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TOPIC HIGHLIGHT

2015 Advances in Alcoholic fatty liver disease

Non-invasive assessment of liver fibrosis in patients with alcoholic liver disease

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Abstract

Alcoholic liver disease (ALD) consists of a broad spectrum of disorders, ranging from simple steatosis to alcoholic steatohepatitis and cirrhosis. Fatty liver develops in more than 90% of heavy drinkers, however only 30%-35% of them develop more advanced forms of ALD. Therefore, even if the current "gold standard" for the assessment of the stage of alcohol-related liver injury is histology, liver biopsy is not reasonable in all patients who present with ALD. Currently, although several non-invasive fibrosis markers have been suggested as alternatives to liver biopsy in patients with ALD, none has been sufficiently validated. As described in other liver disease, the diagnostic accuracy of such tests in ALD is acceptable for the diagnosis of significant fibrosis or cirrhosis but not for lesser fibrosis stages. Existing data suggest that the use of non-invasive tests could be tailored to first tier screening of patients at risk, in order to diagnose early patients with progressive liver disease and offer targeted interventions for the prevention of decompensation. We review these tests and critically appraise the existing evidence.

Key words: Transient elastography; Cirrhosis; Prognosis; Histology; Collagen proportionate area; Fibrotest; AST-to-platelet ratio index; Diagnostic accuracy; Cost-effectiveness; Serum fibrosis markers

Core tip: Although there has been an explosive development and validation of non-invasive fibrosis tests particularly in viral hepatitis, data on patients with alcoholic liver disease are still scarce. We review these tests and critically appraise the existing literature. Evidence suggests that such tests could be tailored to first tier screening of patients at risk, in order to diagnose early patients with progressive liver disease and offer targeted interventions for the prevention of decompensation.

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INTRODUCTION

Chronic liver disease is one of the main causes of morbidity and mortality worldwide, as its most relevant complications, namely cirrhosis and liver cancer, account for approximately 2% and 1.4% of all deaths, respectively[1,2]. Excessive alcohol consumption is a major risk factor for chronic liver disease in industrialized countries, and is the predominant cause of liver disease in 48% cases of cirrhosis in the United States[3].

Alcoholic liver disease (ALD) is defined by anamnestic history of daily alcohol intake of at least 30 g and 20 g for men and women respectively, associated with evidence of liver injury[1].

ALD consists of a broad spectrum of disorders, ranging from simple fatty liver to more severe forms, namely alcoholic steatohepatitis (ASH) and cirrhosis, leading to life-threatening complications such as hepatocellular carcinoma (HCC) and liver failure. Fatty liver develops in more than 90% of heavy drinkers, however only 30%-35% of them develop more advanced forms of ALD. This suggests the role of other contributing factors, such as female sex, obesity, drinking patterns, dietary factors, cigarette smoking and non-sex-linked genetic factors. In particular, genetic factors such as the polymorphism of the patatin-like phospholipase domain-containing protein 3 are currently the focus of further research[3].

Early detection of cirrhosis is important in patients with ALD, as abstinence can prevent the advent of complications and improve prognosis[4,5]. In a cohort of 466 patients with ALD cirrhosis, 1-year mortality was 17% in the absence of baseline complications, progressively increasing to 20%, 29% and 64% in the presence of variceal bleeding, ascites, and encephalopathy, respectively[6]. Abstinence improves survival in patients with established ALD; in a study including 283 patients with ALD cirrhosis and a 5-year follow-up, a significant difference in survival between abstainers and drinkers was demonstrated, with corresponding rates of 63% and 45% respectively[7]. These data were confirmed by Verrill *et al*[8] in a 7-year follow-up of 100 patients with alcoholic cirrhosis.

The current "gold standard" for the assessment of alcohol-related liver injury is histology, obtained through liver biopsy. The histological examination provides information about liver architecture, presence and extent of steatosis, necroinflammation and fibrosis. Nevertheless, it is an invasive procedure with some limitations. Firstly, it is subject to sampling errors and intra and inter-observer interpretation variability, mainly due to the small portion of liver examined. Secondly, it is associated with patient discomfort and a small but significant risk of severe complications, such as hemobilia or bleeding[9].

Therefore, although liver biopsy remains essential in selected cases, there has been a growing interest in non-invasive methods for the assessment of liver fibrosis.

LIVER FIBROSIS AND STAGING ASSESSMENT

The fibrogenic process is a maladaptive wound-healing response to a generic liver injury characterized by excessive production and accumulation of collagen and other extracellular matrix proteins by activated hepatic stellate cells and portal fibroblasts[3,10]. When an imbalance between extracellular matrix production and degradation occurs, fibrosis progresses[11].

In ALD, fibrosis begins in the perivenular regions and extends to portal tracts, leading to the formation of central-portal or portal-portal bridging fibrosis. If the alcoholic injury persists, fibrosis and hepatocyte regeneration result in nodule formation and finally in cirrhosis[10].

Histological examination estimates fibrosis by using a semi-quantitative "staging" scoring system that takes into account both fibrosis and architectural changes[12,13]. Currently different histological semi-quantitative scoring system are available, such as the Ishak and METAVIR scores for viral hepatitis or the Brunt and Kleiner score for non-alcoholic fatty liver disease. These classification systems use numerical categorical labels to describe histological features such as steatosis or necroinflammation. One of their major limitations is the assignment of fixed numerical scores to continuous histological variables, so that the numbers provide more a descriptive feature rather than an actual measurement. Nevertheless, there is no direct correlation of these scoring labels with the amount of fibrosis[12]. This limitation is reflected in the development and evaluation of non-invasive fibrosis markers, where the continuous value provided by the non-invasive fibrosis test is used for the diagnosis of the semi-quantitative stage that describes both architecture and distribution of fibrosis, and thus probably results in a higher number of misclassifications (Table 1).

Recently, a quantitative method of measuring fibrous tissue, through digital image analysis of the proportion of collagen in liver tissue, namely collagen proportionate area (CPA), has been developed[12-14]. CPA is a direct measure of the amount of fibrosis in the liver and could be better used for the validation of non-invasive fibrosis markers but also for the evaluation of future anti-fibrotic treatment.

Table 1 Non-invasive serum tests for the assessment of liver fibrosis and corresponding stages of alcoholic liver disease diagnosed

Test	Variables	ALD stage assessed
AST:ALT ratio	ALT, AST	≥ F1, F4
HA	HA	F4
PGA	PT, GGT, apolipoprotein-A1	F4
PGAA	PT, GGT, apolipoprotein-A1, α2-macroglobulin	
FibroTest®	Haptoglobin, α2-macroglobulin, apolipoprotein-A1, bilirubin, GGT	≥ F3, F4
FibrometerA®	Age, weight, glucose, AST, ALT, PLT count, ferritin	≥ F3, F4
FIB-4	Age, AST, ALT, platelet count	≥ F3
Hepascore®	Age, sex, bilirubin, GGT, α2-macroglobulin, HA	≥ F3, F4
APRI	AST, platelet count	≥ F2, F4
ELF test™	HA, PIIINP, TIMP-1	≥ F3, F4
Forns index	Age, platelet count, total cholesterol, GGT	≥ F3, F4

ALD: Alcoholic liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; GGT: γ-glutamyl transpeptidase; PLT: Platelets; PIIINP: Terminal peptide of procollagen Ⅲ; TIMP-1: Tissue inhibitor of metalloproteinase 1; HA: Hyaluronic acid.

NON-INVASIVE FIBROSIS TESTS

A diversified set of both serum and imaging potential markers has been developed for the non-invasive assessment of liver fibrosis. Serum biomarkers are classed as indirect (class Ⅱ) or direct (class Ⅰ). The development of advanced imaging technique has led to the availability of additional tools to stage liver fibrosis. The advantages of these new methods are the widespread availability, the non-invasiveness and the high reproducibility. Therefore, when validated as sufficiently accurate, they represent a perfect tool for risk stratification, staging fibrosis and long-term follow-up of patients.

Serum biomarkers

Class Ⅱ serum biomarkers or indirect fibrosis tests: Class Ⅱ biomarkers consist of routinely performed serological tests, which evaluate common altered liver parameters, such as transaminases, platelet count or albumin. They are not surrogate markers of matrix turnover or the fibrogenic process in the liver, but rather reflect hepatic function or inflammation. They are usually combined into score systems or panels where other demographic features are included, such as presence of diabetes or age, in order to better classify fibrosis stages[15-17]. These panels have a high and a low cut-off for the diagnosis of a specific fibrosis stage, in order to minimize the number of false positive and false negative respectively. Therefore, a number of patients fall in the "indeterminate zone" between the two thresholds, so that additional investigations to classify such patients are required.

Class Ⅰ serum biomarkers or direct fibrosis tests: Class Ⅰ biomarkers reflect the products derived from the turnover of the extracellular matrix during the fibrogenic process. During this process, there is a consistent increase in the serum levels of fibrogenic cytokines (*e.g.*, tumour-growth factor β), extracellular matrix components [*e.g.*, hyaluronic acid (HA)], degradation products (*e.g.*, procollagen Ⅳ C peptide), and enzymes involved in these processes (*e.g.*, tissue inhibitor of metalloproteinases TIMP-1)[15]. Such biochemical tests are currently performed in designated laboratories and are usually part of complex panels.

IMAGING TECHNIQUES

Ultrasound, CT and MRI can only detect the presence of hepatic steatosis or signs of cirrhosis and portal hypertension, with little contribution to the identification of patients with less advanced stages of fibrosis. Therefore, in recent years new imaging techniques have been developed in order to overcome this limit and emerging data are accumulating, particularly in viral hepatitis. The architectural changes in the liver driven by inflammation and deposition of fibrotic tissue lead to alterations in the microstructure reflected by an increase in the liver stiffness. This can be measured by using elastography principles, which are based on the propagation of a mechanical share wave through the liver parenchyma; the propagation velocity reflects the liver stiffness. Moreover, MRI technique also adapted to assess hepatic fibrosis by modifying phase-contrast imaging sequence to detect the shear waves within the liver.

Transient elastography (TE) or FibroScan® (Echosens; Paris, France) was the first imaging modality used to detect liver fibrosis. It is an ultrasound-based technique that uses an ultrasonic transducer probe (5 MHz), which emits low-frequency vibrations into the liver, creating a propagating shear wave. The latter is detected by a pulse-echo acquisition, which then calculates its velocity. The results are expressed in Kilopascals (kPa) and the final value is the mean of ten valid measurements. In order to ensure a reliable determination of liver stiffness, an interquartile range for measurements within 30% and ratio of success rate of measurements > 60% are required[18]. Liver stiffness is measured in a volume of approximately 1 cm wide and 4 cm long, corresponding to nearly 1/500 of the whole liver volume, thereby representing a sample 100 times greater than the one obtained from a liver biopsy.

The results range from 2.5 to 75 kPa, however a validation of exact stiffness cut-offs for specific fibrosis stages is still lacking[19]. Liver stiffness cut-offs for the diagnosis of extensive fibrosis or cirrhosis could be different according to the cause of the underlying

liver disease, possibly because liver stiffness mainly reflects the amount of liver fibrosis without taking into consideration its distribution within the liver, which the fibrosis staging systems are based on[20].

Fibroscan® has important limitations that need to be taken into account. Firstly, it is technically difficult in patients with visceral obesity, elevated BMI or narrow rib interspaces. Secondly, stiffness values are artificially increased in the presence of congestive heart failure, acute hepatitis, infiltrative liver disease like amyloidosis or if the measurement is performed post-prandially. In a 5-year prospective study by Castéra *et al*[21], which included 13369 patients, the probability of failure and/or unreliable results of Fibroscan® was 18%; this failure was independently associated with obesity, in particular increased waist circumference, and limited operator experience (< 500 examinations performed). The rate of unreliable results is not taken into account when the accuracy of TE is reported in studies, thereby resulting in an overestimation of its performance. A new XL probe for obese patients results in different stiffness cut-offs than the M probe and is still undergoing validation.

Acoustic radio force impulse (ARFI) evaluates the elastic properties of a hepatic region of interest while performing a real-time B-mode conventional hepatic ultrasonography, so that large blood vessels or ribs could be avoided. The elastography system is directly integrated on a standard ultrasonography device (Acuson 2000/3000 Virtual Touch™ Tissue Quantification, Siemens Healthcare, Erlangen, Germany) and short acoustic high-intensity impulses with a fixed frequency of 2.67 MHz are sent into the tissue inducing a tissue displacement and the propagation of shear waves away from the region of excitation. The propagation velocity of these shear waves is expressed in m/s and correlates to the tissue stiffness. The tissue displacements are inversely proportional to the stiffness of the tissue, so that a stiffer region of tissue exhibits smaller displacements than a more compliant region[22]. A high correlation between ARFI elastography and Fibroscan® in staging of liver fibrosis has been demonstrated[23]. ARFI performance seems not to be affected by the presence of hepatic steatosis, whereas the influence of the inflammatory activity in the liver has been confirmed[24].

Supersonic Shear Imaging (SSI), also named ShearWave™ elastography, is a new technique based on the measurement of the velocity of a local shear wave through soft tissues. It uses an ultrasound transducer (Aixplorer, Supersonic Imagine, Aix-en-Provence, France), which emits a series of pulse waves at increasing depths, using a very wide frequency band ranging from 60 to 600 Hz. By generating a real-time colour mapping of the elasticity of the tissue explored coupled with a B-mode image, SSI provides a quantitative imaging of the tissue elasticity. The final value is the average the measurement obtained by selecting the region of interest by using both B-mode and SWE images[25,26]. Unlike Fibroscan, there are no established quality criteria for measurements using ARFI or SSI.

Magnetic resonance elastography (MRE) combines images produced by a traditional magnetic resonance (MR) system with a modified phase contrast technique able to depict the propagation of acoustic shear waves generated by a pneumatic driver. Elasticity values are expressed in KPa and are obtained as mean values measured in a region of interest within the liver[27]. This technique is still undergoing validation and is not used in routine clinical practice.

NON-INVASIVE ASSESSEMENT OF LIVER FIBROSIS IN ALD

Even if data are accumulating on the use of non-invasive tests for the assessment of liver fibrosis in ALD, nevertheless a small number of studies is currently available on such patients compared to other causes of liver disease. Therefore, although non-invasive fibrosis tests have greatly reduced the need for liver biopsy, particularly in patients with HCV, the evidence is still scant in ALD (Table 2).

Serum markers

Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio includes AST and ALT. Values > 1, and especially > 2, are highly suggestive of an alcoholic aetiology of liver disease or the presence of cirrhosis[28,29].

The first serum panel used and validated for the detection of cirrhosis among drinkers is the PGA index, which consists of prothrombin index (PT), gamma glutamyl transferase (GGT) and Apolipoprotein A1[30]. Subsequently α2 macroglobulin has been added to form the PGAA index. PGAA was tested in a cohort of 525 alcoholic patients with different histological stages of fibrosis and performed better than PGA in detecting significant fibrosis or cirrhosis (correct classification in 70% of PGAA and 65% of PGA, $P < 0.001$). The derived PGAA cut-offs for excluding or diagnosing cirrhosis were $\leqslant 3$ and $\geqslant 9$ respectively. Moreover, in a sub-analysis of asymptomatic patients ($n = 316$), a PGAA cut-off of 7 had a sensitivity of 89% and specificity of 79% for the diagnosis of cirrhosis, suggesting a potentially important role in detecting early cirrhosis among drinkers[31].

APRI (AST-To-platelet ratio index) includes AST and platelet count as variables. It is calculated as (AST/upper limit of normal range)/platelet count (10^9/L) X 100. Wai *et al*[32] developed this index in a cohort of 270 HCV mono-infected patients and showed than an APRI cut-off of < 1.0 excluded cirrhosis with a negative predictive value of 98%, whereas a score > 2 was predictive of cirrhosis with a positive predictive value of 93%. On the other hand, cut-offs of < 0.5

Table 2 Non-invasive serum tests to diagnose fibrosis in patients with alcoholic liver disease and corresponding diagnostic indexes

Test	Cut-offs	F3			F4		
		Sensitivity	Specificity	AUROC	Sensitivity	Specificity	AUROC
PGA	< 2	NA	NA	0.84	0%	83%	NA
	> 9	NA	NA	NA	86%	100%	0.89
PGAA	< 3	NA	NA	0.86	NA	NA	NA
	> 12	NA	NA	NA	NA	NA	0.83
Hyaluronic acid, μL	> 55	83.0%	69%	NA	NA	NA	NA
	> 60	NA	NA	NA	100%	60%-86%[2]	NA
	> 100	NA	NA	NA	89%	87%	NA
	> 250	NA	NA	NA	100%	69%	0.78
APRI	< 0.5	NA	NA	NA	NA	NA	NA
	> 1.5	13.2%	77.6%	0.43-0.7[2]	NA	NA	NA
	< 1	NA	NA	NA	NA	NA	NA
	> 2	9.4%	96.6%	NA	16.9%	86.4%	0.56-0.79[2]
FIB-4	< 1.45	NA	NA	0.7	NA	NA	0.8
	> 3.25	NA	NA	0.7	NA	NA	0.8
FibroTest®	< 0.3 (0.3-1.58[1])	84.0%	66%	0.79	100%	50%	0.84
	> 0.7 (0.7-1.0[1])	55.0%	93%	0.83	91%	87%	0.94
FibroMeter®	NA	91.8%	92.3%	0.82-0.88[2]	91.8%	92.3%	0.85-0.94[2]
ELF test™	< 0.431	93.3%	100%	0.94	93.3%	100%	0.94
	> 9.5	74.4%	92.4%	NA	74.4%	92.4%	NA
Hepascore®	NA	NA	NA	0.76-0.83[2]	NA	NA	0.76-0.92[2]
Forns	NA	NA	NA	0.38	NA	NA	0.38

[1]A single cut-off has not been validated; [2]A single value has not been proposed. NA: Not available; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AUROC: Area under receiver operator characteristic curve; GGT: γ-glutamyl transpeptidase; PLT: Platelets; PT: Prothrombin time; PIIINP: Terminal peptide of procollagen Ⅲ; TIMP-1: Tissue inhibitor of metalloproteinase 1; APRI: Aspartate aminotransferase to platelets ratio; ELF: Enhanced liver fibrosis.

and > 1.5 excluded and confirmed the presence of significant fibrosis (METAVIR F2), respectively. Conversely, poorer results have been found in patients with ALD, probably due to the direct effect of alcohol on platelet count and AST[33]. In a cohort of 507 patients with ALD, APRI values of > 1.5 had sensitivity and specificity of 13.2% and 77.6% respectively for the detection of significant fibrosis, and 16.9% and 86.4% respectively for the diagnosis of cirrhosis at a cut-off of 2, thus suggesting a limited utility in clinical practice[33]. The relatively poor diagnostic performance of APRI was confirmed in a comparative study of TE and non-invasive serum tests in a cohort of 103 alcoholic patients. APRI yielded the lowest AUROC at 0.56, while FibroTest and PGAA had AUROCs of 0.84 and 0.83 respectively[34].

The Forns index is based on four routine clinical variables: age, platelet count, cholesterol levels and GGT. It has been developed to predict advanced fibrosis in a cohort of 476 chronic C hepatitis patients[35]. Both APRI and Forns scores showed low performance in detecting both advanced fibrosis and cirrhosis in a cohort of 214 patients with ALD, with AUROCs of 0.38 and 0.59 for the former and 0.67 and 0.38 for the latter, respectively[36]. Similarly, in a cohort of 49 patients with ALD, TE was significantly better for diagnosing advanced fibrosis than APRI and Forns, with corresponding AUROCS of 0.766, 0.611 and 0.648[37].

The performance of single direct serum markers has also been studied in patients with ALD. Of them, more data is available on HA. In a systematic review by Parkes *et al*[38], there were 15 identified studies on HA in ALD, of which only 7 reported cut-offs for the identification of severe fibrosis or cirrhosis. Nevertheless, the number of participants was small (range *n* = 70-247) and varying cut-offs for the diagnosis of cirrhosis were provided (60-300 μg/L). Sensitivity and specificity ranged from 87%-100% and 60%-89%, while only 4 studies provided AUROC values (median 0.79, range 0.69-0.93). Overall, HA was better at excluding severe fibrosis/cirrhosis rather than confirming it, and better in the detection of cirrhosis compared to milder degrees of fibrosis. In particular, in the study of Plevris *et al*[39] including 70 alcoholic patients, a threshold of HA > 100 μg/L had a 89% specificity and 87% sensitivity for diagnosing cirrhosis, with the specificity increasing to 96% for cut-offs of > 300 μg/L, thus reliably ruling out cirrhosis despite the small number on patients considered. Conversely, Tran *et al*[40] considered a lower threshold of HA (60 μg/L) in 146 heavy drinkers and showed a sensitivity of 100% and a specificity of 86% for the detection of cirrhosis. These data suggest that HA could be used as a screening test in patients who abuse alcohol in order to exclude advanced liver disease, provided that a standardized cut-off is adequately validated. Conversely, Lieber[41] evaluated the performance of TIMP1, P3NT and HA among other markers, in a cohort of 247 pre-cirrhotic alcoholic patients. The study reported poor accuracy of all these markers in the prediction of advanced fibrosis, with

corresponding AUROCs of 0.68, 0.67 and 0.69. Plasma YKL-40 was tested in 146 heavy drinkers and its levels increased in parallel with the severity of fibrosis and inflammation. Considering a threshold of 330 mcg/L, YKL-40 had a sensitivity of 50.8% and a specificity of 88.5 for the detection of advanced fibrosis[42]. Therefore, direct serum markers in isolation are inadequate for the diagnosis of pre-cirrhotic fibrosis stages.

A non-commercial panel of indirect and direct non-invasive markers was recently developed to stratify the risk of advanced liver disease and liver-related complications in a cohort of 1038 patients with ALD in primary care. The panel consisted of HA, P3NP and platelet count, and classified patients as high risk (red group), intermediate-risk (amber group) and low-risk (green group). After a mean follow-up of 46 mo, no patients in the green group decompensated or died, compared to 3.3% and 14% of deaths in the amber and red group respectively. The AUROC of this panel was 0.78 and 0.81 for diagnosing any degree or significant fibrosis respectively. Since the red and amber groups had a significant reduction in survival compared to the green one, the panel could be used as a screening test in primary care to guide further secondary care referrals[43].

FibroTest® consists of total bilirubin, haptoglobin, GGT, α2 macroglobulin and Apolipoprotein A1. Imber-Bismut firstly tested its accuracy in 339 HCV-infected patients and reported an AUROC of 0.837 for the detection of significant fibrosis. In a cohort of 221 patients with ALD, FibroTest® values were significantly different among distinct stages of liver fibrosis (except between F0 and F1). In contrast, HA values only differed between advanced stages of fibrosis and F0-F2. Moreover, for ≥ F2, the AUROCs of FibroTest® and HA were 0.84 and 0.79 respectively, while for the diagnosis of cirrhosis the corresponding AUROC were comparable at 0.95 and 0.93 respectively[44].

HepaScore® combines age, gender, bilirubin, GGT, HA, and gamma2-macroglobulin into a score with values ranging from 0 to 1. In a cohort of 512 HCV patients, HepaScore® had acceptable diagnostic accuracy both for significant fibrosis (AUROC = 0.81) and cirrhosis (AUROC = 0.88)[29,45].

The FibroMeter® derives from the combination of several serum markers, such as platelet count, prothrombin index, transaminases, GGT, α2 macro-globulin, HA, blood urea, ferritin, age and sex. It comprises six different tests, one for traditional histological staging and one for fibrosis quantification for each of ALD, NAFLD and viral hepatitis, showing the highest performance in chronic C hepatitis[46]. In a cohort of 478 patients, of which 95 had ALD, Fibrometer® showed a better AUROC (0.96) in diagnosing F2-F4 fibrosis stage in ALD, compared to Forns index, APRI and FibroTest®[47].

In a study by the group that developed FibroTest®, its diagnostic accuracy was compared to that of FibroMeter® and Hepascore® in 218 patients with ALD. Significant correlations between fibrosis stages and each serum panel were found with no significant differences in their AUROC for the diagnosis of advanced fibrosis and cirrhosis, with corresponding values of 0.83 and 0.92-0.94. Nevertheless, in the multivariate analysis, FibroTest® was the only factor independently associated with both advanced fibrosis and cirrhosis, whereas Fibrometer® was independently associated only with cirrhosis. Interestingly, the combination of these indexes did not improve the diagnostic performance of FibroTest®. Moreover, all three scores were predictors of 5 and 10 year overall survival and non liver-related deaths equally well correlated with histological semi-quantitative staging. Once again, at multivariate analysis only Fibrotest® remained an independent prognostic factor of liver-related mortality[36].

ELF™ score was developed by Rosenberg *et al*[48] in 1021 patients with chronic liver disease of mixed aetiologies, showing a high accuracy for the detection of significant fibrosis. Importantly, it performed well in either hepatitis C, NAFLD or ALD; although only 64 patients had ALD in the initial cohort, the sensitivity and specificity for diagnosing significant fibrosis were 93% and 100% respectively. These promising results need further validation in a larger cohort of patients with ALD.

All proprietary serum panels will require independent validation in ALD by groups not involved in their development.

Imaging techniques: Data on transient elastography (TE) are limited in patients with ALD compared to other aetiologies of liver disease. Mueller has shown that the presence of steatohepatitis an/or ongoing alcohol abuse can result in falsely elevated stiffness measurements and suggested that TE should not be performed in patients with AST > 100 IU/L who are actively drinking[49,50].

Similar to other aetiologies of liver disease, there are no validated cut-offs for the diagnosis of specific histological stages in patients with ALD. Nguyen-Khac[34] studied 103 patients with ALD and showed that stiffness cut-off values of 7.8 and 11 kPa were predictive of ≥ F2 and ≥ F3 respectively, with corresponding sensitivity 80% and 86.7% and specificity 90.5% and 80.5%, whereas a cut-off of > 19.5 kPa was suggestive of cirrhosis. Similar results were reported in a study of 711 patients with chronic liver disease, of whom 89 (12.5%) had ALD, where a cut-off value of 17.6 kPa had a sensitivity of 77% and a specificity of 97% for the detection of cirrhosis[51]. In another cohort of 147 alcoholic patients, the AUROC for patients with advanced fibrosis and with cirrhosis were 0.94 and 0.87 respectively. Cut-off values of 12.9 kPa and 22.6 kPa were optimal for the diagnosis of ≥ F3 and F4 respectively[52].

A Cochrane meta-analysis retrieved only 7 studies

on patients with ALD with a total of 834 patients[50]. Although stiffness cut-offs varied among studies and were not defined a priori, the most commonly used cut-offs for the detection of advanced fibrosis and cirrhosis were 9.5 kPa and 12.5 kPa respectively. At these values, TE had a sensitivity of 92% and 95%, and specificity of 70% and 71% for the diagnosis of F3 and F4 respectively. Only one study reported on F1, therefore the performance and cut-off values of TE in mild disease are yet to be established. The wide range of cut-off values for diagnosing specific fibrosis stages significantly affected the specificity of TE. Therefore, the diagnostic accuracy of TE is lower in ALD than in other causes of liver disease, particularly HCV[53]. As previously suggested[50], TE was better in ruling out rather than confirming advanced fibrosis and cirrhosis, with negative likelihood ratios of 0.11 and 0.07 respectively. Before TE can be used in clinical practice, cut-off values need to be sufficiently validated both in patients who continue to abuse alcohol and abstainers.

In order to improve the performance of TE, its combination with FIB4 has been tested in a cohort of 418 patients, showing an improvement in the accuracy in detecting advanced liver fibrosis compared to the performance of each test alone. Indeed, the new score had a sensitivity of 92% and a specificity of 78% compared to 87% and 76% of TE alone[54]. No further data on the combination of non-invasive tests are specifically available in ALD.

ARFI has also been studied in patients with ALD. In a cohort of 99 alcoholic patients, ARFI was significantly better than APRI, with AUROC of 0.875 and 0.893 for diagnosing ≥ S3 and S4 stages of the Scheuer scoring system. The optimum cut-off values for ARFI were 1.40 m/s for S3 and 1.65 m/s for S4. Interestingly, cut-off values decreased in the presence of normal transaminases, suggesting an influence of liver inflammation on ARFI values similar to TE[55].

A recent study by Cassinotto *et al*[26] compared the performance of Fibroscan®, ARFI and SSI in 349 patients with mixed aetiology of liver disease using histology as the gold standard. It demonstrated a superior accuracy of SSI for diagnosing significant fibrosis (≥ F2) compared to ARFI and for diagnosing severe fibrosis (≥ F3) compared to Fibroscan®. Although there were patients with ALD included, no separate analysis was performed according to the aetiology of liver disease. Nevertheless, the comparative accuracy of the technique is not expected to differ according to the underlying aetiology of liver disease.

Bensamoun *et al*[56] compared the diagnostic accuracy of MRE and Fibrometer® in 90 patients with ALD, using TE as the gold standard for fibrosis assessment. The analysis revealed that MRE performed well in the diagnosis of ≥ F1, ≥ F3 and F4, with corresponding AUROCs of 0.94, 0.98 and 0.99; conversely, Fibrometer® could only accurately detect cirrhosis (F4) with an AUROC of 0.95, with lower values for ≥ F1, ≥ F2 and ≥ F3 respectively (0.63, 0.69 and 0.83). As TE has a high number of false positive reading in patients with ALD, it is difficult to interpret the results of this study as liver biopsy was not performed.

CONCLUSION

Currently, although several non-invasive fibrosis markers have been suggested as alternatives to liver biopsy in patients with ALD, none has been sufficiently validated. In contrast to other aetiologies of liver disease, most notably HCV, data are scarce and derive from small cohorts of patients. Indeed, two separate cost-effectiveness analyses of non-invasive fibrosis tests in ALD concluded that such tests cannot be currently recommended for the investigation and management of such patients[57,58]. This was based on both the lack of specific treatment for ALD other than abstinence and the limited data on the diagnostic accuracy of non-invasive fibrosis tests. As described in other liver diseases, the diagnostic accuracy of non-invasive tests in ALD is acceptable for the diagnosis of significant fibrosis or cirrhosis but not for lesser fibrosis stages.

Simple panels that rely on AST, such as APRI and AST/ALT ratio, are of reduced utility in ALD due to the higher AST values in such patients that do not necessarily correlate with severe fibrosis. Proprietary panels such as Fibrotest, Fibrometer and ELF score need further validation. HA has been used either alone or in non-proprietary panels[43], however the cut-offs used for the diagnosis of advanced fibrosis and/or cirrhosis vary across studies and therefore cannot be applied in everyday clinical practice.

The most widely evaluated non-invasive test is Fibroscan, however its specificity is suboptimal and can only be used for ruling out the presence of ≥ F3 or cirrhosis. Therefore, its use as a community-screening tool in patients who abuse alcohol should be further explored. Indeed, the use of non-invasive tests could be tailored to first tier screening of patients at risk, in order to diagnose early patients with progressive liver disease and offer targeted interventions for the prevention of decompensation.

In conclusion, even though evidence supporting the reliability and utility of non-invasive assessment of liver fibrosis in ALD is accumulating, sufficient validation of these tests is still lacking, whereas their accuracy for the detection of earlier stages of fibrosis needs to be improved.

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