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# Clinical Application of Liver Stiffness Measurement Using Transient Elastography: A Surgical Perspective

Seung Up Kim[a–c] Beom Kyung Kim[a–c] Kwang-Hyub Han[a–c]

[a]Department of Internal Medicine, [b]Institute of Gastroenterology, Yonsei University College of Medicine, and [c]Liver Cirrhosis Clinical Research Center, Seoul, South Korea

**Key Words**

Liver stiffness · Transient elastography · Resection · Transplantation · Outcome

**Abstract**

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 ineligible in real clinical practice. Thus, due to the pressing need for non-invasive surrogates, over the past decade, significant progress has been made in non-invasively assessing liver fibrosis. Of the methods now available, transient elastography (TE) appears to be an excellent tool for assessing liver fibrosis and also has some prognostic value in surgical settings. Recent studies have proposed the extended role of TE in the surgical field, based on the concept that TE values show significant correlations with portal hypertension and hepatocellular carcinoma development. TE appears promising in predicting postoperative short-term outcomes such as hepatic insufficiency or complications and long-term outcomes such as recurrence or liver-related death. Furthermore, TE may be useful in predicting the severity of liver fibrosis progression due to recurrence of hepatitis C virus infection or other underlying liver diseases after transplantation. TE cannot completely replace other tests accompanied with hepatic surgical treatments, including LB, endoscopic examination, hepatic venous pressure gradient evaluation, or the indocyanine green retention test. However, TE represents an important non-invasive tool that enables more efficient and tailored management strategies for patients who were treated with liver resection or transplantation. This review discusses extended TE applications in the surgical setting, such as hepatic resection or transplantation. 

## Introduction

The prognosis and management of chronic liver disease (CLD) depend mainly on the amount and progression of liver fibrosis, which results from chronic liver insults [1, 2]. Thus, accurate determination of the presence and degree of liver fibrosis is of paramount importance in choosing treatment strategies, evaluating responses to treatment, assessing the risk of developing liver-related complications, and predicting prognosis in CLD patients. As a surrogate for liver biopsy (LB), which is an invasive

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Beom Kyung Kim
Department of Internal Medicine
Yonsei University College of Medicine
250 Seongsanno, Seodaemun-gu, Seoul 120-752 (South Korea)
E-Mail beomkkim@yuhs.ac

procedure and is often subject to not only sampling error but also intra- and inter-observer variability in histological interpretation [3–7], liver stiffness (LS) measurement using transient elastography (TE) was introduced as a promising non-invasive method for assessing liver fibrosis [8–13]. In many studies, TE proved reliable and accurate in terms of predicting significant fibrosis or cirrhosis [14–19]. More recently, investigators have identified additional important roles for TE, namely predicting long-term disease prognosis and monitoring clinical courses in a longitudinal perspective [20]. These data indicate that TE's role is not merely limited to lessening the frequency of unnecessary LB, but that TE can facilitate establishing tailored CLD management strategies by providing more detailed prognostic information.

Interestingly, recent several pilot studies have proposed an extended role for TE in the surgical field, based on the concept that TE values show significant correlations with portal hypertension and hepatocellular carcinoma (HCC) development [21–24]. Of these, Cescon et al. [22] and Wong et al. [24] tested the predictive performance of TE for postoperative hepatic insufficiency and failure after hepatic resection. Additionally, several studies proved that TE is useful in predicting the severity of liver fibrosis progression due to recurrent hepatitis C virus (HCV) infection after transplantation [25–28]. If future studies validate the usefulness of TE values in the surgical field, TE will rapidly facilitate the risk stratification of patients undergoing surgical management according to different prognoses assessed by this approach.

In this article, we review recent studies that focus on the prognostic value of TE in predicting clinical endpoints after liver resection, from a surgical standpoint. These endpoints include not only postoperative hepatic insufficiency or complications, but also HCC recurrence and liver fibrosis progression after transplantation.

## Prediction of Short- and Long-Term Outcomes Using TE after Hepatic Resection

### *Postoperative Hepatic Insufficiency and Failure*

With considerable improvements in perioperative intensive care and refined surgical techniques, the rates of death and complications after major liver resection surgery have decreased significantly [29–32]. Nevertheless, because many patients still have liver cirrhosis or other CLDs, death and complications may follow liver resection surgery occasionally. Therefore, it is important to investigate the functional liver reserve before hepatic resection. To date, some hepatologists favor assessment of hepatic venous pressure gradient as a preoperative test to estimate the portal pressure and liver reserve; however, it is not widely accepted owing to its invasiveness. Instead, in Eastern countries including Korea and Japan, indocyanine green retention rate at 15 min (ICG R15) has been widely used. Recently, several studies investigated whether TE can assess the hepatic functional reserve and if it can be used as a predictor of short-term surgical outcomes after hepatic resection.

The first study that extended the scope of TE use to the surgical field investigated whether preoperative TE values could predict the development of postoperative hepatic insufficiency after curative resection of HCC [21]. In this study, postoperative hepatic insufficiency was defined as persistent hyperbilirubinemia (total bilirubin level ≥5 mg/dl) for more than 5 days after surgery, or postoperative death without other identifiable causes. Multivariate analysis revealed that TE values >25.6 kPa were identified as the only predictor of postoperative insufficiency. The area under the receiver operating characteristic curve (AUROC) of LS values using TE was higher than that of ICG R15 measurements (0.824 vs. 0.620, respectively). The usefulness of TE in assessing postoperative hepatic insufficiency was also demonstrated in subsequent investigations [33] that compared the predictive ability of TE with another radiological tool, diffusion-weighted magnetic resonance imaging (DW-MRI), using apparent diffusion coefficient values [34, 35]. In patients who underwent liver resection for HBV-related HCC, the predictive performance of TE was superior to that of DW-MRI (AUROC 0.942 vs. 0.797, respectively). The TE cutoff value was set at 22.4 kPa and was similar to that used in a previous study (25.6 kPa) [21]. However, these two pilot studies had several common drawbacks. First, they did not consider other variables such as serum hyaluronic acid level, which is closely correlated with the functional liver reserve and is a useful predictor of liver regeneration [29], or the concept of 'future liver remnant volume' calculated using preoperative helical computed tomography scans. Second, since the primary endpoint of 'postoperative hepatic insufficiency' in these two studies was defined based only on postoperative total bilirubin levels, further studies using more comprehensive endpoints that cover milder degrees of postoperative hepatic dysfunction should be conducted.

Based on a similar hypothesis by Kim et al. [21, 33], a more recent study from Hong Kong [24] also proposed the superior performance of TE to that of the ICG R15 in

predicting major postoperative complications, defined as ≥grade 3 complications based on a modified Clavien classification [36, 37]. The AUROC of TE and ICG R15 in predicting major postoperative complication was 0.79 and 0.51, respectively, and only TE showed a significant positive correlation to the primary endpoint. When the optimal cutoff TE value of 12.0 kPa was used, TE displayed a hazard ratio of 7.33. Interestingly, operative blood loss and blood transfusion rates were significantly higher in patients with preoperative TE value ≥12.0 kPa, consistent with previous studies that observed greater blood loss in cirrhotic patients [38, 39]. Similar results were reported in another recent study [40], wherein even patients without overt hemostatic disorder at preoperative evaluation were also subject to bleeding risk according to the TE values. Whether this higher bleeding tendency in cirrhotic patients depends on physical properties such as technical difficulties during surgical manipulation, or functional properties such as a hemostatic disorder, remains to be determined.

An Italian study which recruited mostly HCV-related HCC also investigated whether preoperative TE can predict the outcome of hepatic resection for HCC [22]. In this study, the primary endpoint was postoperative liver failure (PLF), which was defined more comprehensively to cover milder grades of PLF and included the presence of at least one of the following variables graded according to the Dindo-Clavien classification: occurrence of refractory ascites, increased bilirubin levels to >3 mg/dl, altered coagulation factors requiring fresh frozen plasma infusion, or renal impairment [37]. ROC analysis identified patients with LS values ≥15.7 kPa as being at higher risk of PLF (AUROC = 0.865). Multivariate analysis showed that low preoperative serum sodium levels, histological cirrhosis, and elevated LS values were independent predictors of PLF [22]. The authors concluded that LS measurement using TE is a valid tool for predicting PLF in patients undergoing hepatectomy for HCC. However, ICG R15 data was missing for direct comparison between TE and ICG R15.

Taken together, these two studies confirmed a potential clinical role for TE as a non-invasive and convenient tool for risk stratification or risk disclosure to patients before hepatectomy. Future studies based on various non-invasive preoperative tools to assess reserve liver function including computed tomography volumetry, and serological methods such as FibroTest® (BioPredictive, Paris, France) and the European Fibrosis Panel test, should be compared for their risk stratification utility.

*Predicting HCC Recurrence after Hepatic Resection*

Another issue is using preoperative TE to predict HCC recurrence after curative resection, i.e. de novo recurrence in the background liver with fibrotic burden. In an analysis of 133 patients who underwent preoperative TE and curative resection, HCC recurred in 62 patients [23]. TE was identified as an independent predictor of HCC recurrence, whereas histological fibrosis status was not predictive. This phenomenon can be explained in several ways [23]. First, because high-risk patients with advanced liver cirrhosis where another treatment option such as liver transplantation is generally prepared were excluded as resection candidates, the influence of liver fibrosis on postoperative recurrence may have been underestimated. Second, pathological factors other than liver fibrosis, which greatly contributed to recurrence, may have attenuated the potential influence of liver fibrosis on recurrence. Third, the influence of liver fibrosis also may have been confounded, because liver cirrhosis was analyzed as a single category without considering the wide-range severity of liver cirrhosis. In that study, patients with preoperative TE values >13.4 kPa were at greater risk for HCC recurrence, with a hazard ratio of 1.925 ($p = 0.010$). When HCC recurrence was stratified into early (<2 years) and late (≥2 years) recurrence, TE values were significantly related to late recurrence. These results suggest that preoperative TE could reveal the potential influence of liver fibrosis on HCC recurrence and explain multicentric carcinogenesis in the fibrotic liver. However, more data are needed to clarify this issue.

## Using TE to Predict Short- and Long-Term Outcomes after Orthotopic Liver Transplantation

*Monitoring of Graft Function and Complications in the Peritransplantation Period*

To date, there has been little evidence that supports TE usefulness in monitoring liver grafts in the peritransplantation period. However, some studies indicated that TE values in patients with acute liver damage may increase substantially regardless of chronic structural changes [41, 42]. Thus, TE is hypothesized to be a non-invasive monitoring tool to trace dynamic LS changes in post-transplant liver graft. Inoue et al. [43] measured 678 TE results from 24 living donor orthotopic liver transplantation (OLT) recipients in the peritransplantation period. They reported that TE values were greatest in the first postoperative week (mean 24.8 kPa) and declined thereafter. Furthermore, recipients who had experienced complications such as acute cellular rejection, hepatic arterial

thrombosis, and sepsis had significantly higher TE values than those without complications beyond the fourth ($p = 0.0066$) and fifth postoperative week ($p = 0.003$). Recently, Lee et al. [44] reported that greater TE values are associated with lower graft-to-recipient weight ratios and higher serum bilirubin levels in the first week after liver transplantation. These phenomena are most likely due to persistent hypercirculation and regeneration after transplant, the latter of which is more dynamic during the first week after living donor OLT.

*Predicting Graft Disease in Liver Recipients after Orthotopic Liver Transplantation*

For patients who underwent OLT, LB has been shown to be an important diagnostic and prognostic tool for managing recipients. This is because studies of long-term OLT patients have shown a high prevalence of histological abnormalities in protocol LBs even in the absence of abnormal liver function tests [45–47]. In most OLT patients, several risk factors are presumably involved in allograft fibrosis progression [48–50]. For example, in HCV patients, viral re-infection is likely to be the major factor contributing to hepatocyte injury. Fibrosis progression in non-HCV patients was attributed to risk factors such as metabolic syndrome, non-alcoholic steatohepatitis, and history of biliary obstruction, as well as to surgical factors. Additionally, profibrogenic effects of calcineurin inhibitors have been demonstrated both in vitro and in vivo, and may have contributed to fibrosis progression [51, 52]. Many transplant centers perform protocol LBs to assess fibrosis progression to determine the need for specific intervention and for accurate prognostication. However, because LB has several inherent drawbacks owing to its invasiveness, especially when repeated examinations are required, TE might be a good alternative.

The clinical utility of TE has been investigated to assess the severity of recurrent HCV infection [25, 26, 53, 54]. HCV recurrence in post-OLT patients is nearly universal and has an unpredictable and often accelerated course of disease progression to portal hypertension and liver failure, versus HCV infection of a native liver [55, 56]. This might explain the more rapid liver fibrosis progression in HCV patients when compared with patients transplanted for other indications. Hepatitis and fibrosis occur in 75–80 and 10–30% of recipients, respectively, at 5 years [57, 58]. Furthermore, cholestatic hepatitis occurs in approximately 10% of OLT patients and leads to graft failure and death [59]. The presence of significant liver fibrosis at 1 year after transplantation identifies patients at high risk of graft loss [60, 61]. However, antiviral therapy initiated too early has no mortality benefit but often substantial side effects, whereas therapy initiated too late may decrease efficacy and clinical benefits [62, 63]. Therefore, determining the appropriate timing for commencing antiviral therapy is very important. In this respect [25–28], TE results are well correlated with liver fibrosis histological scores, although some influence of hepatitis-associated necroinflammatory activity is observed. The study by Carrión et al. [26] reported that the AUROC was 0.90 for significant fibrosis and 0.98 for cirrhosis in 124 liver transplant recipients with recurrent HCV infection. Using a cutoff value of 8.5 kPa, the sensitivity, specificity, negative predictive value, and positive predictive value of TE for diagnosing significant liver fibrosis were 90, 81, 79, and 92%, respectively. When using a cutoff value of 12.5 kPa, the sensitivity, specificity, negative predictive value, and positive predictive value for cirrhosis diagnosis were 100, 87, 50, and 100%, respectively. These findings were supported by subsequent studies [27, 28]. In a prospective, longitudinal study of sequential paired examinations using TE and LB in liver graft recipients with recurrent HCV, TE changes over time were dynamically correlated not only with changes in liver fibrosis stage but also with changes in necroinflammatory activity and the occurrence of complications such as cellular rejection, cholestasis, and de novo autoimmune hepatitis [25].

These observations indicate that TE is a reliable predictor of liver graft damage independent of HCV recurrence. However, there remain only limited data about the clinical application of TE in patients undergoing transplantation for end-stage liver diseases other than HCV. Beckebaum et al. [64] prospectively assessed the efficacy of TE, biochemical tests, and more complex scores in determining fibrosis stage in 157 patients transplanted for HCV infection or non-HCV-related liver diseases. Although TE performed better in HCV patients than in non-HCV patients, it is still a reliable method of assessing severe fibrosis in HCV patients: the optimal TE cutoff values were 4.7 and 5.0 kPa for $F \geq 1$, 7.1 and 7.3 kPa for $F \geq 2$, 10.9 and 9.9 kPa for $F \geq 3$, and 17.3 and 12.6 kPa for $F = 4$, respectively, in HCV versus non-HCV patients. The corresponding AUROCs for $F \geq 1$, $F \geq 2$, $F \geq 3$, and $F = 4$ were 0.95 and 0.86, 0.89 and 0.85, 0.97 and 0.88, and 0.99 and 0.97, respectively, for HCV versus non-HCV patients. In another prospective study by Rigamonti et al. [65], TE proved to be an accurate and independent predictor of graft damage regardless of the etiology, which was not an unexpected finding because TE-measured LS was previously shown to correlate not only with liver fibrosis but also with necroinflammatory activity, cho-

lestasis, steatosis, and cellular rejection. They identified two TE cutoffs for diagnosing graft damage: 5.3 kPa with 100% sensitivity and 7.4 kPa with 100% specificity. In patients with TE values ≤5.3 kPa, the post-test probability of graft damage fell to 0%, but in patients with TE results >7.4 kPa, the post-test probability increased to 100% [65].

Because histological changes are potentially clinically significant (e.g. progressive graft fibrosis), monitoring patients with TE to identify the presence of graft damage may be valuable for early identification of OLT patients that require further histological assessment of the graft or modifications of their immunosuppressive therapy regimen [66, 67].

### Limitations of TE and Future Perspectives

Although TE has demonstrated reliable diagnostic accuracy in the surgical setting, it still has a limitation in that space-occupying tissue abnormalities such as edema, inflammation, cholestasis, and congestion after surgery may interfere with TE utility regardless of the liver fibrosis degree. First, the extent of histological necroinflammatory activity influences TE results, resulting in an overestimation of TE values that increases in parallel with the degree of necroinflammatory score [29, 41, 42, 68–74]. Since even mild to moderate ALT elevation is associated with higher LS values, and may cause discrepancies between TE results and the actual underlying fibrosis, physicians should exercise caution in interpreting TE results. Apart from necroinflammation, underlying extrahepatic cholestasis [75] may also contribute to overestimating TE. Because the temporary increase of portal blood flow immediately after hepatic resection can lead to postoperative liver congestion, the optimal timing for acquiring the stabilized LS values should be further investigated. Second, TE performance may be limited in patients with a high body mass index or narrow intercostal space [8]. Although TE reproducibility is typically excellent in terms of inter- and intraobserver agreement, a high body mass index (>28) and waist circumference are significantly associated with TE failure [76]. 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. A new TE probe (the XL probe) was recently introduced to lessen the TE failure rate in obese patients; however, its efficacy requires further validation [77]. Lastly, if patients undergo right hepatectomy, measurement of LS by TE of the right lobe will be no longer possible, and obtaining LS values for the remnant left lobe has not yet been standardized. In such cases, other imaging modalities covering the left lobe such as MR elastography or acoustic radiation force impulse imaging would be potential alternatives. However, their diagnostic performance requires validation in future studies.

Although there are several kinds of non-invasive elastography modalities in addition to TE, including acoustic-radiation-force impulse elastography (ARFI), real-time elastography, and spleen stiffness index, their uses in a surgical field are not widely accepted. Hence, we could not incorporate their predictive performances in this review. Considering that these elastography methods had similar diagnostic performances to predict liver cirrhosis [78–81] and that spleen stiffness had showed the promising results to assess the portal hypertension from more recent investigations [82–84], further studies are required to find whether they have the better predictive performances to predict postoperative outcomes.

Furthermore, in contrast to TE and other elastography methods, ARFI is the only elastography method suitable for quantifying the stiffness of focal liver mass, since it uses elastography with a flexible metering box of the region of the interest. Park et al. [85] and other investigators [86] reported the usefulness of characterization of focal liver masses based on ARFI method, suggesting the higher likelihood of malignancy when the ARFI velocity is >1.82–1.9 m/s. However, these results should be interpreted in a clinical context, because considerable overlap in ARFI values existed among liver masses. Additional roles of ARFI in the surgical perspectives should be investigated in future studies.

### Conclusion

Over the past decade, significant progress has occurred 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 diagnosing cirrhosis, and it also has good prognostic value in the surgical setting. Although TE cannot completely obviate the other tests, such as LB, endoscopic examination, hepatic venous pressure gradient, or ICG R15, it represents an important non-invasive tool which enables more efficient and tailored management strategies for patients with liver resection or transplantation.

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## Disclosure Statement

The authors have no conflicts of interest to disclose.

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