



Review Article

Chronic hepatitis C infection – Noninvasive assessment of liver fibrosis in the era of direct acting antivirals

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ABSTRACT

Significant advancements in the diagnosis and treatment of chronic hepatitis C infection and its associated fibrosis have revolutionized treatment of these patients over the last several years. Liver biopsy, the gold standard diagnostic method for evaluating liver fibrosis level, was routinely used prior to initiation of hepatitis C therapy, placing patients at an inherent risk of adverse events. The recent advent of noninvasive serologic and nonserologic measures of hepatic fibrosis level has reduced the need for liver biopsy significantly, thereby minimizing its associated risks. These noninvasive methods have been extensively studied in the era of interferon therapies and are increasingly recognized in the realm of direct acting antiviral agents as well. Their validation of use after having achieved a sustained virologic response is yet to occur, but the future remains promising.

This review focuses on the various non-invasive diagnostic modalities of liver fibrosis and discusses how they can be applied to the care of patients undergoing direct acting antiviral therapy for hepatitis C. In the constantly evolving landscape of hepatitis C therapy, the review underscores the important prognostic value of fibrosis staging prior to HCV treatment and suggests potential uses for non-invasive fibrosis assessment following successful HCV eradication.

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1. Introduction

Improvements in both noninvasive staging of liver fibrosis and antiviral therapy with Direct Acting Antiviral (DAA) agents have dramatically changed the way chronic hepatitis C virus (HCV) infection is treated. These advances in HCV management have significantly reduced the need for liver biopsy in clinical practice. In this review, we focus on the various modalities for noninvasive assessment of liver fibrosis and discuss how they can be applied to the care of patients with hepatitis C infection. In the evolving landscape of HCV therapy, we underscore the important prognostic value of fibrosis staging prior to treatment and suggest potential uses for noninvasive fibrosis assessment following successful HCV eradication [1–3].

1.1. Noninvasive markers of fibrosis

For years, liver biopsy has been the gold standard to measure hepatic fibrosis [1–3]. However, this method of investigation has

been challenged [4]. The disadvantages of liver biopsy include, but are not limited to, sampling error, increased costs, interobserver and intraobserver variation in interpretation of pathology slides, and the invasive nature of the procedure increasing the inherent risk of complications [5]. In the past decade, multiple serologic and imaging tests (Table 1) have been developed for the assessment of liver fibrosis, reducing the need for an invasive liver biopsy prior to the initiation of HCV treatment.

1.2. Noninvasive serologic markers for fibrosis

There are several noninvasive serum markers commercially available to provide an assessment of liver fibrosis (Table 2). Both direct and indirect serum markers have been discovered and aid in fibrosis assessment before HCV therapy, but still require validation for their use after HCV therapy is completed and SVR is obtained. Indirect serum biomarkers relate to liver damage or liver synthetic dysfunction in the process of fibrosis and cirrhosis, where as direct biomarkers equate to component of extracellular matrix involved in fibrolysis and fibrogenesis.

1.2.1. AST-to-platelet ratio index score

The AST-to-platelet ratio index (APRI) score, originally proposed in 2003 is a publicly available formula consisting of the aspartate aminotransferase (AST) level and platelet count [6–8]. Using a

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Table 1
Comparison of noninvasive tests for detecting HCV fibrosis.

Noninvasive test	Stage of fibrosis	Cut-off	Sensitivity	Specificity	NPV	PPV	Reference
APRI score	F3–F4	1.0	61%	64%	81%	40%	[40]
		1.0	76%	72%	69%	55%	
		2.0	46%	91%	63%	82%	
FIB-4	F3–F4	<1.45	74.3%	80.1%	94.7%	NA	[10]
		>3.25	37.6%	98.2%	NA	82.1%	
FibroTest	F3–F4	0.52	80%	82%	94%	55%	[12]
		0.63	74%	82%	96%	53%	
Fibrometer	F3–F4	0.72	90%	85%	97%	60%	[16]
		0.78	96%	78%	99%	42%	
Hepascore	F3–F4	0.47	79%	85%	95%	53%	[16]
		0.64	78%	82%	97%	34%	
TE	F ≥ 2	7.1	67%	89%	48%	95%	[16]
		9.5	73%	91%	81%	87%	
		12.5	87%	91%	95%	77%	
ARFI	F3–F4	1.55 ^a	86%	86%	89%	82%	[34]
		1.80 ^a	92%	86%	97%	71%	
MRE	F3–F4	4.11 ^a	85%	85%	NA	NA	[59]
		4.71 ^a	91%	81%	NA	NA	

HCV: hepatitis C virus, NPV: negative predictive value, PPV: positive predictive value, APRI: AST-to-platelet ratio index, VCTE: vibration controlled transient elastography, ARFI: acoustic radiation force impulse, MRE: magnetic resonance elastography.

^a Disease-specific cutoffs are still not available for these tests.

Table 2
Test characteristics of noninvasive serologic tests for HCV.

Noninvasive test	Formula/components	Public availability
APRI	AST/[AST upper limit of normal]/platelet count (10 ⁹ /L) × 100	Yes
FIB-4	Age (years) × AST (U/L)/platelets [10 ⁹ /L] × ALT [U/L] ^{1/2}	Yes
FibroTest	α-2 macroglobulin, haptoglobin, apolipoprotein-A, GGT, total bilirubin, age and gender	No (patented formula)
Fibrometer	AST, platelet count, prothrombin index, α-2 macroglobulin, HA, urea and age	No (patented formula)
Hepascore	α-2 macroglobulin, HA, GGT, total bilirubin, age and sex	No (patented formula)

APRI: AST-to-platelet ratio index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyl transferase, HA: hyaluronic acid.

threshold score of 1.0 for severe fibrosis, the sensitivity and specificity are 61% and 64%, respectively [9]. The negative predictive value (NPV) is 81% while the positive predictive value (PPV) is 40% using the same cutoff for severe fibrosis [10]. A threshold of 1.0 for cirrhosis was 76% sensitive and 72% specific, with a NPV and a PPV of 69% and 55%, respectively [10]. For a cutoff of 2.0 in cirrhosis, the NPV and PPV are 63% and 82%, respectively [10].

1.2.2. FIB-4

The FIB-4 index is another publicly available formula consisting of age (years), AST, platelets and alanine aminotransferase (ALT) [10]. FIB-4 index is able to accurately identify individuals with severe fibrosis (F3–F4) and cirrhosis [11]. A value less than 1.45 has a NPV of 94.7% in excluding F3–F4 fibrosis with a sensitivity of 74.3% and a specificity of 80.1% [12]. A value greater than 3.25 has a PPV of 82.1% in confirming F3–F4 fibrosis with a specificity of 98.2% and a sensitivity of 37.6% [12]. In a French study with 847 liver biopsies, 72.8% of the FIB-4 values outside of the 1.45–3.25 range were correctly classified using these cutoffs [12].

1.2.3. FibroTest

The FibroTest is a patented formula which includes five biomarkers with two clinical parameters: α-2 macroglobulin, haptoglobin, apolipoprotein-A, γ-glutamyl transferase, total bilirubin, age and gender [12]. The formula derives a numerical value between 0 and 1 [13–15]. It is a widely available linear score that can be used to risk stratify liver disease ranging from mild disease to cirrhosis [14,15]. For an optimal cutoff of 0.51 for severe fibrosis (F3–F4), the PPV and NPV are 55% and 94%, respectively [8]. The PPV and NPV for cirrhosis (F4) using a higher cutoff of 0.63 are 53% and

96%, respectively [16]. A French study in 2011 showed that noninvasive liver fibrosis assessment with FibroTest was able to reliably predict 5-year survival of patients with HCV infection [17].

1.2.4. Fibrometer

The Fibrometer is another patented formula which combines AST, platelet count, prothrombin index, α-2 macroglobulin, hyaluronic acid (HA), urea and age [16]. Values ranging between 0 and 1 correspond to the probability of advanced fibrosis [18]. Compared to the APRI score and FibroTest, the Fibrometer actually performed better in detecting both significant fibrosis and cirrhosis [8]. The cutoff of 0.72 has a sensitivity of 90%, specificity of 85%, NPV of 97% and PPV of 60% for severe fibrosis [19,20], while the cutoff of 0.78 has a sensitivity of 96%, specificity of 78%, NPV of 99% and PPV of 42% for cirrhosis [16].

1.2.5. Hepascore

The Hepascore is a patented formula which combines age and sex with four biomarkers: α-2 macroglobulin, HA, gammaglutamyl transferase (GGT) and total bilirubin [16]. The Hepascore has been validated by several studies [16,21]. Two great benefits of this noninvasive marker are that it requires only one serum sample and it can be completely automated using a single analyzer [22–27]. Comparative studies have shown that the Hepascore is only slightly better than APRI score and FibroTest for the detection of cirrhosis [24]. With a cutoff of 0.47 for detecting severe fibrosis, the sensitivity and specificity are 79% and 85%, respectively, whereas the NPV is 95% and PPV is 53% [20,28]. A cutoff of 0.64 has a sensitivity of 78%,

specificity of 82%, NPV of 97%, and a PPV of 34% for the detection of cirrhosis [16].

1.3. Noninvasive non-serologic modalities for fibrosis

Liver stiffness measurement (LSM) is a relatively new concept that has transformed the methodology of noninvasive hepatic fibrosis measurement. The newly available diagnostic options have streamlined the approach of fibrosis assessment in clinical practice for HCV. However, each test has its own strengths and limitations. Table 1 illustrates the statistical comparisons between these diagnostic modalities.

1.3.1. Vibration controlled transient elastography

Transient elastography (TE) has been validated for fibrosis assessment in an HCV cohort population. As an FDA approved modality, TE is an excellent noninvasive method that estimates liver stiffness. It is a simple test that uses ultrasound to measure the shear velocity propagating through the liver and expresses it as a volume, which is directly related to hepatic tissue stiffness [16]. The units measured are in kilopascals (kPa) and range from 2.5 to 75 kPa, with the normal value being less than 7 kPa in HCV patients [29].

Since its development, the data on TE has flourished. Zioli et al. first investigated the use of LSM by TE in a prospective study of 327 patients with HCV infection, and found it to be very reliable, particularly for detecting severe fibrosis and cirrhosis [30–32]. Similar results have been reproduced in studies of patients with HCV infection [33]. Furthermore, this technique was validated for the diagnosis of cirrhosis from HCV, as well as from other causes [34]. In comparative studies, TE often outperforms serologic tests, particularly for the diagnosis of cirrhosis [35,36]. Other advantages of this modality include short procedure time, immediate results and its ability to be performed at the bedside [37]. The Baveno VI consensus recommends the use of TE in diagnostic algorithms pertaining to chronic liver diseases [5]. The role of TE in monitoring patients after HCV eradication is currently investigational, but provides an exciting avenue for its potential utilization.

Despite its promising implementation, TE does have its downsides. A significant disadvantage is that the results may be influenced by certain anthropometric and physiological factors such as obesity, waist circumference, thoracic fold thickness, distance between the skin and liver capsule, ascites, hepatic congestion, edema, inflammation, and extrahepatic cholestasis [38]. In addition, increased necroinflammatory activity with ALT levels above 100 U/L can overestimate the degree of fibrosis measured by TE [5,39]. A newer probe, called the XL probe, has greater vibration amplitude and measurement depth, and allows for more accurate measurements, particularly in obese individuals [40]. The limitations of TE pose ongoing challenges in its implementation, and its results should be interpreted in the clinical context of the individual patient.

1.3.2. Magnetic resonance elastography

Magnetic resonance elastography (MRE) is another validated modality for the detection of hepatic fibrosis in HCV patients. This method of noninvasive measurement is costly as it utilizes magnetic resonance imaging (MRI). A probe placed on the patient's back emits low frequency vibrations, which pass through the liver to obtain a LSM. A major advantage of MRE is that it scans the entire liver, allowing it to detect focal hepatic lesions, such as hepatocellular carcinoma (HCC). It can also be used in patients with obesity or ascites, but has limited utility in those with iron overload [39].

The data on MRE continues to emerge as a useful modality of fibrosis assessment, particularly in obese individuals who have unreliable TE scores. A meta-analysis published in 2015, which included 12 studies and 697 patients with chronic liver disease,

devised the optimal cutoff values for each stage of fibrosis [5]. For detection of any fibrosis, the optimal cutoff was 3.45 kPa (sensitivity 73% and specificity 79%) [41]. The optimal cutoff for the detection of advanced fibrosis was 4.11 kPa (sensitivity 85% and specificity 85%) [41]. Lastly, for detecting cirrhosis, the optimal cutoff was 4.71 kPa (sensitivity 91% and specificity 81%) [41]. Studies comparing it to ultrasound-based TE have shown varying results. One prospective study showed MRE to have a higher technical success rate and better diagnostic accuracy [41], while another showed it to have similar test characteristics [42]. The high cost of MRE challenges the full-on implementation of this diagnostic test into clinical practice. As further data emerges, the role of MRE may change drastically, particularly in obese patients with or without nonalcoholic steatohepatitis [43], a cohort where TE remains less reliable [44–46].

1.3.3. Acoustic radiation force impulse imaging

Acoustic radiation force impulse imaging (ARFI) is an ultrasound-based modality that is not as commonly used as VCTE and MRE in liver fibrosis assessment. ARFI uses short duration, high-intensity acoustic pulses, which produce mechanical excitation that results in tissue displacement and shear wave propagation through liver tissue. The shear wave velocity increases with the amount of fibrosis, and therefore correlates with the degree of fibrosis. This method has been extensively studied in HCV infection [47]. Although the optimal cutoff values are different amongst studies, a pooled meta-analysis in 2012 evaluating 518 patients (380 with HCV infection) showed that the optimal cutoffs for advanced fibrosis and cirrhosis were 1.55, and 1.80 m/s, respectively [48–58]. In a prospective study of 321 patients who underwent liver biopsy for chronic liver disease, there was no difference between ARFI and ultrasound-based TE for the diagnosis of severe fibrosis or cirrhosis [59]. However, similar to TE, ARFI performed better in individuals who were not obese compared to obese patients. [60]. In another study, ARFI demonstrated lower reproducibility in patients with high BMI, ascites, women, and those without cirrhosis [60]. The role of this diagnostic modality has not yet been determined in clinical practice, as other clinical techniques have proven to be more effective [61].

1.3.4. Shear wave elastography

A newer, yet not fully validated, technique of noninvasive measurement of liver fibrosis is ultrasound-based shear wave elastography (SWE). Similar to other tests, this modality has been evaluated in the context of HCV infection. One study found patients with SVR to have a lower LSM using SWE compared to treatment-naïve patients [62]. Patients in the treatment-naïve group had an increased shear wave propagation velocity (1.69 ± 0.31 m/s) compared to healthy controls (1.23 ± 0.14 m/s) and those who have achieved SVR (1.56 ± 0.32 m/s). There were significant differences observed between the group that achieved SVR ($n = 51$) and treatment-naïve group ($n = 85$), as well as between the SVR group and the healthy controls ($n = 58$).

Data on SWE in HCV patients continues to emerge. A Japanese study sequentially evaluated LSM using SWE in HCV patients who achieved SVR with DAA therapy [63]. They reported significant differences in LSM at baseline, at end of treatment (EOT) and at SVR24, with median values (interquartile range) of 10.2 (7.7–14.7), 8.8 (7.1–12.1), and 7.6 (6.3–10.3), respectively ($P < 0.001$, baseline vs EOT; $P < 0.001$, EOT vs SVR24). In a multivariate analysis, one study found an LSM of ≥ 11 kPa, measured by SWE, to be independently associated with HCC development (risk ratio = 28.71) after SVR [64]. This data suggests SWE's potential role in risk stratification during and after HCV therapy. Although this modality of noninvasive assessment is promising, investigations remain preliminary and early for routine clinical application.

1.4. Combination tests

A combined approach with the noninvasive strategies to measure fibrosis in HCV infection has been extensively studied [65] and is commonly applied in clinical practice [2,27,66–69]. The different combinations of tests usually include two separate serum markers, or the combination of a serum marker with an imaging modality [2]. In a study population of 180 HCV patients, Leroy et al. evaluated six different noninvasive scores, and found that the combination of APRI and FibroTest could rule out significant fibrosis with a NPV of 94.1% for concordant results below the lower cutoffs (APRI <0.5 and FibroTest <0.22) [2,70]. The PPV for significant fibrosis and extensive fibrosis were 96.7% and 92.2%, respectively, for concordant results above the upper cutoffs (APRI >2 and FibroTest >0.59) [27]. Unfortunately, only 32% of individuals presented with concordant results between the two serum markers, therefore requiring many patients to ultimately undergo liver biopsy [27]. In another study with 2035 HCV patients, the sequential algorithm for fibrosis evaluation (SAFE) biopsy identified cirrhosis with 92.5% accuracy and reduced the need for liver biopsy by 81.5% [27].

A noninvasive strategy devised by Sebastiani et al. simultaneously combined FibroTest and TE, and was compared to the SAFE biopsy in a study with 302 chronic HCV infected patients [66]. The Castera algorithm, also known as Bordeaux algorithm, is based on concordant results for both tests [68]. Those with discordant results, or individuals where LSM was not obtainable, would qualify for liver biopsy [68]. In this study, for the detection of cirrhosis, the Castera algorithm showed significantly higher accuracy than SAFE biopsy (95.7% vs. 88.7%; $P < 0.0001$), but the number of saved liver biopsies was similar (78.8% vs. 74.8%; $P = \text{NS}$). The combination of Fibrometer and FibroScan (TE), termed as the FM + FS classification, has also been proposed in a study with 1785 HCV infected patients [68]. In this study, Boursier et al. found this fibrosis classification to be as accurate (86.7%) as successive SAFE biopsy or Castera algorithm, while simultaneously obviating the need for liver biopsy (0% liver biopsy). These studies, along with many others, suggest that different combinations of noninvasive tests can accurately stage liver fibrosis and prevent the need for liver biopsy prior to HCV therapy.

1.5. Liver fibrosis and its implications

The newly developed and highly effective DAA treatment protocols achieve SVR rates of above 90%, with a proven safety record (even in patients with cirrhosis) in post marketing real world analysis [69]. Even though noninvasive strategies were validated in the interferon era, the improved diagnostic capabilities in the DAA era are key to reducing the need for liver biopsy in the management algorithm for HCV infection. In the interferon era, an invasive liver biopsy to determine the exact stage of liver fibrosis, along with an interferon risk versus benefit analysis, was required to determine if the patient would be suitable for therapy. In modern times, a binary output of cirrhosis versus no cirrhosis is sufficient for standard DAA regimens as these therapies have high potency, high barrier to resistance and minimal side effects regardless of fibrosis level [57]. The idea of stage specific fibrosis assessment prior to HCV therapy is now less important than the identification of cirrhosis itself [71–73].

Identifying cirrhosis is still important as it has implications on DAA treatment duration, response to DAA's with the risk of virological relapse, as well as the important issue of future screening for varices, liver failure and HCC. For instance, randomized trial and real-world cohorts have shown a reduced response to DAA agents in the setting of cirrhosis, particularly in those who are treatment-experienced [74]. In these instances, identification of their cirrhosis status is important and can alter treatment selection

or duration. The diagnosis of cirrhosis and portal hypertension can now be achieved noninvasively in selected patients as described in the Baveno VI recommendations [57].

The identification of advanced fibrosis and cirrhosis has important prognostic value and implications for patient management during treatment and after viral eradication. Advanced liver fibrosis and cirrhosis are linked to worse liver-related outcomes in patients with HCV infection [75]. A long-term follow up study with 642 patients shows the 5-year risk of HCC in patients with cirrhosis is 22.6%, compared to only 3.2% in those without cirrhosis [76]. The stage of fibrosis also plays a role in predicting liver-related outcomes. In a study using an Alaska cohort of patients with hepatitis C, within 5 years, 1% of patients without fibrosis developed HCC compared to 13.4% of patients with cirrhosis ($P < 0.01$) [77]. A systematic review with meta-analysis of 33,000 HCV patients showed the risk of developing HCC at 5 years after achieving SVR was 2.9% in the general cohort and 5.3% in those with cirrhosis [78]. In Fig. 1, we propose the following algorithm for risk stratification and HCV management using non-invasive markers of fibrosis.

1.6. Regression of fibrosis and its implications

Identifying which patients remain at risk of liver-related complications after SVR is challenging [76]. Achieving SVR is known to reduce the risk of portal hypertension and its associated complications [79,80]. The clinical implications of fibrosis regression are controversial. Liver fibrosis regression after SVR may not portend a reduced HCC risk based on a 10-year prospective follow up study in patients treated with interferon regimens [81]. On the contrary, some evidence suggests that reversal of cirrhosis after SVR is associated with an absence of liver-related complications [82]. However, fibrosis regression after SVR is variable and certainly not ubiquitous [7]. In a study of 97 patients with SVR, liver fibrosis measured by biopsy had regressed in 44 patients (45%), progressed in 6 patients (6%), and remained stable in 47 patients (48%) [7]. In those with progressive fibrosis, the incidence of HCC was significantly higher compared to those with regression or stable fibrosis after achieving SVR (33% vs. 4% at 5 years, $P = < 0.05$) [7]. If the regression of fibrosis is to occur, it appears to be a slow process. The mean regression in fibrosis after a median of 3.7 years was -0.28 ± 0.0 unit/year. As shown, fibrosis regression remains variable after achieving SVR with antiviral therapy.

Detecting liver fibrosis noninvasively after achieving SVR has important implications for patient management and risk prediction. The identification of specific cut-offs using noninvasive modalities to predict liver-related outcomes after achieving SVR is still preliminary and has not been extensively studied to date [1]. A study of TE to evaluate liver fibrosis following HCV cure found that LSM measurements were reduced in patients with cirrhosis following SVR, even in those patients who continued to have cirrhosis on post SVR liver biopsy. The authors concluded that a cutoff of 12 kPa for cirrhosis could not be applied to cirrhotic patients who had achieved an SVR [1]. Although the American Gastroenterological Association recommends (based on very low quality of evidence) that low risk individuals without prior known cirrhosis may be considered for discharge from hepatology practice if TE is $\leq 9.5 (\pm 1)$ kPa following SVR, high risk individuals with known pre-treatment cirrhosis or with other risk factors for chronic liver disease (such as obesity, diabetes, HIV or HBV coinfection, or continued excessive alcohol use) may be misclassified as not having advanced fibrosis in 6.6% of cases and require monitoring [58]. How to correctly interpret non-invasive fibrosis assessments in patients after SVR is critical and remains an area of needed investigation.

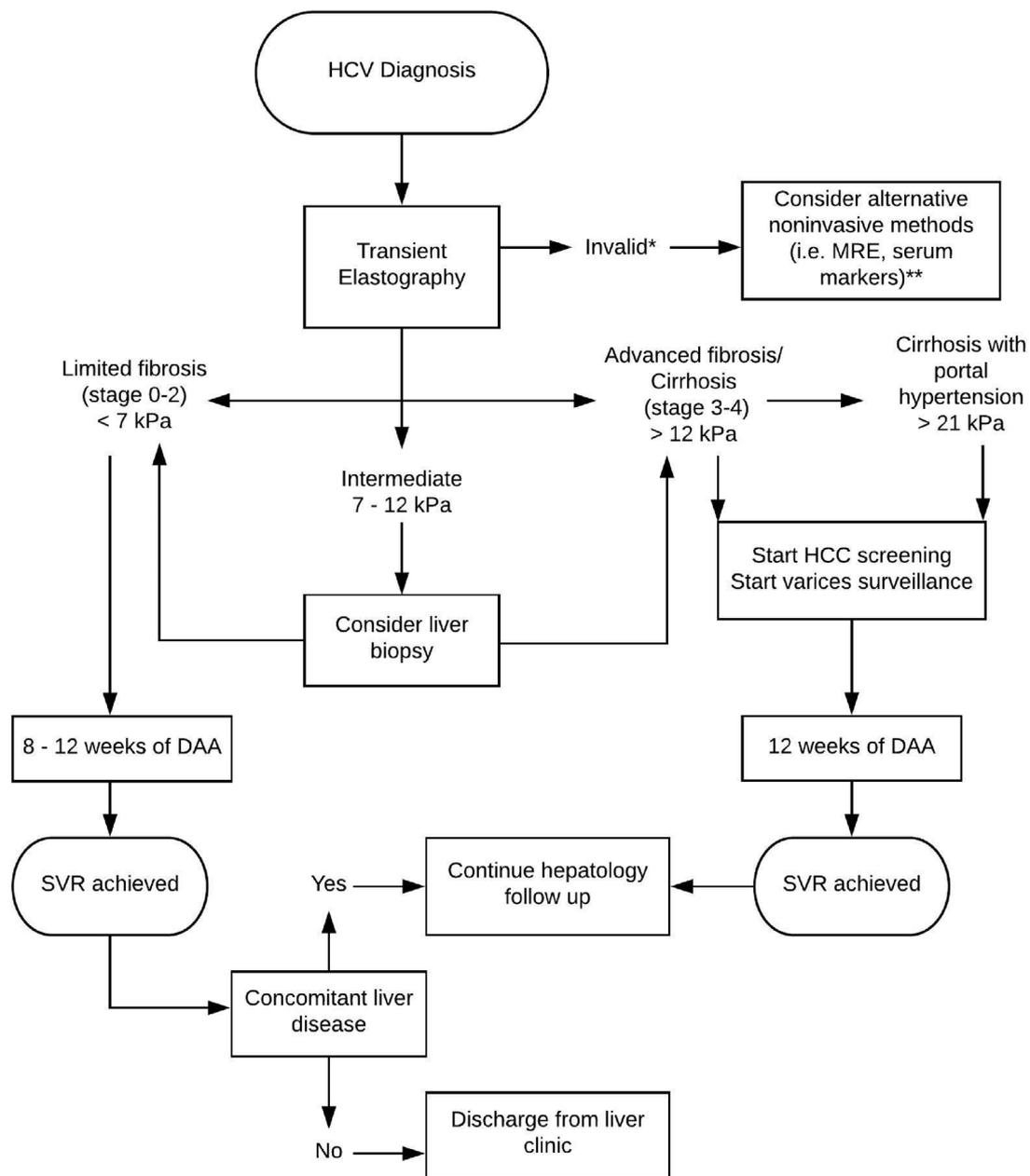


Fig. 1. A stepwise algorithm for noninvasive measurement, treatment and follow up for hepatitis C infection. HCV: hepatitis C virus, MRE: magnetic resonance elastography, kPa: kilopascals, DAA: direct acting antivirals, HCC: hepatocellular carcinoma, SVR: sustained virologic response.

*Invalid measurements can occur in patients with clinical characteristics such as abdominal obesity or ascites.

**MRE or serum markers can be considered if TE is invalid, but TE is the preferred approach due to ease of use, low cost and its applicability at the bedside.

2. Discussion

Several noninvasive modalities have been developed that have revolutionized the way we diagnose liver fibrosis. These noninvasive tests serve multiple purposes in the realm of DAA therapy for treatment of chronic HCV. The American Association for the Study of Liver Disease (AASLD) guidelines recommend risk stratification of patients with HCV infection for advanced liver disease prior to starting DAA therapy as some regimens differ based on the presence or absence of even compensated cirrhosis [83]. We hope our proposed algorithm for the use of non-invasive fibrosis markers prior to HCV treatment will serve as a guide to optimize treatment regimen decisions. The distinction between limited fibrosis and advanced fibrosis/cirrhosis is also important as those in the latter category are at higher risk of HCC, complications of portal

hypertension, and hepatic decompensation, even after achieving SVR [8,84]. These patients require routine surveillance for complications compared to those with limited fibrosis, in whom screening is not required, even after SVR.

There is limited evidence of how to use noninvasive measures in order to risk stratify patients after achieving SVR [76]. Based on the current evidence and experience, we propose an algorithm for the management of a patient who has successfully achieved SVR after DAA therapy (Fig. 1):

We recommend routine use of TE in assessing liver fibrosis level of HCV patients. If there is an invalid result on TE before or after HCV therapy, then we recommend use of a second noninvasive modality (i.e. MRE or serum marker). If the second noninvasive modality is unreliable, or if the initial TE score is in the intermediate range, we then recommend consideration of a liver biopsy. The liver biopsy

would also help characterize co-existing liver diseases that may be complicating the clinical picture.

2.1. Cirrhosis or advanced fibrosis

Patients with advanced fibrosis or cirrhosis prior to HCV therapy should be monitored by a hepatologist routinely for the appropriate surveillance measures, including HCC surveillance with routine abdominal imaging and variceal screening with endoscopy.

It is not yet known whether reductions in noninvasive fibrosis measurement after SVR portends to improved clinical outcomes. It is important to consider whether the reduced fibrosis measurement after HCV eradication is a reflection of fibrosis regression itself or inaccurate fibrosis assessment to begin with during the pre-treatment phase. For instance, fluctuations or falsely elevated VCTE score can certainly occur in the setting of ongoing hepatic inflammation and elevated ALT levels [1]. It is reasonable to monitor liver fibrosis non-invasively on an annual basis following SVR; keeping in mind that reductions may not signify true down-staging of liver fibrosis and vice versa; with additional fibrosis testing required in complex cases. Patients with advanced fibrosis, or cirrhosis, at any point in time, should continue to be monitored in the hepatology clinic on a routine basis.

2.2. Limited fibrosis

Once SVR is achieved in patients with a limited stage of fibrosis, an evaluation for concomitant liver disease should be made. If a patient has coexisting liver disease, we recommend continuing follow up with hepatology, as these patients are at higher risk of fibrosis progression despite achieving SVR. On the other hand, if the patient does not have any features of coexisting liver disease after achieving SVR, they can be safely discharged from the hepatology practice provided they have routine follow up with their primary care physician.

3. Conclusion

The success of DAA therapy in treating HCV infection has been complimented by the advent of valuable, cost-effective and reliable ways to measure liver fibrosis noninvasively in the last decade. New DAA agents treat HCV, with eradication and safety, making HCV cure a reality for many. Non-invasive markers of liver fibrosis have largely reduced the need for liver biopsy in the management of HCV infection. Appropriate use and interpretation of non-invasive markers of fibrosis will be important to making appropriate HCV treatment decisions and optimizing hepatology care following HCV cure. The effect of achieving SVR on regression of fibrosis and how to measure noninvasively remains an exciting avenue for further investigation.

Conflicts of interest

None declared.

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