TOPIC HIGHLIGHT

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Non-invasive prediction of forthcoming cirrhosis-related complications

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Abstract

In patients with chronic liver diseases, identification of significant liver fibrosis and cirrhosis is essential for determining treatment strategies, assessing therapeutic response, and stratifying long-term prognosis. Although liver biopsy remains the reference standard for evaluating the extent of liver fibrosis in patients with chronic liver diseases, several non-invasive methods have been developed as alternatives to liver biopsies. Some of these non-invasive methods have demonstrated clinical accuracy for diagnosing significant fibrosis or cirrhosis in many cross-sectional studies with the histological fibrosis stage as a reference standard. However, non-invasive methods cannot be fully validated through cross-sectional studies since liver biopsy is not a perfect surrogate endpoint marker. Accordingly, recent studies have focused on assessing the performance of non-invasive methods through long-term, longitudinal, follow-up studies with solid clinical endpoints related to advanced stages of liver fibrosis and cirrhosis. As a result, current view is that these alternative methods can independently predict future cirrhosis-related complications, such as hepatic decompensation, liver failure, hepatocellular carcinoma, or liver-related death. The clinical role of non-invasive models seems to be shifting from a simple tool for predicting the extent of fibrosis to a surveillance tool for predicting future liver-related events. In this article, we will summarize recent longitudinal studies of non-invasive methods for predicting forthcoming complications related to liver cirrhosis and discuss the clinical value of currently available non-invasive methods based on evidence from the literature.

Core tip: In this article, we summarized recent longitudinal studies of non-invasive methods - including transient elastography, European Liver Fibrosis scoring system, Fibrotest, and acoustic radiation force impulse technique - for predicting forthcoming complications related to liver cirrhosis. We also discussed the clinical value of currently available non-invasive methods based on evidence from the literature and finally proposed areas for future research directions.

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INTRODUCTION

Viral hepatitis accounts for the majority of chronic liver diseases (CLDs) worldwide[1-4]. In the absence of appropriate therapeutic interventions, CLD can progress to significant liver fibrosis or cirrhosis, resulting in complications, such as portal hypertension, ascites, or hepatocellular carcinoma (HCC)[5-7]. In recent years, secondary prevention of CLD progression to significant liver fibrosis or cirrhosis has been quite successful due to the development and application of antiviral therapies. However, liver-related events (LREs), especially cirrhosis-related complications, occur despite appropriate management with antiviral treatments. These LREs are clinically important and abruptly change the prognosis of patients with CLD.

Therefore, the identification of significant liver fibrosis and cirrhosis is essential for determining treatment strategies, assessing therapeutic response, and stratifying long-term prognosis based on the risk of developing LREs. For evaluating the extent of liver fibrosis, liver biopsy remains the reference standard. However, liver biopsies are often considered "imperfect" surrogate markers for liver fibrosis because of inherent limitations, including invasiveness, risk of life-threatening complications, intra- and inter-observer variability, and sampling error[8-11]. Moreover, monitoring the extent of liver fibrosis through serial liver biopsies during antiviral or antifibrotic treatments is not feasible in practice.

Accordingly, several non-invasive methods have been developed as alternatives to liver biopsies for evaluating the extent of liver fibrosis in patients with CLDs. Alternative approaches include measuring serum hyaluronic acid levels, the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT), AST-to-platelet ratio index (APRI), age-spleen-platelet ratio index (AS-PRI), Fibrosis-4 (FIB-4), Forns' index, Fibrotest (FT), FIBROSpect, Hepascore, Lok index, European Liver Fibrosis (ELF) panel scoring system, and transient elastography (TE, FibroScan®)[12-25]. The diagnostic performance of these non-invasive methods has been assessed in many cross-sectional studies by comparing the area-under-the-receiver operating curves (AUROCs) for these methods with the histological fibrosis stage as a reference standard. Accordingly, some of these tools have demonstrated clinical accuracy for diagnosing significant fibrosis or cirrhosis and have provided reproducible and reliable results[26-30].

However, liver biopsy is not a perfect surrogate endpoint marker for the aforementioned reasons. Thus, non-invasive methods cannot be fully validated through cross-sectional studies[31]. Recent studies have focused on assessing the performance of non-invasive methods through long-term, longitudinal, follow-up studies with solid clinical endpoints related to advanced stages of liver fibrosis and cirrhosis, including liver failure, hepatic decompensation, development of HCC, and/or liver-related death. These longitudinal studies do more than simply comparing the AUROCs with an imperfect histo-

logical reference. They also help to establish the clinical importance of non-invasive methods, including prediction of long-term prognosis[31,32]. Recent studies suggest that serial assessments of non-invasive methods reflect changes in the risk of developing LREs in patients with CLD[33]. Thus, non-invasive methods are proposed to be valuable tools for monitoring changes in prognosis, which cannot be assessed with a liver biopsy.

In this article, we will summarize recent longitudinal studies of non-invasive methods for predicting forthcoming complications related to liver cirrhosis, such as hepatic decompensation, liver failure, development of HCC, or liver-related death. We will also discuss the clinical value of currently available non-invasive methods based on evidence from the literature. Finally, we will discuss future research directions.

TRANSIENT ELASTOGRAPHY

Measurement of liver stiffness (LS) by TE has been proposed as a new non-invasive method for assessing the degree of liver fibrosis. The ability of TE to predict development of cirrhosis-related complications has also been explored in several prospective, longitudinal studies (Table 1).

Gastroesophageal varices

An important cirrhosis-related complication is the development of gastroesophageal varices and bleeding. Gastroesophageal varices are present in 30%-60% of patients with liver cirrhosis. Variceal bleeding is an independent predictor of mortality[34-36]. Although several cross-sectional studies[37-42] have reported significant correlations between TE and the presence of esophageal varices (EVs) and/or EV bleeding, the performance of TE alone as a predictor of EVs is far from satisfactory. Thus, it has been suggested that TE alone cannot replace esophagogastroduodenoscopy for identifying patients with EVs[43]. A novel prediction model was recently introduced by Kim *et al*[44]. This model combines TE with different pathophysiological parameters of liver cirrhosis. The LS-spleen diameter to platelet ratio score (LSPS) combines the LS measurement obtained by TE with the spleen diameter measured by ultrasonography and the platelet count from a routine complete blood count. The LSPS has excellent accuracy for diagnosing and predicting high-risk EVs in patients with compensated hepatitis B virus-related CLD (AUROC = 0.953; negative predictive value 94.7%, positive predictive value 93.3%).

Based on a follow-up prospective, longitudinal study, Kim *et al*[45] concluded that LSPS is a reliable method for predicting variceal bleeding in hepatitis B virus-related liver cirrhosis. In this study, patients with LSPS ≥ 5.5 showed higher cumulative incidences of EV bleeding during the follow-up period. Among those with high-risk EVs, those with an LSPS ≥ 6.5 were at an increased risk of developing variceal bleeding (Figure 1).

The clinical significance of LSPS for predicting EVs in patients with compensated cirrhosis of different eti-

Table 1 Description of prognostic studies assessing non-invasive tools for the prediction of forthcoming cirrhosis-related complications

| Ref.	Etiology of liver disease	*n*	Assessment modality[1]	Endpoint	AUROC
Kim *et al*[45]	LC (HBV)	577	**LSPS**	Esophageal variceal bleeding	0.929
Berzigotti *et al*[46]	LC (mostly HCV)	117 (T)/ 56 (V)	**LSPS**, platelet count, spleen diameter, LS	Esophageal varices	0.882 (T), 0.808 (V)
				Clinically significant portal hypertension	0.918 (T), 0.906 (V)
Masuzaki *et al*[49]	CLD (HCV)	866	**LS**	Hepatocellular carcinoma	N/A
Jung *et al*[33]	LC (HBV)	1130	**LS**	Hepatocellular carcinoma	N/A
Kim *et al*[50]	LC (HBV)	217	**LS, LSPS**	Hepatic decompensation	0.773 (LS); 0.790 (LSPS)
Kim *et al*[51]	CLD (HBV)	128	**LS**	Liver-related events	0.772
Chon *et al*[52]	CLD (HBV)	1126	**LS, LSPS**, ASPRI, P2/MS, FIB-4	Hepatocellular carcinoma	0.789 (LS); 0.790 (LSPS)
				Hepatic decompensation	0.820 (LS); 0.848 (LSPS)
Kim *et al*[53]	CLD (HBV) on antiviral therapy	162	**LS**	Liver-related events	0.736
Kim *et al*[54]	LC (HBV) on antiviral therapy	103	**LS**	Liver-related events	N/A
[2]Singh *et al*[56]	CLD (various)	7058	**LS**	Liver-related events	N/A
Parkes *et al*[58]	CLD (various)	457	**ELF**	Liver-related events	0.82
Kim *et al*[62]	CLD (HBV)	170	**ELF**	Liver-related events	0.808
Vergniol *et al*[66]	CLD (HCV)	1457	**FT**, LS, APRI, FIB-4, LB	Overall survival (5-yr)	0.861 (FT)
de Ledinghen *et al*[67]	CLD (HBV)	600	**FT**, LS, APRI, FIB-4, LB	Overall survival (5-yr)	0.82 (FT)
Park *et al*[68]	CLD (HBV)	151	FT, LS, **FT + LS, FT × LS**, LB	Liver-related events	0.748 (FT + LS); 0.868 (FT × LS)
[3]Morishita *et al*[77]	LC (HCV)	135	ARFI (**LS**)	Esophageal varices (high-risk)	0.890 (0.868)
[3]Takuma *et al*[78]	LC (mostly HCV)	340	ARFI (**SS**, LS)	Esophageal varices (high-risk)	0.993 (0.930)

[1]Bold face denotes main assessment modality; [2]Meta-analysis; [3]Cross-sectional study. AUROC: Area-under-the-receiver-operating curve; LC: Liver cirrhosis; CLD: Chronic liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; T: Training set; V: Validation set; LSPS: Liver stiffness-spleen diameter to platelet ratio score; LS: Liver stiffness; ASPRI: Age-spleen-platelet ratio index; ELF: European Liver Fibrosis; FT: Fibrotest; APRI: Aspartate aminotransferase to platelet ratio index; ARFI: Acoustic radiation force impulse; SS: Spleen stiffness; N/A: Not available.
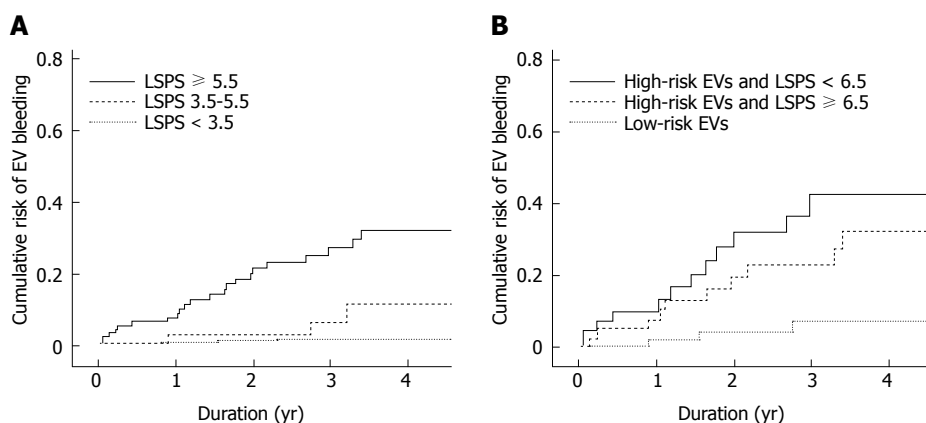
Figure 1 Cumulative incidence rate of variceal bleeding based on liver stiffness measurement-spleen diameter to platelet ratio score values. Reproduced with permission from Kim *et al*[45]. A: Among patients with liver cirrhosis related to hepatitis B virus, those with higher LSPS values had significantly higher cumulative incidences of bleeding from EVs during the follow-up period; *n* = 577; B: Among patients with high-risk EVs, patients with LSPS ≥ 6.5 had higher risks for variceal bleeding; *n* = 150. LSPS: Liver stiffness measurement-spleen diameter to platelet ratio score; EV: Esophageal varice.

ologies was further confirmed by Berzigotti *et al*[46]. In this European multi-center study, which included a training set of 117 patients and a validation set of 56 patients with compensated cirrhosis, LSPS showed good diagnostic performance for predicting the presence of EVs (AUROC = 0.882; negative predictive value 90.8%, positive predictive values 73.2%). Patients with LSPS ≥ 3.21 were considered to have EVs with an accuracy of 84.6% in the training set and 75.0% in the validation set. Interestingly, whereas the diagnostic performance of LSPS by AUROC was similar between the two studies[45,46], the

cut-offs were different: 5.5 *vs* 3.21. The disparity between cut-offs is presumably due to differences in the etiologies of the CLDs. The original publication consisted of patients with hepatitis B virus-related liver cirrhosis only, whereas the latter study included patients with liver cirrhosis of various etiologies, mainly hepatitis C virus. The cross-sectional utility of LSPS demonstrated in Asian studies was validated in a European multicenter trial. However, similar to variceal bleeding, the utility of LSPS as a long-term prognostic factor should be validated through longitudinal, prospective studies performed by

A

B
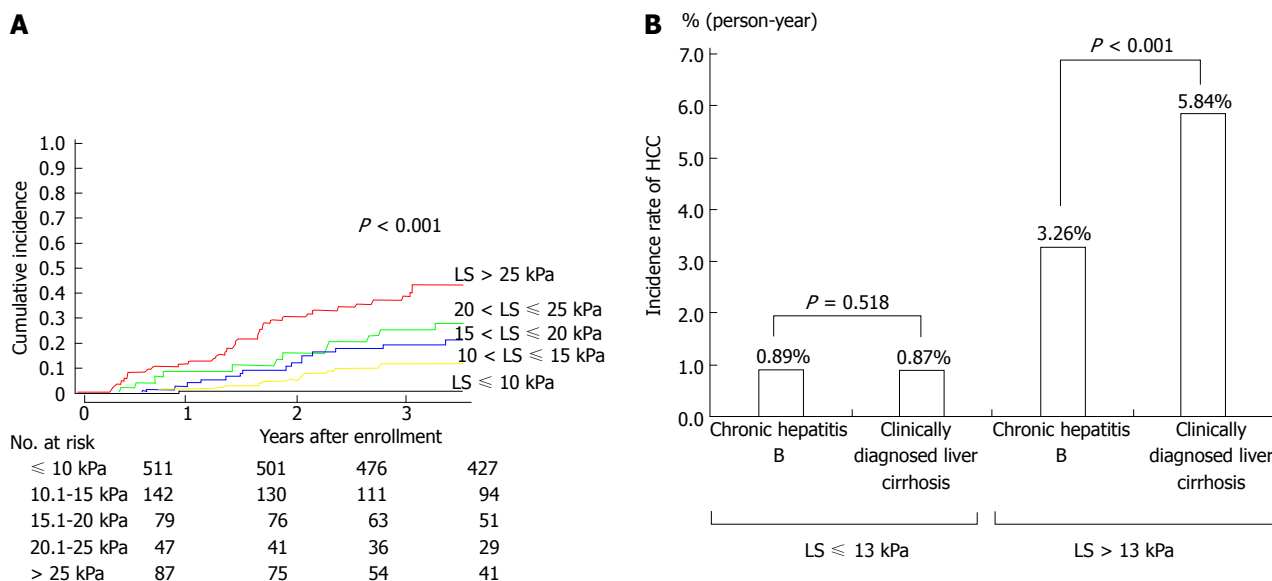
Figure 2 Cumulative incidence of hepatocellular carcinoma. A: The cumulative incidence of hepatocellular carcinoma (HCC) showed a step-wise increase according to the stratified liver stiffness (LS) measurement; *n* = 866. Reproduced with permission from Masuzaki *et al*[49]; B: Patients with higher LS values had significantly higher risks of developing HCC. Transient elastography (TE) and clinical criteria produced conflicting results for diagnosing liver cirrhosis. Patients diagnosed with liver cirrhosis based on TE findings were at higher risk of developing HCC than those diagnosed by clinical criteria (3.26% *vs* 0.87% per person-year); *n* = 1110. Reproduced with permission from Jung *et al*[33].

multiple investigators in patients of varying ethnicities and disease etiologies.

Hepatocellular carcinoma

Advanced liver fibrosis and cirrhosis are regarded as major risk factors for the development of HCC. Early detection of HCC is critical for successful treatment[47,48]. In addition to the clinical application of TE for diagnosing the extent of liver fibrosis and predicting the development of gastroesophageal varices and hepatic decompression, recent studies suggest that TE can predict the development of HCC. Masuzaki *et al*[49] performed a large, prospective cohort study to assess the ability of TE to predict the development of HCC among Japanese patients with hepatitis C-related liver cirrhosis. In addition to age, male gender, and clinical cirrhosis, the LS value stratified by TE was identified as an independent risk factor for developing HCC. Compared to patients with LS values ≤ 10 kPa, patients with higher LS values had a significantly increased risk of developing HCC (LS values, 10.1-15 kPa, HR = 16.7; LS values, 15.1-20 kPa, HR = 20.9; LS values, 20.1-25 kPa, HR = 25.6; and LS values > 25 kPa, HR = 45.5). In addition, the cumulative incidence of HCC increased in a step-wise manner according to the stratified LS value (Figure 2A). These findings suggested that a greater extent of liver fibrosis, as assessed by higher LS values, was closely associated with an increased risk of developing HCC. Thus, TE is a clinically useful method for predicting development of HCC.

The clinical role of TE for predicting the development of HCC was further validated in patients with liver cirrhosis of different etiologies. Jung *et al*[33] conducted a study in Korean patients with chronic hepatitis B. In this

large, prospective cohort study, a significant step-wise association was confirmed between LS values and the risk of developing HCC. Compared to patients with LS values ≤ 8 kPa, patients with higher LS values had significantly increased risks of developing HCC (LS values, 8.1-13 kPa, HR = 3.07; LS values, 13.1-18 kPa, HR = 4.68; LS values, 18.1-23 kPa, HR = 5.55; and LS values > 23 kPa, HR = 6.60). The diagnosis of liver cirrhosis may show conflicting results based on TE findings and clinical criteria. Patients diagnosed with liver cirrhosis based on TE findings showed increased risks of developing HCC than those diagnosed with liver cirrhosis based on clinical criteria (3.26% *vs* 0.87% per person-year) (Figure 2B). These findings indicate that TE might be a more precise indicator of compensated liver cirrhosis in comparison to clinical criteria. Furthermore, changes in the risk of developing HCC according to the pattern of changes in LS values were observed in the study. These data suggest that serial TE measurement may be a dynamic monitoring tool for estimating the risk of developing HCC in patients with liver cirrhosis.

These two large studies confirmed the clinical implications of TE as a non-invasive tool for assessing the risk of developing HCC. However, incorporation of TE into the routine surveillance strategy should be further investigated to determine if this increases the accuracy of detecting risk.

Hepatic decompensation and liver-related events

Development of overall hepatic decompensation, not merely variceal bleeding, is another critical factor related to morbidity in advanced stages of liver fibrosis and cirrhosis. Hence, early prediction of hepatic decompensation is important for establishing therapeutic plans. Kim

et al[50] conducted a prospective, longitudinal study to assess the abilities of TE and LSPS to predict the first event of hepatic decompensation in patients with liver cirrhosis. The study included patients with cirrhosis related to hepatitis B virus without histories of hepatic decompensation, which was defined as a newly-developed ascites, hepatic encephalopathy, variceal bleeding, and/or deterioration of liver function to Child-Pugh class B or C. The risk of hepatic decompensation was stratified into three groups based on the LS or LSPS value. The results suggested that patients with higher LS values (13-18 and $\geq$ 18 kPa) had significantly higher risks of developing hepatic decompensation compared to those with lower values (< 13 kPa) (HR = 4.547, P = 0.044 and HR = 12.446, P < 0.001, respectively). Similarly, the risk of developing hepatic decompensation was increased in patients with higher LSPS values (1.1-2.5 and $\geq$ 2.5) compared to those with lower values (< 1.1) (HR = 5.796, P = 0.004 and HR = 13.618, P < 0.001, respectively).

Another study[51] investigated the potential role of TE for predicting the development of overall LREs in patients with hepatitis B virus-related CLD. Overall LREs included HCC, hepatic decompensation, and liver-related mortality. In this prospective study, 128 patients with chronic hepatitis B who were receiving antiviral therapy and had histologically-confirmed advanced liver fibrosis ($\geq$ F3) and high viral loads (pre-treatment levels of HBV DNA $\geq$ 2000 IU/mL) were stratified into two groups based on the optimal cut-off (19 kPa). The patients with high LS values ($\geq$ 19 kPa) had an increased risk of developing LREs compared with those who had lower LS values (< 19 kPa) (HR = 7.176; P = 0.001). The incidence of LREs in patients with F3 and F4 were not statistically different (22.2% *vs* 13.6%; P = 0.472). However, there was a significant difference in the incidence of LREs between patients with higher and lower LS values (44.4% in $\geq$ 19 kPa *vs* 6.9% in < 19 kPa; P < 0.001). These results suggest that TE has superior performance for predicting LREs compared to that of histology for predicting long-term prognosis.

The role of TE-based non-invasive tools for predicting development of cirrhosis-related events was also analyzed in another study[52]. In this prospective study, the LS values and LSPS showed good performance for predicting the development of HCC (AUROC, 0.789 for LS value, 0.788 for LSPS) and hepatic decompensation (AUROC, 0.820 for LS value, 0.848 for LSPS). Furthermore, the LS value and LSPS were identified as independent predictors of HCC (HR = 1.040 for LS value, 1.001 for LSPS) and hepatic decompensation (HR = 1.033 for LS value, 1.002 for LSPS).

Antiviral treatments are actively administered to patients with hepatitis B virus. It is important to understand if TE can predict the long-term prognosis of patients with advanced liver fibrosis or cirrhosis who are being treated for hepatitis B viral infection. Recently, there were two publications attempting to answer this issue. One study[53] indicated that the LS value can pre-dict the development of LREs in patients with chronic hepatitis B receiving entecavir therapy. Another prospective, longitudinal study[54] showed that stratified LS values based on the Laennec system for histologically sub-classifying liver cirrhosis[55] and dynamic changes in LS values at follow up were significantly related to different risks of developing LREs in patients with advanced liver fibrosis who were receiving antiviral therapy for chronic hepatitis B virus infection.
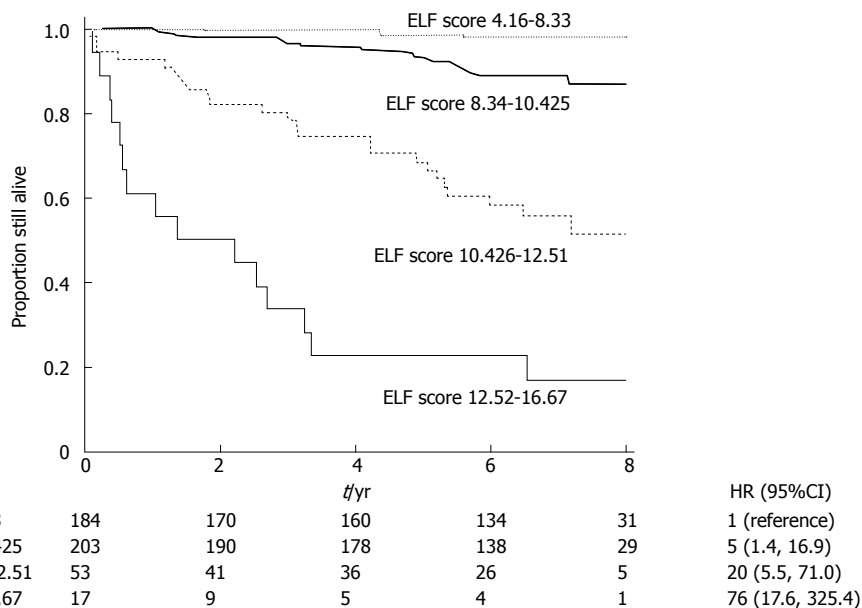
Recently, Singh *et al*[56] performed a comprehensive meta-analysis of 17 prospective cohort studies and confirmed the association between LS values and LREs in patients with CLDs. According to this meta-analysis, a greater degree of LS was significantly associated with an increased risk of developing LREs, including hepatic decompensation (RR = 1.07), HCC (RR = 1.11), overall mortality (RR = 1.22), or a composite of these events (RR = 1.32). Furthermore, a high LS value predicted the development of liver-related events, such as hepatic decompensation, HCC, and overall mortality, in a dose-dependent manner.

Thus, in addition to identifying liver fibrosis, TE appears to accurately predict long-term prognosis. However, several issues, such as determination of cut-off values, TE measurement interval, and cost-effectiveness, remain unresolved.

ELF SCORING SYSTEM

Serum levels of extracellular matrix proteins and degradation products are increased in advanced liver fibrosis. The Original European Liver Fibrosis (OELF) panel of serum markers (aminoterminal propeptide of procollagen type Ⅲ, hyaluronic acid, and tissue inhibitor of matrix metalloproteinases-1), which reflects the dynamics of liver fibrosis, was combined with age in 2004[23]. It showed good diagnostic accuracy for evaluating liver fibrosis in CLDs of different etiologies[23]. Later, this panel was simplified to the ELF scoring system by removing age as a factor from the OELF panel, and the diagnostic accuracy remained intact[57]. ELF accurately predicted the extent of liver fibrosis in several cross-sectional validation studies[58-61]. However, there are limited studies on the longitudinal performance of the ELF scoring system for predicting LREs in patients with liver cirrhosis beyond the cross-sectional aspects of ELF.

Parkes *et al*[58] investigated the performance of the ELF scoring system for predicting the development of LREs in Caucasian patients with diverse etiologies of CLDs using paired ELF scores and liver biopsy data. In this multi-center study from the United Kingdom, the study population was stratified into four groups according to the ELF score for precise assessment of the risk of developing LREs. The performance of the ELF scoring system was compared with that of histopathology of a liver biopsy. The fully adjusted HRs for LREs showed a graded response according to the stratified ELF-score group. Compared to patients with ELF scores < 8.34,

						HR (95%CI)
ELF score 4.16-8.33	184	170	160	134	31	1 (reference)
ELF score 8.34-10.425	203	190	178	138	29	5 (1.4, 16.9)
ELF score 10.426-12.51	53	41	36	26	5	20 (5.5, 71.0)
ELF score 12.52-16.67	17	9	5	4	1	76 (17.6, 325.4)

Figure 3 Kaplan-Meier analysis of liver-related events in patients stratified according to enhanced liver fibrosis scores. Reproduced with permission from Parkes *et al*[58]. The study population was stratified into four groups according to the enhanced liver fibrosis (ELF) score for precise assessment of the risks of developing liver-related events (LREs). LREs showed a graded response according to the stratified ELF score groups. Patients with higher ELF scores had significantly higher risks of having LREs; *n* = 457.

patients with higher ELF scores had significantly higher risks of developing LREs (ELF score, 12.52-16.67, HR = 75; ELF score, 10.426-12.51, HR = 20; and ELF score, 8.34-10.425, HR = 5) (Figure 3). Similarly, compared to patients with no fibrosis or mild fibrosis on liver biopsies, patients with advanced liver fibrosis were at increased risk of developing LREs (HR = 2.4 for moderate fibrosis; 8.3 for severe fibrosis/cirrhosis). Thus, the ELF scoring system was better than a liver biopsy for predicting development of LREs.

In addition, during the follow-up period, 82% of patients within the highest ELF-score group (12.52-16.67) experienced an LRE. In contrast, only 46% of those identified with severe fibrosis/cirrhosis based on a liver biopsy experienced an LRE. Moreover, when the risk of developing an LRE was analyzed with ELF as a continuous variable, the fully-adjusted OR for LRE was 2.2 (95%CI: 1.7-2.9). This result indicates that a unit increase in the ELF score was associated with a two-fold risk of developing an LRE. Furthermore, the ELF scoring system showed better diagnostic performance than a liver biopsy (AUROC, 0.82 for ELF, 0.70 for liver biopsy; *P* = 0.004) for predicting overall mortality.

Recently, the ELF scoring system was further confirmed to predict the development of LREs in a prospective study with a cohort of 170 Asian patients with hepatitis B virus-related CLDs[62]. The ELF scoring system showed good diagnostic performance for predicting the development of LREs (AUROC = 0.808). There was a significant association between the ELF score and the risk of developing LREs (ρ = 0.449; *P* < 0.01). A unit increase in the ELF score was associated with a 1.4-fold increase in the risk of developing an LRE. A higher ELF score at enrollment was correlated with an

increased incidence of LREs (HR = 1.438; *P* < 0.001). Patients were subdivided into two groups based on a calculated optimal cut-off of 10.1. Patients with lower ELF scores had significantly reduced risks of developing LREs compared with those who had higher ELF scores (HR = 0.24; *P* < 0.001). Similar to the original publication[58], stratification of patients into three groups based on the ELF score showed that the fully-adjusted HRs for LREs had a graded response. Compared to patients with ELF score ≥ 10.40, patients with lower ELF scores had significantly lower risks of developing LREs (ELF score, < 8.10, HR = 0.072; and ELF score, 8.10-10.39, HR = 0.286). The superior diagnostic performance of the ELF scoring system for predicting overall mortality compared with a liver biopsy was also confirmed in this study (AUROC, 0.749 for ELF, 0.651 for liver biopsy).

Similar to TE, the ability of ELF to predict the development of cirrhosis-related complications has been confirmed in several studies. However, the clinical utility of the ELF scoring system is limited to centers at which extracellular matrix serum markers can be routinely measured. Thus, the general clinical applicability of the ELF scoring system requires extensive validation and a cost-effective analysis.

FIBROTEST

The FT scoring system was developed by Imbert-Bismut *et al*[17] in 2001. The system is based on a panel of five serum markers, which includes α2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyl transpeptidase (GGT), and total bilirubin adjusted by age and gender. The performance of FT as a surrogate marker for liver biopsy has been extensively studied. FT is ac-
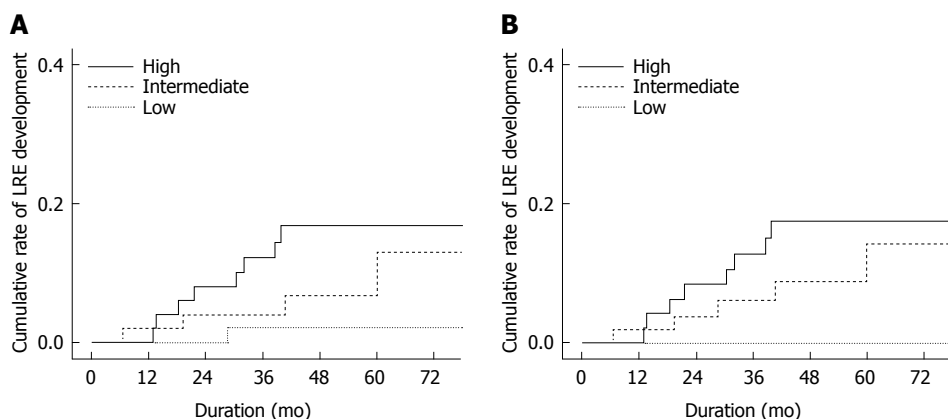
Figure 4 Cumulative rate of liver-related events in patients stratified according to the combination of Fibrotest and liver stiffness values. Reproduced with permission from Park *et al*[68]. The study population was stratified into three groups according to FT + LS (A) and FT × LS (B) values for precise assessment of the risk of developing LREs. The cumulative risk of developing LREs showed a significant graded response according to the stratified groups in both FT + LS (*P* = 0.029) and FT × LS (*P* = 0.008) analyses. *n* = 151. FT: Fibrotest; LS: Liver stiffness; LRE: Liver-related event.

cepted as a promising non-invasive method with a high degree of accuracy and reproducibility for predicting advanced liver fibrosis and cirrhosis in patients with CLDs[63,64]. The prognostic value of FT for predicting five-year survival in patients with CLDs of various etiologies has been previously studied[65-67]. Vergniol *et al*[66] conducted a prospective five-year study to assess whether FT can predict overall survival (OS) in patients with chronic hepatitis C. In this study, FT showed a high level of accuracy for predicting OS with an AUROC of 0.861. The risk of mortality was increased with a cut-off value of 7.4 (adjusted HR = 90). Furthermore, risk stratification based on the FT score was able to predict five-year OS (FT, ≤ 0.75, OS = 97%; FT, 0.75-0.80, OS = 87%; FT, 0.81-0.85, OS = 84%; FT, 0.86-0.90, OS = 75%; FT, 0.91-0.95, OS = 69%; and FT > 0.95, OS = 0%). Comparable results were observed in a similar prospective, single-center study in patients with chronic hepatitis B[67]. The prognostic performance of FT for predicting OS was good with an AUROC of 0.82. The five-year OS rates were 96.8% for FT ≤ 0.73 and 49.2% for FT > 0.85, respectively.

The FT and measurement of LS by TE have high degrees of accuracy and reproducibility for predicting the extent of liver fibrosis and development of LREs in patients with CLDs. Thus, combined application of these two methods may provide additional discriminatory potential for predicting LREs. Indeed, the combination of LS and FT increased the cross-sectional diagnostic performance for assessing the degree of liver fibrosis and the diagnosis of liver cirrhosis (AUROC, 0.910 for LS only; 0.866 for FT only; 0.915 for FT + LS; and 0.929 for FT × LS)[64]. Park *et al*[68] recently conducted a prospective five-year longitudinal study to assess if the combination of FT with LS values enhanced the overall performance of predicting LREs in patients with hepatitis B virus-related liver cirrhosis. The combination was calculated as either the sum or multiplication of the FT score and LS values (FT + LS or FT × LS, respectively).

In this study, 151 patients were analyzed, and the time-dependent AUROCs for predicting LREs were 0.748 (95%CI: 0.621-0.868) and 0.785 (95%CI: 0.647-0.906) at five-year follow-ups of FT + LS and FT × LS, respectively. Data were adjusted for age and histological fibrosis staging, which were the two significant factors according to univariate analysis (*P* < 0.05). Multivariate analysis revealed that FT + LS and FT × LS were independent predictors of LREs (*P* = 0.001, HR = 1.116; *P* = 0.001, HR = 1.137, respectively). Stratification of the study population into three groups showed that the cumulative risk of developing LREs was significantly graded according to the stratification. The study population was stratified with cut-off values of 9.4 and 17.5 for the FT + LS analysis. The cumulative incidence rates of developing LREs at 2, 3, and 5 years were 2.1%, 4.4%, and 6.7%, respectively, for the low group (FT + LS < 9.4); 3.9%, 6.7%, and 13.0%, respectively, for the intermediate group (FT + LS 9.4-17.5); and 8.0%, 12.2%, and 16.8%, respectively, for the high group (FT + LS > 17.5) (*P* = 0.029). Similarly, for the FT × LS analysis, the study population was stratified with cut-off values of 3.6 and 11.0. The cumulative incidence rates of developing LREs at 2, 3, and 5 years were 1.8%, 2.7%, and 4.5%, respectively, for the low group (FT × LS < 3.6); 3.8%, 6.1%, and 14.2%, respectively, for the intermediate group (FT × LS 3.6-11.0); and 8.3%, 12.8%, and 17.5%, respectively, for the high group (FT × LS > 11.0) (*P* = 0.008).

The prognostic role of FT was demonstrated exclusively in a French study of a cohort of patients with chronic hepatitis C. Thus, the clinical value of FT requires further validation in a diverse population of patients with CLDs of varying etiologies. Fortunately, the prognostic performance of FT has recently been demonstrated in several Asian studies of a cohort of patients with chronic hepatitis B in cross-sectional and longitudinal studies[64,69]. Based on current findings, further research is warranted to define the clinical utility of FT for predicting the long-term prognosis of patients with liver cirrhosis.

OTHER MODELS

Several simple non-invasive methods including APRI, FIB-4, Forns' index and Lok index have been found to be useful in assessing the extent of fibrosis in patients with CLD. Given their universal availability without additional economic burden, several studies evaluated the clinical significance of these simple non-invasive scoring systems for prediction of forthcoming complications related to liver cirrhosis.

A retrospective, multicenter, large-scale study of cirrhotic patients by Sebastiani *et al*[70] demonstrated that a combination of the Lok index and the Forns' index had a high negative predictive value (> 90%) to exclude clinically relevant EVs with an AUROC of 0.80, and suggested that these non-invasive markers may be useful as an initial screening tool for cirrhotic patients to exclude the presence of clinically relevant EVs. Another study by Angulo *et al*[71] showed that simple non-invasive methods including APRI and FIB-4 can identify patients with nonalcoholic fatty liver disease at higher risk for development of LREs and higher overall mortality. However, due to the limitations inherent in the retrospective studies, the clinical value of these non-invasive methods needs to be further validated in additional large-scale, prospective, and preferably, longitudinal studies.

Acoustic radiation force impulse (ARFI) elastography is a novel technology based on conventional B-mode ultrasonography, which provides numeric measurements of tissue stiffness as the shear wave velocity[72]. Several publications suggest that LS values and spleen stiffness measured by ARFI elastography both correlate well with the extent of liver fibrosis in patients with CLDs[73-75]. The role of ARFI elastography for assessing the risk of cirrhosis-related complications has been investigated in several studies[76-79].

A recent cross-sectional study by Morishita *et al*[77] showed that LS measurements by ARFI elastography predicted the presence of EVs (cut-off value of 2.05 m/s) or high-risk EVs (cut-off value of 2.39 m/s) in patients with hepatitis C virus-related liver cirrhosis. The diagnostic performance of this method was good (AUROC, 0.890 for EVs; 0.868 for high-risk EVs) with a high negative-predictive value (81% for EVs; 89% for high-risk EVs) and an acceptable positive-predictive value (78% for EVs; 69% for high-risk EVs).

In addition, a study by Bota *et al*[79] proposed a scoring system for predicting high-risk EVs based on liver stiffness and spleen stiffness assessed by ARFI elastography. The diagnostic performance of this scoring system was acceptable (AUROC = 0.721), yet further validation is desired.

Several studies[78,80] also reported that spleen stiffness measurement by TE can provide non-invasive assessment of the presence of EVs in patients with liver cirrhosis. Recently, a prospective study by Takuma *et al*[78] showed that spleen stiffness assessed by ARFI elastography was able to predict the presence of EVs (cut-off value of 3.18 m/s) or high-risk EVs (cut-off value of 3.30 m/s) in patients with liver cirrhosis. This method

showed excellent diagnostic performance (AUROC, 0.933 for EVs; 0.930 for high-risk EVs) and a high negative-predictive value (98.4% for EVs; 99.4% for high-risk EVs). However, the positive-predictive value was low (61.0% for EVs; 47.8% for high-risk EVs). In contrast, Vermehren *et al*[81] reported that the diagnostic performance of spleen stiffness measured by ARFI elastography for predicting large EVs was not satisfactory (AUROC = 0.58). Moreover, Mori *et al*[82] showed that there was no significant association between spleen stiffness measured by ARFI elastography and the presence of EVs in patients with chronic hepatitis C. Furthermore, a recent meta-analysis conducted by Singh *et al*[83] showed that the current techniques of spleen stiffness measurement - either by ARFI or TE - are suboptimal for predicting EVs in patients with CLDs. Hence, further well-designed prospective studies are desired for evaluating the diagnostic role of spleen stiffness measurement in predicting EVs.

There have been no longitudinal studies of the role of LS measurements by ARFI elastography and spleen stiffness measurements with TE or ARFI elastography for risk assessment of LREs in patients with CLDs. Therefore, longitudinal, multi-center studies are warranted to establish a standardized protocol for measuring LS values by ARFI elastography and spleen stiffness by TE or ARFI elastography. Further studies are also needed to validate the clinical role of these non-invasive tools for assessing the risk of liver cirrhosis-related complications.

CONCLUSION

The current view from a limited number of studies is that the recently-introduced non-invasive models can independently predict future cirrhosis-related complications, such as hepatic decompensation, liver failure, HCC, or liver-related death. In addition, some non-invasive tools, such as TE or TE-based models (*i.e.*, LSPS), appear to exhibit superior performance compared to histology and other non-invasive methods for predicting development of LREs.

Non-invasive models may no longer simply be tools for predicting the extent of fibrosis in patients with CLDs. Instead, current literature supports the use of these methods as surveillance tools for predicting future LREs and determining long-term prognosis, which will help to make informed treatment decisions. Future studies should assess whether serial changes in non-invasive measurements or scores reflect the dynamic changes in the risk of developing LREs. In addition, the combination of two or more non-invasive methods should be tested to determine if this approach provides greater discriminatory power for predicting LREs. Significant progress in this field will allow new strategies for risk management in patients with CLD to be developed in the near future.

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