, liver stiffness; MRE, magnetic resonance elastography; ELF, enhanced liver fibrosis; NITs, non-invasive tests.

tive incidence of HCC significantly decreased five years after AVT.<sup>378</sup> Therefore, strategies to identify high-risk patients who require AVT are being explored.

Patients with CHB and ALT levels that are consistently one to two times the ULN are considered to be in the gray zone, and AVT can be initiated if moderate or greater inflammatory necrosis or significant fibrosis is confirmed.<sup>100</sup> The risk of HCC is high in patients with CHB aged 30–40 years or older or with ALT levels at the ULN as well as in patients with normal ALT but persistently high HBV DNA. Therefore, these patients should be assessed for liver fibrosis and AVT should be considered.<sup>100,374</sup> Methods for assessing for liver fibrosis include NITs, such as VCTE and MRE. When significant fibrosis is detected, AVT can be initiated (Fig. 6).<sup>81,379</sup> Although serum markers such as APRI and FIB4 can also be used to assess for liver fibrosis, there is insufficient evidence for their use as a basis for initiating AVT.

### Nonalcoholic fatty liver disease

Liver fibrosis is the most important prognostic factor in patients with NAFLD. Therefore, an accurate assessment of liver fibrosis is crucial in these patients.<sup>380</sup> Although liver biopsy is the standard test for identifying liver fibrosis, it is difficult to perform routinely.

In primary care settings, a thorough history and blood tests are used to check for viral hepatitis, ALD, and other liver diseases when NAFLD is suspected. Several NITs can be used to assess the risk among patients with NAFLD, and serum markers obtained using basic blood tests and clinical information can be used to classify patients into high-risk groups in a cost-effective manner.

FIB-4 is a well-known serum marker; patients with FIB-4 <1.3 are classified as low-risk, while patients with FIB-4 >1.3 should undergo VCTE or be referred to a hepatologist for further risk analysis.<sup>81,381</sup> However, patients aged ≥65 years with FIB-4 <2.0 are not considered high-risk.<sup>35</sup> The diagnostic performance of FIB-4 for advanced fibrosis may be lower in patients with NAFLD and T2DM. If the VCTE test fails or further evaluation of liver fibrosis is necessary, MRE and liver biopsy can be considered.<sup>81,382</sup> Moderate or high-risk patients require a referral to a hepatologist for accurate assessment and appropriate management of liver fibrosis.

The hepatologist will conduct a comprehensive review of the patient's history and liver fibrosis risk, and additional NITs, such as MRE, ELF, and the AGILE score, may be considered to assess liver fibrosis. If cirrhosis is diagnosed, careful monitoring and follow-up are necessary due to the significantly increased risk of liver-related complications and HCC. Liver biopsy can be performed in patients with inconsistent NIT results or when the degree of liver fibrosis is difficult to determine, and follow-up and treatment are considered depending on the progression of the liver fibrosis.

Although guidelines regarding the duration and method of follow-up have not yet been established, FIB-4 can be re-evaluated after one to two years in low-risk patients with prediabetes, T2DM, or two or more metabolic risk factors. FIB-4 can be re-evaluated after two to three years in patients with NAFLD but without T2DM or other metabolic risk factors (Fig. 7).<sup>383,384</sup>

#### [Recommendations]

1. Liver fibrosis should be assessed using VCTE, SWE, and MRE to determine antiviral therapy in patients with CHB who are in the gray zone. (A2)
2. If patients with NAFLD have FIB-4 ≥1.3, referral to a hepatologist or VCTE examination for assessing liver fibrosis can be considered. (B1)

### NONINVASIVE DIAGNOSIS OF PORTAL HYPERTENSION AND PREDICTION OF PROGNOSIS

Portal hypertension (PH) is an abnormal increase in blood pressure of the portal vein and its tributaries. The most common cause of PH is cirrhosis, which leads to increased intrahepatic vascular resistance and portal blood flow. Because PH is a direct cause of various complications related to cirrhosis, evaluation and regular follow-up are necessary for the presence or absence of PH in cirrhosis.<sup>317</sup>

The gold-standard test for PH is the measurement of hepatic venous pressure gradient (HVPG), which is assessed by inserting a balloon catheter directly into the hepatic vein. HVPG is the difference between the wedge hepatic venous

pressure and free hepatic venous pressure measured at the border of the hepatic vein and the inferior vena cava, and is an estimate of the pressure difference between the portal vein and the inferior vena cava. If HVPG is more than 6 mmHg, it is defined as PH, and if it is more than 10 mmHg, it is defined as clinically significant PH (CSPH). Measurement of HVPG has many limitations in clinical practice because it is invasive and can only be performed by experts at institutions equipped with specific facilities. To date, there is no NIT available that can replace HVPG as a quantitative measure of PH, but studies on various NITs to evaluate PH and the risk of developing complications are ongoing.

### Serum markers

There are studies attempting to evaluate PH using serum markers due to the advantages of low cost and high reproducibility, using APRI, FIB-4, Forns index, Lok score, indocyanine green, etc.,<sup>385,386</sup> but these serum markers alone also have limitations in evaluating portal pressure and are not of high clinical utility.

### Imaging markers

Presumption of PH is possible, if portosystemic shunting (recanalization of the umbilical vein, esophageal varices, gastric varices, spleen-kidney shunt) is observed on imaging tests such as abdominal ultrasound, computed tomography (CT), or MRI, regardless of the cause of CLD. In particular, the phenomenon of portal blood flow reversal (reduced portal blood flow velocity due to intrahepatic portal blood flow resistance, loss of physiological respiratory changes in portal flow, and severe portal regurgitation of portal blood flow) on Doppler ultrasound shows high specificity in the diagnosis of CSPH.<sup>387,388</sup> Splenomegaly does not occur only in PH, but spleen size needs to be carefully observed in patients with CLD. Splenomegaly is also related to an increase in splenic venous pressure due to an increase in portal pressure, as well as fibrosis and tissue proliferation of the spleen itself. An increase in splenic artery blood flow in splenomegaly also leads to an increase in splenic venous blood flow, worsening PH.<sup>389,390</sup>

## Vibration-controlled transient elastography

### Portal hypertension

There are many studies on the usefulness of VCTE in screening patients at high risk for CSPH, and it shows excellent overall diagnostic performance. In a recent meta-analysis of 11 studies and 1,451 patients, the hierarchical summary AUC of VCTE for CSPH diagnosis was 0.90, sensitivity 87.5%, specificity 85.3%, and the summary HVPG-LS correlation coefficient was also high at 0.783.<sup>391</sup> In studies including patients with cirrhosis mainly caused by viruses or alcohol, it was suggested that CSPH can be diagnosed when LS exceeds 20–25 kPa,<sup>317,392-394</sup> and it was reported that LS above 21 kPa was specific for CSPH diagnosis.<sup>395</sup>

In the study by Robic et al., no PH-related complications occurred when LS was 20 kPa or less during the 2-year follow-up period.<sup>396</sup> In a study by Vergniol et al., patients with LS exceeding 20 kPa had a survival rate of only 66%.<sup>397</sup> This corresponded to predicting the occurrence of decompensated cirrhosis when HVPG was 10 mmHg or higher.

However, CSPH diagnosis by VCTE has AUC that varies from 0.82 to 0.94 depending on the cause of liver disease or study conditions,<sup>393,395,398</sup> and cannot provide accurate HVPG values as a stand-alone test. In addition, when HVPG becomes more severe than 12 mmHg, the correlation between LS and portal pressure tends to be somewhat lower, which means that in severe PH, the increase in portal blood flow has greater impact on PH than the progression of liver fibrosis and increase in intrahepatic vascular pressure.<sup>398,399</sup>

To overcome these limitations, there are studies attempting to increase diagnostic performance by combining VCTE with other serum or imaging markers. A representative example is LSPS, which was designed by Korean researchers and combines LS measurements on VCTE, spleen size, and platelet count (LS [kPa] × spleen size [cm] / platelet count [mL]).<sup>389</sup> In a cross-sectional study of patients with compensated cirrhosis, the AUC for diagnosing CSPH in LSPS was 0.92, and the specificity was over 90% at a cutoff value of >2.06.<sup>390</sup> In a recent prospective study, LSPS cutoff values of 0.75, 1.70, and 2.65 were associated with a prevalence of PH of 20, 50, and 80%, respectively.<sup>400</sup>

Based on these results, a sequential approach has been proposed to exclude or diagnose CSPH using VCTE and

recommend additional evaluation if necessary, but a consistent cutoff value has not been established depending on the cause and clinical conditions of liver disease therefore, the clinical application is limited yet.

### Esophageal varices

In the past, screening tests using upper gastrointestinal endoscopy were recommended to identify esophageal varices requiring primary prevention in patients with cirrhosis.<sup>401</sup> Recently, with the development of NITs for liver fibrosis, there have been many studies using this method to predict the presence of esophageal varices and clinically significant esophageal varices. In a systematic review and meta-analysis of 3,644 patients in 18 studies, the AUC of VCTE for diagnosing esophageal varices was 0.84, sensitivity 87%, and specificity 53%, and the AUC for diagnosing large esophageal varices was 0.78, sensitivity 86%, and specificity 59%.<sup>402</sup>

The AUC of LSPS for diagnosing all stages of esophageal varices was over 90%, showing high diagnostic performance, and the AUC for diagnosing large esophageal varices was 0.80, sensitivity 93%, and NPV 90%. It has been reported that high-risk esophageal varices can be excluded or predicted in more than 90% of patients using two cutoff values of 3.5 and 5.5.<sup>389,390,400</sup>

In 2015, BAVENO VI suggested a standard for avoiding upper gastrointestinal endoscopy to screen for esophageal varices in patients with cACLD if LS is less than 20 kPa and platelet count is more than 150,000/mL.<sup>317</sup> These BAVENO VI criteria have been validated in many studies, avoiding endoscopy in approximately 20% of cases and missing less than 4% of patients with esophageal varices requiring treatment.<sup>400,403,404</sup> In order to reduce the probability of screening failure of large esophageal varices and additional upper gastrointestinal endoscopy, various studies evaluated different cutoffs for LS and platelet count, the two indicators used in the BAVENO VI standard, in patients with cirrhosis of various causes. Additional verification is required prior to application.<sup>404-408</sup>

Thus, the Baveno VI criteria can be helpful in screening for large esophageal varices. In low-risk cases, VCTE and platelet count can be measured and re-evaluated annually without performing invasive endoscopy for screening. However, in high-risk groups potentially requiring primary bleeding prevention treatment, selective endoscopy is neces-

sary.

## Other noninvasive tests

### Shear wave elastography

A few studies have investigated the diagnostic performance of pSWE for PH, and overall, it overcomes the limitations of VCTE and has a high measurement success rate, with an AUC for diagnosing PH of 0.82–0.90.<sup>409-411</sup> 2D-SWE showed excellent performance with an AUC of 0.88, sensitivity of 85%, and specificity of 85% in a meta-analysis including nine studies.<sup>412</sup> However, both methods have insufficient validation compared to VCTE, and clinical application is difficult due to differences in the cause and severity of liver disease included depending on the study, as well as the various cutoff values used.

### Magnetic resonance elastography

Limited data is available on the direct correlation between MRE and portal pressure. In cross-sectional studies, the combination of a cutoff value of 4.2 kPa and platelet count >180,000/mL showed a high NPV for high-risk esophageal varices, and prospective validation studies are needed.<sup>413</sup>

### Spleen stiffness

Spleen stiffness (SS) shows a high correlation with HVPG. However, there is heterogeneity in the etiologies of liver diseases and patient groups included in each study, and additional research is needed. In a systematic literature review including 12 studies, SS showed 78% sensitivity and 76% specificity regardless of the stage of esophageal varices. In a meta-analysis including nine studies, SS showed 81% sensitivity and 66% specificity for clinically significant esophageal varices, and was more specific for large esophageal varices at a cutoff value of 50–75 kPa.<sup>414</sup>

A limitation of SS measured by VCTE in PH evaluation is that VCTE is not optimized for measuring SS because it uses a LS measurement method. SS is generally higher than LS; in VCTE, the maximum measurable value is 75 kPa, but SS often exceeds this.<sup>415,416</sup> Additionally, the spleen is smaller than the liver, is more mobile due to its proximity to the left ventricle, and is often not visible on left intercostal approach.<sup>417</sup> However, it was recently reported that CSPH can be more accurately predicted with a sensitivity of 83% and a specificity of 82% when the cutoff value

exceeds 26.5 kPa through SS measurement using 100-Hz-probe VCTE dedicated to spleen measurement.<sup>418</sup>

### Noninvasive follow-up of portal hypertension

There is a lack of research on whether the Baveno VI criteria can be used as noninvasive follow-up for CSPH. In a study on patients with cirrhosis caused by HBV and HCV, there was no development of large esophageal varices in patients who met the Baveno VI criteria and showed sustained viral suppression. Patients who did not meet the Baveno VI criteria did not show progression of PH if they maintained consistently good viral suppression.<sup>419</sup> Additional research is needed to determine the most appropriate interval for follow-up depending on the patient's clinical condition, the presence and size of esophageal varices, and the cause and treatment of liver disease.

Research on noninvasive monitoring following nonselective beta-blocker treatment is also limited. One study identified hemodynamic parameters associated with the hemodynamic response to intravenous infusion of propranolol,<sup>420</sup> another study showed an association between hemodynamic response to carvedilol and SS changes as a primary preventive treatment for large esophageal varices,<sup>421</sup> but further validation is needed.

#### [Recommendations]

1. Patients with cACLD and LS on VCTE greater than 20 kPa or platelet count less than 150,000/mL require upper gastrointestinal endoscopy to screen for esophageal varices. (A2)
2. CSPH and large esophageal varices can be predicted using LSPS, a combination of LS on VCTE, spleen size, and platelet count. (B1)
3. CSPH and large esophageal varices can be predicted using SS on VCTE, SWE, and MRE. (B2)

## PREDICTION OF HEPATOCELLULAR CARCINOMA, HEPATIC DECOMPENSATION, AND DEATH

Liver fibrosis is a risk factor for the development of hepatic decompensation and HCC, as well as liver-related

death.<sup>4</sup> Consequently, several studies utilizing NITs to predict liver-related complications have been conducted. Among NITs, meta-analyses of VCTE, which has been most extensively studied, are summarized in Table 21.

Moreover, for early-stage HCC, curative treatments such as hepatectomy and radiofrequency ablation (RFA) show favorable clinical outcomes, but there is a risk of recurrence and complications following those treatments. Therefore, accurately assessing the degree of liver fibrosis before hepatectomy or RFA is necessary in selecting treatment modality and evaluating prognosis. Predicting post-hepatectomy liver failure is particularly crucial in making these decisions.

### Development of hepatocellular carcinoma

#### Serum markers

Among serum markers, the predictive performance for HCC development has been relatively well studied in FIB-4. The predictive performance of FIB-4 for HCC development in patients with CHB has been primarily reported in Korean studies.<sup>422-425</sup> In a study involving 986 Korean patients with CHB, the hazard ratio (HR) was 4.57 for the FIB-4 group of  $1.7 \leq \text{FIB-4} < 2.4$ , and 21.34 for  $\text{FIB-4} \geq 2.4$ , indicating a higher risk of HCC development compared to patients with  $\text{FIB-4} < 1.25$ .<sup>425</sup> Additionally, a decrease in FIB-4 after 1 year of AVT in patients with HBV-related cirrhosis was associated with reduced risk of HCC development.<sup>426</sup> In a Korean study of 1,193 patients who achieved SVR after interferon or direct-acting antiviral (DAA) treatment, a high FIB-4 significantly predicted HCC development (HR=1.08).<sup>427</sup> High FIB-4 before DAA treatment<sup>428</sup> and after SVR significantly predicted HCC development in patients with CHC,<sup>428,429</sup> and a decrease in FIB-4 after achieving SVR was also a significant predictor of reduced risk of HCC development.<sup>429</sup> In particular, patients with a high FIB-4 of more than 3.25 after SVR maintained a high annual incidence rate of HCC of 2.39%.<sup>429</sup> Additionally, high FIB-4 was a significant risk factor for HCC development in patients with NAFLD<sup>430</sup> and ALD.<sup>431</sup> In a European multinational study on patients with NAFLD, patients were classified into three groups based on FIB-4 cutoff values of 1.45 and 2.67, and the group with consistently high FIB-4 above 2.67 both at baseline and at 3 years had a significantly higher risk of HCC development, with a HR of 57.69 com-

**Table 21.** Meta-analyses of studies on predictive performance of VCTE for the development of liver-related complications

References	Study number	Patient number	Liver-related complications HR (95% CI)	HCC HR (95% CI)	Decompensation HR (95% CI)	Liver-related death HR (95% CI)
Baseline LS value						
Singh et al. <sup>436</sup> (2013)	17	7,058	1.32 (1.16–1.51)	1.11 (1.05–1.18)	1.07 (1.03–1.11)	1.22 (1.05–1.43)
Wang et al. <sup>437*</sup> (2018)	44	35,249	7.90 (5.65–11.05)	4.2 (3.41–5.18)	13.1 (7.85–21.93)	2.73 (1.74–4.29)
Per 1 kPa						
Wang et al. <sup>437</sup> (2018)	44	35,249	1.07 (1.06–1.07)	1.05 (1.04–1.06)	1.06 (1.05–1.07)	1.09 (1.06–1.12)
Shen et al. <sup>438</sup> (2019)	62	43,817	1.07 (1.04–1.09)	1.08 (1.05–1.11)	1.08 (1.06–1.10)	1.11 (1.05–1.17)
LS cutoff value <sup>†</sup>						
Shen et al. <sup>438</sup> (2019)	62	43,817	9.7 kPa 2.83 (1.73–4.62)	7.2 kPa 1.80 (1.49–2.18)	8.6 kPa 1.50 (0.92–2.44)	8.5 kPa 1.34 (0.86–2.07)
			14.0 kPa 4.49 (2.77–7.29)	12.5 kPa 5.38 (3.38–8.56)	13.5 kPa 4.69 (2.63–8.37)	13.5 kPa 3.25 (1.90–5.56)
			20.5 kPa 6.72 (4.13–10.91)	19 kPa 9.05 (5.78–14.17)	20.2 kPa 16.23 (9.63–27.35)	19.8 kPa 7.72 (4.51–13.22)
			34.5 kPa 14.88 (6.49–34.12)	35 kPa 14.36 (9.10–22.67)	37.5 kPa 21.29 (11.98–37.83)	37.5 kPa 14.25 (8.22–24.73)

CI, confidence interval; HR, hazard ratio; kPa, kilopascal; LS, liver stiffness; VCTE, vibration-controlled transient elastography.

\*Comparing highest and lowest cutoff values.

<sup>†</sup>Compared to 5 kPa.

pared to the group with FIB-4 lower than 1.45.<sup>432</sup>

Other serum markers such as NFS have also been shown to predict HCC development in patients with NAFLD.<sup>430</sup> M2BPGi,<sup>433</sup> APRI,<sup>434</sup> and ELF<sup>435</sup> are also serum markers that can predict HCC development in CLDs. However, serum markers including FIB-4 lack international validation and are mostly based on retrospective studies. Serum markers can predict the degree of liver fibrosis, but their accuracy is relatively low compared to imaging-based fibrosis tests, making them useful as initial screening tools for diagnosing liver fibrosis. Similarly, in predicting HCC development, they can be used as a supplement to other tests or as one risk factor in prediction models for HCC development. The accuracy of the cutoff values of each test or comparative accuracy with other NITs is also unclear in predicting HCC development.

#### **Vibration-controlled transient elastography**

More studies have explored the prediction of HCC development using VCTE compared to serum markers. A meta-analysis including 17 studies on patients with CLD showed a significant correlation between LS measured by VCTE and the HR of HCC development at 1.11.<sup>436</sup> A meta-analysis including 54 studies on patients with CLD showed that high LS, compared to low LS, had significantly increased the risk of HCC development with a HR of 4.20, and a dose-response correlation with a HR of 1.05/kPa.<sup>437</sup> In a meta-analysis involving 62 studies, similar results were observed with a HR of 1.08/kPa. Specifically, a detailed analysis of six studies with 5,566 patients revealed that, compared to LS of 5 kPa, the HRs of HCC development at cutoff values of 7.2 kPa, 12.5 kPa, 19 kPa, and 35 kPa were 1.80, 5.38, 9.05, and 14.36, respectively.<sup>438</sup>

Among patients with CHB, Korean cohort studies linked VCTE to a prediction of HCC development at LS cutoff values of 8–14.1 kPa.<sup>439–445</sup> Notably, in a Korean prospective study, LS exceeding 8 kPa was a significant risk factor for HCC development, with HRs of 3.07, 4.68, 5.55, and 6.60 at LS of 8.1–13 kPa, 13.1–18 kPa, 18.1–23 kPa, and >23 kPa, respectively.<sup>444</sup> Another Korean study found that LS on VCTE of above 13 kPa, indicating subclinical cirrhosis, was an independent risk factor for HCC development regardless of AVT, with a risk ratio of 4.68 in patients with CHB without clinical cirrhosis.<sup>441</sup> This suggests the additional value of VCTE in predicting HCC development

alongside morphological assessments like abdominal ultrasonography and CT scans.

In a Korean study of 190 patients with CHC who achieved SVR after interferon and ribavirin combination therapy, post-SVR LS exceeding 7.0 kPa on VCTE significantly increased the risk of liver-related complications, including HCC, with a HR of 8.23.<sup>446</sup> The VCTE LS cutoff values predicting HCC in patients with CHB who achieved SVR after DAA therapy ranged from 9.2 to 17.3 kPa,<sup>428,447,448</sup> with post-SVR LS cutoff values reported between 8.4–10 kPa at 6–12 months post-treatment.<sup>447,449,450</sup> A multicenter study in Europe found that high LS value prior to DAA treatment was a significant risk factor for HCC development in patients with CHB, with a cutoff value of 17.3 kPa.<sup>428</sup> However, LS values at 1-year post-SVR were not a significant factor for HCC development, though a significant reduction in LS of more than 25.5% did reduce the risk of HCC.<sup>428</sup> Other retrospective European studies also indicated that LS values greater than 30.0 kPa before DAA treatment were an independent predictor of HCC development and recurrence.<sup>451</sup> European prospective studies showed that LS value  $\geq 10.0$  kPa 1 year post-SVR was a significant risk factor for HCC development, although changes in LS or baseline LS did not predict HCC development.<sup>450,452</sup>

In addition, a multinational retrospective cohort study on patients with NAFLD identified LS on VCTE as an independent risk factor for HCC development, although specific cutoff values were not provided.<sup>453</sup> This study also found that a VCTE LS increase of more than 20% during follow-up significantly raised the risk of HCC development, but the timing of follow-up varied among patients.<sup>453</sup> In patients with ALD, a LS cutoff value of 15 kPa significantly increased the risk of HCC development, hepatic decompensation, and liver-related death, with a HR of 27.9.<sup>454</sup> In summary, these findings suggest that while VCTE is helpful in predicting the risk of HCC development in patients with CLDs regardless of the underlying cause, there is relatively less evidence for its utility in ALD and NAFLD, underscoring the need for further detailed analysis and validation of follow-up tests in each disease etiology.

#### **Shear wave elastography**

Studies on the predictive performance of SWE for HCC development are limited. Retrospective studies focusing on patients with CHB<sup>455,456</sup> and CHC<sup>457</sup> demonstrated that

SWE can predict HCC development. Notably, a small-scale Korean study analyzing patients with CHB found that LS greater than 10 kPa on 2D-SWE was a significant risk factor for HCC development, with a HR of 4.08.<sup>456</sup> Similarly, a small-scale retrospective study in Japan reported that LS values greater than 11 kPa were significantly associated with HCC development in patients who achieved SVR after DAA treatment, with a HR of 28.71.<sup>457</sup>

### **Magnetic resonance elastography**

An international multicenter study on patients with CLD showed that increased LS on MRE was associated with HCC development, with a HR of 1.28. The LS value exceeding 4.7 kPa significantly increased the risk of HCC development compared to the LS value below 3 kPa, with a HR of 4.20.<sup>458</sup> A Korean study on patients with CLD also confirmed this dose-response relationship, with a HR of 1.59 per 1 kPa increase in the LS value.<sup>459</sup> In patients with CHC who achieved SVR after DAA treatment, LS exceeding 3.75 kPa was a significant predictor of HCC development.<sup>460</sup> A meta-analysis of six studies with 2,018 patients with NAFLD explored the predictive performance of the MEFIB index and MRE alone for HCC development,<sup>261</sup> and found that patients with LS above 8 kPa were at significantly higher risk of HCC development compared to those with LS value below 5 kPa, with a HR of 33.8, and a HR of 23.4 when comparing the 5–8 kPa group to the <5 kPa group. The incidence rates of HCC at three years were 0.35%, 5.25%, and 5.66% for <5 kPa, 5–8 kPa, and >8 kPa groups, respectively. High MEFIB patients had a HR of 40.5 for HCC development.

### **Models predicting hepatocellular carcinoma development based on vibration-controlled transient elastography**

Efforts to enhance the performance of models for HCC development using LS on VCTE have been reported. In particular, various predictive models for HCC development in Korean patients with CHB have incorporated clinical factors, blood tests, and LS as components of these prediction models (Table 22). Models such as the LS model using age, sex, HBV DNA, and LS values<sup>461</sup>; the LSPS model combining LS, spleen size, and platelet count<sup>462</sup>; the CAM-PAS model incorporating LS, age, sex, platelet count, serum albumin, and cirrhosis detected by ultrasound<sup>463</sup>; and

the SAGE-B model combining LS and age at 5 years post-treatment for CHB<sup>464</sup> all showed good predictive accuracy with AUCs above 0.8. The mREACH-B model, which incorporates LS values in place of HBV DNA in the REACH-B model for Korean patients with CHB, showed superior predictive performance for HCC development compared to the original model.<sup>465</sup> Furthermore, significant reduction of mREACH-B after AVT was observed,<sup>466</sup> indicating the dynamic assessment of HCC risk through predictive models incorporating LS measured via VCTE might be feasible. The modified PAGE-B<sup>LS</sup> model, combining VCTE LS with the existing PAGE-B model for patients with CHB undergoing AVT, exhibited superior predictive accuracy,<sup>467</sup> demonstrating the potential of VCTE to enhance the predictive performance of existing HCC development models. The LS-HCC model, which adds VCTE LS to the CU-HCC score, also accurately predicted HCC development in patients with CHB, showing superior predictive performance compared to the original CU-HCC score.<sup>439</sup> Similarly, a predictive model for HCC development in patients with NAFLD incorporating age, platelet count, and LS measured by VCTE accurately predicted HCC development.<sup>468</sup> In summary, VCTE can enhance the predictive performance of HCC development models when combined with other clinical factors in patients with CLD. However, validation studies outside Korea or Asia are necessary, and whether the current HCC screening strategy needs to be adjusted based on these predictive models including VCTE requires further research.

## **Prognosis prediction after curative treatment for hepatocellular carcinoma**

### **Prognosis prediction after hepatectomy**

Prognosis following hepatectomy of HCC can be predicted using NITs (Table 23). A FIB-4 cutoff value above 3.25 is associated with a 5-year recurrence rate of 47.2%, while a value above 2.7 correlates with a 77.2% recurrence rate.<sup>469,470</sup> In regions with a high prevalence of CHB, other indices such as APRI, AAR, AAR-to-platelet ratio index (AARPRI), and albumin-bilirubin (ALBI) score were related to survival and disease-free survival, albeit with lower predictive performance compared to FIB-4.<sup>471</sup> Combining FIB-4 and PIVKA-II offers more accurate prediction of overall survival (OS) and disease-free survival (DFS) than using



**Table 22.** HCC prediction models using LS measurement by VCTE

Model	Region	Etiology	Study number	Age	Sex	Risk factors							AUC
						HBV DNA	HBeAg	ALT	Serum albumin	Platelet count	Cirrhosis in USG	Spleen size	
LS <sup>461</sup>	Korea	HBV	1,250	0	0	0	0	0	0	0	0	0	0.81
LSM-HCC <sup>439</sup>	Hong Kong	HBV	1,555	0	0	0	0	0	0	0	0	0	0.83–0.89
LSPS <sup>462</sup>	Korea	HBV	227						0	0	0	0	0.83
mREACH-B <sup>465</sup>	Korea	HBV (complete VR)	192	0	0	0	0	0	0	0	0	0	0.81
CAMPAS <sup>463</sup>	Korea	HBV (VR)	1,511	0	0	0	0	0	0	0	0	0	0.87
mPAGE <sup>LS-B</sup> <sup>467</sup>	Korea	HBV (AVT)	2,184	0	0	0	0	0	0	0	0	0	0.76
SAGE-B <sup>464</sup>	Europe	HBV (5-year post-AVT)	734	0									0.78–0.80
Alonso López et al. <sup>428</sup>	Spain	HCV (SVR after DAA)	1,046				0						0.78
Lee et al. <sup>468</sup>	Korea	NAFLD	3,133	0					0				0.94–0.95

ALT, alanine aminotransferase; AVT, antiviral therapy; AUC, area under the curve; DAA, direct acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LS, liver stiffness; SVR, sustained virologic response; USG, ultrasonography; VCTE, vibration-controlled transient elastography; VR, virologic response.

either test alone.<sup>472</sup> A nomogram for predicting recurrence using FIB-4 and ALBI has also been reported.<sup>473</sup>

Recent studies using VCTE have presented varying LS cutoff values ranging from 8.5–22 kPa, with each value associated with major post-hepatectomy complications (Clavien-Dindo Grade 3a or higher), OS, and DFS. These studies predominantly involved patients with CHB, with LS cutoff values generally between 8.5–13.4 kPa.<sup>474-479</sup> A Korean study reported a HR of 19.14 for post-resection liver failure development at a LS cutoff value of 25.6 kPa,<sup>480</sup> while a study from China found an OR of 1.21 for liver failure at a LS cutoff value of 14 kPa.<sup>481</sup> A retrospective study analyzing 471 patients from Korean and European cohorts developed a nomogram using LS value by VCTE, age, Model for End-Stage Liver Disease (MELD) score, and serum albumin, significantly predicting post-hepatectomy complications.<sup>482</sup>

Although models using VCTE for predicting HCC recurrence based on prospective cohorts have been reported,<sup>483</sup> applications in clinical practice might be limited due to the need for histological examination results including the intrahepatic inflammation and histologic fibrosis grade, in addition to VCTE, number of intrahepatic tumors and indocyanine green R15% value. Furthermore, the heterogeneity in LS cutoff values among the reports emphasizes the need for the future studies.

In addition, most recent studies, primarily those conducted in China, Japan, and Korea, involve patients with HBV-related cirrhosis, making it difficult to apply LS values obtained via VCTE to pre-surgical evaluations in liver diseases of various etiologies (Table 23). The included studies exhibit clear limitations due to the wide variation in HCC size,  $\alpha$ -fetoprotein level, and the inclusion rate of major hepatectomy. Variability in follow-up duration also necessitates caution in interpreting outcomes such as recurrence rates, patient survival, and post-hepatectomy complication rates.

Studies using 2D-SWE have suggested that a LS cutoff value of 9.5 kPa in patients with Child-Pugh A liver function can predict post-hepatectomy liver failure, aiding in pre-surgical patient selection.<sup>484</sup> Another study introduced a nomogram predicting post-hepatectomy liver failure using a 2D-SWE LS measurement >9.5 kPa, residual liver volume, Child-Pugh grade, and the presence of PH, providing safe residual liver function parameters based on the de-

gree of fibrosis and PH.<sup>485</sup> A study utilizing MRE reported that LS >4.53 kPa is associated with a HR of 1.27 for DFS.<sup>486</sup> Another prospective study indicated that a threshold of 4.3 kPa could predict a higher rate of major post-hepatectomy complications.<sup>487</sup>

Histological staging of HCC and non-tumorous tissue findings post-hepatectomy provide more accurate prognostic information than NITs. However, preoperative serum markers and NITs such as VCTE, SWE, and MRE aid in determining the extent of hepatectomy and predicting post-hepatectomy residual liver function.

### Radiofrequency ablation

NITs are useful in predicting the recurrence rate and survival of HCC patients following RFA (Table 24). Relevant studies from Korea, Taiwan, China, and France, published between 2015 and 2020, include three retrospective and three prospective studies investigating the utility of NITs for prognosis prediction post-RFA. These studies utilized various methods such as pSWE, 2D-SWE, and VCTE. When LS measured by pSWE exceeded 1.5–1.6 m/s, the HR for HCC recurrence ranged from 2.87–4.1.<sup>488,489</sup> Although LS cutoff values for VCTE ranged from 13–14 kPa, the HRs varied between 1.03–3.12 across studies.<sup>488,490,491</sup> The association between high LS on VCTE and poor OS was also noted, with HRs ranging from 1.02–9.80.<sup>488-491</sup> In patients with cirrhosis due to various etiologies such as ALD, NAFLD, CHB, and CHC who underwent RFA, significant differences in survival periods were observed when a VCTE LS cutoff value of 40 kPa was used (59 vs. 34 months).<sup>492</sup> However, the inclusion of patients with multiple tumors and large tumors, as well as the lack of observation period data in several studies, should also be considered limitations when interpreting the results.

## Development of hepatic decompensation

### Serum markers

Similar to HCC development, the role of serum markers in predicting the development of hepatic decompensation is limited and has primarily been reported in retrospective cohorts for various liver diseases.<sup>430,493-496</sup> According to a study from Taiwan, CHB patients who received AVT for more than a year and who had a low FIB-4 of less than 3 showed a cumulative 8-year incidence rate of 1.03%,

**Table 23.** Predictive values of pre-operative NITs for prognosis after hepatectomy for HCC

Reference	Study design	Region	Patient number	Outcome	NIT	Cutoff value	Post-hepatectomy complications	OS	DFS	HR (95% CI)	OR (95% CI)
Toyoda et al. <sup>469</sup> (2015)	Retrospective	Japan	431	Recurrence, survival	FIB-4	≥3.25	NR	5-year 72.2% vs. 67.1%	5-year 69.6% vs. 54.8%	OS 1.72 (1.20–2.51) DFS 1.66 (1.28–2.17)	NR
Okamura et al. <sup>470</sup> (2016)	Retrospective	Japan	140	Recurrence, survival	FIB-4	≥2.7	Major complication: 10.4% vs. 12%	3-year 84% vs. 69.3%	3-year 81.7% vs. 45.4%	OS 2.11 (1.06–4.18) DFS 2.21 (1.38–3.54)	NR
Yun et al. <sup>471</sup> (2023)	Retrospective	Korea	962	Recurrence, survival	FIB-4	≥1.67	NR	94.1% vs. 90.2%	75.5% vs. 69.0%	2-year OS 2.36 (0.99–5.65) 2-year DFS 1.81 (1.18–2.77)	NR
Tortajada et al. <sup>476</sup> (2022)	Retrospective	France	66	Recurrence, survival	Score +1 for each factor (age ≥70, LS value by VCTE ≥11.0 kPa, PT INR ≥1.2, Largest tumor ≥3 cm)	Score <2	NR	Mean OS 69.7 vs. 54.8 months	Mean DFS 52.2 vs. 34.7 months	NR	NR
Kim et al. <sup>480</sup> (2008)	Prospective	Korea	72	PHLF	VCTE	≥25.6	NR	NR	NR	PHLF 19.14 (2.71–135.36)	NR
Jung et al. <sup>479</sup> (2012)	Prospective	Korea	133	Recurrence, survival	VCTE	≥13.4	Major complication 8.2% vs. 20.8%	NR	Overall 37.6% vs. 28.5%	DFS 1.925 (1.17–3.168)	NR
Wong et al. <sup>474</sup> (2013)	Prospective	Hong Kong	59	Recurrence, survival	VCTE	≥12.0	Major complication: 33.3% vs. 4.3%	NR	NR	NR	Major complications 7.33 (95% CI: NR)
Lei et al. <sup>481</sup> (2017)	Retrospective	China	247	PHLF	VCTE	≥14	NR	NR	NR	NR	PHLF 1.21 (1.13–1.29)
Rajakannu et al. <sup>477</sup> (2017)	Prospective	France	106	Recurrence, survival	VCTE	≥22.0	Complication 66.7% in LS value ≥22 kPa	NR	NR	NR	NR
Qi et al. <sup>478</sup> (2017)	Retrospective	China	263	Recurrence, survival	VCTE	≥13.2	NR	Median OS 61.3 vs. 48.2 months	Median DFS 60.4 vs. 47.0 months	OS 0.15 (0.09–0.25) DFS 0.32 (0.04–1.02)	NR

Table 23. Continued

Reference	Study design	Region	Patient number	Outcome	NIT	Cutoff value	Post-hepatectomy complications	OS	DFS	HR (95% CI)	OR (95% CI)
Wang et al. <sup>495</sup> (2021)	Prospective	Taiwan	94	Recurrence, survival	VCTE	≥8.5	NR	NR	3-year DFS 81.3% vs. 48.2% 5-year DFS 74.9% vs. 40.7%	1.03 (1.01–1.05)	NR
Long et al. <sup>494</sup> (2022)	Prospective	China	119	PHLF	2D-SWE	≥9.5	PHLF Minor hepatectomy 3.7% vs. 22.7% Major hepatectomy 70.4% vs. 17.6%	NR	NR	NR	PHLF 10.89 (3.86-30.75)
Abe et al. <sup>496</sup> (2021)	Retrospective	Japan	156	Recurrence, survival	MRE	≥4.53	NR	NR	Median DFS 22.5 months vs. 11.3 months	3.17 (1.96–5.24)	NR

2D-SWE, two-dimensional shear wave elastography; CI, confidence interval; DFS, disease-free survival; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HR, hazard ratio; kPa, kilopascal; LS, liver stiffness; MRE, magnetic resonance elastography; NIT, noninvasive fibrosis test; NR, not reported; OR, odds ratio; OS, overall survival; PHLF, post-hepatectomy liver failure; VCTE, vibration-controlled transient elastography.

whereas those with a high FIB-4 demonstrated a significantly higher incidence rate of 8.62%.<sup>495</sup> In patients with CHC treated with DAA therapy, the development of liver-related complications, including hepatic decompensations, was higher with a FIB-4 cutoff value of 2.9, showing a HR of 2.6.<sup>497</sup> In NAFLD patients, NFS, FIB-4, APRI, and BARD significantly predicted the development of hepatic decompensation.<sup>430,496</sup> Specifically, a study from the US reported risk ratios of 34.2, 20.9, 14.6, and 6.6 for the development of hepatic decompensation in high-risk groups with cutoff values of NFS 0.676, APRI 1.5, FIB-4 2.67, and BARD 4, respectively, although it did not specify which test was superior.<sup>496</sup> ELF was significantly predictive of hepatic decompensation development in NAFLD<sup>493</sup> and PSC.<sup>494</sup>

### Vibration-controlled transient elastography

The usefulness of VCTE in predicting the development of hepatic decompensation has been extensively studied across various liver diseases, showing more promise than serum markers. A meta-analysis including 17 studies of patients with CLD found a significant correlation between increased LS on VCTE and the development of hepatic decompensation, with a HR of 1.07.<sup>436</sup> Another meta-analysis of 54 studies found a significant correlation between high VCTE LS and the development of hepatic decompensation, with a HR of 13.1, and a dose-response correlation with a HR of 1.06/kPa.<sup>437</sup> This is similar to another meta-analysis of 62 studies that found a HR of 1.08/kPa, particularly in a subgroup analysis of four studies with 6,368 patients, where the HRs for the development of hepatic decompensation at LS cutoff values of 8.6 kPa, 13.5 kPa, 20.2 kPa, and 37.5 kPa were 1.50, 4.69, 16.23, and 21.29, respectively.<sup>438</sup> These findings suggest that VCTE can be used to predict the development of hepatic decompensation in patients with CLD.

A prospective study in Europe on patients with CLD showed that VCTE had equivalent performance to HVPG measurement in predicting the development of hepatic decompensation, with both LS cutoff values of 21.1 kPa and HVPG cutoff values of 10 mmHg showing a NPV of 100%.<sup>396</sup> A retrospective study in Europe of patients co-infected with HCV/human immunodeficiency virus showed that VCTE had similar predictive performance to liver biopsy for the development of hepatic decompensation.<sup>498</sup> While evidence is still insufficient, VCTE may be a useful

**Table 24.** Predictive values of pre-treatment NITs for prognosis after RFA for HCC

Reference	Study design	Region	Patient number	NIT	Cutoff value	OS	DFS	HR (95% CI)
Lee et al. <sup>491</sup> (2015)	Retrospective	Korea	111	VCTE	≥13 kPa	NR	NR	DFS 3.12 (1.24–7.84) OS 9.83 (1.15–84.21)
Lee et al. <sup>490</sup> (2017)	Retrospective	Korea	247	VCTE	≥13 kPa	NR	3-year 82.8% vs. 47.8% 5-year 77.0% vs. 23.5% 7-year 77.0% vs. 9.0%	OS 1.03 (1.02–1.04)
Rekik et al. <sup>492</sup> (2020)	Retrospective	France	159	VCTE	≥40 kPa	Median OS 59.0 vs. 34.0 months	NR	OS 1.02 (1.01–1.04)
Yoon et al. <sup>488</sup> (2018)	Prospective	Korea	130	pSWE	≥1.6 m/s	NR	NR	DFS 2.873 (1.81–4.57)
Lee et al. <sup>489</sup> (2020)	Prospective	Taiwan	173	pSWE	≥14 kPa	NR	NR	DFS 1.028 (1.01–1.04)
Lee et al. <sup>511</sup> (2018)	Retrospective	Korea	134	pSWE	≥1.5 m/s	NR	NR	OS 4.11 (1.16–14.52) DFS 2.00 (1.08–3.69)
Xie et al. <sup>512</sup> (2020)	Prospective	China	273	2D-SWE	≥13.3 kPa	1-year 98.3% vs. 94.4% 3-year 96.3% vs. 76.8%	NR	OS 4.30 (1.26–14.7)
				2D-SWE	≥13.4 kPa	Mean OS 62.6 vs. 48.5 months	Mean DFS 60.4 vs. 47.3 months	OS 3.68 (1.22–9.86) DFS 2.87 (1.03–9.15)

2D-SWE, two-dimensional shear wave elastography; CI, confidence interval; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; kPa, kilopascal; NIT, noninvasive fibrosis test; NR, not reported; OS, overall survival; pSWE, point shear wave elastography; RFA, radiofrequency ablation; VCTE, vibration-controlled transient elastography.

test for predicting the development of hepatic decompensation.

In Korean patients with CHB, LS measurement by VCTE above 19 kPa was associated with an increased risk of developing hepatic decompensation, with a HR of 7.18.<sup>499</sup> Another Korean study on CHB patients found a HR of 12.4 when comparing patients with LS cutoff value above 18 kPa to those with LS cutoff value below 13 kPa.<sup>500</sup> A Korean study on CHB patients showed that the development of liver-related complications, including hepatic decompensation, was 5.9% versus 23.1% with a LS cutoff value of 11.6 kPa, and 9.8% versus 33.3% for 18.2 kPa, and noted that the risk of liver-related complications decreased when LS decreased during follow-up.<sup>443</sup>

In a study from the US, CHC patients who achieved SVR after antiviral therapy and had LS on VCTE above 20 kPa had a HR of 3.85 for the development of hepatic decompensation compared to those with LS below 12.5 kPa.<sup>501</sup> A small retrospective study reported that liver-related complications, including hepatic decompensation, were significantly higher in patients with LS >8 kPa 1 year post-SVR, with a HR of 5.04.<sup>502</sup> In patients with ALD, LS >15 kPa significantly increased the risk of liver-related complications, including HCC, hepatic decompensation, and death, with a HR of 27.9.<sup>454</sup>

A prospective study in Europe analyzing patients with NAFLD found that LS >12 kPa significantly increased the risk of hepatic decompensation.<sup>503</sup> Another study analyzing patients with advanced fibrosis on liver biopsy or VCTE LS >10 kPa retrospectively found that higher baseline LS and a 20% or more increase in LS during follow-up of at least 6 months significantly increased the risk of hepatic decompensation and liver-related death.<sup>453</sup> Therefore, VCTE appears useful for predicting the development of hepatic decompensation in CLD, although the predictive performance and cutoff values may vary based on the cause of liver disease and patient characteristics, making direct clinical application challenging. Moreover, whether VCTE is superior to direct HVPG measurement or liver biopsy in predicting the development of hepatic decompensation and the usefulness of follow-up VCTE remains unclear.

### Shear wave elastography

Evidence for the usefulness of SWE in predicting the development of hepatic decompensation in patients with CLD

is limited. However, a recent multinational, multicenter cohort study involving 5,648 patients with cACLD reported significant differences in the incidence rates of hepatic decompensation among low-, medium-, and high-risk groups classified based on a 2D-SWE LS <20 kPa and MELD <10, LS ≥20 kPa or MELD ≥10, and both LS ≥20 kPa and MELD ≥10, respectively, with 1-year incidence rates of 0.7%, 7.7%, and 26.6%, respectively, and 2-year rates of 4.1%, 20.0%, and 61.8%, respectively.<sup>504</sup>

### Magnetic resonance elastography

An international multicenter study on patients with CLD showed that increased MRE LS was associated with the development of hepatic decompensation, with a HR of 1.34, and patients with LS >4.7 kPa had a significantly higher risk of developing hepatic decompensation compared to those with LS <3 kPa, with a risk ratio of 67.5.<sup>458</sup> This was also confirmed in a Korean retrospective study.<sup>459</sup> A meta-analysis using IPMA from six cohorts and 2,018 patients with NAFLD reported that the MEFIB index and MRE alone showed predictive performance for the development of hepatic decompensation, with HRs of 15.9 for LS >8 kPa compared to <5 kPa, and 11.0 when comparing 5–8 kPa to <5 kPa groups.<sup>261</sup> Patients with a high MEFIB index showed a risk ratio of 20.6 for the development of hepatic decompensation compared to the patients with a low MEFIB index. Thus, MRE seems useful for predicting the development of hepatic decompensation in patients with NAFLD, and further research is needed in patients with CLDs of other etiologies.

## Death

### Serum markers

A study involving 46,456 adults without CLD in Korea reported that the group with FIB-4 >2.67 had a HR of 1.64 for all-cause death and 10.50 for liver-related death.<sup>505</sup> In patients with CHB, a FIB-4 score >2.67 was associated with higher liver-related death.<sup>506</sup> A systematic review including 13 studies on NAFLD reported predictive AUCs for FIB-4, NFS, and APRI between 0.67–0.82, 0.70–0.83, and 0.52–0.73, respectively, for predicting death.<sup>507</sup> A large study of 437,828 individuals in Korea categorized patients into low-, intermediate-, and high-risk groups based on FIB-4 cutoff values of 1.3 and 2.67. Compared to healthy individuals,

HRs for death in patients with NAFLD were 0.43, 2.74, and 84.66, respectively, and 0.67, 5.44, and 59.73 in patients with ALD.<sup>508</sup> Meta-analyses of 10 studies with 3,485 HCC patients and 15 studies with 5,051 HCC patients found that increases in FIB-4 and APRI were associated with poor survival rates, with HRs of 1.74<sup>509</sup> and 1.62,<sup>510</sup> respectively.

### Vibration-controlled transient elastography

A meta-analysis of 17 studies on patients with CLD showed that an increase in VCTE LS measurements had a relative risk ratio of 1.22 for liver-related mortality.<sup>436</sup> Another meta-analysis including 54 studies found that high VCTE LS was associated with a HR of 4.2 for liver-related death, with a dose-response correlation of 1.11/kPa.<sup>437</sup> This is consistent with another meta-analysis of 62 studies showing a similar result with a relative HR of 1.08/kPa, especially in a subgroup analysis of three studies with 4,374 patients, where liver-related death HRs at cutoff values of 8.5 kPa, 13.5 kPa, 19.8 kPa, and 37.5 kPa were 1.34, 3.25, 7.72, and 14.25, respectively.<sup>438</sup> A retrospective study in Europe on patients co-infected with HCV/human immunodeficiency virus showed that a predictive model including LS from VCTE was equivalent to liver biopsy in predicting death.<sup>498</sup>

In Korea, the development of liver-related death and complications in CHB patients showed significant differences at LS cutoff values of 11.6 kPa and 18.2 kPa, with rates of 5.9% vs. 23.1% and 9.8% vs. 33.3%, respectively. Moreover, a decrease in LS during follow-up was associated with reduced liver-related complications.<sup>443</sup> A small study in Taiwan showed that CHC patients treated with DAA therapy had a significant difference in liver-related death or complications with a LS cutoff value of 8 kPa 1-year post-SVR, showing a HR of 5.04.<sup>502</sup> For ALD, LS >15 kPa was associated with a significantly higher risk of liver-related complications, including HCC development and death, with a HR of 27.9.<sup>454</sup> A prospective study in Europe on patients with NAFLD showed that LS >12 kPa significantly increased mortality risk,<sup>503</sup> and another study found that higher baseline LS and a 20% or more increase in LS over a six-month follow-up period were associated with increased risks of liver-related death.<sup>453</sup> Thus, VCTE can aid in predicting death in patients with CLD, in addition to its predictive value for the development of HCC and hepatic decompensation.

### Shear wave elastography

While evidence on the predictive performance of SWE for death is limited, a recent multinational, multicenter cohort study involving 5,648 patients with cACLD reported significant differences in mortality rates when classified by 2D-SWE LS and MELD score into low-, intermediate-, and high-risk groups. The death rates at 1 year were 0.3%, 4.6%, and 15.7%, and at two years were 1.5%, 11.7%, and 38.8%, respectively.<sup>504</sup>

### Magnetic resonance elastography

An international multicenter study on patients with CLD found that an increase in MRE LS was associated with increased death rate, with a HR of 1.17. Patients with LS >4.7 kPa had a higher risk of death compared to those with LS <3 kPa, with a HR of 2.90.<sup>458</sup> A Korean study on patients with CLD also showed similar results.<sup>459</sup> A meta-analysis of six studies with 2,018 patients with NAFLD reported a HR of 4.78 for death in patients with LS >8 kPa compared to those <5 kPa, and a HR of 2.31 when comparing the 5–8 kPa group to the <5 kPa group. Patients with a high MEFIB index had a HR of 3.78 for death.<sup>261</sup> Therefore, MRE can be useful in predicting death in patients with CLD.

### [Recommendations]

1. Serum markers (B2), VCTE (A2), and MRE (B2) can be used to assess the risk of HCC, hepatic decompensation, and death in patients with CLD.
2. In patients with CHC, VCTE before and after DAA therapy can assess the risk of HCC (B2).
3. In patients with HCC, VCTE before hepatectomy or RFA can predict prognosis (B2).

## MONITORING OF CHRONIC LIVER DISEASE

### Chronic hepatitis B

Long-term AVT in patients with CHB is closely related to improvement of liver fibrosis.<sup>513-515</sup> NITs are good tools for monitoring change in liver fibrosis. In many studies, LS on VCTE in patients with CHB who received AVT showed significant improvement (Table 25).<sup>516</sup> In a recent systematic review and meta-analysis including 24 studies that continu-

ously measured VCTE LS values during AVT in patients with CHB, LS decreased by -2.56 kPa (21.3%) compared to baseline after 1 year of AVT.<sup>517</sup> Among patients who were expected to have cirrhosis due to having LS >11 kPa, approximately 30.4% showed a decrease in LS to less than 11 kPa after one year. Reductions in LS after AVT in these studies may not only reflect improvement in liver fibrosis but also improvement in inflammation. However, liver biopsy, which is the reference standard, was not performed before or after AVT in most studies; thus, it was difficult to determine correlations between the degree of improvement in liver fibrosis or inflammation and improvement in LS measurements. In a recent Chinese multicenter prospective study conducted by Dong et al., 182 patients underwent liver biopsy and VCTE simultaneously before and after 78 weeks of entecavir treatment.<sup>518</sup> In this study, LS showed an excellent diagnostic performance for each stage of fibrosis before treatment, but the decrease in LS during 78 weeks of AVT appeared to reflect improvement in inflammation rather than liver fibrosis. The only predictor of improvement in histological liver fibrosis after AVT was the Ishak fibrosis score before treatment. Therefore, when measuring LS using VCTE before and after AVT, clinicians should consider that when ALT is elevated, LS can be overestimated independently from liver fibrosis.<sup>49,127</sup> Improvements in LS after AVT may be related to improvement in inflammation represented by normalization of ALT rather than improvement in liver fibrosis.

VCTE can also be used to monitor the natural history of patients with CHB who are naïve to AVT.<sup>41,519-521</sup> According to one study, in CHB patients with normal ALT who did not meet the requirements for AVT and were being monitored, an LS increase of more than 20% showed an excellent AUC of 0.79 in predicting the progression of liver fibrosis defined as a one-point increase in METAVIR fibrosis score on liver biopsy.<sup>519</sup> Continuous measurement of LS using VCTE had better predictive performance for the progression of liver fibrosis than serum markers. However, as the above studies included a small number of patients and had a retrospective study design, additional research is needed to determine the usefulness and optimal interval for VCTE in patients with inactive CHB who are not receiving AVT.

Many studies have reported that monitoring the improvement of liver fibrosis in CHB patients receiving long-term AVT through APRI and FIB-4 is useful in evaluating treat-

ment effectiveness.<sup>522-524</sup> However, some studies have shown that APRI and FIB-4 have poor diagnostic performance for evaluating improvement in liver fibrosis compared to VCTE.<sup>518,525</sup> According to a comprehensive study of two phase 3 clinical trials that repeated liver biopsies before and after tenofovir disoproxil fumarate (TDF) treatment, decreases in APRI or FIB-4 scores after 240 weeks of treatment with TDF did not correlate with the improvement in liver fibrosis observed on liver biopsy.<sup>525</sup> In this study, baseline APRI and FIB-4 scores correlated with the histological stage of liver fibrosis; however, the APRI and FIB-4 scores after long-term AVT tended to underestimate the degree of liver fibrosis compared to liver biopsy. Therefore, follow-up studies are needed to determine whether APRI and FIB-4 can predict improvement in liver fibrosis after AVT.

In a study of 71 CHB patients, pSWE LS values continued to decrease during long-term AVT,<sup>526</sup> but these results should be supported by future research with a larger number of patients.

## Chronic hepatitis C

After the introduction of highly potent DAAs for CHC worldwide, there has been an increasing need for NITs to confirm improvement of liver fibrosis in patients who have achieved a SVR after CHC treatment. In a meta-analysis that investigated changes in VCTE LS before and after AVT in patients with CHC, LS measurements decreased in approximately 28.2% of patients who achieved SVR after AVT.<sup>527</sup> Post-treatment LS compared to baseline decreased more in patients who received DAA treatment compared to those who received interferon treatment, in patients with cirrhosis compared to those without, and in patients with a high liver enzyme level compared to those with low levels. In particular, among patients who were considered to have advanced fibrosis because their baseline LS value was higher than 9.5 kPa, 47% showed decreased LS to less than 9.5 kPa after treatment.<sup>527</sup> In an Italian study of 749 CHC patients with advanced fibrosis, VCTE-measured LS significantly reduced from 19.3 kPa to 14.2 kPa in patients who achieved SVR after DAA treatment.<sup>528</sup> In another study of 84 patients who received DAA due to recurrence of HCV after liver transplantation and achieved SVR, liver biopsy and VCTE were repeatedly measured before and 12



**Table 25.** Changes in LS measurement by VCTE before and after AVT in patients with CHB

Study	Research type	Nation	Patient number	Type of AVT	Observation period	Baseline LS (kPa)	Follow-up LS (kPa)	P-value
Gou et al. <sup>575</sup> (2010)	Prospective cohort	China	74	TLV (n=74)	6 months	16.5±8.9	10.5±4.1	0.003
Enomoto et al. <sup>576</sup> (2010)	Retrospective cohort	Japan	20	ETV (n=20)	1 year	11.2 (7.0–15.2)	7.8 (5.1–11.9)	0.009
Kim et al. <sup>577</sup> (2010)	Retrospective cohort	Korea	23	LMV (n=11), ETV (n=7), ADF (n=5)	1 year	13.7±7.9	11.3±5.3	0.018
Wong et al. <sup>578</sup> (2011)	Prospective cohort	Hong Kong	71	ADV or CLV (n=71)	1 year	8.8 (3.1–26.3)	6.6 (3.3–18.8)	<0.001
Fung et al. <sup>579</sup> (2011)	Retrospective cohort	Hong Kong	58	CLV (n=24), ETV (n=20), ADV (n=14)	Less than 6 months	7.9 (3.6–34.3)	6.4 (3.2–26.3)	<0.001
Lim et al. <sup>580</sup> (2011)	Retrospective cohort	Korea	62	ETV (n=62)	1 year	15.1 (5.6–75.0)	8.8 (3.0–33.8)	NR
Fung et al. <sup>581</sup> (2011)	Prospective cohort	Hong Kong	110	LAM (n=49), ETV (n=41), combination (n=10), ADV (n=6), TDF (n=3), TLV (n=1)	3 years	7.3	6.1	<0.001
Ogawa et al. (2011)	Retrospective cohort	Japan	22	LMV or ETV (n=22)	3 years	8.2 (4.2–28.5)	5.3 (2.5–18.0)	0.006
Osakabe et al. <sup>583</sup> (2011)	Retrospective cohort	Japan	29	ETV (n=21), LMV (n=8)	3 years	12.9 (6.2–17.9)	4.7 (3.1–7.9)	0.006
Yan et al. <sup>584</sup> (2013)	Prospective cohort	China	58	TLV (n=26), ETV (n=22), LMV (n=8), ADV (n=2)	1 year	8.8 (3.2–47.3)	5.5 (2.8–21.5)	NR
Kim et al. <sup>585</sup> (2013)	Prospective cohort	Korea	121	ETV (n=121)	3 years	14.3 (9.0–23.5)	7.3 (5.3–11.8)	<0.001
Wong et al. <sup>586</sup> (2013)	Prospective cohort	Hong Kong	106	NR	4 years	6.4±2.1	5.6±2.7	<0.001
Yang et al. <sup>587</sup> (2014)	Retrospective cohort	China	65	TLV (n=65, compensated cirrhosis)	2 years	19.1 (7.3–32.6)	14.8 (7.4–32.5)	<0.001
Kim et al. <sup>588</sup> (2014)	Retrospective cohort	Korea	83	TLV (n=62, decompensated cirrhosis)	1 year	30.5 (9.1–55.0)	29.9 (8.4–53.2)	0.085
Zhang et al. <sup>589</sup> (2015)	Retrospective cohort	China	12	ETV 0.5 mg (n=28), LMV (n=22), CLV (n=14), Combination (n=11), ADF (n=4), ETV 1.0 mg (n=4)	6 months	16.2±12.4	11.3±7.4	<0.001
Wang et al. <sup>590</sup> (2016)	Retrospective cohort	Taiwan	80	NR	3 years	12.0±9.3	11.1±10.3	0.695
				TDF (n=80)		10.2±6.2	7.3±5.7	<0.001

Table 25. Continued

Study	Research type	Nation	Patient number	Type of AVT	Observation period	Baseline LS (kPa)	Follow-up LS (kPa)	P-value
Chon et al. <sup>591</sup> (2017)	Prospective cohort	Korea	120	ETV (n=78), LAM (n=42)	5 years	14.5±7.2	8.3	<0.001
Zeng et al. <sup>592</sup> (2017)	Retrospective cohort	China	108	ETV (n=87), combined (n=9), TLV (n=8), ADV (n=4)	2 years	8.7±3.1	5.9±1.6	<0.001
Stasi et al. <sup>593</sup> (2017)	Retrospective cohort	Italy	20	ETV or TDF (n=20)	2 years	12.6±6.3	7.3±3.2	0.001
Liang et al. <sup>594</sup> (2017)	Prospective cohort	China	534	TLV or TLV + ADV (n=534)	2 years	8.6 (2.6–49.5)	5.3 (2.7–36.8)	<0.001
Wu et al. <sup>595</sup> (2018)	Prospective cohort	China	120	ETV (n=120)	1.6 years	13.8 (9.6–20.3)	7.7 (5.7–12.0)	<0.05
Dong et al. <sup>518</sup> (2019)	Prospective cohort	China	182	ETV based treatment (n=182)	1.6 years	11.3 (7.8–16.7)	6.4 (5.1–8.8)	NR
Wei et al. <sup>596</sup> (2022)	Retrospective cohort	China	23	ETV or TDF or TAF (n=23)	2 years	8.9	6.4	<0.001
Hu et al. <sup>597</sup> (2023)	Retrospective cohort	China	102	TDF (n=49), ETV (n=40), TAF (n=13)	2 years	8.3±3.9	6.2±1.9	<0.001

LS, liver stiffness; TE; transient elastography; AVT, antiviral therapy; CHB, chronic hepatitis B; LAM, lamivudine; ETV, entecavir; ADV, adefovir; CLV, clevudine; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; NR, not reported.

months after treatment, and LS significantly decreased in the group showing improvement in liver fibrosis compared to the group without improvement (47% vs. 30%).<sup>529</sup> Although LS on VCTE 12 months after SVR had a high AUC of 0.90 for diagnosing advanced fibrosis, the AUC of LS improvement for predicting the degree of improvement in liver fibrosis was low, at 0.65.<sup>529</sup> In addition, other studies investigated improvement in liver fibrosis in patients with CHC by measuring LS on VCTE before and after DAA treatment.<sup>530-536</sup> However, the European Association for the Study of the Liver currently does not recommend performing VCTE routinely to confirm improvement of liver fibrosis after CHC treatment, as it cannot distinguish whether a decrease in LS reflects an improvement in inflammation or improvement in liver fibrosis.<sup>537</sup> Moreover, applying the same cutoff value for diagnosing advanced fibrosis or cirrhosis used in untreated patients to patients who have achieved SVR may underestimate the degree of liver fibrosis.<sup>529,537,538</sup> According to one study with 33 CHC patients with SVR achievement, 24 (73%) were considered to have improved cirrhosis at an LS value less than 12 kPa, but five (21%) still had cirrhosis on liver biopsy.<sup>538</sup> This may be related to the liver remodeling process during the AVT, and if the VCTE before treatment is applied to patients who achieve SVR, the diagnostic performance for liver fibrosis after treatment may be reduced. Further research is needed to determine an appropriate cutoff value to evaluate the stage of liver fibrosis after AVT in NITs, including VCTE.

There are studies on LS measurements obtained via p-SWE<sup>534,536,539-543</sup> and MRE<sup>544-546</sup> after achieving a SVR in CHC patients, which showed a significant reduction compared to baseline values.

## Nonalcoholic fatty liver disease

Assessment of treatment response and disease progression via NITs is increasingly crucial for patients with NAFLD. Serum ALT serves as the most accessible serum marker in clinical practice and has been widely used as an indicator of liver damage in various studies. The TONIC study, which focused on pediatric patients with NAFLD, highlighted a correlation between the mean change in ALT from baseline to 96 weeks and histologic improvement.<sup>547</sup> Similarly, the FLINT study identified a significant association between a decline in ALT levels of at least 17 IU/L after

24 weeks of treatment and histological improvement (AUC 0.83, odds ratio 11.0).<sup>548</sup> A retrospective, longitudinal study in the US, covering 292 patients with biopsy-proven NAFLD and monitored through serum markers and liver biopsies over a median of 2.6 years, found significant associations between changes in the APRI, FIB-4, and NFS scores and the progression of fibrosis (the cross-validated C-statistic for detecting progression to advanced fibrosis: APRI 0.82, FIB-4 0.81, NFS 0.80).<sup>549</sup> APRI, FIB-4, and NFS demonstrated a high NPV of over 90% for predicting progression to advanced fibrosis, although their PPV was limited to the 40% range. In simtuzumab trials, an ELF score exceeding 9.76 predicted progression to cirrhosis with a sensitivity of 77% and specificity of 66% in patients with bridging fibrosis at baseline. Furthermore, changes in ELF score from baseline were associated with progression to cirrhosis in a multivariable model.<sup>493</sup> Conversely, a retrospective study in Sweden with 135 NAFLD patients revealed the limited clinical applicability of APRI, FIB4, and NFS for detecting fibrosis progression as assessed by liver biopsy or VCTE (AUC 0.56–0.64, PPV 0.28–0.36).<sup>550</sup> In addition, a systematic review based on three studies similarly showed inconsistent performance of serum markers in predicting the progression of hepatic fibrosis.<sup>507</sup>

Research on noninvasive evaluation of treatment response remains limited in the literature. An Indian study evaluating LS measurements and paired liver biopsy before and after one year of bariatric surgery among 58 patients showed no significant difference in LS cutoff values for diagnosing various stages of hepatic fibrosis.<sup>551</sup> A Japanese study based on 14 patients revealed a modest association (correlation coefficient 0.56) between 10-year changes in LS and fibrosis stage, suggesting the feasibility of repeated LS measurements for monitoring treatment response.<sup>552</sup> An analysis of 1,135 patients with compensated cirrhosis involved in the selonsertib and simtuzumab trials indicated that those exhibiting fibrosis regression (176 patients) demonstrated significant improvements in ELF, LS, and fibrosis markers based on machine learning algorithms compared to those without fibrosis regression.<sup>553</sup> Furthermore, in the REGENERATE study evaluating the effects of obeticholic acid in patients with NASH, patients with  $\geq 1$ -stage fibrosis improvement showed a decrease in LS at month 18 (mean kPa, -3.68; percentage change, 19.8%).<sup>554</sup> However, univariate logistic regression analysis showed a

weak association between changes in LS and fibrosis improvement (odds ratio 1.10 per 10% decrease in LS, AUC 0.62), suggesting the need for improvement in the performance of NITs through combination with other clinical measurements. Although recent clinical trials evaluated changes in LS as a candidate biomarker for monitoring treatment response, the exact thresholds correlating with treatment-induced fibrosis improvement are not well established. Thus, liver biopsy remains the reference for evaluating treatment response in patients with NAFLD.<sup>4,555</sup>

MRI-PDFF provides precise, sensitive, and reproducible quantification of steatosis.<sup>297,556,557</sup> A recent meta-analysis demonstrated that a  $\geq 30\%$  relative decline in MRI-PDFF is associated with higher odds of histologic response (odds ratio 6.98) and NASH resolution (odds ratio 5.45).<sup>558</sup> Therefore, MRI-PDFF appears as a promising tool for monitoring steatosis evolution and was used as a reference in recent clinical trials.<sup>559-562</sup> Given that MRE can be used to image the entire liver without operator dependency and is unaffected by obesity, it represents the most accurate NIT for staging liver fibrosis. However, its use in routine clinical practice is limited by its high cost and limited availability.<sup>258,259</sup> A prospective cohort study evaluating paired liver biopsy in 102 NAFLD patients over a median period of 1.4 years showed that a 15% increase in MRE was associated with histologic fibrosis progression and progression to advanced fibrosis.<sup>563</sup> Another retrospective study of 128 patients undergoing at least two serial MREs (median interval 3.4 years) reported that those with an increase in LS of 19% or more from baseline had a significantly higher risk of developing cirrhosis, hepatic decompensation, or mortality compared to non-progressors.<sup>564</sup> However, a study involving 54 patients with NASH and stage 2 or 3 fibrosis failed to show a significant difference in the change in LS on MRE between fibrosis responders ( $\geq 1$ -stage reduction) and non-responders (median relative change,  $-2.3\%$  vs.  $3.0\%$ ).<sup>565</sup>

In summary, the potential of NITs for assessing therapeutic response to inflammation and fibrosis in patients with NAFLD is highlighted. MRI-PDFF stands out as a promising test in noninvasive evaluation of steatosis evolution during treatment; however, overcoming challenges related to high cost and limited accessibility is required.

## Alcohol-related liver disease

A recent systematic review of 11 studies involving over 20,000 patients with ALD reported that NITs such as FIB-4, ELF, VCTE, and FibroTest can predict mortality and liver-related events with an AUC exceeding 0.7.<sup>566</sup> However, due to heterogeneity among these studies, a direct comparison between these NITs was not feasible, and the number of included studies was limited. Currently, there is insufficient evidence to support the use of NITs for monitoring disease progression, treatment response, and prognosis in alcohol-related liver disease, highlighting the need for further research.

## Cholestatic and autoimmune liver disease

Research on the course of AIH using NITs remains scarce. A retrospective study in Germany involving 125 AIH patients reported that those who failed to achieve complete biochemical remission exhibited an increasing trend in LS values ( $+1.7\%/year$ ;  $P=0.19$ ), while a significant decrease in LS was observed in the complete biochemical remission group ( $-7.5\%/year$ ), indicating that fibrosis regression can be monitored by VCTE.<sup>567</sup> However, further validation studies are needed. Moreover, since hepatic inflammation impacts LS, it is recommended to stage liver fibrosis using VCTE after at least 6 months of treatment.<sup>343</sup>

Despite the small number of studies, there is evidence to support the use of NITs in the monitoring of cholestatic liver disease. In PBC, a LS cutoff value of  $\geq 10.2$  kPa by VCTE and  $\geq 4.3$  kPa by MRE was acceptable for identifying PBC patients with advanced fibrosis and increased risk of future hepatic decompensation.<sup>337,568</sup> In another study, an increase of 2.1 kPa/year in VCTE LS was associated with an 8.4-fold increase in the risk of liver-related complications.<sup>331</sup> The European Association for the Study of the Liver recommends repeating LS measurement every 2 years in patients with early stage and annually in patients with advanced stage disease.<sup>81</sup> More studies are required to define the optimal interval between repeated tests.

In patients with PSC, liver fibrosis can progress unevenly or locally due to irregular narrowing of the bile ducts and cholestasis, frequently leading to sampling error during liver biopsy. Therefore, VCTE or MRE is preferred over liver biopsy in clinical practice.<sup>569</sup> A recent study reported that

baseline VCTE LS exceeding 9.9 kPa was associated with increased risk of hepatic decompensation, liver transplantation, or mortality, and an increase of 1.3 kPa/year was associated with a 10.4-fold increase in the risk of adverse outcomes.<sup>348</sup> Therefore, despite the lack of solid evidence regarding the optimal timeframe, the European Association for the Study of the Liver recommends the implementation of repeated VCTE LS measurement in patients with PSC.<sup>81</sup> In 204 PSC patients who underwent repeated MRE with a median interval of 1.1 years, the overall change in LS value was only 0.05 kPa/year. However, the change in LS value was ten-fold higher in patients with cirrhosis (0.31 kPa/year), with the highest risk of hepatic decompensation seen with a LS value increased of >0.34 kPa/year, indicating the potential of MRE in monitoring disease progression.<sup>570</sup> As LS can be significantly influenced by biliary obstruction and stasis in PSC, hepatic imaging is recommended before LS measurement in patients with PSC to accurately interpret the results.<sup>350,571</sup>

The ELF test showed good performance in predicting transplant-free survival in several studies of patients with PSC (AUC 0.78–0.81) and can be useful as a surrogate marker in clinical trials.<sup>572-574</sup> Furthermore, in a phase 2 simtuzumab trial, patients with a change in ELF  $\geq 0.19$  at week 12 showed an increased risk of hepatic decompensation, cholangitis, or cholangiocarcinoma compared to those with a lesser change.<sup>325</sup> However, the commercial availability of the ELF test is limited.<sup>569</sup>

#### [Recommendations]

1. VCTE can assess changes in liver fibrosis during AVT in patients with CHB (B1).
2. In patients with NAFLD, serum markers, VCTE, and MRE can monitor changes in liver fibrosis. (B1)
3. In patients with PBC and PSC, VCTE can assess treatment response and monitor disease course. (B1)

## PEDIATRIC PATIENTS

CLD in children and adolescents encompasses a wide range of conditions resulting from congenital or metabolic disorders, autoimmune diseases, and viral hepatitis. The incidence and prevalence of pediatric chronic liver disease

is increasing worldwide and, if not managed appropriately, can progress to significant fibrosis or cirrhosis.<sup>598-600</sup>

Although liver biopsy is the standard test for assessing the degree of liver fibrosis in CLDs among children and adolescents, there are several ethical concerns, including the need for general anesthesia, which significantly limits its application in the pediatric population. Research on NITs for assessing liver fibrosis in this group has mostly been reported through cross-sectional studies.

## Serum markers

### AST to platelet ratio index

The APRI has been extensively studied as a serum marker in pediatric patients with CLDs. In a study involving 48 infants with biliary atresia, the mean APRI was 1.38 for those with advanced fibrosis or less and 3.74 for those with cirrhosis. Using an APRI of 1.38 as a cutoff value, the sensitivity and specificity for diagnosing advanced fibrosis were 100% and 21.43%, respectively.<sup>601</sup> In a prospective cohort study of 260 infants with biliary atresia who underwent Kasai operation, the AUC for diagnosing cirrhosis was 0.83 using an APRI of 1.22 as the cutoff value.<sup>602</sup> In 46 patients with CHC, the APRI cutoff value for diagnosing significant fibrosis was 0.62, with sensitivity and specificity of 16.43% and 94.4%, respectively.<sup>603</sup> A study involving 92 patients with NAFLD found that the AUC of APRI for diagnosing advanced fibrosis was 0.628.<sup>604</sup> In a study of 204 patients with NAFLD, the AUCs of PIIINP, APRI, and FIB-4 for diagnosing significant fibrosis were 0.92, 0.77, and 0.74, respectively, while AUCs for diagnosing advanced fibrosis were 1.00, 0.85, and 0.77, respectively.<sup>605</sup>

These studies indicate that APRI is useful for assessing the degree of liver fibrosis in pediatric populations, but also highlight the need for larger validation studies.

### Fibrosis-4 index

In pediatric studies, FIB-4 generally demonstrates lower diagnostic performance for liver fibrosis compared to the APRI across various liver conditions, including NAFLD,<sup>604-606</sup> CHC,<sup>607</sup> CHB,<sup>608</sup> choledochal cysts,<sup>609</sup> and other CLDs.<sup>610-613</sup> However, an exception was noted in a study of 77 patients with NAFLD, where FIB-4 showed superior diagnostic performance for significant fibrosis compared to APRI (AUC of 0.81 vs. 0.70).<sup>614</sup>

### **Pediatric NAFLD Fibrosis Index and Pediatric NAFLD Fibrosis Score**

The Pediatric NAFLD Fibrosis Index (PNFI) was developed based on age, waist circumference, and triglyceride levels in a cohort of pediatric NAFLD.<sup>615</sup> In a study of 111 pediatric patients with NAFLD, the PNFI had a diagnostic AUC of 0.618 for advanced fibrosis.<sup>616</sup> Alkhoury et al. reported an AUC of 0.747 for diagnosing significant fibrosis.<sup>617</sup>

In 2014, the Pediatric NAFLD Fibrosis Score (PNFS) was initially developed based on ALT, ALP, platelet count, and GGT in a cohort of 242 pediatric patients with NAFLD and the AUC for diagnosing advanced fibrosis was 0.7.<sup>613</sup> However, the PNFS lacks external validation.

#### **Other serum markers**

Serum markers of liver fibrosis in children and adolescents have been studied, including HA,<sup>612,618-628</sup> type IV collagen,<sup>612,621,622,624,629</sup> PIIINP,<sup>623</sup> laminin,<sup>623,626-628</sup> YKL-40,<sup>618,626,630</sup> monocyte chemoattractant protein,<sup>612</sup> soluble Fas,<sup>612</sup> cytokeratin-18 fragments,<sup>620,626,631,632</sup> autotaxin,<sup>629,633</sup> and M2BPGi.<sup>621,629,634</sup> However, serum markers for diagnosing liver fibrosis need to be studied on a larger scale in the pediatric population.

### **Vibration-controlled transient elastography**

VCTE has been extensively researched for diagnosing liver fibrosis in children and adolescents.<sup>155</sup> In a study involving 83 healthy pediatric participants, the median LS measurement was 4.1 kPa.<sup>635</sup> Another study with 123 healthy children and adolescents reported median LS values of 3.4 kPa for ages 1–5, 3.8 kPa for ages 6–11, and 4.1 kPa for ages 12–18, indicating an increase in LS values according to age.<sup>636</sup> Recently, a prospective population-based cohort study in Germany (LIFE Child cohort) involving 482 healthy adolescents aged 10–18 demonstrated sex differences in LS value percentiles, with significant increases observed in males during puberty but not in females.<sup>637</sup> Based on these findings, when interpreting VCTE LS measurements in pediatric populations, it is crucial to consider factors such as age, sex, and pubertal status.

Studies of pediatric patients with chronic liver disease of various etiologies have suggested a LS cutoff value of 7.5–13 kPa for advanced fibrosis.<sup>618,620,638</sup> Looking at the cutoff values for each etiology, Luo et al. reported a cutoff value

of 5.9 kPa (diagnostic AUC 0.74) for significant fibrosis in 43 patients with CHB.<sup>608</sup> In studies assessing the diagnostic performance of preoperative VCTE in infants with biliary atresia, Shen et al. identified a cutoff value of 15.5 kPa (diagnostic AUC 0.87) for cirrhosis in a study of 31 patients,<sup>639</sup> while Shin et al. reported cutoff values of 9.6 kPa (diagnostic AUC 0.86) for advanced fibrosis and 18.1 kPa (diagnostic AUC 0.96) for cirrhosis in a study of 47 patients.<sup>640</sup> In a study of patients with NAFLD by Nobili et al, the cutoff value for advanced fibrosis was 9 kPa.<sup>641</sup> A cutoff value of 9.7 kPa (range, 6.2–12.7 kPa) has been proposed for diagnosing PH.<sup>642</sup>

In a meta-analysis of 11 studies involving 723 pediatric patients in 2018, VCTE had an AUC of 0.96 for diagnosing significant fibrosis (sensitivity 95%, specificity 90%).<sup>643</sup>

### **Shear wave elastography**

Research on normal values of SWE in pediatric populations is limited. In a recent study, 2D-SWE LS values in 32 pediatric patients with liver disease (mean age 2.1 years) and 15 controls (mean age 11.8 years) were compared, and the mean LS in patients with liver disease was significantly higher than in controls (6.2 kPa vs. 4.6 kPa).<sup>644</sup>

A meta-analysis of 10 studies reported a LS cutoff value of 9.4 kPa by SWE (diagnostic AUC 0.91)<sup>645</sup> for significant fibrosis. In a prospective cross-sectional study involving 213 patients with chronic liver diseases, the cutoff value for advanced fibrosis was 12 kPa (diagnostic AUC 0.91).<sup>646</sup> Another study involving 160 patients showed AUCs of 0.990, 0.923, 0.819, and 0.884 for diagnosing each fibrosis stage ( $\geq F1$ ,  $\geq F2$ ,  $\geq F3$ , and  $F4$ ), respectively.<sup>647</sup>

Regarding specific etiologies, 46 patients with CHC exhibited higher LS values than those without (10.43 vs. 4.26 kPa).<sup>603</sup> In a study of 68 pediatric patients with biopsy-proven NASH, the AUC for diagnosing stage 1 or greater liver fibrosis and stage 2 or greater liver fibrosis was 0.92 and 0.97, respectively.<sup>648</sup> In a prospective cohort study of 69 patients with biliary atresia, LS on 2D-SWE showed a strong correlation with fibrosis stage (correlation coefficient 0.79), with cutoff values of 9.1 kPa, 11.6 kPa, 13.0 kPa, and 15.7 kPa for each fibrosis stage ( $\geq F1$ ,  $\geq F2$ ,  $\geq F3$ , and  $F4$ ), respectively.<sup>628</sup>

SWE demonstrates good sensitivity and specificity for diagnosing liver fibrosis, but shear wave velocity may be in-

fluenced by age and height.<sup>649</sup>

## Magnetic resonance elastography

Normal values for MRE are limited in pediatric populations. In a prospective study of 81 healthy children and adolescents (mean age 12.6 years), mean LS was 2.45 kPa, which was higher than values reported in healthy adults.<sup>650</sup>

Trout et al. reported an AUC of 0.70 for diagnosing significant fibrosis using MRE in pediatric liver transplant candidates,<sup>651</sup> and Xanthakos et al. reported a cutoff value of 2.71 kPa (AUC >0.90) for significant fibrosis in various chronic liver disease patients.<sup>652</sup> In a recent multi-center, prospective study, the AUC for diagnosing liver fibrosis was 0.93.<sup>653</sup>

In a cohort study including 93 pediatric patients with various liver diseases, the AUCs for diagnosing advanced fibrosis using SWE, VCTE, and MRE were 0.80, 0.86, and 0.90, respectively.<sup>654</sup> Although there are studies indicating high diagnostic performance of MRE for liver fibrosis in pediatric populations, the number of these studies remains limited.

### [Recommendations]

1. VCTE can assess the degree of liver fibrosis in pediatric patients with chronic liver disease. (B2)

## Authors' contributions

List of author contributions is available at the official website of Clinical and Molecular Hepatology (Supplementary Table 1, <https://doi.org/10.3350/cmh.2024.0506>).

## Conflicts of Interest

Conflicts of interest statement is available at the official website of Clinical and Molecular Hepatology (Supplementary Table 2, <https://doi.org/10.3350/cmh.2024.0506>).

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**Supplementary Table 1.** Committee members of KASL Clinical Practice Guidelines for Noninvasive Tests to Assess Liver Fibrosis in Chronic Liver Disease

	<b>Name</b>	<b>Institution/Department</b>	<b>Role/Part</b>
Chair	Seung Up Kim	Yonsei University College of Medicine, Internal Medicine	Guide the whole process
Deputy	Mi Na Kim	Yonsei University College of Medicine, Internal Medicine	Organize the whole process
Member	Beom Kyung Kim	Yonsei University College of Medicine, Internal Medicine	TYPES OF NONINVASIVE TESTS
	Moon Young Kim	Yonsei University Wonju College of Medicine, Internal Medicine	SCREENING HIGH-RISK GROUPS
	Sang Gyune Kim	Soonchunhyang University College of Medicine, Internal Medicine	Advise for the whole process
	Seung-seob Kim	Yonsei University College of Medicine, Radiology	TYPES OF NONINVASIVE TESTS
	Won Kim	Seoul National University College of Medicine, Internal Medicine	Advise for the whole process
	Hee Yeon Kim	The Catholic University of Korea, Internal Medicine	DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS, and systematic review
	Yu Rim Shin	Yonsei University College of Medicine, Thoracic and Cardiovascular Surgery	DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS
	Jihyun An	Hanyang University College of Medicine, Internal Medicine	DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS, and systematic review
	Jung Hwan Yu	Inha University School of Medicine, Internal Medicine	SCREENING HIGH-RISK GROUPS, and systematic review
	Minjong Lee	Ewha Womans University College of Medicine, Internal Medicine	DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS
	Eun Joo Lee	Yonsei University College of Medicine, Pediatrics	PEDIATRIC PATIENTS
	Han Ah Lee	Chung-Ang University College of Medicine, Internal Medicine	DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS, and systematic review
	Dae Won Jun	Hanyang University College of Medicine, Internal Medicine	Guide the whole process of systematic review
	Young Eun Chon	CHA University, Internal Medicine	SCREENING HIGH-RISK GROUPS, and systematic review
	Yuri Cho	National Cancer Center, Internal Medicine	DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR LIVER FIBROSIS
	Eun Ju Cho	Seoul National University College of Medicine, Internal Medicine	SCREENING HIGH-RISK GROUPS
	Young-Joo Jin	Inha University School of Medicine, Internal Medicine	TYPES OF NONINVASIVE TESTS, and systematic review
	YoungRok Choi	Seoul National University College of Medicine, Surgery	SCREENING HIGH-RISK GROUPS
	Ji Won Han	The Catholic University of Korea, Internal Medicine	SCREENING HIGH-RISK GROUPS, and systematic review

**Supplementary Table 1.** Continued

Delphi Committee

<b>Name</b>	<b>Institution</b>
Oh Sang Kwon	Gachon University College of Medicine, Internal Medicine
In Hee Kim	Jeonbuk National University Medical School,, Internal Medicine
Ji Hoon Kim	Korea University College of Medicine, Internal Medicine
Soo Young Park	Kyungpook National University School of Medicine, Internal Medicine
Byung Kuk Jang	Keimyung University College of Medicine, Internal Medicine
Jae Youn Cheong	Ajou University School of Medicine, Internal Medicine
Byung Seok Lee	Chungnam National University School of Medicine, Internal Medicine
Jung Il Lee	Yonsei University College of Medicine, Internal Medicine
Tae Hee Lee	Konyang University College of Medicine, Internal Medicine
Hyung Joon Yim	Korea University College of Medicine, Internal Medicine
Yong Kyun Cho	Sungkyunkwan University School of Medicine, Internal Medicine

Advisory Committee

<b>Name</b>	<b>Institution</b>
Young Seok Kim	Soonchunhyang University College of Medicine, Internal Medicine
Jin Wook Kim	Seoul National University College of Medicine, Internal Medicine
Jong Eun Yeon	Korea University College of Medicine, Internal Medicine
Young Suk Lim	University of Ulsan College of Medicine, Internal Medicine
Won Young Tak	Kyungpook National University School of Medicine, Internal Medicine
Moon Seok Choi	Sungkyunkwan University School of Medicine, Internal Medicine



**Supplementary Table 2.** Disclosure of conflict of interest

All committee members who participated in the development of the guidelines prepared a declaration of interests consisting of the following questions, and information on conflicts of interest within the last three years was as follows.

1. Do you have intellectual property rights such as patents, trademarks, licensing, and royalties in relation to interventions (drugs, medical technologies, etc.) covered by the clinical practice guidelines?
2. Are you employed (if you have an official/informal title) or have you ever been employed by a company or organization that is commercially related to the interventions covered by the clinical practice guidelines (drugs, medical technology, etc.)?
3. Do you have unlisted shares (stock options, non-trading stocks) or listed shares (over 10 million won, including stock options, but excluding indirect investment through mutual funds, etc.) of a company or organization that is commercially related to clinical practice guidelines?
4. Have you ever received research funds, grants, or equipment support from a company or organization that is commercially related to clinical practice guidelines?
5. Have you ever received honoraria, consulting fees, or payments (travel expenses, etc.) exceeding KRW 3 million each year or a total of KRW 10 million or more from companies or organizations that are commercially related to clinical practice guidelines?
6. Do you have any of the relationships described above in your family (parents, spouse, children) or the company in which a family member is involved?

Name	Details
Development Committee	
Seung Up Kim	Participation in research sponsored by Abbvie, Gilead, BMS, EchoSens Medical consultation/lecture fee for BMS, Abbvie, Gilead, Bayer, Eisai, Sirtex, Boston Scientific, Novo Nordisc, Samil, Ildong, Hanmi, Yuhan, Daewoong, Samjin, Chong Kun Dang, Inoen, Pharmaking, GC Wellbeing, GC cell, Acme medical
Mi Na Kim	Nothing to disclose
Beom Kyung Kim	Nothing to disclose
Moon Young Kim	Nothing to disclose
Sang Gyune Kim	Nothing to disclose
Seung-seob Kim	Nothing to disclose
Won Kim	Honoraria/Advisory role: Gilead, Boehringer-Ingelheim, GSK, Novo Nordisk, Samil, Ildong, LG Chemistry, YUHAN, Hanmi, HK Inoen, Standigm, PharmaKing, KOBIO LABS, Olix Pharma, TSD Life Sciences, Daewoong, QUEST, Therasid Bioscience, Korea United Pharm, and Eisai Research funding: GSK, Gilead, Novartis, Pfizer, Roche, Springbank, Altimmune, Ildong, DaeWoong, Dicerna, Celgene, Hanmi, Novo Nordisk, Galmed, Enyo, and KOBIO LABS Stock: KOBIO LABS and Lepidyne Founder: Remedygen Incorporation
Hee Yeon Kim	Nothing to disclose
Yu Rim Shin	Nothing to disclose
Jihyun An	Nothing to disclose
Jung Hwan Yu	Nothing to disclose
Minjong Lee	Nothing to disclose
Eun Joo Lee	Nothing to disclose
Han Ah Lee	Nothing to disclose
Dae Won Jun	Nothing to disclose
Young Eun Chon	Nothing to disclose
Yuri Cho	Nothing to disclose
Eun Ju Cho	Nothing to disclose
Young-Joo Jin	Nothing to disclose
YoungRok Choi	Nothing to disclose
Ji Won Han	Participation in research sponsored by Daewoong, Gilead, and LG Chem

**Supplementary Table 2.** Continued

Name	Details
Delphi Committee	
Oh Sang Kwon	Nothing to disclose
In Hee Kim	Nothing to disclose
Ji Hoon Kim	Nothing to disclose
Soo Young Park	Nothing to disclose
Byung Kuk Jang	Nothing to disclose
Jae Youn Cheong	Nothing to disclose
Byung Seok Lee	Nothing to disclose
Jung Il Lee	Nothing to disclose
Tae Hee Lee	Nothing to disclose
Hyung Joon Yim	Nothing to disclose
Yong Kyun Cho	Nothing to disclose
Advisory Committee	
Young Seok Kim	Nothing to disclose
Jin Wook Kim	Nothing to disclose
Jong Eun Yeon	Nothing to disclose
Young Suk Lim	Nothing to disclose
Won Young Tak	Nothing to disclose
Moon Seok Choi	Nothing to disclose