

## Clinical application of liver stiffness measurement using transient elastography in chronic liver disease from longitudinal perspectives

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### Abstract

Accurate determination of the presence and degree of fibrosis in liver is of great importance, because the prognosis and management strategies for chronic liver disease depend mainly on these factors. To date, liver biopsy (LB) remains the "gold standard" for assessing the severity of liver fibrosis; however, LB is often limited by its invasiveness, sampling error, and intra/inter-observer variability in histological interpretation. Furthermore, repeated LB examinations within a short time interval are indeed ineligible in a real clinical practice. Thus, due to the pressing need for non-invasive surrogates for liver fibrosis, transient elastography (TE),

as a novel ultrasound based technology, has allowed a noninvasive measurement of liver stiffness and has gained in popularity over recent years. In the past few years, additional roles for transient TE beyond the initial purpose of a non-invasive surrogate for LB have included the prediction of the most two critical consequences of fibrosis progression: the development of portal hypertension-related complications and hepatocellular carcinoma. This indicates that the role of transient TE is not merely limited to reducing the need for LB, but transient TE can enable the establishment of tailored management strategies by providing more detailed prognostic information. In particular, under the concept in which the clinical course of liver fibrosis is dynamic and bidirectional, especially when appropriate intervention is commenced, transient TE can be used to track the dynamic changes in fibrotic burden during antiviral or antifibrotic treatment. This review discussed extended applications of transient TE in prediction of the development of real clinical endpoints from a longitudinal perspective.

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**Key words:** Liver stiffness; Transient elastography; Fibroscan; Fibrosis; Longitudinal; Outcome

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### INTRODUCTION

The prognosis and management of chronic liver disease (CLD) depend mainly on the amount and progression

of liver fibrosis, which is defined as the excessive accumulation of extracellular matrix proteins, resulting from chronic liver insults<sup>[1,2]</sup>. The initiation of its deposition is an important phase of CLD. As liver fibrosis eventually progresses without appropriate intervention, this process will lead to architectural change of the liver, followed by deterioration of liver function and hemodynamics, complications due to portal hypertension, and an increased tendency for hepatocarcinogenesis<sup>[3]</sup>.

Thus, accurate determination of the presence and degree of liver fibrosis is of paramount importance in choosing treatment strategies, evaluating responses to treatment and the risks of developing liver-related complications, and predicting prognosis in patients with CLD. To assess the severity of liver fibrosis, liver biopsy (LB) remains the “gold standard”. However, LB is often limited by its invasiveness and rare, but serious, complications, including bleeding, pneumothorax, and procedure-related death<sup>[4,5]</sup>. Moreover, repeated LB examinations within a short time interval are impractical. Additionally, concerning the reliability of pathological examinations, not only sampling error inherent in the percutaneous approach, but also intra- and inter-observer variability in histological interpretation may still occur<sup>[6]</sup>. Even if the LB is performed by an experienced physician and interpreted by an expert pathologist, it has an up to 20% error rate in disease staging<sup>[7,8]</sup>.

Ideally, a method of evaluating liver fibrosis should accurately determine the presence of significant fibrosis, and be readily available, highly reproducible, and widely applicable to liver diseases of various etiologies. Although LB does not fulfil all these criteria, it has remained the gold standard, likely due to the absence of a better alternative. Recently, liver stiffness measurement using transient elastography (TE) was introduced as a promising non-invasive method for assessment of liver fibrosis<sup>[9-15]</sup>. In many studies, TE proved to be a reliable and accurate surrogate for LB in terms of prediction of significant fibrosis or cirrhosis<sup>[8,16-19]</sup>. In a large-scale meta-analysis including 50 studies, the mean areas under the receiver operating characteristic curves (AUROCs) for the diagnosis of significant fibrosis and cirrhosis were 0.84 and 0.94, respectively, with optimal cutoff values of 7.6 and 13.1 kPa, respectively<sup>[20]</sup>.

Most studies to date have focused on assessing the performance of TE, reflected by AUROC, from a cross-sectional perspective, with reference to histological fibrosis. However, because LB as a reference standard is imperfect, it may have only limited clinical implications in terms of increasing the AUROC of TE to 1 (*i.e.*, perfect concordance with LB). Thus, additional roles for TE, namely prediction of long-term prognosis of the disease and monitoring clinical courses, have recently begun to attract attention. This indicates that the role of TE is not merely limited to lessening the frequency of unnecessary LB, but TE can also enable establishment of tailored management strategies by providing more detailed prognostic information<sup>[21]</sup>. In this regard, the “classical” end-points of “static” liver fibrosis in recent cross-sectional

studies on TE are shifting to the “real and solid” end-points of the development of clinical events related to liver fibrosis progression, including hepatic decompensation, hepatocellular carcinoma (HCC), or liver-related death in a longitudinal study from a prospective cohort with long-term follow-up. Additionally, the performance of non-invasive methods is being judged and compared from this viewpoint.

In this article, we reviewed recent studies that focused on the prognostic value of TE for prediction of clinical end-points related to liver fibrosis progression, such as decompensation events, HCC development, or liver-related death, from a longitudinal perspective.

## PREDICTION OF THE DEVELOPMENT OF LIVER-RELATED COMPLICATIONS

### *Portal hypertension-related complications*

The development of portal hypertension is a common consequence of fibrosis progression, leading to the formation of esophageal and gastric varices responsible for variceal bleeding, and other severe complications, such as portosystemic encephalopathy, spontaneous bacterial peritonitis and sepsis<sup>[22-24]</sup>. Measurement of the hepatic venous pressure gradient (HVPG) is the gold standard for portal hypertension assessment in patients with cirrhosis; however, it is invasive and is routinely available only in experienced centers<sup>[25-29]</sup>. Although TE was initially proposed for assessment of liver fibrosis, a good correlation between TE values and HVPG has been reported, as well as the presence of esophageal varices, suggesting that it may be a valuable tool for the non-invasive evaluation of portal hypertension<sup>[30-32]</sup>. Subsequent studies have investigated correlations between TE values and the hepatic decompensation due to increased portal hypertension. A significant correlation between TE values and portal hypertension, expressed as the HVPG, was reported by Vizzutti *et al.*<sup>[33]</sup> suggesting that TE may reflect a progressive rise in portal pressure due primarily to increased hepatic vascular resistance, caused by fibrillar extracellular matrix accumulation. Based on this concept, Foucher *et al.*<sup>[34]</sup> first reported that cutoff values of 27.5, 37.5, 49.1, 53.7 and 62.7 kPa had > 90% negative predictive values for the presence of large esophageal varices (stage 2/3), Child-Pugh score B or C, past history of ascites, HCC and esophageal bleeding, respectively.

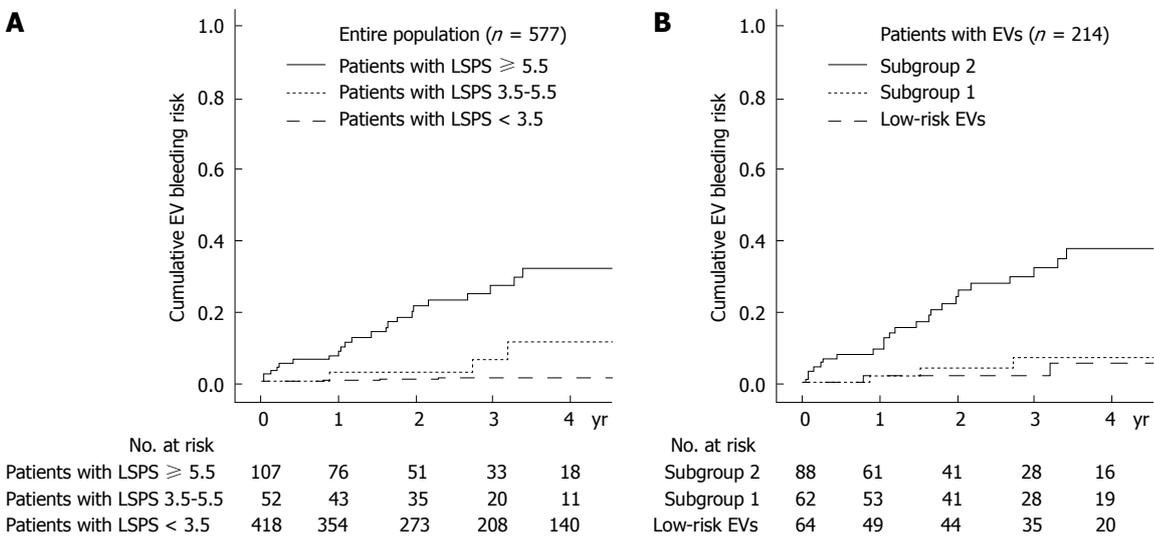
As variceal bleeding is a life-threatening complication of portal hypertension, the relationship between TE values and the presence of esophageal varices has been investigated in several studies<sup>[35-40]</sup>. All demonstrated a significant correlation between TE values and the presence of esophageal varices and that TE values could predict the presence of large varices (more than grade 2)<sup>[38,40]</sup>. Table 1 summarizes reports of the relationship between TE values and esophageal varices<sup>[33,38,40-44]</sup>.

Although TE can predict the presence of esophageal varices and consequently assist in selection of candidates for endoscopic screening or prophylactic treatment, sever-

**Table 1 Diagnostic performance of transient elastography for prediction of esophageal varices or large esophageal varices**

Ref.	No. of patients (etiology)	Endpoints	AUROC	Cutoffs (kPa)	Sensitivity	Specificity	PPV	NPV
Vizzutti <i>et al</i> <sup>[33]</sup>	47 (HCV)	EV	0.76	17.6	90%	43%	77%	66%
Castéra <i>et al</i> <sup>[38]</sup>	70 (HCV)	EV	0.84	21.5	76%	78%	68%	84%
Kazemi <i>et al</i> <sup>[40]</sup>	165 (CLD)	Large EV	0.87	30.5	77%	85%	56%	94%
		EV	0.83	13.9	95%	43%	57%	91%
Bureau <i>et al</i> <sup>[41]</sup>	89 (CLD)	Large EV	0.84	19.0	91%	60%	48%	95%
		EV	0.85	21.1	84%	71%	NA	NA
Pritchett <i>et al</i> <sup>[42]</sup>	211 (CLD)	Large EV	0.76	29.3	81%	61%	NA	NA
		EV	0.74	19.5	76%	66%	56%	82%
Nguyen-Khac <i>et al</i> <sup>[43]</sup>	183 (CLD)	Large EV	0.76	19.8	91%	56%	91%	55%
		Large EV	0.76	48.0	73%	73%	44%	90%
Malik <i>et al</i> <sup>[44]</sup>	124 (CLD)	Large EV	0.73	19.8	89%	55%	27%	97%
		Large EV	0.77	47.2	85%	64%	44%	93%
		EV	0.85	20.0	NA	NA	80%	75%

AUROC: Area under the receiver operating characteristic curve; PPV: Positive predictive value; NPV: Negative predictive value; CLD: Chronic liver disease; EV: Esophageal varix; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NA: Not available.

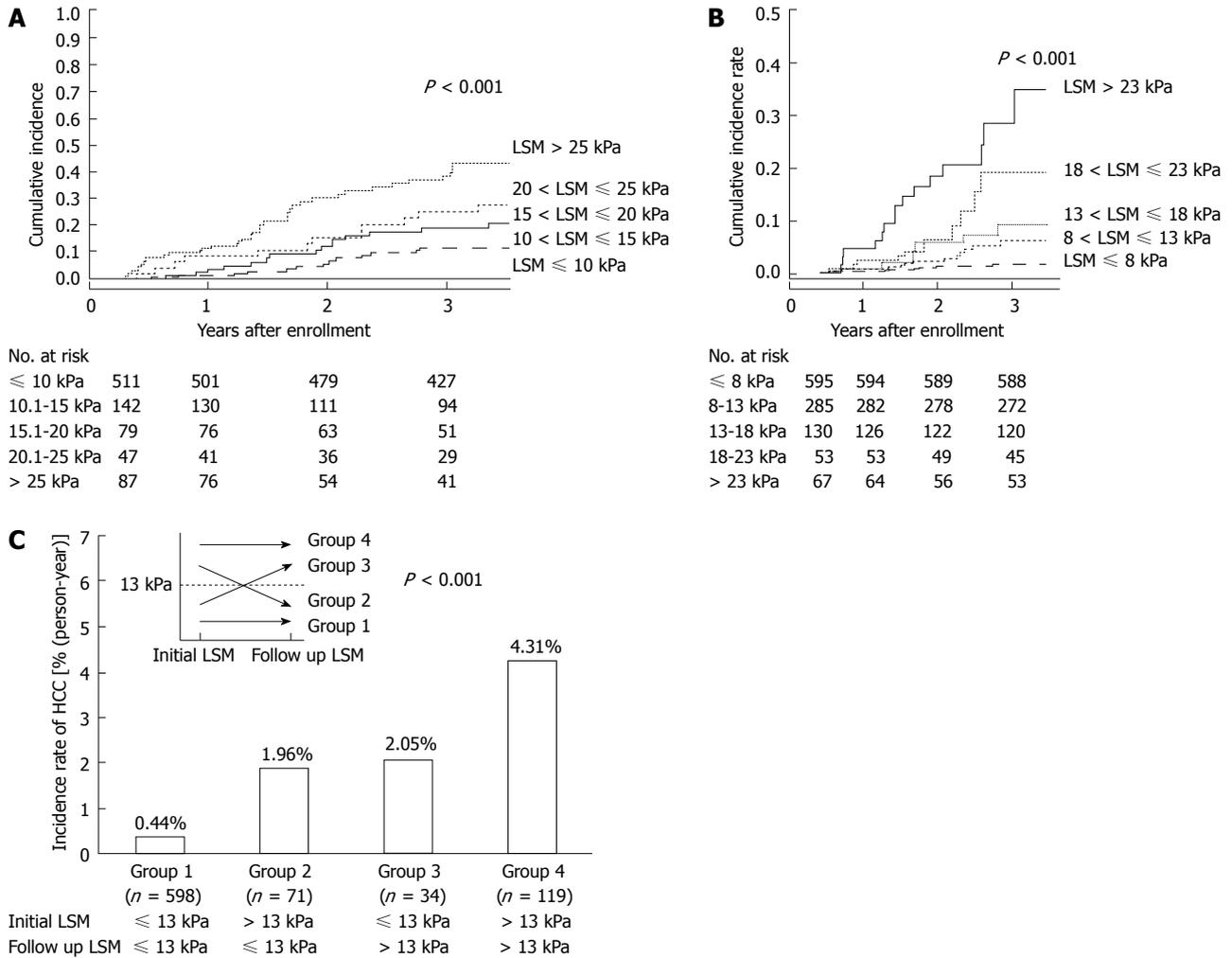


**Figure 1 Cumulative incidences of variceal bleeding based on liver stiffness-spleen diameter to platelet ratio score values.** A: The incidence of variceal bleeding increased significantly in association with higher liver stiffness-spleen diameter to platelet ratio score (LSPS) values (long-rank test,  $P < 0.001$ ); B: In particular, among patients with high risk esophageal varices (EV), the incidence of variceal bleeding was significantly higher in patient with LSPS 6.5 (subgroup 2) than those with LSPS < 6.5 (subgroup 1).

al issues remain unresolved. First, the cutoff values (range, 13.9-21.5 kPa) and performance of TE varied (AUROC range, 0.76-0.85) among studies<sup>[38-40]</sup>. Second, from data currently available, diagnostic performances of TE are acceptable for the prediction of esophageal varices, but far from satisfactory for screening cirrhotic patients without endoscopy confidently. Thus, Kim *et al*<sup>[45]</sup> recently proposed a novel prediction model [liver stiffness-spleen diameter to platelet ratio score (LSPS)] to address this issue, achieving higher accuracy using TE values and other parameters simultaneously that reflect portal hypertension as constituent variables. Overall, this model had excellent diagnostic accuracy for the prediction of high-risk esophageal varices (HEV, AUROC = 0.953; negative predictive value 94.7%, positive predictive value 93.3%).

Beyond this cross-sectional analysis, a subsequent study by the same group recently showed that LSPS can be a reliable predictor of the development of variceal

bleeding<sup>[20]</sup>. In this prospective, longitudinal study analyzing 577 patients with hepatitis B virus-related cirrhosis, those with LSPS ≥ 5.5 had higher cumulative incidences of esophageal variceal bleeding during the follow-up period and LSPS score ≥ 6.5 was an independent risk factor of variceal bleeding among those with HEV, indicating that further prophylactic treatment such as endoscopic ligation in addition to a non-selective beta-blocker should be considered in these high-risk patients (Figure 1). In a similar context, Kim *et al*<sup>[46]</sup> stratified the risk of hepatic decompensation, such as ascites, hepatic encephalopathy, variceal hemorrhage, and deterioration of liver function to Child-Pugh class B or C, based upon three classes of TE values (TE value < 13, 13-18 and ≥ 18 kPa) in histologically proven hepatitis B virus-related cirrhosis with well-preserved liver function and no history of decompensation. In a multivariate analysis, patients with a TE value of 13-18 kPa [hazard ratio (HR), 4.547;  $P = 0.044$ ] and ≥ 18



**Figure 2** Cumulative incidence of hepatocellular carcinoma development based on stratified transient elastography values in patients with chronic hepatitis C (A,  $n = 866$ ) and those with chronic hepatitis B (B,  $n = 1130$ ). The cumulative incidences increased significantly in association with higher TE values (log-rank test, all  $P < 0.001$ ). In particular, the overall incidence of HCC differed significantly among the four groups (C) (both initial and follow-up TE values ≤ 13 kPa (group 1), initial TE value > 13 kPa and follow-up TE value ≤ 13 kPa (group 2), initial TE value ≤ 13 kPa and follow-up TE value > 13 kPa (group 3), and both initial and follow-up TE values > 13 kPa (group 4) according to changing patterns of TE value during follow-up ( $P < 0.001$ ; Figure 2C). A: Cited from Masuzaki *et al.*<sup>[52]</sup>; B and C: Cited from Jung *et al.*<sup>[53]</sup>. HCC: Hepatocellular carcinoma; TE: Transient elastography; LSM: Liver stiffness measurement.

kPa (HR, 12.446;  $P < 0.001$ ) showed independently higher risks than patients with TE value < 13 kPa.

### HCC

Another promising area for the application of TE, other than portal hypertension-related decompensation events, is the prediction of HCC development. Unless HCC is diagnosed at an early stage, a poor prognosis is expected due to the limited treatment options<sup>[47-51]</sup>. Thus, early prediction of HCC development is of great importance, especially in high-risk patients. Among traditional risk factors, advanced liver fibrosis and cirrhosis is known to have a close association with risk of HCC development<sup>[47]</sup>. Thus, assessment of the severity of liver fibrosis at a given time point with subsequent monitoring of liver fibrosis progression by serial check-up is essential for effective and optimized surveillance strategies for the early detection of HCC<sup>[3]</sup>.

Recently, several Asian studies have investigated the

clinical role of TE in the noninvasive prediction of HCC development<sup>[52-56]</sup>. The first large prospective cohort study of 866 Japanese patients with chronic hepatitis C (CHC) tested whether TE can predict the future development of HCC<sup>[52]</sup>. During a mean follow-up of 3 years, 77 patients developed HCC. By multivariate analysis, together with age, male gender, and clinical cirrhosis, stratified TE value was identified as an independent risk factor for HCC development, with relative risks of 16.7, 20.0, 25.6 and 45.5 for TE values of 10-15, 15-20, 20-25 and > 25 kPa, respectively, *vs* an TE value of < 10 kPa as the reference and the cumulative incidence of HCC showed a step-wise increase according to stratified TE value (Figure 2A). Despite there being no histological analysis in relation to TE values and inclusion of patients with high alanine aminotransferase (ALT) levels [ $> 5 \times$  upper limit of normal (ULN)] both of which can attenuate the accuracy of TE, this study confirmed that severity of liver fibrosis, reflected by higher TE values, was closely associated with higher

risk of HCC development and suggested a clinical role for TE in a longitudinal setting using HCC development as a solid clinical endpoint. Interestingly, in this study, even patients with not so high level of TE (10-15 kPa) were still more subject to HCC development with an adjusted HR of 16.7, compared to those with a TE value < 10 kPa.

Another large Korean cohort study with 1130 patients with chronic hepatitis B (CHB) also confirmed the longitudinal role of TE on HCC development<sup>[53]</sup>. Together with age, male gender, heavy alcohol consumption, lower serum albumin, and HBeAg positivity, stratified TE value was identified as an independent risk factor for HCC development, with relative risks of 3.07, 4.68, 5.55 and 6.60 for liver stiffness measurement (LSM) values of 8-13, 13-18, 18-23 and > 23 kPa, respectively, when compared with a LSM value of < 8 kPa as a reference (Figure 2B). In contrast to the Japanese study<sup>[52]</sup>, several additional issues were further analyzed in this Korean study. First, when the diagnosis of cirrhosis showed discordant results between TE-based and clinical-based criteria, patients with cirrhosis based on TE were at a higher risk of HCC development than those with cirrhosis based on clinical criteria, indicating the superiority of TE for diagnosis of compensated liver cirrhosis. Second, patients with TE values below the cutoff level for cirrhosis, 8-13 kPa, had a higher relative risk of HCC development than those with LSM values < 8 kPa. Although this finding should be validated in large prospective studies, the issue of expansion of the high-risk group for HCC surveillance to include those with significant fibrosis was raised by this study. Furthermore, when patients with available follow-up TE values were analyzed, the risk of HCC development changed according to the pattern of the changes in TE values, suggesting a potential role for serial measurements of TE as a dynamic monitoring tool for risk estimation of HCC development (Figure 2C). However, other confounding factors including lack of histological information, insensitive HBV DNA tests, and heterogeneity in antiviral treatment should be noted when interpreting these results. Recently, Chon *et al.*<sup>[56]</sup> compared the performance of various noninvasive fibrosis prediction methods [aspartate aminotransferase-to-platelet ratio index (ARRI), age-spleen-to-platelet ratio index (ASPRI), TE, LSPS, P2/MS and FIB-4] for prediction of HCC development in patients with CHB and concluded that TE and LSPS showed the best performance (AUROC = 0.789 and 0.788, respectively). Using multivariate analyses, TE and LSPS were identified as independent predictors of HCC development.

In another study<sup>[54]</sup> from Hong Kong, which followed up 528 patients with HBeAg negative CHB for a median length of 35 mo and identified seven patients with HCC development, the cumulative incidence of HCC was higher in patients with TE values  $\geq$  10 kPa than those with TE values < 10 kPa (9% *vs* 0%, respectively;  $P < 0.001$ ), and the cumulative liver-related mortality was also higher in patients with TE values < 10 kPa compared with those with TE values  $\geq$  10 kPa (4% *vs* 0%, respec-

tively;  $P < 0.001$ ). By multivariate analysis, only TE value was significantly associated with HCC development and liver-related mortality.

Similarly, Kim *et al.*<sup>[55]</sup> investigated the prognostic role of TE in predicting the development of overall liver-related events (LREs), defined as development of HCC, hepatic decompensation, or liver-related mortality, among 128 patients with CHB showing histologically advanced liver fibrosis ( $\geq$  F3) and high viral loads (HBV DNA  $\geq$  2000 IU/mL) before starting nucleos(t)ide analogs. When the study population was stratified into two groups using the optimal cutoff value (19 kPa), patients with TE values > 19 kPa were at significantly greater risk for LRE development than those with TE values  $\leq$  19 kPa (HR, 7.176;  $P = 0.001$ ). Moreover, the incidence of LREs was similar in patients with F3 and F4 (22.2% *vs* 13.6%;  $P = 0.472$ ); however, it differed significantly between patients with TE values  $\leq$  19 kPa and those with TE values > 19 kPa (6.9% *vs* 44.4%;  $P < 0.001$ ), indicating the superior performance of TE to that of histology in prediction of LRE development.

Apart from predicting HCC development, the application of TE was validated in a study by Vergniol *et al.*<sup>[57]</sup>, in which 1457 patients with CHC were followed up; 5-year survival outcomes worsened as TE values increased. The prognostic values of TE were demonstrated to be statistically significant ( $P < 0.0001$ ) after adjustment for other important factors, including treatment response, patient age, and estimates of necroinflammatory grade. For example, the 5-year overall survival was 96% in patients with TE value < 9.5 kPa, and 47% in patients with TE value > 40 kPa.

Overall, TE has shown the potential for a clinical role in predicting the development of portal hypertension-related hepatic decompensation and/or HCC and, in part, demonstrated superior performance to histology and other noninvasive tools<sup>[41,58-63]</sup>. This is most likely due to the wider dynamic range of TE values in the evaluation of liver cirrhosis. In fact, as the stage of "cirrhosis" has to date been defined by histopathological evidence of one or two qualitative categories (METAVIR stage F4 or ISHAK S5-S6), or more generally by the presence of so-called "regenerative" or "cirrhotic nodules", an interval scale cannot be used in this setting<sup>[64-66]</sup>. However, the degree of liver fibrosis may vary widely among patients in this category, and the risk of hepatic decompensation and HCC may not be uniform. Thus, in this regard, because TE value, expressed in kPa as a continuous variable, has a wide dynamic range within the cirrhotic stage from the cutoff level from non-cirrhosis (15-17 kPa) to the upper measurement limit of present devices (75 kPa), it would seem to be a more reasonable tool for detailed prognostication.

## UTILITY OF TE IN THE SURGICAL SETTING

Because TE values show significant correlations with portal hypertension and HCC development, prediction

of postoperative short-term outcomes, such as hepatic insufficiency, and long-term outcomes, such as recurrence or liver-related death using TE has been tested in several pilot studies<sup>[67-69]</sup>. Although further studies are required to validate these results, TE may facilitate stratification of patients undergoing curative resection according to different prognoses.

In the first place, Kim *et al.*<sup>[67]</sup> investigated whether preoperative TE values could predict the development of postoperative hepatic insufficiency after curative resection of HCC. In this study, multivariate analyses revealed that a TE value > 25.6 kPa was the only predictor of postoperative insufficiency. The AUROC of 25.6 kPa was higher than that of indocyanine green R15, which is a popular method for assessment of preoperative functional reserve liver function (0.824 *vs* 0.620, respectively). Similar results were obtained in a subsequent investigation by the same group<sup>[68]</sup>. In this study, the performance of TE was superior to that of diffusion-weighted magnetic resonance imaging, which has also been shown to be a noninvasive fibrosis prediction tool for the assessment of liver fibrosis and the prediction of postoperative hepatic insufficiency.

Another issue is prediction of HCC recurrence after curative resection, that is, *de novo* recurrence in the background liver with fibrotic burden, using preoperative TE. In an analysis of 133 patients who underwent preoperative TE and curative resection (HCC recurred in 62 patients), TE was selected as an independent predictor of recurrence, whereas histological fibrosis status was not<sup>[69]</sup>. In the study, patients with preoperative TE values > 13.4 kPa were at a greater risk of recurrence, with an HR of 1.925 ( $P = 0.010$ ). More specifically, when recurrence was stratified into early (< 2 years) and late ( $\geq 2$  years), TE values were significantly related to late recurrence, thus supporting the hypothesis. These results suggest that preoperative TE could reveal the potential influence of liver fibrosis on recurrence and explain multicentric carcinogenesis in a fibrotic liver. However, more data are needed to clarify this issue.

## ROLE OF TE IN MONITORING FIBROTIC BURDEN DURING ANTIVIRAL THERAPY

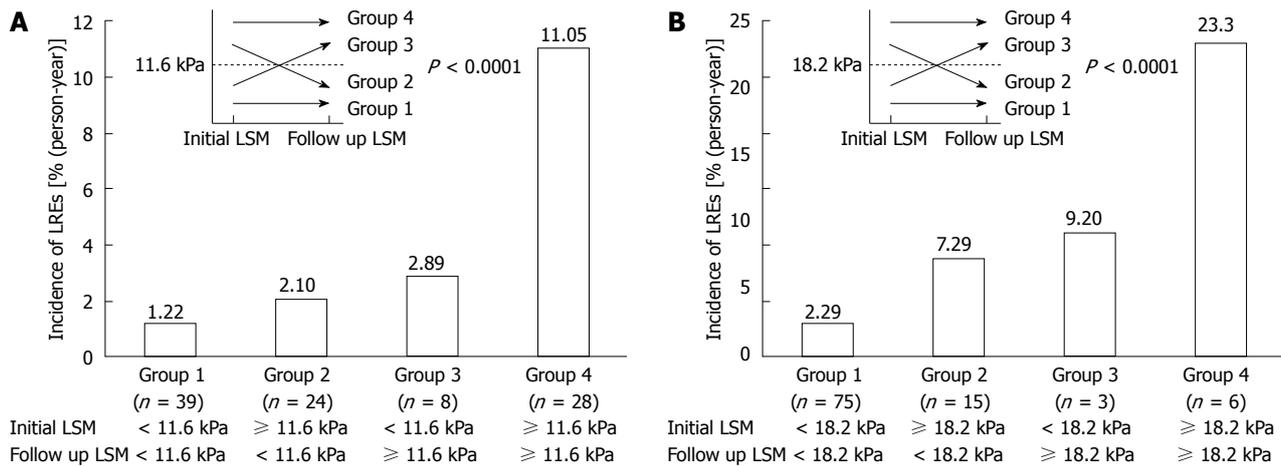
Recently, the concept of “cirrhosis” has changed from static and uncompromisingly progressive to rather dynamic and bidirectional, especially when treatment against the causative agent of tissue damage (*i.e.*, antiviral agents against CHB or CHC and antifibrotic agents) can be introduced successfully at this stage of the disease. The ideal approach to evaluate histological outcomes during antiviral therapy, such as fibrosis regression and necroinflammation stabilization, is serial LB examinations. However, this is impractical, primarily due to the inherent invasiveness of LB. Instead, because of the ease, safety, and rapidity of TE, it may be useful for monitoring the dynamic changes in liver fibrosis during antiviral or antifibrotic treatment. Indeed, several studies have reported

the clinical usefulness of TE for monitoring potential fibrosis regression during antiviral treatment in patients with CHC and CHB<sup>[57,70-77]</sup>.

Kim *et al.*<sup>[71]</sup> analyzed 41 patients with CHB who received antiviral treatment using nucleos(t)ide analogs. To prevent the confounding effect of high ALT, patients with high ALT levels more than 2 $\times$  ULN, were excluded. Although ALT levels did not show a statistically significant change during the first 12 or 24 mo of antiviral treatment, TE values decreased significantly, indicating potential fibrosis regression due to prolonged antiviral treatment. Indeed, fibrosis regression and stabilization of necroinflammation was noted in two patients with available paired LBs. Enomoto *et al.*<sup>[70]</sup> reported the changes in LSM values during the first 12 mo of entecavir treatment in 20 patients. Median TE values decreased significantly from 11.2 to 7.8 kPa after 12 mo of treatment, and serum fibrosis markers, such as PIIINP and type IV collagen 7S domain, also decreased significantly. In one patient with available paired LBs, histological fibrosis regression and stabilization of necroinflammation were noted. Although these studies suggest a role for TE for monitoring fibrosis regression due to prolonged antiviral treatment, the short duration of observation and small sample sizes with paired biopsies are major limitations of these studies.

Recently, data regarding a longer antiviral treatment duration (more than 3 years) have become available<sup>[72-74,78]</sup>. Fung *et al.*<sup>[72]</sup> reported a significant decline in TE values from baseline after subsequent ALT normalization with 3-year treatment ( $n = 110$ , 7.8 to 6.1 kPa;  $P = 0.002$ ). In this study, independent factors associated with a significant decline in TE value of  $\geq 1$  kPa included antiviral therapy and ALT levels at the follow-up time point. Another study by Andersen *et al.*<sup>[78]</sup> also noted significant declines in TE values after a median antiviral treatment duration of 50.5 mo ( $n = 66$ ), and concluded that prolonged antiviral treatment in patients with CHB resulted in significant declines in TE values, suggesting regression of fibrosis in a majority of patients with advanced fibrosis or cirrhosis.

Likewise, for patients with CHC, changes in TE values during antiviral treatment have been investigated in several studies. Two prospective studies by Vergniol *et al.*<sup>[57]</sup> and Ogawa *et al.*<sup>[75]</sup> demonstrated that patients with CHC showing sustained virological responses to pegylated interferon-ribavirin combination therapy had significantly reduced TE values at the end of follow-up. Moreover, Ogawa *et al.*<sup>[75]</sup> reported that patients with non-sustained virological responses, but with a biochemical response, showed a greater reduction in TE values than did those with a non-biochemical response. Subsequent studies reported similar results, suggesting that changes in TE values during antiviral treatment in patients with CHC may represent alterations in the severity of liver fibrosis<sup>[76,77]</sup>. However, it should be further confirmed whether the favorable changes in LSM values during or after antiviral treatment does have a significant influence



**Figure 3** Incidence of liver-related events according to changes in transient elastography values after 6 mo of antiviral therapy. The overall incidence of liver-related events differed significantly among the four groups using TE value cutoffs of 11.6 kPa (A) and 18.2 kPa (B) (both  $P < 0.0001$ ). Adapted from Kim *et al.*<sup>[79]</sup>. TE: Transient elastography; LSM: Liver stiffness measurement; LREs: Liver-related events.

on the long-term prognosis such as disease-specific survival in patients with CHC.

Taken together, TE value seems to decrease during and after antiviral therapy. However, without paired histological results through repeated LB, whether the reduction in TE values is closely correlated with regression of liver fibrosis or improvement in necroinflammatory scores remains unclear. To clarify this, Lim *et al.*<sup>[73]</sup> investigated patterns of TE values among patients who were treated with entecavir. In all subjects, the median TE value at baseline was 15.1 (range, 5.6-75.0) kPa and decreased significantly, to 8.8 (range, 3.0-33.8) kPa after 12 mo of therapy, and a decrease in TE values correlated significantly with increase in albumin, decrease in bilirubin, decrease in ALT level, and decrease in aspartate aminotransferase levels (all  $P < 0.05$ ). However, among 15 patients with available paired LBs, decreases in TE values were correlated significantly with improved necroinflammatory scores, but not with fibrosis regression. Similarly, Wong *et al.*<sup>[74]</sup> insisted that the decline in absolute TE values during antiviral treatment did not reflect the change in histologically assessed liver fibrosis, probably due to the confounding influence of ALT reduction caused by antiviral treatment.

However, regardless of whether TE values during antiviral treatment are due to fibrosis regression, activity stabilization, or both, changes in TE value during antiviral treatment can be translated into the overall response of chronically diseased liver to antiviral treatment from the viewpoint of its long-term clinical implications. Thus, it is more logical to investigate whether the decline in TE value can be used as a favorable predictor of long-term prognosis. Encouraging results were recently published by Jung *et al.*<sup>[53]</sup> suggesting that the change in TE values in patients with CHB showed a significant correlation with differential future risk of HCC development. Additionally, Kim *et al.*<sup>[79]</sup> insisted that changes in TE values were significantly associated with the difference risk of liver-related event occurrence, such as hepatic decompensation, HCC

development, and LREs (Figure 3). This would suggest that the assessment of overall background liver status using TE may be an important end-point in the management of CHB and prediction of long-term outcomes. Further research is needed to evaluate the reproducibility of such findings in independent populations.

### LIMITATIONS OF TE

Although TE has demonstrated reliable diagnostic accuracy with excellent inter-observer and intra-observer agreement, additional space-occupying tissue abnormalities, such as edema and inflammation, cholestasis, and congestion may interfere with TE, regardless of the degree of liver fibrosis, because the liver is wrapped in a distensible, but non-elastic, envelope (Glisson's capsule)<sup>[80]</sup>.

First, the extent of histological necroinflammatory activity has been shown to influence TE results in patients with viral hepatitis, resulting in an overestimation of TE values that increases in parallel with the degree of necroinflammatory score<sup>[81-85]</sup>. Consistent with these results, a risk of overestimation of TE values has been reported in cases of ALT flares in patients with acute viral hepatitis or CHB<sup>[86-92]</sup>. Thus, in such subjects, TE examinations should be delayed until ALT levels have stabilized. In this regard, several studies have investigated the optimal period (3 to 6 mo) for restoration of the reliability of TE values in patients with acute flares<sup>[88,91,93,94]</sup>. Furthermore, even mild to moderate elevation in ALT can be associated with higher liver stiffness values, and may cause discrepancies between TE results and the actual underlying fibrosis. Apart from necroinflammation, extrahepatic cholestasis<sup>[95]</sup> and congestive heart failure<sup>[96-98]</sup> may also contribute to the overestimation of TE.

Additionally, the performance of TE may be limited in patients with a high body mass index (BMI), narrow intercostal space, or ascites<sup>[9]</sup>. Although TE reproducibility has been shown to be excellent in terms of inter-observer and intra-observer agreement, a high BMI (> 28

**Table 2** Proposal of application of transient elastography in each clinical setting

Clinical setting	Role of TE
Prediction of portal hypertension	TE with platelet counts and spleen size complementary to HVPG
Prediction of esophageal varices	TE with platelet counts and spleen size complementary to endoscopy
Prediction of developing esophageal variceal bleeding	TE with platelet counts and spleen size
Prediction of developing portal hypertension-related complications	TE with platelet counts and spleen size
Prediction of developing hepatocellular carcinoma	TE
Prediction of developing postoperative hepatic insufficiency after surgical resection	TE
Prediction of developing recurrence of hepatocellular carcinoma after curative resection	TE
Monitoring of fibrotic burden during antiviral treatment	TE

TE: Transient elastography; HVPG: Hepatic venous pressure gradient.

kg/m<sup>2</sup>) and waist circumference were significantly associated with TE failure<sup>[99]</sup>. These results emphasize the need for adequate operator training and for technological improvements in specific patient populations, such as those with non-alcoholic fatty liver disease. For this, a new TE probe (the XL probe) was recently introduced to lessen the TE failure rate in obese patients; however, its efficacy should be further validated<sup>[100]</sup>.

## CONCLUSION

Over the past decade, significant progress has been made in the non-invasive assessment of liver fibrosis in patients with CLD. Of the methods now available, TE appears to be an excellent tool for assessing liver fibrosis, particularly for diagnosis of cirrhosis, and also has prognostic value from a longitudinal perspective. Although TE cannot completely obviate the need for invasive tests, such as LB, endoscopic examination for identification of varices, or HVPG, it represents an important non-invasive tool, enabling more efficient and tailored management strategies for patients with CLD (Table 2). We hope that other researchers will evaluate the usefulness of other similar techniques such as the measurement of spleen stiffness in comparison or in combination with TE in the future.

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