INTRODUCTION

Early identification of fibrosis recurrence is essential in the management of liver transplant (LT) recipients as it permits appropriate interventions and management modifications. Liver biopsy is the established method for assessing hepatic fibrosis, particularly in the post-transplant setting. LT recipients require longitudinal follow-up to assess allograft fibrosis. Thus, it is impractical to use liver biopsy as a tool for serial monitoring in the post-transplant setting due to its invasiveness, cost, and potential for sampling error.1,2 Liver stiffness (LS) as measured by transient elastography (TE) has been validated in immunocompetent patients with various liver diseases.3-6 Concurrent use of controlled attenuation parameter has been validated in quantifying steatosis in patients having non-alcoholic fatty liver disease (NAFLD). Few published studies have evaluated the usefulness of TE in the LT setting. The purpose of this review is to examine the current literature that evaluates the utility of TE in the LT recipient.
drug therapy for HCV infection. Protocol liver biopsies helped show that mild acute cellular rejection (ACR) could be present in the setting of normal liver chemistry tests and not be clinically relevant, and that often long-term survivors of LT had abnormal liver histology.7 Protocol liver biopsies are much less frequently performed in non-HCV patients.

TE was first introduced as a non-invasive tool to assess the degree of LS in patients with chronic liver disease in 2003.8 Since then, it has found wide-ranging acceptance for staging disease prior to LT. Several studies have demonstrated good reproducibility of TE results in a wide array of liver diseases, with an intra-observer agreement of 96%-96% and an inter-observer agreement of 89%-98%.9-12 The system is equipped with an ultrasound transducer that transmits vibrations of mild amplitude and low frequency to tissues. It involves assessing the velocity rate of propagation of an elastic shear wave generated by mechanical impulse from an applied transducer. This rate is determined by cohesiveness of the liver. The degree of cohesiveness increases in direct proportion to the degree of fibrosis. A measurement depth of 25-45 mm is considered reliable and 10 successful measurements are required. The velocity measurements are computer-processed and an average of the 10 measurements is reported in kilopascal (kPa). The addition of CAP, introduced in 2010,13 has allowed the grading of steatosis by assessing the degree of ultrasound attenuation due to hepatic fat using the TE probe simultaneously with LS measurements. CAP has been an important addition to the applicability of TE, but important caveats apply. Whereas an elevated LS is uniformly associated with worse clinical outcomes in patients with chronic liver disease, such as a higher risk of decompensating events,14 HCC development,15,16 and decreased survival,17 steatosis as measured by CAP has not been associated with the development of liver cancer or decompensating events.18,19 Thus, steatosis is an unreliable marker for disease progression and does not portend a poor clinical course, unlike elevations in LS.

Overall, TE is a novel, adjunctive modality that may replace the gold standard, liver biopsy, when clinically warranted. By comparison, ultrasonography, frequently used as a non-invasive method to assess for liver cirrhosis, has been demonstrated to have a low sensitivity, particularly in diagnosing non-nodular forms of cirrhosis.20,21 The recent European Association for the Study of the Liver guidelines on non-invasive diagnosis of liver fibrosis suggest that non-invasive methods could replace liver biopsy when used in combination with the pre-transplant setting.22 In 2013, the Food and Drug Administration approved the use of TE in both adults and children with liver disease. In the post-LT population, however, data regarding the use of TE are sparse.

2.2 | Clinical applications of transient elastography in LT patients

2.2.1 | Graft selection

The optimal selection of a liver graft is essential to the success of the transplant.23 Determination of graft steatosis is a key segment of the selection process. The precise estimation of graft steatosis is challenging, and although a liver biopsy is most commonly performed to evaluate this, it remains prone to sampling error.24-26 CAP measured using TE is a potentially rapid, non-invasive, reliable tool to pre-operatively assess and quantify graft steatosis.13,27-32 Pichon et al33 failed to confirm that LS alone using TE could adequately assess liver allografts. A pilot study by Mancia et al34 used the combination of CAP and LS in 23 donors with brain death. The different predictive models of liver retrievability using liver biopsy as the gold standard led to the following area under receiver operating characteristic (AUROC) curve: 76.6% (95% confidence intervals [95% CIs], 48.2%-100%) when based solely on CAP, 75.0% (95% CIs, 34.3%-100%) when based solely on LS, and 96.7% (95% CIs, 88.7%-100%) when based on combined indices. The authors concluded that the combination of CAP and LS could successfully predict the histological status and steatosis grade of the liver allograft.

Although performance of bedside and operative TE with CAP is feasible using portable devices, we believe its utility in assessing the deceased donor is low, however. Deceased donors with obvious cirrhosis or advanced fibrosis can be detected radiologically and thus obviate the need for biopsy or failed procurement of the organ. Liver biopsies are not performed on potential patients being evaluated for donation after cardiac death. Cirrhosis and appreciable steatosis may be noted during cross-sectional imaging; confirmatory TE could be utilized to more confidently exclude a potential donor. Even in potential donors showing negligible fibrosis or steatosis on TE, exclusion of other confounding histology, such as microvesicular steatosis, is important however, especially in the setting of abnormal liver chemistry tests. TE thus is not expected to replace liver biopsy and histological evaluation in assessment of the donor.

2.2.2 | Live donors

The application of CAP with LS has subsequently been evaluated in the living liver donor population. Kim et al evaluated a group of 79 living donors by TE using LS and CAP; computed tomography (CT), and magnetic resonance imaging and compared these non-invasive modalities to intra-operative frozen sections. The authors found that CT liver-spleen attenuation differences and the measurements obtained via TE correlated with hepatic steatosis present on biopsy, and a weighted combination of these two modalities yielded a higher predictive capability of hepatic steatosis, with an AUROC of 86.6% (P = .001).35 In another study by Hong and colleagues, 55 potential live donors were evaluated by CAP and the results were compared with biopsy. CAP had an AUROC of 78% for detecting at least S1 steatosis and 88% for at least S2.36 Most recently, Yen et al37 compared TE with intra-operative liver biopsy in 54 living donors. Using a cut-off of 257 dB/m, the authors were able to achieve a 100% sensitivity for hepatic steatosis, though only 7 of the 12 patients with CAP values >257 had biopsy-proven steatosis. Although these results are promising, this study was performed in an East Asian population with an average BMI of 24 kg/m²; potentially limiting its applicability to a Western population. Most potential donors undergo MRI for...
assessment of vascular and biliary anatomy. As part of this evaluation, elastography and assessment for steatosis can be performed. Both have similar sensitivities as TE in quantifying fibrosis and steatosis, respectively. Exclusion of other important liver histology in the setting of abnormal liver tests is not possible with TE or CAP, so liver biopsy appears warranted in this setting, especially if baseline MRI does not suggest steatosis or fibrosis.

### 2.2.3 Acute cellular rejection

The inflammatory cascade driving acute cellular rejection (ACR), as with any inflammatory process, might be expected to increase LS. Crespo et al. evaluated the association between LS and severity of biopsy-proven ACR in liver transplanted patients. In their prospective study, TE achieved highest diagnostic accuracy, with an AUROC of 0.924 to discriminate mild from moderate/severe rejection. A LS measurement of 8.5 kPa had a positive predictive value of 100% to diagnose moderate/severe rejection. Rigamonti et al. studied 65 LT recipients who underwent liver biopsy, either for a clinical need or per protocol (1 year and 5-10 years post-transplant), and subsequent TE. Twenty-eight patients exhibited graft damage, including three with ACR. Using a receiver operating characteristic curve analysis, a TE reading of 5.3 kPa was 100% sensitive in detecting graft damage, whereas a TE reading of 7.4 kPa was 100% specific. The authors concluded that using these dual cutoffs could help predict and exclude patients suspected of having any form of allograft injury.

Overall, data are limited regarding this population; a recent systematic review found only 3 studies comprising 33 total patients with ACR who were evaluated with TE. Further, although an increased LS may in fact suggest underlying ACR, it does not add much to a clinician’s decision-making process in the acute setting, that is, whether a liver biopsy is necessary or whether an empiric increase in immunosuppression is warranted. Liver histology would be invaluable in assessing the degree of ACR and whether there was evidence of chronic ductopenic rejection, plasma cell hepatitis rejection, or antibody-mediated rejection that might influence the timing and duration of therapy. Thus, we feel that TE plays little role in the diagnosis and management of ACR.

### 2.2.4 Recurrent fibrosis post-transplant

Progression of graft fibrosis is significantly accelerated in immunosuppressed patients, particularly those receiving calcineurin inhibitors post-transplant. TE is an ideal, non-invasive, and accessible method for diagnosing the degree of hepatic fibrosis. In a meta-analysis evaluating non-invasive methods of diagnosing recurrent fibrosis post-LT, Bhat et al. compared TE, AST-to-platelet ratio index (APRI), and fibrosis score 4 (FIB-4). A total of 12 studies evaluating TE were included in the analysis, six of which only evaluated patients with HCV. The authors found TE performed the best of the three measures, with significant differences noted between TE and APRI as well as between TE and FIB-4. The accuracy of TE in evaluating post-transplant fibrosis was consistent among those with viral hepatitis and those transplanted for other etiologies. This could potentially be of value in assessing patients with mild liver chemistry test abnormalities in whom immunosuppression minimization is being considered. Those patients having high or increasing LS readings over time might be identified as requiring a liver biopsy before proceeding with further immunosuppression withdrawal, whereas those with stable or declining LS may be candidates for immunosuppression minimization.

### 2.2.5 Hepatitis C

Many transplant centers have traditionally had protocols that called for routine biopsy post-LT to evaluate allograft injury. With the advent of the DAA to treat recurrent HCV, the need for serial biopsies to monitor fibrosis progression and to exclude other coexistent pathologies (ie, ACR) before embarking upon antiviral therapy is no longer clinically relevant. Several studies previously evaluated the role of TE in assessing fibrosis progression in LT patients with recurrent HCV. Rigamonti et al. provided data on sequential TE of patients with recurrent HCV. Patients with Ishak fibrosis scores of 0-1 had an average LS of 5.6 kPa, while those with fibrosis of biopsy stages 2-3 had an average of 7.6 kPa and those with scores of 5-6 had measurements averaging 16.7 kPa. AUROC was 0.85 (95% CI, 0.76-0.92) for scores ≥3 and 0.90 (95% CI, 0.82-0.85) for those with scores ≤4. During post-LT follow-up, TE results changed in parallel with HCV grading (r = 0.63) and staging (r = 0.71), having a sensitivity of 86% and a specificity of 92% in predicting staging increases. The authors concluded that TE may accurately predict fibrosis progression in LT patients with recurrent HCV, ameliorating the need for protocol biopsy in patients with improving or stable TE values.

In a prospective study, Beckebaum et al. assessed the efficacy of TE, biochemical testing, and scoring systems in determining fibrosis staging for both HCV- and non-HCV-related liver diseases post-LT. TE showed excellent sensitivity for differentiating fibrosis stages compared with biopsy. Berrault and colleagues evaluated the accuracy of TE compared with biopsy in 43 patients with and without a history of HCV. A cutoff of 7 kPa was able to reliably distinguish patients with Metavir score 2 fibrosis, with similar results among both groups. Similarly, Kampsheus et al. compared TE with liver biopsy and composite scores for evaluation of fibrosis in patients transplanted for HCV and alcoholic liver disease. In the HCV group, the AUROC for diagnosis of significant fibrosis (F ≥ 2) and cirrhosis (F = 4) was 0.81 (negative predictive value [NPV] = 0.58, positive predictive value [PPV] = 0.9) and 0.87 (NPV = 0.94, PPV = 0.56), respectively. Thinner patients had more accurate results. The authors concluded that TE could reliably exclude cirrhosis in the HCV post-transplant population but was not sufficient in excluding significant liver fibrosis. In patients achieving sustained virologic response (SVR) with DAA post-LT, especially those who were transplanted some time ago and who have already developed advanced fibrosis, TE is important in identifying those persons who have developed cirrhosis in order to individualize hepatocellular carcinoma surveillance strategies.
Finally, in patients transplanted for HCV who were treated post-LT and achieved SVR, LS has been shown to accurately assess the presence of advanced fibrosis and clinically significant portal hypertension.53 LS measurements to rule out and rule in advanced fibrosis were 10.6 and 14 kPa, respectively, with an AUROC of 0.902. LS cutoffs to rule out and rule in clinically significant portal hypertension were 11.3 kPa and 23 kPa, respectively, with an AUROC of 0.888. Given that patients with lower hepatic venous pressure gradient have been shown to have a lower incidence of clinical decompensation,54 LS may be an important prognostic tool in the post-transplant population who have achieved an SVR.

2.2.6 Non-alcoholic fatty liver disease

NAFLD affects about 24% of the world population and is becoming the most common etiology of end-stage liver disease in the industrial world.55,56 Patients on immunosuppression are at risk of developing or exacerbating risk factors that lead to progression of NAFLD, such as weight gain, diabetes, hyperlipidemia, and hypertension. This places these patients at risk for the development of hepatic graft steatosis and recurrence of non-alcoholic steatohepatitis (NASH) post-LT.57-59 Additionally, de novo NAFLD in LT patients not transplanted due to NASH is being increasingly observed. One systematic review reported a 26% pooled weighted prevalence of biopsy-proven de novo NAFLD in a LT patient population.60 In a single-center study of patients undergoing LT for NASH, Malik et al identified recurrent NAFLD, NASH, and stage 2 fibrosis in 70%, 25%, and 18% of patients, respectively, with a mean follow-up time of 18 months.61 In another study, recurrent steatohepatitis was noted in one third of patients transplanted for NASH.62

Accuracy of TE in diagnosing fatty liver disease in non-transplant patients has been established and validated.63 The utility of TE in detecting NAFLD post-LT has not yet been corroborated. One concern regarding the use of TE is that severity is affected by obesity, resulting in 15% of readings being unreliable.64 Given obesity is a common comorbidity in the NAFLD population, the utility of TE could be called into question. The XL probe was designed to improve the usefulness of TE in the obese patient, allowing for measurements of depths ≥35 mm below the skin, compared with 25 mm for the M probe.65 In one study comparing use of TE using the XL probe and the standard probe (M) to liver biopsy, the XL probe gave reliable results 23% more often than the M probe.64 With the addition of CAP, a program designed to measure hepatic steatosis, the accuracy of the XL probe increases even more.56

Karlas et al67 evaluated post-LT steatosis by TE using CAP measurements in a population of 204 patients who underwent LT, 50% of whom were transplanted for alcoholic cirrhosis and only 2% transplanted for NASH. At the time of the study, CAP was not available using the XL probe and thus only the M probe was used. Perhaps as a result, only 157 of the cases were able to achieve valid results; however, TE detected steatosis in 44% of these patients, with 24% having advanced steatosis, indicating a high prevalence of post-LT de novo steatosis. Although it has not been compared with biopsy in the evaluation of grafts post-LT, the promise of non-invasive evaluation of graft steatosis with CAP and TE using the XL probe is compelling and is worthy of further study. Recurrent or de novo NASH may be present in the setting of normal or near normal aminotransferases. Demonstration of NASH via TE and CAP should alert the clinicians and patient to this additional comorbidity and the potential greater likelihood for complications related to insulin resistance. In some recipients, despite achieving SVR fibrosis may continue to progress. The presence of appreciable steatosis in the setting of advanced fibrosis will identify patients for both closer follow-up and for HCC surveillance.68

2.3 Limitations of transient elastography

The limitations of TE are important and impact its use in clinical practice. For instance, different cutoff values have been reported for the prediction of fibrosis or cirrhosis in the post-LT setting compared with the non-transplant setting. The optimal LS cutoff for detecting liver fibrosis post-LT, particularly in the intermediate stages, has not been established. Many of the studies evaluating fibrosis in the post-LT setting have focused on HCV-related disease and have proposed different values of LS for staging fibrosis. For example, in a systematic review by Cholongitas and colleagues, the proposed LS cutoffs for patients with post-LT cirrhosis varied greatly—from 10.5 kPa to 26.5 kPa—across four different studies.69 The cutoffs for “significant fibrosis” also varied from 7.9 kPa to 10.1 kPa.

In a large, more recent prospective study of 259 patients evaluated by TE and liver biopsy, the cutoffs proposed for all patients to achieve a specificity of ≥90% were 8.1 kPa for F ≥ 1, 12.3 kPa for F ≥ 2, 15.1 kPa for F ≥ 3, and 16.7 kPa for F = 4. When only patients with HCV were analyzed, the cutoffs were adjusted to 8.1 kPa for F ≥ 1, 12.3 kPa for F ≥ 2, 16.5 kPa for F ≥ 3, and 17.6 kPa for F = 4 to achieve a specificity of ≥90%.70 Although a large study such as this shows promise, many of the other published studies dedicated to post-LT TE have been small, single-center series and have lacked a validation cohort.

Other difficulties complicate the regular use of TE in the post-LT population. These patients may have differences relative to the anatomic position of the liver due to instances of hemi-diaphragmatic elevation or geometric mismatch between graft and abdominal cavity.

Liver stiffness, traditionally associated with degree of fibrosis, has also been shown to correlate with factors that affect sinusoidal pressure (SP). Factors that affect SP, such as inflammation and hepatic congestion (see below), alter LS even prior to the development of fibrosis.71 Similarly, factors that increase mean arterial pressure, such as vasopressors or aerobic exercise, increase LS measurements in both animal and human models.72 Changes in portal venous flow, as in the setting of pharmacologic effect on hepatic hemodynamics, transjugular intrahepatic portosystemic shunt (TIPS) placement or variceal ligation, also affect LS.73,74 For example, in a group of 14 patients undergoing TIPS placement, LS decreased by 9.2 kPa on average, whereas in a group of 11 patients undergoing esophageal ligation, LS increased by roughly 16 kPa post-ligation.74
The presence of active inflammation increases LS measurements regardless of fibrosis stage. For example, one study found that among patients with the same level of fibrosis by histology, those with concurrent increased histological inflammation had higher LS than those with less inflammation.\textsuperscript{75} LS is elevated in a number of co-morbid conditions in the absence of liver fibrosis.\textsuperscript{71,76} For instance, factors that increase central venous pressure, such as right heart failure, have been shown to increase LS.\textsuperscript{77,78} Extra-hepatic cholestasis has also been shown to affect LS measurements. In a study of 15 patients undergoing endoscopic retrograde cholangiopancreatography for biliary obstruction in the absence of liver disease, successful biliary drainage reduced LS by 8.1 kPa.\textsuperscript{79} In sum, understanding the clinical context is critical when interpreting TE results (Table 1).

The presence of obesity has historically limited the use of TE in patients with suspected liver disease.\textsuperscript{80,81} The development of the XL probe has improved the usefulness of TE in this population; however, limitations remain. In a meta-analysis of studies comparing the use of the XL probe to the M probe, the former was found to have lower rates of failure in patients with a BMI $\geq 30$ kg/m$^2$ (RR 0.16, 95% CI 0.08-0.32, $P < .00001$).\textsuperscript{82} However, the rates of unreliable measurements were not significantly different between the two probes (RR 0.63, 95% CI 0.30-1.32, $P = .22$). The addition of CAP to the XL probe, as mentioned earlier, is a promising tool that may increase the utility of TE in the obese population.

Lastly, the need for well-trained operators is paramount, as there is established variation in TE results based on technical experience and expertise.\textsuperscript{80,83}

### 2.4 Future directions

Transient elastography in post-LT patients has not yet been fully studied; however, potential future diagnostic roles exist. For example, it is known that graft fibrosis occurs often in the setting of normal liver biochemistry tests, making non-invasive detection of post-LT injury difficult.\textsuperscript{7,84,85} TE also presents a novel approach to re-calibrating our understanding and thus definition of normal liver biochemistry tests in transplant recipients. By comparing LS values and liver chemistry tests, it may be possible to create more reliable liver chemistry test cutoffs in the post-LT population that allow for detection of graft fibrosis earlier.

Hepatic steatosis in patients transplanted for both NASH and those with de novo NASH is an important, emerging issue in the LT population. Utilizing TE to assess the degree of steatosis in these patients may provide useful information for clinicians treating patients in the post-transplant setting. In particular, it may motivate physicians to aggressively treat exacerbating co-morbidities such as obesity and diabetes mellitus. Further, the armamentarium of agents to treat NASH as well as anti-fibrotic agents is expected to grow as compounds currently being evaluated in clinical trials become available.\textsuperscript{56,87} The utility of these agents in the post-LT setting will ultimately need to be examined. One can envision TE as a tool to better understand and study patients who may be enrolled in trials evaluating these agents in the post-LT setting.

Feng et al\textsuperscript{88} have recently demonstrated the development of progressive liver fibrosis and chronic allograft injury in serial liver biopsies of long-term pediatric liver transplant recipients. Many such patients had normal aminotransferases with protocol biopsies being performed as part of a prospective, multicenter trial of immunosuppression withdrawal for stable pediatric LT recipients. Appreciable fibrosis was noted in a subset of patients. TE was not performed in patients but could have identified these patients possibly without the need of protocol biopsy or if the biopsy was precluded. Thus, performance of TE could be considered in patients undergoing active immunosuppression withdrawal with the detection of appreciable fibrosis triggering the need for liver biopsy or precluding immunosuppression withdrawal. Late graft hepatitis and fibrosis is increasingly being found in pediatric liver allograft recipients and adult survivors of pediatric transplantation.\textsuperscript{89-91} TE may become important in identifying such patients earlier without the performance of protocol liver biopsy. There is little published experience so far using TE in the pediatric post-LT setting.\textsuperscript{92}

### 2.5 Summary

The long-term results of liver transplantation are excellent. Liver fibrosis induced by various causes remains one of the principle reasons for graft dysfunction. Early identification of appreciable fibrosis or allograft injury in LT recipients is of paramount importance to permit risk stratification, ascertain prognosis, and thereby provide targeted interventions. It is important to establish the utility of new non-invasive methods, including TE, in this population. LS measurement by TE appears to be a promising tool for non-invasive monitoring of liver fibrosis progression after LT. Further studies with validation in large cohorts are needed to establish the precise association of TE values and cutoff values, with corresponding histological lesions and collagen content of liver biopsies using optimally sized biopsy specimens as a reference standard. Longitudinal assessment of fibrosis by means of these non-invasive tests may reduce the need for serial liver biopsies.

 Given the non-invasive nature and ability to perform serial measurements, non-invasive testing for liver fibrosis could be used in the post-transplant clinical setting as an adjunctive tool for suspected recurrent or de novo liver disease. The high accuracy noted in the few published post-LT studies, especially for TE, suggests that these tests have similar diagnostic value as in the pre-transplant setting.

### Table 1 Factors affecting liver stiffness measurements

| Factors          | Effect                                      |
|------------------|---------------------------------------------|
| Cholestasis      | Increases LS\textsuperscript{79}            |
| Obesity          | Unreliable LS measurements\textsuperscript{80} |
| Operator inexperience | Higher rates of invalid and unreliable LS measurements\textsuperscript{80} |
| Hepatic inflammation | Increases LS\textsuperscript{75}       |
| Right heart failure  | Increases LS\textsuperscript{77,78}      |
More data are necessary in assessing the sensitivity of CAP for hepatic steatosis in the post-LT setting.

Of course, liver biopsy remains a cornerstone for the clinical management of LT recipients, as non-invasive tests cannot differentiate between pathologies that may coexist in this setting, such as acute or chronic rejection. Nonetheless, when the etiology of recurrent or de novo disease has been established, these non-invasive tests may be helpful in following fibrosis progression longitudinally and implementing preventive therapies in a timely manner.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD, American Association for the Study of Liver Diseases. Liver biopsy. Hepatology. 2009;49(3):1017-1044.
2. Sebastiani G. Non-invasive assessment of liver fibrosis in chronic liver diseases: implementation in clinical practice and decisional algorithms. World J Gastroenterol. 2009;15(18):2190-2203.
3. Poynard T, de Ledinghen V, Zarski JP, et al. Performances of Elasto-FibroTest®, a combination between FibroTest® and liver stiffness measurements for assessing the stage of liver fibrosis in patients with chronic hepatitis C. Clin Res Hepatol Gastroenterol. 2012;36(5):455-463.
4. Poynard T, de Ledinghen V, Zarski JP, et al. FibroTest and Fibroscan performances revisited in patients with chronic hepatitis C. Impact of the spectrum effect and the applicability rate. Clin Res Hepatol Gastroenterol. 2011;35(11):720-730.
5. Yoneda M, Yoneda M, Fujita K, et al. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). Gut. 2007;56(9):1330-1331.
6. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol. 2016;65(5):570-578.
7. Slapak GJ, Saxena R, Portmann B, et al. Graft and systemic disease in long-term survivors of liver transplantation. Hepatology. 1997;25(1):195-202.
8. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol. 2003;29(12):1705-1713.
9. Fraquelli R, Tateishi R, Yoshida H, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology. 2009;49(6):1954-1961.
10. Jung KS, Kim SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology. 2011;53(3):885-894.
11. Fraquelli M, Rigamonti C, Casazza G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut. 2007;56(7):968-973.
12. Maor Y, Halton P, Bashari D, et al. Fibrotest or fibroscan for evaluation of liver fibrosis in haemophilia patients infected with hepatitis C. Haemophilia. 2010;16(1):148-154.
13. Sasso M, Beaupré M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol. 2010;36(11):1825-1835.
14. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut. 2004;55(3):403-408.
15. Masuzaki R, Tateishi R, Yoshida H, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology. 2009;49(6):1954-1961.
16. Liu K, Wong VW, Lau K, et al. Prognostic value of controlled attenuation parameter by transient elastography. Am J Gastroenterol. 2017;112(12):1812-1823.
17. Scheiner B, Steininger L, Semmler G, et al. Controlled attenuation parameter does not predict hepatic decompensation in patients with advanced chronic liver disease. Liver Int. 2019;39(1):127-135.
18. Ong TZ, Tan HJ. Ultrasoundography is not reliable in diagnosing liver cirrhosis in clinical practice. Singapore Med J. 2003;44(6):293-295.
19. Allan R, Thoirs K, Phillips M. Accuracy of ultrasound to identify chronic liver disease. World J Gastroenterol. 2010;16(28):3510-3520.
20. EuropeanAssociation for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado, EASL-ALA clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63(1):237-264.
21. Chen YS, Cheng YF, De Villa VH, et al. Evaluation of living liver donors. Transplantation. 2003;75(3 suppl):S16-19.
22. Yersiz H, Lee C, Kaldas FM, et al. Assessment of hepatic steato- sis by transplant surgeon and expert pathologist: a prospective, double-blind evaluation of 201 donor livers. Liver Transpl. 2013;19(4):437-449.
23. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology. 2005;128(7):1898-1906.
24. Vuppalarangi R, Unalp A, Van Natta ML, et al. Effects of liver biopsy sample length and number of readings on sampling variability in nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7(4):481-486.
25. Shen F, Zheng RD, Mi YQ, et al. Controlled attenuation parameter for non-invasive assessment of hepatic steatosis in Chinese patients. World J Gastroenterol. 2014;20(16):4702-4711.
26. Chan WK, Nik Mustapha NR, Mahadeva S. Controlled attenuation parameter for the detection and quantification of hepatic steatosis in nonalcoholic fatty liver disease. J Gastroenterol Hepatol. 2014;29(7):1470-1476.
27. Wang Y, Fan Q, Wang T, Wen J, Wang H, Zhang T. Controlled attenuation parameter for assessment of hepatic steatosis grades: a diagnostic meta-analysis. Int J Clin Exp Med. 2015;8(10):17654-17663.
28. Berzigotti A. Getting closer to a point-of-care diagnostic assessment in patients with chronic liver disease: controlled attenuation parameter for steatosis. J Hepatol. 2014;60(5):910-912.
29. de Ledinghen V, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled
attenuation parameter (CAP) and transient elastography. Liver Int. 2012;32(6):911-918.

32. Myers RP, Pollett A, Kirsch R, et al. Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. Liver Int. 2012;32(6):902-910.

33. Pichon N, Loustaud-Ratti V, Clavel M, Carrier P, Amiel JB, Labrousse F. Value of liver stiffness measured by transient elastography in the liver transplant pre-operative evaluation of the potential deceased liver donors: preliminary study. Clin Transplant. 2011;25(2):205-210.

34. Mancia C, Loustaud-Ratti V, Carrier P, et al. Controlled attenuation parameter and liver stiffness measurements for steatosis assessment in the liver transplant of brain dead donors. Transplantation. 2015;99(8):1619-1624.

35. Kim JM, Ha SY, Joh JW, et al. Predicting hepatic steatosis in living liver donors via noninvasive methods. Medicine (Baltimore). 2016;95(7):e2718.

36. Hong YM, Yoon KT, Cho M, et al. Clinical usefulness of controlled attenuation parameter to screen hepatic steatosis for potential donor of living donor liver transplant. Eur J Gastroenterol Hepatol. 2017;29(7):805-810.

37. Yen YH, Kuo FY, Lin CC, et al. Predicting hepatic steatosis in living liver donors via controlled attenuation parameter. Transplant Proc. 2018;50(10):3533-3538.

38. Crespo G, Castro-Narro G, Garcia-Juarez I, et al. Usefulness of liver stiffness measurement during acute cellular rejection in liver transplantation. Liver Transpl. 2016;22(3):298-304.

39. Rigamonti C, Fraquelli M, Bastiampli AI, et al. Transient elastography identifies liver recipients with nonviral graft disease after transplantation: a guide for liver biopsy. Liver Transpl. 2012;18(5):566-576.

40. Nacif LS, Gomes C,Misciatielli MN, et al. Transient elastography in acute cellular rejection following liver transplantation: systematic review. Transplant Proc. 2018;50(3):772-775.

41. Koo J, Wang HL. Acute, chronic, and humoral rejection: pathologic features under current immunosuppressive regimes. Surg Pathol Clin. 2018;11(2):431-452.

42. Frizell E, Abraham A, Doolittle M, et al. FK506 enhances fibrogenesis in in vitro and in vivo models of liver fibrosis in rats. Gastroenterology. 1994;107(2):492-498.

43. Khanna A, Kapur S, Sharma V, Li B, Suthanthiran M. In vivo hyperexpression of transforming growth factor-beta1 in mice: stimulation by cyclosporine. Transplantation. 1997;63(7):1037-1039.

44. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus infected patients. The Multivirc Group. Hepatology. 1999;30(4):1054-1058.

45. Benhamou Y, Di Martino V, Bochet M, et al. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-infected patients: impact of protease inhibitor therapy. Hepatology. 2001;34(2):283-287.

46. Berenguer M. Host and donor risk factors before and after liver transplantation that impact HCV recurrence. Liver Transpl. 2003;9(11):S44-47.

47. Bhat M, Tazari M, Sebastiani G. Performance of transient elastography and serum fibrosis biomarkers for non-invasive evaluation of recurrent fibrosis after liver transplantation: a meta-analysis. PLoS ONE. 2017;12(9):e0185192.

48. Firpi RJ, Abdelmalek MF, Soldevila-Pico C, et al. One-year protocol liver biopsy can stratify fibrosis progression in liver transplant recipients with recurrent hepatitis C infection. Liver Transpl. 2004;10(10):1240-1247.

49. Rigamonti C, Donato MF, Fraquelli M, et al. Transient elastography predicts fibrosis progression in patients with recurrent hepatitis C after liver transplantation. Gut. 2008;57(6):821-827.

50. Beckebaum S, Iacob S, Klein CG, et al. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. Transplantation. 2010;89(8):983-993.

51. Barrault C, Roudot-Thoraval F, Tran Van Nhieu J, et al. Non-invasive assessment of liver graft fibrosis by transient elastography after liver transplantation. Clin Res Hepatol Gastroenterol. 2013;37(4):347-352.

52. Kamphues C, Lotz K, Rocken C, et al. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. Clin Transplant. 2010;24(5):652-659.

53. Mauro E, Crespo G, Montironi C, et al. Portal pressure and liver stiffness measurements in the prediction of fibrosis regression after sustained virological response in recurrent hepatitis C. Hepatology. 2018;67(5):1683-1694.

54. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical compensation in patients with compensated cirrhosis. Gastroenterology. 2007;133(2):481-488.

55. Younossi Z, AnsteeQM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11-20.

56. Karlas T, Wiegand J, Berg T. Gastrointestinal complications of obesity: non-alcoholic fatty liver disease (NAFLD) and its sequelae. Best Pract Res Clin Endocrinol Metab. 2013;27(2):195-208.

57. Charlton M. Evolving aspects of liver transplantation for nonalcoholic steatohepatitis. Curr Opin Organ Transplant. 2013;18(3):251-258.

58. Friman S. Recurrence of disease after liver transplantation. Transplant Proc. 2013;45(3):1178-1181.

59. Ong J, Younossi ZM, Reddy V, et al. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. Liver Transpl. 2001;7(9):797-801.

60. Losurdo G, Castellaneta A, Rendina M, Carparelli S, Leandro G, Di Leo A. Systematic review with meta-analysis: de novo non-alcoholic fatty liver disease in liver-transplanted patients. Aliment Pharmacol Ther. 2018;47(6):704-714.

61. Malik SM, Devera ME, Fontes P, Shaikh O, Sasatomi E, Ahmad J. Recurrent disease following liver transplantation for nonalcoholic steatohepatitis cirrhosis. Liver Transpl. 2009;15(12):1843-1851.

62. Bhagat V, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. Liver Transpl. 2009;15(12):1814-1820.

63. Wong VW, Vergniol J, Wong GL, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51(2):454-462.

64. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology. 2012;55(1):199-208.

65. de Ledinghen V, Vergniol J, Foucher J, El-Hajbi F, Merrouche W, Bedossa P, Paradis V. Controlled attenuation parameter (CAP) with the XL probe of the Fibroscan®: a comparative study with the M probe and liver biopsy. Dig Dis Sci. 2017;62(9):2569-2577.

66. Karlas T, Kollmeier J, Bohn S, et al. Noninvasive characterization of graft steatosis after liver transplantation. Scand J Gastroenterol. 2015;50(2):224-232.

67. Whitcomb E, Choi WT, Jerome KR, et al. Biopsy specimens from allograft liver contain histologic features of hepatitis C virus infection after virus eradication. Clin Gastroenterol Hepatol. 2017;15(8):1279-1285.

68. Cholongitas E, Tsoschatzis E, Goulis J, Burroughs AK. Noninvasive tests for evaluation of fibrosis in HCV recurrence after liver transplantation: a systematic review. Transpl Int. 2010;23(9):861-870.
70. Della-Guardia B, Evangelista AS, Felga GE, Marins LV, Salvalaggio PR, Almeida MD. Diagnostic accuracy of transient elastography for detecting liver fibrosis after liver transplantation: a specific cut-off value is really needed? Dig Dis Sci. 2017;62(1):264-272.

71. Mueller S. Does pressure cause liver cirrhosis? The sinusoidal pressure hypothesis. World J Gastroenterol. 2016;22(48):10482-10501.

72. Piecha F, Peccerella T, Bruckner T, Seitz HK, Rausch V, Mueller S. Arterial pressure suffices to increase liver stiffness. Am J Physiol Gastrointest Liver Physiol. 2016;311(5):G945-G953.

73. Piecha F, Mandorfer M, Peccerella T, et al. Pharmacological decrease of liver stiffness is pressure-related and predicts long-term clinical outcome. Am J Physiol Gastrointest Liver Physiol. 2018;314(2):G179-G187.

74. Piecha F, Paech D, Sollors J, et al. Rapid change of liver stiffness after variceal ligation and TIPS implantation. Am J Physiol Gastrointest Liver Physiol. 2018;314(5):G945-G953.

75. Arena U, Vizzutti F, Corti G, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology. 2008;47(2):380-384.

76. Mueller S, Sandrin L. Liver stiffness: a novel parameter for the diagnosis of liver disease. Hepat Med. 2010;2:49-67.

77. Millonig G, Friedrich S, Adolf S, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol. 2010;52(2):206-210.

78. Hopper I, Kemp W, Porapakkham P, et al. Impact of heart failure and changes to volume status on liver stiffness: non-invasive assessment using transient elastography. Eur J Heart Fail. 2012;14(6):621-627.

79. Millonig G, Reiman FM, Friedrich S, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology. 2008;48(5):1718-1723.

80. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology. 2010;51(3):828-835.

81. Wong GL, Wong VW, Chim AM, et al. Factors associated with unreliable liver stiffness measurement and its failure with transient elastography in the Chinese population. J Gastroenterol Hepatol. 2011;26(2):300-305.

82. Xia B, Wang F, Friedrich-Rust M, et al. Feasibility and efficacy of transient elastography using the XL probe to diagnose liver fibrosis and cirrhosis: a meta-analysis. Medicine (Baltimore). 2018;97(39):e11816.

83. Pang JX, Pradhan F, Zimmer S, et al. The feasibility and reliability of transient elastography using Fibroscan®: a practice audit of 2335 examinations. Can J Gastroenterol Hepatol. 2014;28(3):143-149.

84. Sebagh M, Samuel D, Antonini TM, et al. Twenty-year protocol liver biopsies: invasive but useful for the management of liver recipients. J Hepatol. 2012;56(4):840-847.

85. Gane EJ, Portmann BC, Naoumov NV, et al. Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med. 1996;334(13):815-820.

86. Banini BA, Sanyal AJ. Current and future pharmacologic treatment of nonalcoholic steatohepatitis. Curr Opin Gastroenterol. 2017;33(3):134-141.

87. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53(3):362-376.

88. Feng S, Bucuvalas JC, Demetris AJ, et al. Evidence of chronic allograft injury in liver biopsies from long-term pediatric recipients of liver transplants. Gastroenterology. 2018;155(6):1838-1851 e7.

89. Neves Souza L, de Martino RB, Sanchez-Fueyo A, et al. Histopathology of 460 liver allografts removed at retransplantation: a shift in disease patterns over 27 years. Clin Transplant. 2018;32(4):e13227.

90. Ekong UD. The long-term liver graft and protocol biopsy: do we want to look? What will we find? Curr Opin Organ Transplant. 2011;16(5):505-508.

91. Kelly D, Verkade HJ, Rajanayagam J, McKiernan P, Mazariogos G, Hubschner S. Late graft hepatitis and fibrosis in pediatric liver allograft recipients: current concepts and future developments. Liver Transpl. 2016;22(11):1593-1602.

92. Goldschmidt I, Stieghorst H, Munteanu M, et al. The use of transient elastography and non-invasive serum markers of fibrosis in pediatric liver transplant recipients. Pediatr Transplant. 2013;17(6):525-534.

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