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Non-invasive Fibrosis Assessment of Patients with Hepatitis C: Application of Society Guidelines to Clinical Practice

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Abstract

Purpose of Review Chronic hepatitis C (CHC) infection remains a significant global public health burden and is associated with significant morbidity and mortality due to complications of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). All oral direct-acting antivirals (DAAs) are associated with high rates of sustained virologic response (SVR). Pre-treatment assessment for liver fibrosis remains of high importance as it may impact treatment choice, treatment duration, and signal the presence of cirrhosis for which variceal screening and HCC surveillance are warranted.

Recent Findings Non-invasive fibrosis assessment tools have largely replaced gold standard liver biopsy in routine clinical practice. Herein, we review key modalities of noninvasive testing with serum and imaging biomarkers, summarize current guideline recommendations, and propose an algorithm for real-world application in clinical practice.

Summary Careful history and exam, laboratory assessment, liver imaging, and a two-test noninvasive fibrosis strategy can reliably identify cirrhosis in patients with CHC infection.

Keywords Hepatitis C · Liver fibrosis · Serum fibrosis assay · Liver elastography

Introduction

Chronic hepatitis C virus infection (CHC) remains a substantial global public health burden despite the recent advent of oral direct-acting antivirals (DAAs) due to its association with significant morbidity and mortality related to CHC-associated cirrhosis and hepatocellular carcinoma (HCC) [1–3]. While identification of patients with end-stage liver disease is often clinically evident, assessment of those with advanced liver fibrosis at risk for cirrhosis and HCC relies on an accurate assessment of liver fibrosis [4, 5]. Liver biopsy remains the gold standard for fibrosis assessment, and although generally safe and well-tolerated, the procedure is associated with rare but potentially serious complications and is limited by sampling bias and both intra-observer and inter-observer variability [6–9]. In one study of 124 CHC patients, simultaneous paired left and right hepatic lobe biopsies demonstrated a discordance of one fibrosis stage in 33% of subjects, and sampling error may have classified cirrhosis as stage three fibrosis in up to 15% of subjects [10]. Due to these limitations and poor acceptance by patients, noninvasive fibrosis assays represent attractive options for assessment of liver fibrosis in clinical practice.

Numerous direct and indirect serum biomarkers, imaging studies, elastography methods, genomic tests, and combination algorithms have been developed to evaluate fibrosis stage in context of CHC infection. This review aims to concisely summarize the most widely used and evidence-based modalities, focusing on how they should be utilized in today's clinical management of adult patients with CHC. The use of noninvasive testing in fibrosis assessment of other chronic liver diseases (CLD) and in the assessment of portal hypertension and liver outcomes has been extensively reviewed elsewhere [11–14]. Specific attention is paid to recently published major society guidelines and the role of noninvasive markers before and after antiviral therapy.

This article is part of the Topical Collection on *Hepatitis C*

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Clinically Relevant Endpoints for Fibrosis Detection

With more than 10 DAA regimens approved by the United States (U.S.) Food and Drug Administration (FDA) which are associated with SVR rates exceeding 90%, the National Academies of Science, Engineering, and Medicine has proposed a strategy to eliminate 90% of CHC by 2030 [15, 16••]. Prior to treatment, fibrosis assessment is important for several reasons. The stage of liver fibrosis directly impacts clinical management, informs the decision to pursue antiviral therapy, as well as the selection of an appropriate DAA regimen, and fulfills fibrosis assessment requirements for public and private payors. The identification of stage 4 fibrosis or cirrhosis represents the primary objective of fibrosis assessment as it signals the need for screening endoscopy for evaluation of gastroesophageal varices and for HCC surveillance imaging, and influences treatment duration (requirement for minimum of 12 week course) and DAA selection due to restrictions on the use of protease inhibitor-based regimens among patients with decompensated cirrhosis [17, 18••, 19]. Although identification of moderate (F2) or advanced (F3) fibrosis influences prognosis [20] and may signal priority candidates for antiviral therapy in settings with restricted access to DAAs [19], given the excellent safety, tolerability, and efficacy of all-oral regimens, antiviral therapy is recommended for all patients except those with limited life expectancy [18••, 19]. Furthermore, although distinguishing between significant (F2) and advanced (F3) fibrosis does not meaningfully alter HCV treatment approach, the current AASLD/IDSA HCV guidance document does suggest that patients with F3 fibrosis are at risk for HCC and require lifelong surveillance imaging including in the post-SVR context, although updated AASLD and EASL HCC guidelines suggest that the benefit of this approach remains uncertain, and requires individualized risk assessment [17, 21]. Finally, fibrosis assessment represents a required step in accessing DAAs through private and public payors, many of whom continue to restrict access to patients with significant liver fibrosis [22, 23].

Noninvasive Modalities

Conventional Imaging Methods

Conventional imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) have a limited role in the evaluation of fibrosis in patients with CHC. They are unable to reliably assess early stages (F0-F2) of fibrosis or definitively rule out cirrhosis [24–28]. In general, they are best utilized in the initial assessment of patients with CHC to rule in cirrhosis when history, physical exam, or laboratory parameters are suggestive of this diagnosis, and to exclude the presence of HCC in patients with advanced disease [19, 29, 30••]. The presence of characteristic findings such as nodular liver contour, left lobe or caudate lobe hypertrophy, recanalization of the umbilical vein, and splenomegaly in patients with other clinical signs or symptoms of cirrhosis may confirm the diagnosis without the need for additional fibrosis assessment with non-invasive tests or biopsy, unless other etiologies for liver disease are suspected [19].

Serum Tests

Numerous serum tests have been evaluated both individually and in combination to identify surrogates for evaluating the degree of fibrosis in patients with CHC. These tests have generally been dichotomized into those directly arising from the fibrotic process (e.g., α2-macroglobulin, hyaluronic acid [HA], tissue inhibitors of metalloproteinase-1 [TIMP-1], procollagen type III N-terminal peptide [PIIINP]) and those indirectly affected by it (e.g., AST, platelet count, INR). No individual biomarker has shown adequate performance characteristics to reliably distinguish between stages of fibrosis, but have acceptable test characteristics in identifying no or mild fibrosis versus advanced liver fibrosis/cirrhosis in a binary fashion. Multiple linear regression models evaluating combinations of biomarkers have derived at least 20 serum-based tests which have been validated in CHC cohorts and have confirmed excellent predictive value in the identification of cirrhosis. Many of these algorithms have been commercialized as proprietary serum fibrosis assays (e.g., Fibrotest, Fibrosure, ELF, Hepascore), while others such as the AST-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) utilize only indirect and widely available components. The performance characteristics of the most commonly used serum tests have been previously reviewed in detail [31, 32•, 33–35].

Vibration-Controlled Transient Elastography

Vibration-controlled transient elastography (VCTE) utilizes an ultrasound probe that delivers both ultrasound and low-frequency elastic waves to calculate a propagation velocity measured in kilopascals (kPa) that correlates to liver stiffness and fibrosis. This represents the most commonly used and validated imaging-based fibrosis biomarker used in the care of patients with CHC infection. It has important advantages including rapid point-of-care performance in a physician office, wide dynamic range of liver stiffness measurement (2–75 kPa), high reproducibility, quality criteria are well defined, and established cut-offs are available for identification of significant fibrosis, cirrhosis, and cirrhosis with portal hypertension which impact patient care decisions. However, VCTE is limited by obesity, ascites, narrow intercostal spaces, acute

inflammatory states, extrahepatic cholestasis, excess alcohol consumption, hepatic congestion, meal intake, and steatosis [36–43]. In clinical trials, over one in five scans could not be interpreted [44–46].

In the earliest study examining VCTE, FibroScan (Echosens, Paris, France) was used to evaluate 106 patients with CHC, with an area under the receiver operator characteristic curve (AUROC) of 0.88 for detecting significant fibrosis (F2–4) compared to liver biopsy [47]. Two subsequent prospective studies validated these results in CHC cohorts, with an AUROC of 0.79–0.83 and 0.95–0.99 for significant fibrosis and cirrhosis, respectively [48, 49]. An early systematic review of the accuracy of VCTE incorporated four studies with 546 CHC patients and found the AUROC for significant fibrosis and cirrhosis to be 0.83 and 0.95, respectively [50]. A meta-analysis which evaluated 50 studies examining VCTE in assessment of various forms of chronic liver disease found the mean AUROC for detecting significant fibrosis and cirrhosis to be 0.84 and 0.94, respectively [51]; among CHC patients, the mean AUROC for significant fibrosis was 0.85 (95% CI, 0.80–0.89).

In two large multicenter studies comparing VCTE to serums biomarkers, VCTE performed equally well or better for the diagnosis of cirrhosis and comparably for the diagnosis of significant fibrosis [44, 45]. In the FIBROSTIC study, 1037 patients with chronic viral hepatitis (913 with CHC) who underwent liver biopsy, FibroScan was compared with FibroTest, Fibrometer, APRI, and Hepascore [45]. For the diagnosis of cirrhosis, FibroScan had an AUROC of 0.90 compared to 0.77–0.86 for the serum tests; however, the diagnostic accuracy for the detection of significant fibrosis was poorer for all non-invasive modalities without differences between VCTE and serum tests. In the ANRS HCEP-23 study comparing interpretable VCTE examinations with nine serum biomarker tests in 382 CHC patients, VCTE performance was not statistically different from serum biomarker tests for the diagnosis of both significant fibrosis and cirrhosis [45]. A large two-phase U.S. multicenter study compared VCTE to liver biopsy in patients with viral hepatitis (93% with CHC) [52]. In the development phase (188 patient cohort), the authors reported superior performance for the identification of cirrhosis (definition 12.8 kPa, AUROC 0.92, 84% sensitivity, 86% specificity, cirrhosis prevalence 20%) than significant fibrosis (definition 8.4 kPa, AUROC 0.89, 82% sensitivity, 79% specificity). In the validation cohort of 560 patients, the authors similarly reported superior performance for the identification of cirrhosis (AUROC 0.92, 76% sensitivity, 85% specificity, cirrhosis prevalence 15%) than significant fibrosis (AUROC 0.73, 58% sensitivity, 75% specificity). Notably, overall performance of VCTE was limited by technical failure with non-interpretable results across studies, including in 10% in the U.S. multicenter study and 22–25% in the FIBROSTIC and ANRS HCEP-23 protocols. Several systematic reviews and meta-analyses have confirmed that VCTE has excellent diagnostic performance in the detection of cirrhosis and liver outcomes in patients with CHC, including those with HCV/HIV coinfection and recurrent HCV post-transplant [53–56].

2D-Shear Wave Elastography

2D-shear wave elastography (2D-SWE), also known as supersonic shear imaging (SSI), is an ultrasound-based technique that enables real-time 2D quantitative mapping of shear elasticity in tissue [57, 58]. Several studies have reported excellent diagnostic performance in the identification of significant fibrosis and cirrhosis in patients with CHC infection [59, 60]. The advantages include the ability to implement the technology on conventional U.S. machines, operator choice of region and size, high range of values, low failure rate, and improved accuracy in obese patients [61]. Disadvantages include a reliance on operator experience and readings influenced by food intake [62–64].

Acoustic Radiation Force Impulse Imaging

Acoustic radiation force impulse imaging (ARFI), also known as point shear wave elastography (pSWE), uses focused ultrasound to deliver localized radiation force to a small area of tissue for a very brief period of time to generate displacement in the tissue that can be correlated in an inverse manner to stiffness (Nightingale et al. 2002). Advantages of ARFI for liver fibrosis evaluation include implementation on conventional U.S. machines, capacity for operator-identified regions of interest, wide dynamic range of liver stiffness (2–150 kPa), and a lower failure rate in the presence of obesity or ascites than VCTE. Several studies have reported excellent diagnostic performance in the detection of cirrhosis in patients with HCV and HCV-HIV coinfection [65–68]. The key disadvantages of ARFI include a narrow range of liver stiffness measurement (0.5–4.4 m/s), confounding by food intake and inflammation, and poorer discrimination between intermediate stages of liver fibrosis region [69, 70].

Magnetic Resonance Elastography

Magnetic resonance elastography (MRE), which utilizes a modified MR phase-contrast sequence t image propagating shear waves in tissue, was first developed and validated to measure liver stiffness in the mid-2000s [71–74]. Since then, MRE has been studied in multiple cohorts and validated in comparative studies with non-invasive serum tests and biopsy gold standard for the identification of significant fibrosis and cirrhosis [75–78]. The primary advantages of MRE include implementation on standard MRI machines and capacity to overcome interference from obesity or ascites. Furthermore, in contrast to VCTE and 2D SWE, which have a region of

interest (ROI) of 4–20 cc, MRE provides examination of the whole liver with estimated ROI of approximately 250 cc. Multiple studies have reported excellent diagnostic performance of MRE in the detection of cirrhosis in patients with CHC infection. In a pooled analysis performed within a technical review, a liver stiffness cutoff of 4.71 was associated with the highest accuracy for detection of cirrhosis with sensitivity and specificity of 0.94 (95% CI, 0.87–0.97) and 0.81 (95% CI, 0.61–0.98), respectively [79•]. These values are comparable to those reported for VCTE, and therefore, MRE does not appear to be associated with higher diagnostic performance than VCTE, although no validated head-to-head studies comparing the two modalities have been reported. The primary disadvantages of MRE include the requirement for facility-based rather than office-based radiology exam, significant exam time requirement, and high cost.

Novel Modalities

Genomics offers the potential to predict fibrosis progression and response to therapy in patients with CHC by correlating genetic variants, often through genome-wide association studies (GWAS). Specific variants correlated to fibrosis progression in CHC have been reviewed elsewhere [80–83]. While some loci such as interleukin 28B (IL28B) and interferon-λ (IFNL) have shown promise as individual tests when utilized within clinical context [84, 85], attempts to identify genomic signatures to predict the risk of fibrosis progression have had only modest success [86, 87]. Unfortunately, the generalizability of genetic variants is often limited to narrow populations under investigation. Other techniques incorporating proteomics, metabolomics, microRNA signatures, and other novel serum biomarkers remain under evaluation. In the context of the simplicity, access, and excellent diagnostic performance of existing serum and imaging biomarkers, the role of new modalities may remain limited, although it may have particular importance in specific contexts including patients being monitored followed SVR.

Guideline Recommendations

Major societal guidelines have recently proposed recommendations for the use of non-invasive biomarkers to assess fibrosis stage and decrease the use of liver biopsy [18••, 19, 88••, 89••]. Major guideline recommendations addressing the use of serum and imaging biomarkers are summarized in the **Table**. All guidelines recommend pre-treatment fibrosis testing in all patients with CHC, and preferentially suggest the use of non-invasive markers over liver biopsy in most clinical settings.

The 2018 AASLD-IDSA hepatitis C guidance document recommends that all patients with CHC undergo fibrosis assessment, with direct biomarkers and VCTE suggested as the most efficient approach [19]. VCTE and direct serum tests are reported as having high diagnostic performance for both significant fibrosis and cirrhosis, citing a systematic review that compared over 15 serum tests in 172 studies [90]. The guidance panel recommends that in settings where direct biomarkers or VCTE are not available, APRI or FIB-4 indices may be incorporated into clinical decision making, although with caution that these indirect serum tests performed more poorly for exclusion of significant fibrosis.

The 2015 European Association for the Study of the Liver (EASL) and Asociación Latinoamericana para el Estudio del Hígado (ALEH) joint guidelines on non-invasive testing recommend combining serum tests and VCTE as the most attractive and best-validated approach to assess fibrosis stage in patients with CHC [88••]. The author panel offered a strong recommendation that VCTE be used to screen patient to exclude cirrhosis due to superior test characteristics by VCTE to rule out rather than rule in cirrhosis. In the absence of VCTE, the guidelines recommend the use of serum tests to exclude cirrhosis, with preference for direct serum tests which may have stronger performance characteristics than indirect serum assays such as APRI and FIB-4. Both VCTE and serum test are identified as having strong diagnostic performance for cirrhosis than significant fibrosis. Alternative imaging-based elastography methods including ARFI and 2D-SWE are identified as having similar test characteristics as VCTE but require further investigation. MRE is not recommended for routine clinical practice. The 2018 EASL hepatitis C treatment guideline recommendations are aligned with the 2015 fibrosis testing guidelines, with emphasis on the recommendation for the use of multiple tests to improve diagnostic accuracy [18••].

The 2017 American Gastroenterological Association (AGA) guideline on the role of liver elastography in assessment of liver fibrosis recommends that VCTE, where available, should be used over nonproprietary indirect serum tests such as APRI or FIB-4 to diagnose cirrhosis in adults with CHC infection [89••]. This recommendation was supported by an evidence-based technical review of 36 studies evaluating VCTE versus serum tests and revealed superior sensitivity (0.89) and specificity (0.91) compared with APRI/FIB-4 for the detection of cirrhosis. A VCTE cutoff of 12.5 kPa is recommended to detect cirrhosis, based on a pooled effect estimate for VCTE cutoff from 17 studies with 5812 patients which revealed a sensitivity of 0.86 and specificity of 0.9. The technical review and guideline panels did not address other direct serum biomarkers or non-VCTE elastography methods in its evaluation process and focused only on the detection of cirrhosis rather than significant or advanced fibrosis. Based on pooled effect estimates from 13 studies evaluating the performance of MRE, overall test characteristics were similar to that reported with VCTE, and therefore, the guidance panel recommended preferential use of VCTE over MRE for the detection of cirrhosis in patients with CHC infection.

Proposed Algorithm

All patients with CHC should undergo a thorough clinical evaluation including history and physical exam to identify symptoms and signs suggestive of liver cirrhosis. This should be accompanied by an initial laboratory investigation and standard liver imaging study to characterize the infection and assess for signs of cirrhosis, including low platelet count, high AST/ALT ratio, decreased serum albumin, prolonged prothrombin time, and radiographic features of cirrhosis. In patients with overt features of cirrhosis and/or hepatic decompensation, no further fibrosis testing is warranted and the clinician may proceed to enact cirrhosis-specific management and CHC treatment. In patients without overt features of cirrhosis, two non-invasive fibrosis tests are recommended, ideally consisting of a serum test plus VCTE (or equivalent elastography method) to increase confidence in the non-invasive fibrosis estimate [91–94]. Although VCTE is widely available in many clinical settings and has been validated across multiple HCV subgroups, alternative elastography methods such as ARFI, 2D-SWE, and MRI may be reasonably used. In resource-limited settings, indirect serum tests such as APRI or FIB-4 may be used in place of proprietary direct serum tests, although ideally should be performed in combination with VCTE or a second fibrosis test. We have outlined a flow diagram proposing a potential algorithm (Fig. 1).

When the results of two non-invasive tests are concordant, the diagnosis or exclusion of cirrhosis can be presumed with reasonable confidence. However, when results are discordant, consideration should be given repeat noninvasive testing, testing with alternative noninvasive tests, and/or liver biopsy, particularly in patients in whom advanced (F3) fibrosis or more is suspected. Despite its limitations, liver biopsy remains the diagnostic gold standard for the assessment of liver fibrosis and cirrhosis and should be used selectively in patients in whom alternative or concomitant etiologies for liver disease are suspected (e.g., autoimmune hepatitis) or there is ongoing discordance between noninvasive fibrosis tests. Caution is needed in the interpretation of all noninvasive serum and imaging biomarkers for liver fibrosis, and should be evaluated in context of all clinical information and with careful assessment of confounding factors which may limit the diagnostic performance of individual fibrosis tests (e.g., significant alcohol consumption).

Non-invasive Modalities After SVR

With the advent of DAAs, SVR has become attainable in the vast majority of CHC patients. As more people are cured, the paradigm in management is shifting to post-SVR surveillance and identifying patients who require continued close follow-up for complications of advanced disease, including HCC. Non-invasive fibrosis assessment in the post-SVR setting represents an area of active investigation. Multiple studies have reported significant declines in serum and imaging-based fibrosis assays following virologic cure, although the diagnostic performance of these tests have been validated in the viremic rather than the cured patient, and may be subject to significant error.

The 2015 EASL guideline addressing non-invasive fibrosis testing does not recommend the use of non-invasive tests following SVR (Table 1) [89••]. The guideline panel authors suggest no added benefit of non-invasive fibrosis testing in patients who are non-cirrhotic pretreatment and raise concern

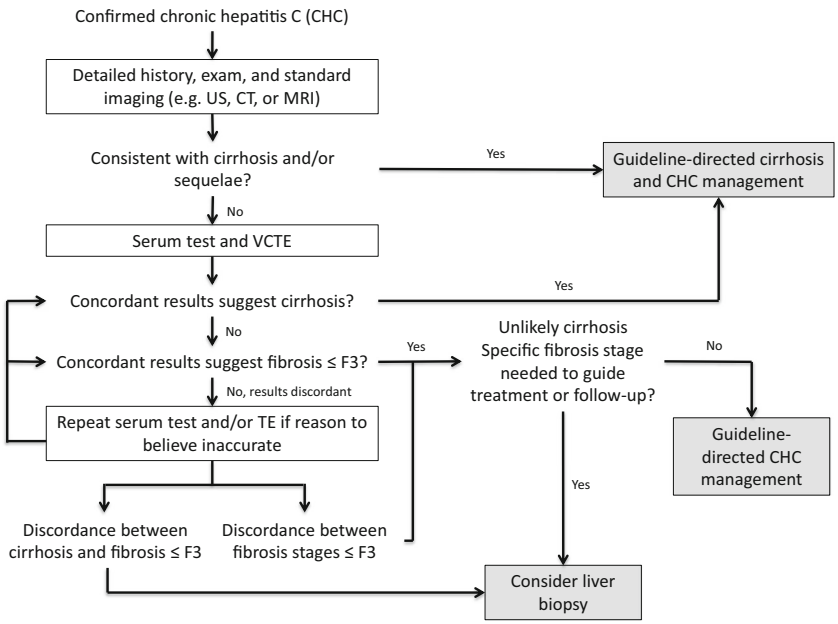

Fig. 1 Proposed algorithm for non-invasive assessment of liver fibrosis in patients with chronic hepatitis C infection

Table 1 Major societal guidelines for the use of non-invasive modalities for fibrosis assessment in patients with hepatitis C

Guideline	Year published	Serum tests (ST)	VCTE	Other elastography modalities	Combination algorithms	Use after SVR
AASLD-IDSA HCV guidance	2014/2018	ST are moderately useful for identifying clinically significant fibrosis or cirrhosis; if direct ST or VCTE are not available, APRI and FIB-4 can be helpful, though neither is sensitive enough to rule out substantial fibrosis	VCTE correlates well with measurement of substantial fibrosis or cirrhosis	NR	The most efficient approach is to combine direct ST and VCTE	NR
EASL HCV Treatment (EASL 2018)	2018	APRI and FIB-4 are generally available, simple, cheap, and reliable	Liver stiffness measurements can be used to assess liver fibrosis	NR	Non-invasive tests should be used instead of liver biopsy; the combination of ST or a ST and liver stiffness improves accuracy	Non-invasive tests should not be used to assess fibrosis stage after therapy
AGA elastography (Lim et al. 2017)	2017	VCTE, if available, should be used over nonproprietary, noninvasive ST (e.g., APRI, FIB-4) to diagnose cirrhosis (strong)	A cutoff of 12.5 kPa should be used to detect cirrhosis (conditional)	VCTE should be used rather than MRE to detect cirrhosis (conditional)	NR	A VCTE cutoff of 9.5 kPa can be used to rule out advanced liver fibrosis in patients without pre-treatment F3-F4 (conditional)
EASL-ALEH Non-Invasive Testing (EASL-ALEH 2015)	2015	ST are well-validated and are better at detecting cirrhosis than significant fibrosis (strong); ST have equivalent performance to VCTE to detect significant fibrosis (strong); ST can be used to screen patients to exclude cirrhosis in the absence of VCTE (strong); patented ST have similar levels of performance in detecting significant fibrosis and cirrhosis (strong); non-patented ST might have lower diagnostic accuracy than patented ST, but are cheaper and widely available (weak)	VCTE is more accurate for detecting cirrhosis than significant fibrosis (strong); VCTE generally performs better at ruling out than ruling in cirrhosis (strong); all patients should be screened to exclude cirrhosis by VCTE, if available (strong)	ARFI performs better for detecting cirrhosis than significant fibrosis (strong); ARFI shows equivalent performance to VCTE for detecting significant fibrosis and cirrhosis (strong); 2D-SWE seems to be equivalent to VCTE and ARFI but requires further investigation (strong); MRE is currently too costly and too time consuming for routine clinical practice (strong); further data are needed before MRE can be recommended (strong)	Either ST or VCTE are adequate for diagnosing severe fibrosis and cirrhosis (strong); algorithms combining ST and VCTE are the most attractive and validated (weak); a combination of tests with concordance may provide the highest diagnostic accuracy for significant fibrosis (weak)	In non-cirrhotic patients, non-invasive tests do not add to clinical disease management (strong); in cirrhotic patients, they have a high false-negative rate and cannot be used to determine which patients no longer need HCC screening or for the diagnosis of cirrhosis reversal (weak); thresholds to predict low risk of liver-related events not yet established (strong)

2D-SWE, 2-dimensional shear wave elastography; *AASLD-IDSA*, American Association for the Study of Liver Disease-Infectious Diseases Society of America; *AGA*, American Gastroenterological Association; *ALEH*, Asociacion Latinoamericana para el Estudio del Higado; *APRI*, AST-to-platelet ratio index; *ARFI*, acoustic radiation force impulse imaging; *HCV*, hepatitis C virus; *EASL*, European Association for the Study of the Liver; *FIB-4*, fibrosis-4 index; *MRE*, magnetic resonance elastography; *NR*, no recommendation; *ST*, serum tests; *SVR*, sustained virologic response; *VCTE*, vibration controlled transient elastography

for a high false-negative rate for cirrhosis in patients with pretreatment evidence of cirrhosis. On this basis, the guideline recommends that clinicians avoid the use of non-invasive fibrosis tests to determine fibrosis regression or to inform

decisions on the need for long-term HCC surveillance in patients with advanced fibrosis or cirrhosis prior to DAA therapy. The 2018 EASL guideline panel additionally recommended against the use of non-invasive tests to assess fibrosis stage following SVR [18••].

The 2017 AGA guidelines suggest that VCTE may be utilized as an adjunct to clinical decision making in the assessment of non-cirrhotic CHC patients who are classified as low risk for developing liver complications following SVR [89••]. The committee conditionally recommends a VCTE cutoff of 9.5 kPa to rule out advanced fibrosis only in patients without advanced fibrosis or cirrhosis at baseline, with caveat that the guidance panel rated the evidence as of very low quality. The use of VCTE to assess fibrosis is not recommended in patients with advanced fibrosis or cirrhosis at baseline pretreatment. The 2017 AGA Clinical Practice Update addressing the care of patients following SVR does not recommend routine fibrosis testing after viral eradication but may be considered on a case-by-case basis, and importantly should not be used to determine eligibility for HCC surveillance among patients with advanced liver disease at baseline [95•]. The 2018 AASLD-IDSA hepatitis C guidance document does not make recommendations for or against the use of non-invasive fibrosis testing following SVR [16••].

Based on current guidelines and best evidence, routine post-SVR fibrosis testing is not recommended. Multiple studies have demonstrated a significant decline in fibrosis scores with both serum and imaging biomarkers with viral eradication, although it may potentially overestimate fibrosis regression, including among individuals who have ongoing advanced liver fibrosis or cirrhosis who may require ongoing HCC surveillance. On this basis, the use of non-invasive fibrosis tests should be pursued with caution, although with expectation that future studies will further clarify and validate the potential role for biomarkers in assessing regression of fibrosis and portal hypertension.

Conclusions

The assessment of liver fibrosis remains an essential step in the initial evaluation of a patient with CHC infection and directly impacts clinical management and approach to antiviral therapy. Non-invasive testing has largely supplanted gold standard liver biopsy as the preferred strategy in contemporary clinical practice and is supported by society guidelines including those of the AASLD, IDSA, EASL, ALEH, and AGA. Both serum fibrosis tests and liver elastography are associated with excellent diagnostic performance and have been validated in patients with CHC, and should ideally be used in combination as part of a two-test strategy to increase clinician confidence in the identification and/or exclusion of cirrhosis. Liver biopsy remains an important tool in the minority of patients in whom alternative causes of liver disease are suspected, or there remains uncertainty in the assessment of liver fibrosis. Future studies will help further clarify the role of non-invasive fibrosis testing in emerging clinical contexts, including the care of patients who have achieved SVR following DAA therapy.

Compliance with Ethical Standards

Conflict of Interest Joseph K. Lim reports grants from Allergan, AbvVie, Conatus, Genfit, and Intercept, as well as grants and personal fees from Gilead outside the submitted work.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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