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Liver fibrosis markers in alcoholic liver disease

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Abstract

Alcohol is one of the main factors of liver damage. The evaluation of the degree of liver fibrosis is of great value for therapeutic decision making in patients with alcoholic liver disease (ALD). Staging of liver fibrosis is essential to define prognosis and management of the disease. Liver biopsy is a gold standard as it has high sensitivity and specificity in fibrosis diagnostics. Taking into account the limitations of liver biopsy, there is an exigency to introduce non-invasive serum markers for fibrosis that would be able to replace liver biopsy. Ideal serum markers should be specific for the liver, easy to perform and independent to inflammation and fibrosis in other organs. Serum markers of hepatic fibrosis are divided into direct and indirect. Indirect markers reflect alterations in hepatic function, direct markers reflect extracellular matrix turnover. These markers should correlate with dynamic changes in fibrogenesis and fibrosis resolution. The assessment of the degree of liver fibrosis in alcoholic liver disease has diagnostic and prognostic implications, therefore noninvasive assessment of fibrosis remains important. There are only a few studies evaluating the diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with ALD. Several noninvasive laboratory tests have been

used to assess liver fibrosis in patients with alcoholic liver disease, including the hyaluronic acid, FibroTest, FibrometerA, Hepascore, Forns and APRI indexes, FIB4, an algorithm combining Prothrombin index (PI), α -2 macroglobulin and hyaluronic acid. Among these tests, Fibrotest, FibrometerA and Hepascore demonstrated excellent diagnostic accuracy in identifying advanced fibrosis and cirrhosis, and additionally, Fibrotest was independently associated with survival. Therefore, the use of biomarkers may reduce the need for liver biopsy and permit an earlier treatment of alcoholic patients.

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Key words: Liver fibrosis markers; Alcoholic liver disease

Core tip: Monitoring the stage of liver fibrosis in alcohol abusing persons is important in order to undertake proper therapeutic decisions. The usefulness of liver biopsy in the diagnostics of liver fibrosis is indisputable with the only limitation being its invasive character. Thus, non-invasive tests and biochemical markers determining the stage and dynamics of liver fibrosis in alcohol liver disease are of great significance.

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INTRODUCTION

The diagnosis of alcoholic liver disease (ALD) is based on the following features: history of alcohol abuse, clinical evidence of liver disease and the results of laboratory tests. First, alcoholic patients develop fatty liver, and then more severe consequences such as perivenular fibrosis and alcoholic hepatitis^[1,2] can occur. The most common clinical sign of alcoholic fatty liver is hepatomegaly, but

the majority of patients are asymptomatic. The presence of steatosis in alcoholic liver disease is associated with progression of fibrosis and with necroinflammatory lesions^[3,4]. The precursors of fibrosis are necrosis and inflammation, albeit the cirrhosis commonly develops without overt alcoholic hepatitis^[5]. Perivenular fibrosis can rapidly develop to alcoholic cirrhosis. The incidence of cirrhosis in patients with alcoholic hepatitis is nine times higher than in those with fatty liver. Nevertheless, alcoholic hepatitis develops in only a fraction of heavy drinkers. The prevalence of alcoholic steatohepatitis (ASH) in alcoholics was about 10%-35%^[6]. Taking into account the fact that about 30%-35% of heavy drinkers developed advanced forms of ALD such as advanced fibrosis and cirrhosis, the prevalence of presumed and confirmed fibrosis in alcoholic liver disease is established in 7% and 8%, respectively^[7,8]. In another study, advanced fibrosis (F2-F4) confirmed by biopsy examination was present in 63% of patients with chronic alcoholic liver disease^[4].

The treatment of ALD is focused on the psychological and behavioral effects of alcohol consumption, but should also affect severe medical complications. The detection of precursor lesions facilitates early intervention to prevent irreversible liver damage. Therefore, the evaluation of the degree of liver steatosis, fibrosis, and ASH is of great value for therapeutic decision making in patients with ALD. Staging of chronic liver disease, especially liver fibrosis, is essential to define prognosis and management of the disease. According to the METAVIR classification, fibrosis is defined as two stages that significantly modify the management of liver disease. There is advanced fibrosis which is defined as $F \geq 2$, and cirrhosis defined as $F \geq 4$ ^[9].

Liver biopsy, which is considered a gold standard for evaluation of the stage of liver fibrosis, is an invasive procedure and leads to complications in 0.6%-5.0% of patients^[10]. Additionally, the liver samples can be a cause of a diagnostic error, *e.g.*, in almost 30% of patients with chronic hepatitis C provided we underestimate the stage of liver fibrosis^[11]. There are three limitations that prevent its use as a routine clinical tool. The fibrosis staging system is not appropriate to describe the linear relationship between amount of fibrosis and fibrosis stage, sampling error and inter-observer variation^[12]. On the other hand, biopsy is not recommended for alcohol dependent patients with symptoms of alcoholic liver disease. Taking into account these limitations of liver biopsy, there is an urgent need to introduce non-invasive serum markers for fibrosis that are in a position to replace liver biopsy. Additionally, liver biopsy is not useful for regular testing of fibrosis progression and effectiveness of the therapy. There are several non-invasive imaging techniques for fibrosis evaluation. These include positron emission tomography, transient elastography, and magnetic resonance imaging. In the past decade, serum tests, as non-invasive assessment of liver fibrosis that can accurately evaluate degree of liver fibrosis, were introduced. Serum markers are offered as an alternative to liver biopsy as

less invasive but effective in the diagnosis, prognosis and management of liver disease. The diagnostic performance of serum markers in chronic hepatitis C and non-alcoholic liver disease have been reported many times but just a few times in ALD.

SERUM MARKERS

Ideal serum markers should be specific for the liver, freely available and easy to measure, independent of inflammation, not influenced by excretion, capable of identifying the stage of fibrosis and correlate with dynamic changes in fibrogenesis and fibrosis resolution^[12]. Serum markers of hepatic fibrosis can be divided into direct or indirect. Indirect markers reflect alterations in hepatic function, *e.g.*, platelet count, coagulation factors and transaminases. Direct markers of fibrosis reflect extracellular matrix turnover. These include the products of matrix synthesis or degradation and the enzymes involved in these processes^[13]. The markers of matrix deposition are procollagen I C terminal, procollagen III N terminal, tenascin, tissue inhibitor of metalloproteinases, and tumor growth factor- β . The markers of matrix removal are procollagen IV C peptide, procollagen IV N peptide, collagen IV, undulin, matrix metalloproteinases, urinary desmosine, and hydroxylsypyridinoline.

There are only a few studies evaluating the diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with ALD. The first generation panel is the PGA index, which includes the Prothrombin index (PI), Gamma-glutamyl transferase (GGT) and Apolipoprotein A1^[14]. When the PGA index involves α -2 macroglobulin it is called the PGAA index^[15]. FibroTest, Hepascore and FibrometerA are second generation panel tests that provide useful information regarding different fibrosis stages and have discriminating power between mild fibrosis and clinical significant fibrosis, and between advanced fibrosis and cirrhosis. FibroTest combines a panel of five biochemical markers: α -2 macroglobulin, apolipoprotein A1, haptoglobin, GGT, and total bilirubin adjusted by age and gender^[16]. Fibro Test scores from 0 to 0.10 had 100% negative predictive value for the absence of significant fibrosis (F2 or higher by Metavir) while scores from 0.60 to 1.00 had > 90% positive predictive value for significant fibrosis for hepatitis C patients. For intermediate scores from 0.11 to 0.59, liver biopsy is recommended. In an independent validation of FibroTest, the negative predictive value of a score < 0.10 was 85% and the positive predictive value of a score > 0.60 was 78%^[17]. Hepascore uses a panel of 4 biochemical tests: α -2 macroglobulin, hyaluronic acid (HA), GGT, and total bilirubin adjusted by age and gender^[18]. A hepascore value ≥ 0.50 indicates significant liver fibrosis, whereas for a value < 0.50 significant fibrosis is absent. If the value is ≥ 0.84 , cirrhosis is likely present and if the value is < 0.84 cirrhosis is absent^[19]. FibrometerA combines α -2 macroglobulin, hyaluronic acid, PI, aspartate aminotransferase (AST), platelet count, urea and age

Table 1 Characteristic of studies concerning alcoholic liver disease

Study	Number of patients	Age (yr)	Alcohol consumption	Exclusion criteria
Rosenberg <i>et al</i> ^[24] (2004)	64	18-74	No data	Any disorder associated with extrahepatic fibrosis; cardiovascular disease or cancer; advanced cirrhosis; regular consumption of aspirin; hepatocellular carcinoma or drug-induced liver disease
Calès <i>et al</i> ^[20] (2005)	95	18-74	≥ 50 g/d for the previous 5 yr (mean: 94 g/d ± 50)	Other causes of LD or complicated cirrhosis or received antifibrotic treatment within the previous 6 mo
Naveau <i>et al</i> ^[4] (2005)	221	47 (SE = 0.7)	at least 50 g/d over the previous year	Concomitant liver disease, HIV antibodies, immune-suppression, hepatic surface antigen, antibodies to HCV, associated severe diseases
Naveau <i>et al</i> ^[22] (2009)	218	47.1 (SE = 0.7)	≥ 50 g/d during the preceding y (mean 146 g/d, SE = 80 g/d for 17 yr)	Concomitant liver disease, human immunodeficiency virus antibodies, immunosuppression
Poynard <i>et al</i> ^[23] (2012)	218	47 (SD = 10.3)	No data	HIV co-infection

HCV: Hepatitis C virus; LD: Liver disease; HIV: Human immunodeficiency virus.

of patients^[20]. Calès *et al*^[20] reported superior diagnostic accuracy of Fibrometer to Forns index, Fibrotest, and APRI. APRI (AST to Platelet Ratio Index) is calculated as a ratio of AST to platelet count^[11]. Using optimized cut-off values, significant fibrosis could be predicted accurately in 51% and cirrhosis in 81% of chronic hepatitis C patients (CHC). Using readily available laboratory results can identify CHC patients with significant fibrosis and cirrhosis with a high degree of accuracy. Application of this index may decrease the need for liver biopsy among CHC patients. Forns index is derived from GGT, cholesterol, platelet count, and age^[21]. This test was useful at excluding patients with minimal fibrosis, but was of limited value for the identification of patients with more advanced liver disease^[13].

This paper concerns the diagnostic and prognostic values of noninvasive markers in alcoholic liver disease and is based on the study of Calès *et al*^[20] (2005), Naveau *et al*^[15,22] (2005, 2009) and Poynard *et al*^[23] (2012), Rosenberg *et al*^[24] (2004). Inclusion and exclusion criteria were given in Table 1.

The following parameters were assessed: alanine aminotransferase, AST, GGT, bilirubin, PI, α -2 macroglobulin, apolipoprotein A1, haptoglobin, HA, FibroTest, Hepascore, FibrometerA, FIB-4, Forns and APRI indexes, an algorithm combining age, hyaluronic acid, amino-terminal propeptide of type III collagen (P11NP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). In these studies patients were classified according to the severity of fibrosis. Advanced fibrosis was defined as stage F2 or higher according to METAVIR scoring system and cirrhosis as stage F4.

PRESENCE OF FIBROSIS

The majority of patients with alcoholic liver disease (93%) had fibrosis; 69.5% had clinically significant fibrosis (F2 or higher), 31% had cirrhosis, and 29% had alcoholic hepatitis (Naveau 2005). In the recent study of Naveau *et al*^[22] the prevalence of clinically significant fibrosis was 63% (minimal fibrosis in 30% of patients) and the

prevalence of cirrhosis was 31%. In the study of Calès *et al*^[20], the distribution of fibrosis was as follows: 46.3% had fibrosis, 41.1% had cirrhosis and 29% had alcoholic hepatitis. In the study of Poynard *et al*^[23] minimal fibrosis was present in 63% of patients and cirrhosis in 31% of patients. Discrepancy between the outcomes of Naveau *et al*^[4,22], and Calès *et al*^[20] and Poynard *et al*^[23] should be attributed to different lengths of liver specimen taken by biopsy, 18.4 mm (SD = 6.0) in the study of Calès *et al*^[20] and 15.0 mm (SE = 0.5) in the study of Naveau *et al*^[4], and 15.0 mm (SD = 6.5) in the study of Poynard *et al*^[23]. According to experimental data, sampling error is especially evident in small biopsies. A sample of tissue may vary from lobule to lobule, although the error is usually not greater than one fibrosis stage. Biopsies obtained from the right and left lobes from patients with hepatitis C proved to make a difference of at least one stage, between right and left lobes, in 33% of patients and two patients had a difference of two fibrosis stages^[25].

DIAGNOSIS OF FIBROSIS

The performance of tests was expressed by the diagnostic accuracy and by the area under the receiver operating characteristic (AUROC). For predicting fibrosis and cirrhosis the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated.

According to the results of Naveau *et al*^[4,22] AUROC of FibroTest for the detection of moderate to severe fibrosis (F2-F4) was higher for patented biomarkers (FibroTest, Fibrometer A and Hepascore) than for non-patented scores (Forns, APRI and FIB4) (Table 2). The accuracy of these tests for discriminating between advanced (stage F2 or higher) versus non-advanced fibrosis (stage F < 2) reached the same value of AUROC = 0.83. For the diagnosis of cirrhosis (F4) the AUROC of patented biomarkers was higher than that of non patented. The diagnostic values of Fibrometer A and Hepascore did not differ from that of FibroTest for advanced fibrosis and cirrhosis. There were also no differences between

Table 2 Area under the curves receiver operating characteristic for the diagnosis of fibrosis in patients with alcoholic liver disease

Test	F2-F4 vs F0-F1	F4 vs F0-F3
FibroTest ^[22]	0.83 (95% CI: 0.77-0.88)	0.94 (95% CI: 0.90-0.96)
FibrometerA ^[22]	0.83 (95% CI: 0.77-0.87)	0.94 (95% CI: 0.90-0.97)
Hepascore ^[22]	0.83 (95% CI: 0.77-0.88)	0.92 (95% CI: 0.87-0.97)
Forns ^[22]	0.38 (95% CI: 0.30-0.46)	0.38 (95% CI: 0.27-0.47)
APRI ^[22]	0.59 (95% CI: 0.51-0.67)	0.67 (95% CI: 0.59-0.75)
FIB4 ^[22]	0.70 (95% CI: 0.62-0.76)	0.80 (95% CI: 0.72-0.86)
FibroTest ^[4]	0.84 ± 0.03 (SD)	0.95 ± 0.01 (SD)
Hyaluronic acid ^[4]	0.79 ± 0.03 (SD)	0.93 ± 0.02 (SD)
The algorithm combining PI, α-2 macroglobulin and hyaluronic acid ^[20]	0.962 ± 0.018 (SD)	

diagnostic accuracy for FibroTest and HA. These results confirm previous observations that serum HA had good diagnostic values for the diagnosis of cirrhosis^[26]. As for other tests, only the apolipoprotein A1 and α-2 macroglobulin had independently predictive values of significant fibrosis (from multivariate analysis). The results indicate that the FibroTest had the highest sensitivity for the detection of cirrhosis, because all cirrhotic patients had FibroTest scores ≥ 0.3 (sensitivity and NPV = 100%). For advanced fibrosis (F2-F4) FibroTest scores ≥ 0.3 had lower sensitivity (84%) and NPV (70%). Therefore, the patients with a score < 0.3 had a low probability of cirrhosis. When the score increased above 0.7, sensitivity and NPV for the diagnosis of advanced fibrosis and cirrhosis decreased but the specificity and PPV increased. 91% of patients with FibroTest score > 0.7 had cirrhosis. There was a significant concordance between FibroTest and biopsy with intra-class coefficient of correlation = 0.961 for F4 and 0.899 for F1^[23]. Most discordances between FibroTest and liver biopsy were attributable to errors in biopsy interpretation. The study of Naveau *et al*^[22] showed significant correlation between fibrosis stages and FibroTest ($R = 0.71$), FibrometerA ($R = 0.72$) and Hepascore ($R = 0.71$). All three tests (Fibrotest, FibrometerA, Hepascore) demonstrated excellent diagnostic accuracy in identifying advanced fibrosis and cirrhosis.

According to study of Calès *et al*^[20], the AUROC for clinically significant fibrosis (F2 or higher) in a test combining PI, α-2 macroglobulin, hyaluronic acid and age was higher than that of FibroTest (Table 2). The diagnostic indexes of these blood tests for predicting clinically significant fibrosis were: 91.8% for sensitivity, 92.6% for specificity, 96.6% for PPV and 83.3% for NPV.

The performance of the algorithm of panel serum markers (HA, PIIINP and TIMP-1) was compared with histologic staging^[27]. The AUC for the differentiation of “mild” and “moderate/severe” alcoholic liver disease (Scheuer stages 0-2 vs 3 and 4) was 0.944 and was higher than that for hepatitis C and for NAFLD. In ALD, for detecting fibrosis stage 3 or 4, using a threshold score of 0.087, the sensitivity and NPV was equal 100%, while a threshold of 0.431 yielded a sensitivity of 93.3%, speci-

ficity and PPV of 100%, and NPV of 85.7%. For the comparison, the algorithm was capable of detecting Scheuer fibrosis stages 3 and 4 in hepatitis C with a sensitivity of 95% and an NPV of 94.9% (at a threshold score of 0.063). For NAFLD, fibrosis stage 3 or 4 was detectable with a sensitivity of 89%, specificity of 96%, PPV of 80%, and NPV of 98% (using a threshold value of 0.375). Therefore, it can be concluded that the algorithm may prove very useful in monitoring alcoholic disease progression. The negative and positive predictive values for the algorithm in ALD must be interpreted with caution because the number of patient was relatively small, but the high sensitivity and specificity provide evidence of good assay performance.

In summary, patented biochemical biomarkers of fibrosis (FibroTest, Fibrometer A and Hepascore) have a high diagnostic power to identify and discriminate advanced fibrosis and cirrhosis in ALD. Therefore, the use of these biomarkers may decrease the need for liver biopsy examination.

PROGNOSTIC VALUE

Hazard function, log-rank test, and proportional hazard regression analysis were used for validation of liver fibrosis biomarkers and assessing liver fibrosis progression in alcoholic liver disease^[22]. The biomarkers prognostic value of fibrosis was also estimated in survival analysis^[21]. The 5-year and 10-year survival or non-liver related death were main endpoints used to compare the prognostic value of biomarker with histological staging. Survival was calculated from the date that the biomarkers were carried out to the endpoint date. According to data presented by Naveau *et al*^[22], the cumulative global survival, regardless the cause of death, at 5-year survival reached a value of $79 \pm 3\%$ and at 10-years survival reached $62 \pm 4\%$. In turn, the cumulative survival and non-liver-related death was $84 \pm 3\%$ at 5-years survival and $78 \pm 3\%$ at 10-years survival.

Survival was tested according to the three categories of baseline FibroTest. At a cut-off of FibroTest value < 0.32 (no or minimal fibrosis) 5-years survival or non-liver-related death was 98.7%, at baseline FibroTest value > 0.32 and at < 0.58 (moderate fibrosis) it was 92.1%, and at baseline FibroTest value > 0.58 (severe fibrosis) it was 68.3%^[22]. At cut-off of FibroTest value < 0.32 (no or minimal fibrosis) 10-years survival or non-liver-related death was 92.0%, at baseline FibroTest value > 0.32 and < 0.58 (moderate fibrosis) it was 87.5%, and at baseline FibroTest value > 0.58 (severe fibrosis) the survival or non-liver-related death was 62.6%.

The accuracy of biomarkers and liver biopsy for the prognosis of patients with ALD was as follows: FibroTest, FibrometerA and Hepascore have AUROC (diagnostic accuracy) than Pugh scores and non-patented markers (FIB-4, APRI and Forns), but the prognostic values of FibroTest, FibrometerA and Hepascore do not significantly differ from biopsy staging. Additionally, FibroTest was well associated with overall survival and

survival or non-liver-related deaths^[22].

The estimation of liver fibrosis progression (LFP) to cirrhosis in alcoholic fatty liver disease could be done by time-dependent statistics and non-invasive biomarkers such as FibroTest that can be used as an alternative to liver biopsy. The transition of fibrosis to cirrhosis and its complications are always due to mortality associated with ALD^[27]. If the exposure time is known, one biopsy is necessary to estimate the transition rate from normal liver to minimal fibrosis stage (it concerns chronic hepatitis C). Poynard *et al.*^[28] proposed the time-dependent statistics to assess LFP from birth to first biopsy in chronic liver disease. According to the results of Poynard *et al.*^[23] the transition rate to minimal fibrosis (F1 in METAVIR scores for biopsy) in ALD estimated by biopsy and FibroTest is concordant with intra class coefficient ICC = 0.864. Biopsy and FibroTest were also in significant concordance for estimation of LFP to cirrhosis, with ICC = 0.970. A more rapid transition of LFP to minimal fibrosis and cirrhosis was observed for men with ALD, for both biopsy and FibroTest. The multivariate analysis showed the similar transition rates to cirrhosis in ALD and non-alcoholic fatty liver disease (NAFLD) using biopsy and FibroTest, but the transition to minimal fibrosis in ALD was higher than in NAFLD using FibroTest^[24].

In summary, patented biomarkers (FibroTest, FibrometerA and Hepascore) and liver biopsy similarly predict overall survival in alcoholic liver disease. However, they more accurately predict non-liver related survival and death in ALD. FibroTest allows the estimation of liver fibrosis progression in alcoholic liver disease similar to liver biopsy.

CONCLUSION

Several noninvasive laboratory tests have been used to assess liver fibrosis in patients with alcoholic liver disease, including the hyaluronic acid, FibroTest, FibrometerA, Hepascore, Forns and APRI indexes, FIB4, an algorithm combining PI, α -2 macroglobulin and hyaluronic acid. The assessment of the degree of liver fibrosis in alcoholic liver disease has diagnostic and prognostic implications and thus, noninvasive assessment of fibrosis remains important. Among these tests, Fibrotest, FibrometerA and Hepascore demonstrated excellent diagnostic accuracy in identifying advanced fibrosis and cirrhosis, and additionally, Fibrotest was independently associated with survival. Therefore, the use of biomarkers may reduce the need for liver biopsy and permit an earlier treatment of alcoholic patients.

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