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## Non-invasive diagnosis of advanced fibrosis and cirrhosis

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## Abstract

Liver cirrhosis is a common and growing public health problem globally. The diagnosis of cirrhosis portends an increased risk of morbidity and mortality. Liver biopsy is considered the gold standard for diagnosis of cirrhosis and staging of fibrosis. However, despite its universal use, liver biopsy is an invasive and inaccurate gold standard with numerous drawbacks. In order to overcome the limitations of liver biopsy, a number of non-invasive techniques have been investigated for the assessment of cirrhosis. This review will focus on currently available non-invasive markers of cirrhosis. The evidence behind the use of these markers will be highlighted, along with an assessment of diagnostic accuracy and performance characteristics of each test. Non-invasive markers of cirrhosis can be radiologic or serum-based. Radiologic techniques based on ultrasound, magnetic resonance imaging and elastography have been used to assess liver fibrosis. Serum-based biomarkers of cirrhosis have also been developed. These are broadly classified into indirect and direct markers. Indirect biomarkers reflect liver function, which may decline with the onset of cir-

rhosis. Direct biomarkers, reflect extracellular matrix turnover, and include molecules involved in hepatic fibrogenesis. On the whole, radiologic and serum markers of fibrosis correlate well with biopsy scores, especially when excluding cirrhosis or excluding fibrosis. This feature is certainly clinically useful, and avoids liver biopsy in many cases.

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**Key words:** Cirrhosis; Biomarker; Non-invasive; Fibrosis; Viral; Non-alcoholic fatty liver disease; Primary biliary cirrhosis; Autoimmune hepatitis; Hepatitis B virus; Hepatitis C virus

**Core tip:** There has been considerable research in recent years towards the development of non-invasive markers of cirrhosis. These include novel radiologic techniques, serum biomarkers and panels of fibrosis. In this review, we outline the current state of knowledge on the most commonly used radiologic and serum biomarkers of cirrhosis. The pathophysiologic principles behind the use of these markers are discussed. In addition, we focus on the evidence behind the use of these markers, and highlight their performance characteristics. This review is intended to provide an overview of the current knowledge in this area, and to encapsulate the evidence for the reader.

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## INTRODUCTION: HOW COMMON IS LIVER CIRRHOSIS?

Liver cirrhosis is an important and growing global health

problem. In the United States alone, approximately 400000 people (0.15% of the population) are estimated to have cirrhosis<sup>[1]</sup>. In 2010, cirrhosis was listed as a diagnosis in 727000 hospital discharges in the United States, while it was the primary diagnosis in approximately 101000 discharges<sup>[2]</sup>. Cirrhosis-related complications resulted in 31903 deaths in 2010, making it the 12<sup>th</sup> leading cause of mortality in the country<sup>[2]</sup>. Recent projections from the United States show that the prevalence of cirrhosis is expected to peak at 1 million patients by 2020, attributable largely to the ageing population of baby-boomers with chronic hepatitis C<sup>[3]</sup>.

## WHY IS IT IMPORTANT TO DIAGNOSE CIRRHOSIS?

Patients with non-cirrhotic chronic liver disease may have an increased mortality rate when compared to controls<sup>[4]</sup>. However, mortality and morbidity rates increase exponentially once cirrhosis develops. A large prospective study ( $n = 838$ , median follow-up 50 mo) of chronic hepatitis C (CHC) patients from Germany showed that the SMR for non-cirrhotic patients younger than 50 was 3.1, whereas cirrhotic patients had an SMR of 26.2 in the same age group<sup>[5]</sup>. Therefore, the ability to reliably rule out cirrhosis may be considered an important characteristic of any test designed to assess liver fibrosis.

The diagnosis of cirrhosis also portends an increased risk of liver related morbidity<sup>[6]</sup> as well as mortality<sup>[7]</sup>. A systematic review of 118 studies involving 23797 patients by D'Amico *et al*<sup>[7]</sup> showed a distinct increase in mortality risk with development of each successive decompensation - varices, variceal bleed and ascites. The overall survival was only 64% over a median follow-up of 31 mo.

Moreover, the rate of progression of fibrosis to liver cirrhosis can be variable. A study of 2235 treatment-naïve CHC patients showed a median time of 30 years to development of cirrhosis<sup>[8]</sup>. However, the rate of progression was faster in heavy alcohol users, older patients, males and patients with high indices of inflammatory activity on biopsy.

Liver-related mortality and decompensation is expected to continue to increase over the next decade, due to the projected increase in the number of patients with cirrhosis in the population<sup>[9]</sup>. Therefore, an accurate and timely diagnosis of liver cirrhosis is critical to identify patients in need of close monitoring, management of complications and treatment of the underlying liver disease.

## LIVER BIOPSY: A FLAWED GOLD STANDARD

Liver biopsy is the traditional gold standard for staging of fibrosis and diagnosis of cirrhosis. Under local anesthesia, a core of liver tissue is obtained for pathologic analysis. Several scoring systems exist to stage the degree of fibrosis in the biopsy specimens. These include the

Ishak, METAVIR, Scheuer and Batts-Ludwig score. The METAVIR and Ishak scores are used most commonly. The METAVIR system scores fibrosis on a 5-point scale, with F0 equating to no fibrosis, and F4 equating to cirrhosis. Patients with F2 or higher are considered to have "significant fibrosis" and patients with F3 or higher are considered to have advanced fibrosis. The Ishak system uses a 7-point scale with F0 indicating no fibrosis; F5, incomplete cirrhosis; and F6, definite cirrhosis.

However, many factors impact on the accuracy of fibrosis staging with liver biopsy. For example, diagnostic accuracy is correlated with the length of the biopsy specimen<sup>[10,11]</sup>. A study of 17 patients with CHC used explant livers to obtain whole liver fibrosis assessments, and also random biopsies of varying length, which were used to assess for fibrosis stage<sup>[11]</sup>. Core biopsies that were 25 mm or more correctly classified the fibrosis stage 75% of the time, whereas biopsies that were 15 mm had only 65% accuracy. Another study of biopsy quality in 537 CHC patients showed that only 31% of biopsies were considered "adequate" (at least 15 mm and  $\geq 5$  portal tracts) and only 14% were considered "ideal" ( $\geq 25$  mm)<sup>[10]</sup>.

The etiology of chronic liver disease (CLD) may also impact on biopsy results<sup>[12,13]</sup>. A retrospective study of NASH and CHC patients found that biopsies  $< 16$  mm had increased and significant heterogeneity in reported fibrosis stage for NASH patients, but not in HCV patients<sup>[12]</sup>. Fibrosis staging may also differ by location of biopsy<sup>[14]</sup>. A study of laparoscopic right and left lobe biopsies in 124 patients found 33.1% variation of  $\geq 1$  fibrosis stage between right and left lobes, and 2.4% had variation of  $\geq 2$  stage<sup>[14]</sup>. Significantly, 14.5% of patients were rated as stage F3 in one lobe, but F4 (cirrhotic) in another.

There is also significant intra- and inter-observer variability in the assessment of fibrosis stages. One study showed up to 10% variability in staging upon repeat assessments of the same specimen by a single observer<sup>[15]</sup>. The inter-observer variability in fibrosis assessments was assessed in a study of 30 biopsy specimens reviewed by 10 pathologists<sup>[15]</sup>. The inter-observer agreement ( $\kappa$ ) value for cirrhosis was 0.91 (excellent), the value for score of fibrosis (F0-3) was 0.78 (moderate). Inter-observer agreement was even lower for scores of disease activity ( $\kappa = 0.2-0.5$ ). Reliability of fibrosis scoring is improved with 2 pathologists reading each biopsy as a pair, although this may not be practical in the clinical setting<sup>[16]</sup>.

Complications from liver biopsy have been well characterized in a large retrospective study of over 68000 biopsies<sup>[17]</sup>. The mortality rate was found to be 9 per 100000 procedures (about 0.01%). Deaths were attributed to hemoperitoneum and occurred exclusively in patients with cirrhosis or HCC. The rate of complications in this study was found to be 278 per 100000 procedures (about 0.3%). Another retrospective review of 1000 biopsies found a complication rate of 5.9%, with 5.3% hospitalizations, mainly due to post-procedural pain or hypotension<sup>[18]</sup>.

**Table 1** Summary performance characteristics for selected serum- and radiology-based noninvasive markers for the diagnosis of cirrhosis

Test	Etiology (Ref.)	Cutoff	Sens (%)	Spec (%)	AUC	Advantage	Disadvantage
Serum markers							
APRI	HCV <sup>[59]</sup>	> 2.0	48	94	0.84	Easy to calculate	Lower diagnostic value in comparative studies
FIB-4	HCV <sup>[71]</sup>	< 1.45	74	80	0.85	Easy to calculate	Not well validated in all etiologies of CLD (e.g., Autoimmune liver disease)
		> 3.25	38	98			Patented formula (\$)
Fibrotest	HCV <sup>[59]</sup>	> 0.66	77	82	0.89	Validated in a number of etiologies; may correlate with fibrosis progression	
	HBV <sup>[64]</sup>	> 0.68	80	84	0.87		
ELF	Mixed <sup>[92]</sup>	> 0.025	91	69	0.89	Validated in a number of etiologies, may have prognostic value	Requires levels of HA, TIMP1 and PIIINP
Radiologic markers							
TE	Mixed <sup>[38]</sup>	> 15 (9-26)	83	89		Easy to use, validated in a number of etiologies, predicts complications of cirrhosis	Requires expensive equipment, less reliable in obese patients and acute hepatitis
ARFI	Mixed <sup>[48]</sup>	> 1.87	84	92	0.91	Easy to use, validated in a number of etiologies, allows measurement away from masses/lesions	Requires expensive equipment, less reliable in obese patients, smaller region of interest than standard TE
MRE	Mixed <sup>[57]</sup>	> 4.13	100	96	0.998	Highly accurate, fibrosis estimation over a much larger area than TE or ARFI	Requires expensive equipment and radiology expertise, results may change with patient positioning

APRI: AST to platelet ratio index; FIB-4: Fibrosis-4; ELF: Enhanced liver fibrosis; TE: Transient elastography; ARFI: Acoustic radiation force impulse; MRE: Magnetic resonance elastography; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CLD: Chronic liver disease.

## NON-INVASIVE ASSESSMENT OF FIBROSIS AND CIRRHOSIS

Despite its universal use in the staging of fibrosis, liver biopsy is an invasive and inaccurate gold standard with numerous drawbacks. In order to overcome the limitations of liver biopsy, a number of non-invasive techniques have been investigated for the assessment of fibrosis. This review will focus on the non-invasive diagnosis of cirrhosis using these modalities. The performance characteristics, advantages and drawbacks of selected non-invasive markers are summarized in Table 1.

## RADIOLOGIC TECHNIQUES

### Conventional ultrasound

Ultrasound (US) has become a well-established modality for the non-invasive diagnosis of cirrhosis. The progression of fibrosis in patients with chronic liver disease is detected sonographically through characteristic changes such as a coarse or nodular appearance of the parenchyma, hepatomegaly and caudate lobe hypertrophy, among others<sup>[19]</sup>. US can also detect the development of portal hypertension by measuring portal vein diameter, velocity of flow, flow reversal, ascites and splenomegaly<sup>[20]</sup>.

The performance characteristics of each of the above features have been evaluated. Early studies of the accuracy of US criteria found caudate hypertrophy (defined as ratio of caudate and right lobe) had a sensitivity of 84%, specificity of 100% and area under the curve (AUC, a measure of accuracy) of 94%<sup>[21]</sup>. However, subsequent studies have shown that these estimates were optimistic. A later study examined the performance of a 2 (nodularity and portal velocity) or 7 (nodularity, portal velocity, liver size, caudate hypertrophy, echogenicity, portal vein diam-

eter and spleen size) component score for the diagnosis of cirrhosis<sup>[22]</sup>. The sensitivity was 82.2% and 78.7%, while specificity was 79.9% and 80.1% respectively. AUC values were 80.4% and 80.2%.

The performance characteristics of each of the above features have been evaluated individually. Hepatic surface nodularity, especially detected by a linear probe, has been shown to be the most direct sign of advanced fibrosis, with reported sensitivity and specificity of 54% and 95% respectively<sup>[23]</sup>. The addition of other signs, such as caudate-right lobe ratio, increased the sensitivity but diminishes the specificity of US.

The use of additional modalities such as Doppler enhances the specificity and sensitivity of greyscale US. For example, the measurement of the “vascular index” (ratio of portal vein velocity and hepatic artery pulsatility index) using Doppler was assessed in one study<sup>[24]</sup>. At a value of 12 cm/s, the sensitivity was 97% and specificity was 93% for a diagnosis of cirrhosis. However, subsequent studies have shown mixed results, with a high degree of overlap between the stages of chronic hepatitis and limited diagnostic utility<sup>[25,26]</sup>.

Contrast enhanced US can also be used for the accurate detection of cirrhosis<sup>[27-31]</sup>. The “arrival time” of contrast agents into the hepatic vein is reduced in patients with cirrhosis. In one study, an arrival time of sulphur hexafluoride microbubble (Sonovue) contrast below 17 s had 100% sensitivity and 93% specificity for cirrhosis<sup>[30]</sup>. A review of studies using hepatic vein transit time showed a pooled sensitivity of 79% and specificity of 78%, with an AUC of 79%<sup>[31]</sup>. Contrast-enhanced US requires additional expertise and adds cost, and this may limit its availability for the routine detection of cirrhosis.

In summary, US is a cheap and widely available modality for the diagnosis of cirrhosis. Greyscale US has

moderate sensitivity and moderate-high specificity, but this can be enhanced by the use of adjuvant technologies.

### Computed tomography

Morphological findings of cirrhosis and portal hypertension have traditionally been used in the diagnosis of cirrhosis, showing high sensitivity but moderate specificity. Because computed tomography (CT) images the entire abdomen, small varices at various typical locations can easily be identified, increasing the sensitivity of the modality. In a recent report, CT was reported to have a sensitivity of 77.1% but specificity of 67.6%<sup>[32]</sup>.

More recent studies have used physiological parameters calculated from multiple measurements of enhancement during a dynamically enhanced CT studies as markers for fibrosis. For example, Van Beers *et al*<sup>[33]</sup> identified three parameters - changes in liver perfusion, arterial fraction and mean transit time of contrast that correlated well with severity of liver disease by Child-Pugh classification. Zissen *et al*<sup>[34]</sup> have demonstrated high sensitivity and specificity for increased fractional extracellular fluid space in the identification of cirrhosis. These techniques are currently investigational and need to be validated in multicenter trials. Furthermore, CT subjects the patients to ionizing radiation and intravenous contrast material, and can significantly increase the cost of the procedure, limiting its practical clinical use in assessment of cirrhosis.

### Magnetic resonance imaging

The increased fibrotic tissue within the liver leads to expansion of the extracellular fluid space and restricted movement of water, which can be measured using diffusion-weighted techniques. The same restriction results in slow washout of intravenous contrast in fibrotic areas. These principles have been exploited by magnetic resonance imaging (MRI) techniques to quantify fibrosis using Diffusion-Weighted MRI (DW-MRI) and contrast enhanced MRI<sup>[35,36]</sup>. Patel *et al*<sup>[35]</sup> showed the combination of three parameters (diffusion coefficient, time to peak and distribution volume) had a sensitivity of 85% and specificity of 100% for cirrhosis. DW-MRI can also be used to identify the stage of cirrhosis (sensitivity 89%, specificity 80%)<sup>[36]</sup>. MRI-based techniques are subject to the limited availability, and significantly increased cost when compared to US-based techniques. Furthermore, they require high degree of technical expertise, limiting their practicality in the clinical setting.

## NOVEL ELASTOGRAPHY TECHNIQUES

### Transient elastography

Transient elastography (TE) (Fibroscan; Echosens, Paris, France) is a novel technique used for the non-invasive assessment of liver fibrosis. This technique involves the use of transducer on the end of an US probe that transmits 50 MHz pressure waves through the liver tissue. The velocity of the resultant “shear wave” is measured by the US. This shear wave velocity correlates with liver stiff-

ness, thus providing an estimate of liver fibrosis.

Since its development, the use TE has been evaluated for many etiologies of chronic liver disease<sup>[37,38]</sup>. A large meta-analysis by Tsochatzis *et al*<sup>[38]</sup> included 40 studies and patients with chronic hepatitis B, C, alcohol and other causes of cirrhosis. In this analysis, TE had a pooled sensitivity of 83% and specificity of 89% for the diagnosis of cirrhosis (F4 on biopsy). A mean cutoff of 15 kPa was used in the included studies for the diagnosis of cirrhosis (range: 9-26.5 kPa).

Transient elastography can also be used to predict complications of cirrhosis, such as portal hypertension. In a large meta-analysis by Shi *et al*<sup>[39]</sup> ( $n = 18$  studies, 3644 patients), TE had 90% sensitivity and 79% specificity for the diagnosis of significant portal hypertension (defined as hepatic vein portal gradient above 10 mmHg), with an AUC of 93%. TE cutoffs used for the diagnosis of significant portal hypertension ranged from 13.6-34.9 kPa. Area under the curve for the prediction of varices and large varices were 0.84 and 0.78, respectively, in this analysis.

TE may also have a role in the post-transplant setting<sup>[40]</sup>. A meta-analysis of 6 studies enrolling post-transplant HCV patients showed an 83% sensitivity and 83% specificity of elastography in the diagnosis of significant fibrosis (F2 or greater)<sup>[40]</sup>. Cutoff values used varied from 7.1-10.1 kPa.

TE fulfills many of the requirements of an ideal non-invasive marker of cirrhosis - it is easy to perform, reproducible, and tolerated well by patients. However, the limitations of this technique include the requirement for expensive equipment, and lack of standardized cutoffs for diagnosis of fibrosis stages, as noted in the meta-analyses above<sup>[37-39]</sup>.

The diagnostic accuracy of TE is lowered in obese patients<sup>[41]</sup>. In order to improve the accuracy of readings in obese patients, an extra-large (XL) probe has been developed. This probe allows for increased reliability and validity of measurements when compared with the standard (M) probe<sup>[42]</sup>. In a study of 193 patients (35% had BMI > 30), the XL probe obtained 10 or more valid readings in 95% of patients, as opposed to 81% with the M probe. Similarly, the consumption of a meal prior to the test has been shown to elevate TE readings for up to 120 minutes following the meal<sup>[43]</sup>.

Moreover, TE readings are also elevated in the presence of active hepatitis. Studies in patients with chronic hepatitis B and C<sup>[44,45]</sup> have shown that liver stiffness readings increase in patients with elevated ALT.

Similarly, the consumption of a meal prior to the test has been shown to elevate TE readings for up to 120 min following the meal<sup>[43,46,47]</sup>. Berzigotti *et al*<sup>[46]</sup> administered a 7 mg/kg milkshake to 19 patients who underwent TE before and after the standardized meal. There was a significant increase in post meal liver stiffness readings, with an average increase of 27%.

Therefore, while TE remains a well-validated and reliable non-invasive modality for the diagnosis of cirrhosis,



these limitations should be kept into account in order to interpret the results in a meaningful manner.

### Acoustic radiation force imaging

This technique uses conventional US to generate a shear wave directly within the liver tissues. This allows the sonographer to obtain both conventional US images and also specify a region of interest (ROI) for estimation of liver stiffness. The propagation velocity of the shear wave is reported in meters per second, and correlates with the liver stiffness. The direct generation of shear wave within the liver tissue holds advantages over TE since it is not subject to the chest/abdominal wall distortion of the waves, and not affected by presence of ascites.

In a meta-analysis of 36 studies involving 3951 patients, Nierhoff *et al.*<sup>[48]</sup> showed that acoustic radiation force imaging (ARFI) had excellent accuracy for the diagnosis of cirrhosis (AUC 0.91 for F4). At a cutoff value of 1.87 m/s, ARFI had 84% sensitivity and 92% specificity for the diagnosis of cirrhosis. This analysis included patients across many etiologies of chronic liver disease (HBV, HCV, NASH, autoimmune liver diseases).

The accuracy of ARFI measurements is adversely affected by obesity<sup>[49-51]</sup>. In one study, up to 49% of patients had unreliable results with ARFI measurements when the BMI was above 30<sup>[51]</sup>.

The accuracy of ARFI has been compared with standard transient elastography using the Fibroscan device<sup>[50]</sup>. In a study of 114 patients (including 23 with cirrhosis), both modalities demonstrated comparable accuracy for the diagnosis of cirrhosis (AUC 0.99 for TE, 0.95 for ARFI). However, TE performed better than ARFI in the diagnosis of significant fibrosis (AUC 0.90 *vs* 0.77 for ARFI).

The location of the region of interest is an important variable when using ARFI to estimate liver stiffness<sup>[50]</sup>. Measurements made at least 1-2 cm below the liver capsule offer the best predictive value. The region of interest in ARFI (1-2 cm) is smaller than TE (5 cm), thus providing a smaller region of liver tissue for measurement of shear wave velocity<sup>[48]</sup>. On the other hand, the dynamic visualization of the liver parenchyma allows the placement of the region of interest directly on the liver tissue and exclusion of any liver masses from the measurements.

### Supersonic shear wave imaging

Also known as real-time shear wave elastography, this technique also generates shear waves directly within the liver tissue using the Mach cone of supersonic US waves. This technique also holds the same advantages as ARFI over TE. It also uses conventional US to simultaneously produce images the liver and measure the velocity of the shear wave, allowing calculation of the hepatic stiffness. In direct comparison to TE, supersonic shear wave imaging (SSWI) exhibits improved differentiation of mild fibrotic stages, but similar performance in detection of cirrhosis<sup>[52]</sup>. SSWI has shown mild improvement in assessment of hepatic fibrosis when directly compared to

TE and ARFI<sup>[53]</sup>.

### MR elastography

MR elastography (MRE) involves the use of a transducer placed under the rib cage of patients that transmits mechanical waves into the liver. MR imaging is performed concurrently, and the images processed to obtain shear elasticity and viscosity maps. This allows the estimation of fibrosis over a much larger area<sup>[54]</sup>.

The accuracy of MRE for the estimation of cirrhosis has been evaluated<sup>[55]</sup>. In a study of 88 patients with chronic liver disease, MRE had an AUC of 1.0 for the diagnosis of cirrhosis.

MRE can also be used to quantify the progression of steatosis to steatohepatitis and fibrosis in patients with non-alcoholic fatty liver disease (NAFLD)<sup>[56]</sup>. In a study of 58 patients with NAFLD, the mean liver stiffness was higher in patients with steatohepatitis and fibrosis than those with simple steatosis (4.16 kPa with fibrosis, 3.24 kPa with NASH and 2.51 with steatosis). In this study, MRE had an AUC of 0.93 for the diagnosis of NASH, with a sensitivity of 94% and specificity of 73%.

Huwart *et al.*<sup>[57]</sup> compared the accuracy of MRE with TE in a study of 141 patients with chronic liver disease. The success rate of MRE was 94%, significantly higher than that of TE (84%). The diagnostic accuracy of MRE was significantly higher than TE for both cirrhosis and significant fibrosis.

While MRE is highly accurate and reliable in the diagnosis of cirrhosis, it requires the use of expensive equipment, and considerable expertise. Additionally, repositioning of the patient during the study or with subsequent studies may significantly alter the diagnostic yield<sup>[58]</sup>.

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## SERUM BIOMARKERS

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Many serum biomarkers and biomarker panels have been studied for the assessment of fibrosis and diagnosis of cirrhosis. Overall, these markers are good indicators of the presence or absence of fibrosis, or the presence of cirrhosis. However, their use in distinguishing between fibrosis stages or the rate of fibrosis progression has not been well established. Similarly, the prognostic value of many serum biomarkers has not been studied.

These biomarkers can be divided into two broad categories - direct and indirect. Indirect biomarkers reflect liver function, which may decline with the onset of cirrhosis. Direct biomarkers, on the other hand, reflect extracellular matrix turnover, and include many molecules involved in hepatic fibrogenesis.

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## INDIRECT MARKERS

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### APRI

AST-Platelet Ratio Index [APRI = (AST/upper limit of normal)\*100/platelet count] is a simple and easily available biomarker panel for the estimation of fibrosis. APRI

values increase as fibrosis-induced portal hypertension results in a decline in platelet count.

APRI has been extensively validated in chronic hepatitis C. In a meta-analysis of 18 studies<sup>[59]</sup>, APRI > 2 had a specificity of 94% for the diagnosis of cirrhosis (sensitivity 48%), with a pooled AUROC of 0.84 across 40 studies. APRI > 0.5 was found to have a sensitivity of 81% and specificity of 55% (AUROC = 0.77) for the diagnosis of fibrosis ( $n = 28$  studies).

APRI has also been studied in non-alcoholic fatty liver disease (NAFLD)<sup>[60]</sup>. In a systematic review of 242 NAFLD patients, an APRI cutoff of 0.54 was found to have an AUROC of 0.75 (Sensitivity 77.3%, Specificity 70.9%).

The use of APRI is not as well validated in other etiologies. In a study of 178 Chinese CHB patients<sup>[61]</sup>, APRI > 1.0 was found to have an AUROC of 0.83 (sensitivity 75.9% and specificity 69.2%) for the diagnosis of cirrhosis. Similarly, a study of 218 patients with alcoholic liver disease (ALD) showed an AUROC of 0.67 for cirrhosis<sup>[62]</sup>. In this study, APRI had lower predictive value than Fibrotest and Hepascore (described below). In addition, APRI was found to be of little prognostic value in this cohort, with an AUROC of 0.60 for survival or non-liver related mortality.

Overall, while APRI is an inexpensive and readily accessible marker, its accuracy has not been clearly established over a broad range of etiologies. It may also have lower diagnostic and prognostic value than other serum biomarkers, especially in ALD.

### Fibrotest

Fibrotest (marketed as Fibrosure in the US) is a patented biomarker panel using 5 biochemical markers and 2 clinical parameters<sup>[63]</sup>. These include alpha-2 macroglobulin, haptoglobin, total bilirubin, apolipoprotein-A, GGT, age and gender. Using a patented formula, these biomarkers are combined to yield a numerical value between 0.0 and 1.0. The resulting score correlates with METAVIR fibrosis stages.

Fibrotest was originally developed using a population of 205 HCV patients, and validated in 134 patients<sup>[63]</sup>. Chou *et al.*<sup>[59]</sup> conducted a meta-analysis of 9 studies using Fibrotest in CHC. The pooled AUROC for the diagnosis of cirrhosis was 0.89 (sensitivity 56%, specificity of 81% at cutoff > 0.75; sensitivity 77%, specificity 82% at cutoff > 0.66). Similarly, a study of 194 CHB patients showed an AUROC of 0.87 for diagnosis of cirrhosis (sensitivity 80%, specificity 84% at cutoff > 0.68)<sup>[64]</sup>.

Fibrotest has subsequently been validated in several etiologies of cirrhosis. Poynard *et al.*<sup>[65]</sup> conducted a meta-analysis of 30 studies ( $n = 6378$  patients) including patients with CHC, CHB, ALD, and NAFLD. Overall, Fibrotest had an AUROC of 0.84, with no significant difference between etiologic categories. This study also demonstrated that Fibrotest was moderately accurate in distinguishing between adjacent fibrosis stages (*e.g.*, AUROC 0.69 for F3 vs F4), when compared to biopsy

(AUROC = 0.82). The authors concluded that Fibrotest is a viable alternative to liver biopsy in the diagnosis and staging of fibrosis.

The combination of Fibrotest with transient elastography has also been assessed<sup>[66]</sup>. In this study, 183 patients with CHC underwent Fibrotest, TE and liver biopsy. The AUROC for the diagnosis of cirrhosis was 0.87 for Fibrotest alone, but 0.95 with the combination of TE and Fibrotest. When Fibrotest and TE results were concordant, liver biopsy confirmed the diagnosis of cirrhosis in 94% of patients, suggesting that the combination of these two tests may be used to avoid liver biopsy in a large proportion of patients.

In addition to its use as a diagnostic test, Fibrotest may also have value in monitoring fibrosis progression. Poynard *et al.*<sup>[67]</sup> studied the progression of fibrosis in 2472 patients with chronic liver disease of various etiologies. Fibrotest and liver biopsy had a high degree of concordance for the estimation of liver fibrosis progression (intraclass correlation coefficient 0.961). Therefore, the authors concluded that Fibrotest may be used for the monitoring of liver fibrosis progression, avoiding the need for repeated biopsies.

Fibrotest has been combined with ALT to yield a newer measure, the Actitest. This measure has been validated for the diagnosis of cirrhosis in CHC, and has the added advantage of correlating with histologic necroinflammatory activity grade. A meta-analysis of 6 studies showed that Actitest had an AUROC of 0.79 for histologic activity grade, and performed significantly better than ALT<sup>[68]</sup>.

### FIB4

FIB4 is a biomarker panel using Age, AST, platelet count and ALT [ $FIB4 = (age * AST) / (Platelets * \sqrt{ALT})$ ]<sup>[69]</sup>. This marker was originally developed and validated in a cohort of HIV/HCV co-infected patients<sup>[70]</sup>. In a study of 832 patients, FIB4 > 3.25 had a specificity of 97% for the diagnosis of cirrhosis (AUROC = 0.76). The authors estimated that 71% of biopsies could be avoided by using FIB4 in this cohort.

FIB4 was subsequently validated in a series of 592 patients with CHC<sup>[71]</sup>. In this study, a value > 3.25 had an AUROC of 0.91 for cirrhosis, while a value < 1.45 had a sensitivity of 74% for excluding severe fibrosis. These results have been validated in other studies, showing that FIB4 > 3.25 has a high specificity (92%) and predictive value (AUROC = 0.87) for the diagnosis of cirrhosis<sup>[59,69]</sup>.

In addition to its use in HCV, FIB4 is also a useful marker in NAFLD<sup>[72]</sup>. In a series of 541 adults with NAFLD, FIB4 had an AUROC of 0.8, superior to other markers of fibrosis, and could correctly avoid a biopsy in approximately 60% of patients.

### NAFLD fibrosis score

The NAFLD fibrosis score (NFS) is comprised of diabetes/impaired fasting glucose, age, AST, ALT, platelets, BMI and albumin<sup>[73]</sup>. The NFS was developed and vali-

dated in a series of 733 patients<sup>[74]</sup>. NFS had an AUROC of 0.84, with 98% specificity for advanced fibrosis/cirrhosis above a value of 0.676. The authors estimated that biopsy could be avoided in 75% of patients in this study. A meta-analysis of 13 studies shows a pooled AUROC of 0.85 for the diagnosis of advanced fibrosis using the NFS<sup>[75]</sup>.

### Fibroindex

Fibroindex consists of platelet count, AST and GGT. It was developed and validated in a cohort of 360 patients with CHC (240 development cohort, 120 validation cohort)<sup>[76]</sup>. In this study, the AUROC of fibroindex was 0.82 for significant fibrosis. In validation studies, the pooled AUROC for cirrhosis was 0.86 ( $n = 5$  studies)<sup>[59]</sup>.

## DIRECT MARKERS

### Hyaluronic acid

Hyaluronic acid (HA) is an unbranched, high molecular weight glycosaminoglycan that is found in the extracellular matrix. It enters the circulation *via* the lymphatic system during matrix turnover, and is rapidly taken up and degraded in the liver through hepatic endothelial cells. Elevated HA levels may reflect increased production of HA within a fibrotic liver, or reduced clearance of circulating HA. Serum HA concentrations may correlate with both inflammatory activity and fibrotic stages in the liver.

The utility of HA has been studied in CHC. In a study of 486 CHC patients, cirrhotic patients had a significantly higher circulating HA level than non-cirrhotic patients (382 mcg/L *vs* 110 mcg/L)<sup>[77]</sup>. An HA level < 60 mcg/L excluded cirrhosis (Sensitivity 98%), while a score > 110 mcg/L had a 78% specificity and AUROC of 0.79 for cirrhosis.

HA has also been studied in ALD. In a study of 45 patients with ALD, HA correlated with both fibrosis stage as well as inflammatory activity (AUROC = 0.91 for presence of fibrosis)<sup>[78]</sup>. Similar performance characteristics were seen in a study of 79 patients with NAFLD, with an AUROC of 0.92 for cirrhosis (sensitivity 85%, specificity 79% at cutoff > 46.1 mcg/L)<sup>[79]</sup>.

HA has also been combined with indirect markers (bilirubin, GGT, alpha-2 macroglobulin), age and gender, to formulate the Hepascore. This panel was developed and validated in 221 patients with CHC<sup>[80]</sup>. Hepascore had an AUC of 0.89 in the validation set for the diagnosis of cirrhosis.

Subsequent studies have validated the use of Hepascore, with studies mainly in CHC patients. Hepascore has a pooled AUROC of 0.89 ( $n = 8$  studies) for the diagnosis of cirrhosis (sensitivity 72%, specificity 86%, cutoff > 0.80)<sup>[59]</sup>.

### PIIINP

PIIINP (amino terminal of serum procollagen III peptide) is a marker of collagen turnover. Increased levels occur with tissue repair and fibrosis. It has been studied

as a non-invasive marker for liver fibrosis, with the earliest studies in primary biliary cirrhosis (PBC)<sup>[81,82]</sup>. In these studies, raised PIIINP was found to correlate with the histological stage of PBC and degree of cholestasis. PIIINP levels were also elevated in patients on chronic methotrexate therapy, with levels being particularly increased in patients with fibrosis or cirrhosis<sup>[83]</sup>.

PIINP has also been studied in patients with NAFLD<sup>[84]</sup>. In this study, PIIINP was the only biomarker that distinguished between simple steatosis and NASH. It also correlated with the NAFLD Activity Score (NAS) as well as its components. Similar results have been seen in patients with alcoholic liver disease, with PIIINP values increased in patients with septal fibrosis or cirrhosis<sup>[85]</sup>.

Among patients with viral hepatitis, PIIINP was found to be an independent predictor of cirrhosis<sup>[86]</sup>. In a study of 280 patients (121 development, 159 validation), the authors found the combination of platelet count and PIIINP to have an AUC of 0.88 for cirrhosis, showing better diagnostic accuracy than APRI, FIB4 and enhanced liver fibrosis (ELF) scores.

### TIMP-1

The development of hepatic fibrosis represents an imbalance between collagen production and degradation, with decreased levels of serum collagenase. Tissue inhibitors of metalloproteinase are a family of enzymes that inactivate collagenase (and other metalloproteinase). The levels of TIMP-1 were found to be higher in alcoholic patients with fibrosis and cirrhosis compared to those with steatosis alone<sup>[85]</sup>.

TIMP-1 was also studied in a cohort of 194 patients with CHC<sup>[87]</sup>. TIMP-1 correlated significantly with fibrosis stage, with an AUROC of 0.82 for the diagnosis of extensive fibrosis (cutoff 1300 ng/mL, sensitivity 75%, specificity 70%). Among patients with CHB, TIMP-1 correlated significantly with both inflammatory activity and fibrosis stage in one study<sup>[88]</sup>. In this study, TIMP-1 had an AUROC of 0.92 for advanced fibrosis (> F2), with better accuracy than other direct markers of fibrosis.

### YKL-40

YKL-40 (chondrex) is a mammalian member of the bacterial Chitinase enzyme family. It is thought to have a role in extracellular matrix remodeling, and may function as a growth factor for connective tissue and endothelial cells<sup>[89]</sup>. Levels of YKL-40 have been found to correlate with the presence of fibrosis in ALD<sup>[89]</sup>. YKL-40 may also carry prognostic value, as patients with elevated YKL-40 were found to have lower survival in this study.

YKL-40 has also been studied in CHC, with one study showing an AUROC of 0.79 for the diagnosis of cirrhosis (Sensitivity 80%, Specificity 71%)<sup>[90]</sup>. YKL-40 levels also declined with interferon therapy, in both responders and non-responders<sup>[90]</sup>. In another study of 132 CHC patients, the AUROC of YKL-40 for cirrhosis was 0.70, lower than other serum markers such as HA and Fibrospect<sup>[91]</sup>.



**ELF**

The ELF score was developed in a cohort of 1021 patients with chronic liver disease<sup>[92]</sup>. It combined age, HA, TIMP1 and P3NP. The model predicts cirrhosis with an AUROC of 0.89 (sensitivity 90%, specificity 69%). The AUROC of ELF was particularly high in patients with ALD or NAFLD (0.87-0.94). This was validated in a further study using a modified ELF (without age), with an AUROC of 0.90 for severe fibrosis in NAFLD patients<sup>[93,94]</sup>.

The ELF score has been validated in both CHB and CHC, with AUROC values of 0.85 (CHC) and 0.86 (CHB) for severe fibrosis (> F3)<sup>[95,96]</sup>. In patients with CHB, ELF performed as well as TE for prediction of significant fibrosis (> F2), although TE was superior for prediction of severe fibrosis<sup>[96]</sup>.

**CONCLUSION**

The development of cirrhosis is a significant clinical landmark in patients with chronic liver disease. It portends an increased risk of morbidity, and declining probability of survival. The diagnosis of cirrhosis using liver biopsy carries a small but definite risk of complications. It is also prone to variability in the assessment of fibrosis stage depending on biopsy size, location and pathologist interpretation.

The non-invasive assessment of fibrosis and cirrhosis attempts to overcome some of the drawbacks of liver biopsy - by eliminating the risk of peri-procedural complications. On the whole, radiologic and serum markers of fibrosis correlate well with biopsy scores, especially when excluding cirrhosis (F4 or F < 4) or excluding fibrosis (F0 *vs* F > 0). This feature is certainly clinically useful, and avoids liver biopsy in many cases. However, the accurate distinction of stage of fibrosis is less reliable with these modalities. In addition, the progression or regression of fibrosis may not be easily detectable with many non-invasive markers, since their use has not been universally validated in this context. Future research in this area may include prospective studies using panels of serum and/or radiologic markers of fibrosis. Further research on the pathophysiology of liver fibrosis may identify novel markers that are able to accurately detect both progression and regression of liver fibrosis.

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