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MINIREVIEWS

Noninvasive markers of liver steatosis and fibrosis after liver transplantation – Where do we stand?

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Abstract

In the last two decades, advances in immunosuppressive regimens have led to fewer complications of acute rejection crisis and consequently improved short-term graft and patient survival. In parallel with this great success, long-term post-transplantation complications have become a focus of interest of doctors engaged in transplant medicine. Metabolic syndrome (MetS) and its individual components, namely, obesity, dyslipidemia, diabetes, and hypertension, often develop in the post-transplant setting and are associated with immuno-suppressive therapy. Nonalcoholic fatty liver disease (NAFLD) is closely related to MetS and its individual components and is the liver manifestation of MetS. Therefore, it is not surprising that MetS and its individual components are

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associated with recurrent or "*de novo*" NAFLD after liver transplantation (LT). Fibrosis of the graft is one of the main determinants of overall morbidity and mortality in the post-LT period. In the assessment of post-LT steatosis and fibrosis, we have biochemical markers, imaging methods and liver biopsy. Because of the significant economic burden of post-LT steatosis and fibrosis and its potential consequences, there is an unmet need for noninvasive methods that are efficient and cost-effective. Biochemical scores can overestimate fibrosis and are not a good method for fibrosis evaluation in liver transplant recipients due to frequent post-LT thrombocytopenia. Transient elastography with controlled attenuation parameter is a promising noninvasive method for steatosis and fibrosis. In this review, we will specifically focus on the evaluation of steatosis and fibrosis in the post-LT setting in the context of *de novo* or recurrent NAFLD.

Key Words: Steatosis; Fibrosis; Noninvasive methods; Transient elastography; Transplantation; Nonalcoholic fatty liver disease

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Core Tip: Fibrosis of the graft is one of the main determinants of overall morbidity and mortality in the post-transplantation period. In the assessment of post-transplantation steatosis and fibrosis, we have biochemical markers, imaging methods and liver biopsy. Because of the significant economic burden of post-transplantation steatosis and fibrosis and the potential consequences, there is an unmet need for noninvasive methods that are efficient and cost-effective.

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INTRODUCTION

The prevalence of metabolic syndrome (MetS) and obesity is increasing; hence, nonalcoholic fatty liver disease (NAFLD)-induced chronic liver disease (CLD) is more frequent[1-4]. NAFLD has become the most common CLD today and has a high socioeconomic impact. This CLD is becoming a focus of interest of many authors in the transplant population because it has multiple impacts on liver transplantation (LT); influencing the number of patients on the waiting list for transplantation, number and quality of organ donors and increasingly important graft and recipient post-transplant outcome[1,2]. NAFLD-related end-stage liver disease (ESLD) is currently assumed to be the second most common cause of LT in the United States[1].Growing prevalence of NAFLD in the West, advancements in hepatitis C virus infection (HCV) therapy, and the aging population, will have NAFLD-driven ESLD emerge as the leading cause for LT in the Western world in the decades to come[5]. Therefore, NAFLD and diagnostic approach in LT setting has been the center-point of LT academic interest and this review[1].

Liver transplantation is the optimal treatment method for most patients with ESLD and for some patients with hepatocellular carcinoma or acute liver failure[6]. In the last two decades, advances in immunosuppressive regimens have led to fewer complications of acute rejection crisis and consequently improved short-term graft and patient survival. In parallel with this great success, long-term post-LT complications have become a focus of interest of doctors engaged in transplant medicine. MetS and its individual components, namely, obesity, dyslipidemia, diabetes, and hypertension are highly present in LT candidates, in addition it often develops *de novo* or deteriorates in the posttransplant setting as a consequence of prescribed immunosuppressive therapy[6,7]. NAFLD is closely related to MetS and its individual components and is the liver manifestation of MetS. Therefore, it is not surprising that

MetS and its individual components are associated with recurrent or "*de novo*" NAFLD after LT. Consequently, MetS and NAFLD after LT potentially impact recipients' post-LT survival[2,6].

As there are no specific or well-validated pharmaceuticals currently available for NAFLD, treatment options are focused on the identification of high-risk patients. It is well known that liver fibrosis is the main driver of CLD as well as the main factor influencing post-LT morbidity and mortality. The gold standard for the diagnosis and staging of all CLD is liver biopsy (LB). However, LB is an invasive procedure. Because of the significant economic burden of post-LT steatosis and fibrosis (*i.e.*, NAFLD) and its potential consequences, there is an unmet need for noninvasive methods that will be efficient and cost-effective[8]. In the last decade, numerous laboratory tests and biomarkers for steatosis, inflammation and fibrosis detection as well as imaging methods have been intensively investigated.

In this review, we will specifically focus on the evaluation of steatosis and fibrosis in the post-LT setting in the context of *de novo* or recurrent NAFLD.

NONALCOHOLIC FATTY LIVER DISEASE AFTER LIVER TRANSPLANTATION

As mentioned, notable development of immunosuppressive treatment and progress of transplant surgery has resulted in improvement in survival rates after LT, with an approximately 90% survival rate at the first year and a survival rate of more than 70% five years after the surgical procedure[2]. With these excellent post-LT survival rates, research interest is now focusing on long-term complications, such as MetS, cardiovascular disease (CVD) and chronic kidney disease (CKD). Immunosuppressive therapy, such as calcineurin inhibitors (CNIs), mTOR inhibitors (sirolimus and everolimus) and steroids that we use today in the transplant setting, promotes the development of MetS and its individual components[6]. Immunomodulatory and steroid therapy post-LT promotes the advancement of preexisting and *de novo* MetS features, such as weight gain (> 90% of all recipients), hypertension (50%-100%), dyslipidemia (45%-69%) and diabetes (10%-40%)[6,9-13]. According to relevant studies, MetS develops in up to 60% of liver recipients and is related to CVD, CKD, NAFLD/fatty allograft disease and progression of recurrent HCV[9-19]. As a liver manifestation of MeS, NAFLD can reoccur in a previously NAFLD/MetS burdened patient, facilitate accelerated progression toward ESLD, leading to possible retransplantation, or appear *de novo* in pre-LT NAFLD naive patients. Recurrent steatosis and steatohepatitisare very common (30%-100%)[7] and were present in 1/3 of the cases at 6 months postoperatively in a study by Bhagat *et al*[11]; specifically, they were present in 33% of the group transplanted for NAFLD *vs* 0% of the group transplanted for alcoholic liver disease, $P < 0.0001$. Most important study data about incidence and outcome of recurrent and *de novo* NAFLD in posttransplant setting are summarized in Table 1[4,12,14,15,19]. Interestingly, in most studies the serum amino-transferase levels did not correlate with NAFLD recurrence or the fibrosis progression rate[12,14].

According to a meta-analysis published a year ago, the recurrence rate of both NAFLD/nonalcoholic steatohepatitis (NASH) and the occurrence rates of new-onset NAFLD/NASH are highly variable across studies[13] due to most studies dealing with the recurrence of NAFLD/NASH being retrospective, single-centered, and lacking a universal post-LT biopsy regimen, standardized histological criteria and consistent study inclusion/exclusion criteria. The authors also found that NAFLD after LT is associated with metabolic risk factors, especially high BMI.

Important point in the context of recurrent or *de novo* NAFLD after LT needs to be addressed. Although NAFLD is very common after LT, there are no clear data regarding whether NAFLD in allografts is histologically the same or different from NAFLD in native livers. The limited data that address histologic findings in *de novo* or recurrent NAFLD after LT did not address that question clearly. Thus, investigations that determine NAFLD in the allograft histologically like NAFLD in native livers are needed[16-18].

The real impact of NAFLD recurrence or *de novo* disease on allograft and patient outcomes is unclear. New-onset NAFLD appears more benign than recurrent NAFLD, with a later onset and favorable clinical course, rarely resulting in NASH. Most of the available knowledge about recurrent or *de novo* NAFLD comes from data that are based on a small number of patients, and in the majority of them, there are no protocolar biopsies, and the follow-up time is short[15,16]. Further prospective research

Table 1 Studies investigating the role of nonalcoholic fatty liver disease in post-liver transplant setting

Ref.	Type of the study	Study population	Follow up	Diagnostic method	Incidence of NAFLD	Major outcomes
Bhagat *et al*[11]	Retrospective	71 NAFLD, 81 alcoholic liver disease	Median 1517-1686 d	43.4% biopsy, 56.6% US	30% NAFLD, 0% alcoholic liver disease	NAFLD recurrence more common than *de novo*; acute cellular rejections more common in NAFLD group; no influence on CVD and overall mortality
Bhati *et al*[12]	Retrospective	103 NAFLD	Median 47-78 mo	90% biopsy or TE	87.5% steatosis (TE), reccurent NAFLD 88.2% (biopsy)	20.6% had bridging fibrosis (TE); advanced fibrosis (> F3) was seen in 26.8% (biopsy)
Seo *et al*[4]	Retrospective	68 non-NAFLD	Median 28 mo		18% *de novo* NAFLD, 9% NASH	Increase in BMI > 10% risk factor for *de novo* NAFLD; ACE-I protective role
Dumortier *et al*[14]	Retrospective	421 non-NAFLD	48 mo	Biopsy	53% had steatosis grade 1, 31% grade 2 and 16% grade 3 steatosis; 29% perisinusidal fibrosis; 3.8% NASH. 2.25% cirrhosis	MetS and its individual components, tacrolimus-based immunosuppressive therapy, alcoholic liver disease as the primary indication for LT and liver graft steatosis were associated with post-LT steatosis
Vallin *et al*[15]	Retrospective	80 *de novo* NAFLD, 11 recurrent NAFLD	5 yr		NASH and severe fibrosis (stages 3 and 4) were more common in recipients with recurrent than in those with *de novo* NAFLD (71.4% *vs* 12.5% and 71.4% *vs* 17.2%, respectively)	Recurrent NAFLD is a more severe disease with an earlier onset; prevalence of diabetes mellitus was higher in patients with recurrent NAFLD
Narayanan *et al*[19]	Retrospective	588 LT recipients; 9.7% NAFLD; 90.3% non-NAFLD	10 yr	41.5% biopsy, other US, CT, MR	Recurrent steatosis developed 77.6% and *de novo* 44.7%	Allograft steatosis did not influence post-LT survival or adverse CVD events, while underlying; NAFLD diagnosis was associated with a 2.04 increased risk of adverse cardiovascular events

LT: Liver transplantation; NAFLD: Nonalcoholic liver fatty disease; NASH: Nonalcoholic stetohepatitis, MeS: Metabolic syndrome; TE: Transient elastography; US: Ultrasound; CT: Computed tomography; BMI: Body mass index; ACE-I: Angiotensin converting enzyme inhibitors; MR: Magnetic resonance; CVD: Cardiovascular disease.

on the matter is warranted as clinical courses of new onset and recurrent NAFLD differ[13,15,16]. According to the available data, one more point in the context of post-LT NAFLD should be addressed: the definition of recurrence *vs de novo* NAFLD requires identification of preexisting NAFLD, which is often difficult to define and thus can be underrecognized. Additionally, we must think about steatosis and even fibrosis that can occur from other secondary etiologies, such as recurrence disease or some drugs; therefore, it should be excluded, although it is often difficult since many etiological factors can overlap in the same patient. Further studies should address this point and may find some biomarker that will truly identify these patients[16].

Finally, there are no proven drugs for NAFLD treatment; thus, the management of post-LT NAFLD is based on the identification of risk factors. The most common risk factors are hypertension, diabetes, dyslipidemia, and weight gain. Other factors, such as immunosuppressive drugs, have not been clearly identified to date. In the general population, the use of steroids relates to MetS and steatosis. However, in the post-LT setting, this effect could be different because most transplant centers taper steroids in the 3-6-mo period after LT. Therefore, the impact of steroids on post-LT NAFLD could be minimal. However, further studies on this topic are needed in the population of patients with liver transplant. On the other hand, CNIs are known to promote insulin resistance and MetS development. Both CNIs are related to hypertension and diabetes mellitus, but tacrolimus is a more diabetogenic medication, and cyclosporin is more related to hypertension development. From the general population, we know that MetS is related to NAFLD development. However, the development of steatosis in relation to CNIs after LT is not well investigated[16-22]. A small retrospective study investigated the posttransplant recurrence of NAFLD as well as outcomes after LT in recipients who underwent LT for NAFLD-related cirrhosis. They analyzed 88 patients. The authors have reported that the choice of CNIs (tacrolimus *vs* cyclosporine) was not significantly different among patients with NAFLD recurrence and those without[17]. On the other hand, Dumortier *et al*[14] reported that steatosis is a frequent complication after LT. In their multivariate analysis, factors that were independently related to post-LT steatosis were diabetes mellitus, post-LT obesity, hypertension, dyslipidemia,

tacrolimus-based regimen, alcoholic cirrhosis as the primary indication for LT, and pretransplant liver graft steatosis[14]. Therefore, this topic requires further long-term prospective studies with protocolar liver biopsies. Additionally, some nonmodifiable risk factors are recognized as potential factors for steatosis development, such as age, sex, and genetics[16]. Studies have shown that the PNPLA-3 non-CC genotype is associated with posttransplant obesity[22]. Additionally, Finkenstedt *et al*[23] found that recipients who carry rs738409-G in PNPLA3 have a risk for hepatic triglyceride accumulation. Interestingly, some other genetic associations, such as the transmembrane gene (TM6SF), are not investigated in the context of LT and should be investigated in upcoming investigations[16].

Another less known factor that is possibly involved in NAFLD pathogenesis and that has attracted much research interest in the general population is the gut microbiome. To the best of our knowledge, no studies have investigated gut dysbiosis in liver transplant recipients in relation to NAFLD recurrence or development. The link with MetS and obesity in the general population requires translation into the liver transplant recipient.

DIAGNOSIS OF STEATOSIS AND FIBROSIS AFTER LIVER TRANSPLANTATION – WHAT IS THE OPTIMAL DIAGNOSTIC METHOD?

Transplanted liver is prone to complications specific to transplant procedures, as well as to liver diseases like the general population. The causes partially depend on the time after LT, but there is no universal prevalence or time distribution of the various causes of graft injury. Most commonly, graft injury is related to vascular, biliary, or infective complications; toxic hepatitis; acute and chronic cellular rejection; preservation injury; or recurrence of previous liver disease. In routine practice, graft dysfunction is suspected by an increase in liver enzymes. Unfortunately, enzyme levels do not correlate with the cause or severity of liver disease. Furthermore, many diseases may be evident by a combination of clinical, microbiological, or serological findings and imaging methods. Nevertheless, in most situations, LB is needed to confirm the diagnosis[21]. Studies on long-term LT recipients and graft outcomes have shown a high prevalence of histological changes in protocolar biopsies even in the absence of abnormal liver enzymes and function tests. Therefore, occasionally, biopsy alterations may be the first sign of graft disease. Since usually more than one risk factor could be related to the development and progression of allograft fibrosis, LB is still the most performed and golden standard procedure. Knowing the challenges related to sampling error, interpretation variability, significant costs and repeatability, the major limitation in the performance of LB is the risk of complications. This allows the opportunity for noninvasive methods as a screening and monitoring method for subclinical changes in liver grafts after LT[21].

Liver allograft fibrosis is one of the main determinants of allograft survival and the need for retransplantation; therefore, early recognition of fibrosis is of great clinical interest in the management of liver transplant recipients[24-26]. Patients with LT can have many risk factors for fibrosis recurrence after LT. For example, until the era of direct anti-viral agents, patients who were transplanted due to end-stage liver disease as a consequence of HCV infection had almost universal recurrence of HCV infection with the development of cirrhosis in up to 30% by 5 years post-LT[24-26]. Furthermore, due to the high incidence of MetS after LT, recurrent or *de novo* NAFLD after LT is an important cause of post-LT recurrent fibrosis. Hepatic fibrosis is likely be more common in recurrent disease and may occur in younger individuals with NAFLD[13]. Except for HCV and NAFLD, there are other factors that may have a negative effect on fibrosis recurrence after LT, such as demographic factors (*i.e.*, recipient and donor age), immunosuppressive therapy and cytomegalovirus infection[24-26]. In the assessment of post-LT steatosis and fibrosis, we have biochemical markers, imaging methods and LB. Liver biopsy is the gold standard for diagnosing and grading all stages of liver disease and the best available standard of reference for fibrosis evaluation. The usefulness of LB is even more pronounced in post liver transplant, where today, there is no single method that can assess steatosis, necroinflammation and fibrosis concurrently in a population at risk for other concomitant causes of liver injury[16]. Knowing the practical challenges and possible complications of LB, in routine clinical practice, even in LT setting, noninvasive markers are needed to assess fat in the liver, as well as inflammation and fibrosis of the liver.

The usefulness of biochemical markers after liver transplantation

In the general population, several algorithms, based on clinical and biochemical factors, have been developed to detect individuals with advanced fibrosis. It is believed that serum fibrosis biomarkers have the potential to reflect dynamic changes in fibrogenesis and thus the ability to assess matrix turnover earlier in the disease process, allowing earlier intervention or closer surveillance. Unfortunately, none of the routinely available serum fibrosis biomarkers were designed to reflect the dynamic process of fibrogenesis, differentiate between adjacent disease stages, diagnose NAFLD, or follow longitudinal changes in fibrosis or disease activity caused by natural history or therapeutic interventions.

Biochemical markers are based on readily available parameters. According to data, few studies have investigated the usefulness of biochemical markers for fibrosis detection in the post-LT setting. The most investigated biomarkers in the post-LT setting are the asparthate-aminotraspherase-to-platelet ratio index (APRI) and the Fibrosis score 4 (FIB-4)[24,25]. Studies that investigated the diagnostic accuracy of the APRI and FIB-4 to predict fibrosis F2-4 in LT recipients are shown in Table 2.

One of the first studies that was published in 2007 included 51 patients who were transplanted due to HCV[27]. In this analysis, the area under the receiver operating characteristic curves (AUROC) of the APRI was better in female than in male recipients (0.871 *vs* 0.753). At the cut-off value of > 1.4, the APRI in women had 91% sensitivity and 75% specificity in detecting a staging score of fibrosis > 2, while in men, the corresponding values were 60% and 77%, respectively[27]. Later, Pissaia *et al*[28] analyzed the APRI and FIB-4 in 50 liver transplant recipients[28]. The primary etiologies of end-stage liver disease were HCV in 23% of cases, hepatitis B virus (HBV) infection in 14%, alcoholic disease in 33%, cholestatic disease in 19%, and others in 11% of recipients. The mean period after LT was 30.7 mo (range, 12-108 mo). The AUROC of the APRI and FIB-4 to predict fibrosis were 0.87 and 0.78, respectively. Kamphues *et al*[29] prospectively analyzed the stage of fibrosis in 135 Liver transplant recipients (94 HCV, 41 alcoholic cirrhosis)[29]. According to this study, both the APRI and FIB-4 failed to assess liver fibrosis with satisfactory accuracy. Furthermore, Pinto *et al*[30] analyzed the accuracy of the APRI score in 30 children/adolescents with LT[30]. The AUROC for significant fibrosis detection was 0.74. However, in multivariate analysis, the APRI failed to be an independent predictor of significant fibrosis. Unfortunately, most of the studies evaluated biochemical markers in LT recipients with diseases other than NAFLD, consequently mora data and validation in NAFLD LT recipients are needed. The NAFLD fibrosis score (NFS) was designed to assess liver fibrosis exclusively in patients with NAFLD and has been well investigated in the general population[31]. It's accuracy in the post-LT setting is not well investigated. Kabbany *et al*[32] investigated 93 LT recipients who were transplanted due to HCV- or NAFLD-related ESLD[32]. In addition to APRI and FIB-4, NFS was also studied. The authors found that the APRI and FIB-4 could not accurately predict advanced fibrosis in LT recipients, while NFS correlated with advanced fibrosis in the graft when the indication of LT was NAFLD[32]. An interesting study was published five years ago by Bhat *et al*[33]. They retrospectively analyzed the usefulness of FIB-4, APRI and NFS in 547 liver transplant recipients in predicting death and graft loss after LT[33]. The authors found that serum fibrosis biomarkers 1 year after LT and changes in serum fibrosis biomarkers predict death and graft loss in LT recipients[33]. Given the encouraging results of the aforementioned studies, further prospective, controlled, multicenter studies in the NAFLD population with protocol biopsies as gold standard are needed. Also, the validation in routine practice is necessary, mainly with the aim of defining its role in assessing the course and outcome of the disease. However, we have to draw attention to the fact that the main limitation of the biomarkers that are well investigated and validated in the pre-LT setting is that all three biomarkers (APRI, FIB-4 and NFS) have thrombocytes in their formulas. According to earlier data, thrombocytopenia can persist after LT even though portal hypertension has reversed following LT. Therefore, these scores can overestimate fibrosis and are not a good method for fibrosis evaluation in LT recipients[16]. Serum biomarkers are well investigated in the pre-LT setting and are recommended by the guidelines of the European Association for the Study of the Liver (EASL). It is recommended that noninvasive methods could substitute for LB when combined in the pretransplant setting[34]. However, due to the abovementioned limitation (*i.e.*, post-LT thrombocytopenia), their use in the post-LT setting possibly could not be as useful as it is in the pre-LT setting.

Various other combinations of cytokines, chemokines, genetic polymorphisms, microRNAs, and post-translationally modified glycoproteins have also been proposed as candidate biomarkers of fibrosis but have not yet been validated or made available outside research laboratories[35]. Their application is difficult given the heterogeneity of

Table 2 Asparthate-aminotraspherase-to-platelet ratio index and fibrosis score 4 for fibrosis detection in liver transplant recipients

Ref.	Study population and etiology of ESLD	Prevalence F2-F4 (%)	Months after LT	Biochemical marker	Cut-off	Se	Sp	AUC	PPV	NPV
Toniutto *et al*[27], 2007	51 patients; HCV	32.4	24	APRI	1.4	76	77	0.80	46	93
Pissaia *et al*[28], 2009	50 patients; various etiologies	28	30.7	APRI	0.5	81	80	0.87	62	91
Kamphues *et al*[29], 2010	135 recipients; 94 HCV, 41 alcoholic cirrhosis	68.1	80.6	APRI	0.48	70	63	0.68	80	80
Pinto *et al*[30], 2014	30; biliary atresia, metabolic disease, other	20	60	APRI	0.4	83	58	0.74	31	94
Crespo *et al*[31], 2016	72; HCV	33	12	APRI	1.36	69	87	0.83	75	83
Pissaia *et al*[28], 2009	50 patients; various etiologies	28	30.7	FIB-4	3.25	31	94	0.78	67	77
Kamphues *et al*[29], 2010	135 recipients; 94 HCV, 41 alcoholic cirrhosis	68.1	80.6	FIB-4	2.8	44	87	0.66	88	42
Crespo *et al*[31], 2016	72; HCV	33	12	FIB-4	3.23	77	80	0.81	69	86

ESLD: End-stage liver disease; F: Fibrosis; Se: Sensitivity; Sp: Specificity; AUC: The area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; HCV: Hepatitis C; APRI: AST-to-platelet ratio index; FIB-4: Fibrosis score 4.

liver diseases, especially regarding the detection of specific histological changes. Recent studies aiming to investigate markers related to the risk of NASH incorporated PNPLA3 I148M and rs738409 polymorphisms as well as other molecules related to inflammation (*e.g.*, K18), lipid metabolism, peptides, gut microbiome, circulating mRNA, DNA methylation, *etc*[35]. Investigations in genomics, epigenomics, metabolomics, lipidomics and proteomics have led to the identification of new markers able to define the type and severity of NAFLD as a long disease course. Before their routine application proof of concept is needed in the clinical field along with further validation.

In conclusion, there is a need to further investigate noninvasive biomarkers to decrease reliance on LB in assessing the progression of fibrosis in LT patients.

ULTRASOUND

Imaging of the liver by ultrasound (US) represents a valuable asset in addressing the characteristics of the liver graft in a pre-transplant setting and helps quickly identify some of the acute post-LT complications concerning vascular structures, especially when paired with contrast enhancement[36]. Ultrasound is noninvasive, widely available, inexpensive and portable method. Hepatic steatosis is seen on liver ultrasound as a hyperechoic (bright) liver compared with parenchyma of the ipsilateral kidney, while in a liver without steatosis, the liver and the renal parenchyma should exhibit similar echogenicity[37,38].

A meta-analysis of forty-nine studies with 4720 participants compared ultrasound with the gold standard LB in detecting liver steatosis. The overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of US for the detection of moderate-severe fatty liver compared to histology were 84.8% (95% confidence interval: 79.5-88.9), 93.6% (87.2-97.0), 13.3 (6.4-27.6), and 0.16 (0.12-0.22), respectively[39]. However, the sensitivity of ultrasound decreases with the decrement of fatty infiltration, so in the presence of a hepatic fat content of 10% to 19%, it had a sensitivity of only 55% shown in a study on 100 Living liver donor candidates[40]. As mentioned earlier, the presence of morbid obesity (BMI greater than 40 kg/m^2) also lowers the sensitivity and specificity of ultrasound in detecting steatosis, which fall to 49% and 75%, respectively, as well as detecting the presence of severe fibrosis[39,41].

Simply classifying liver steatosis by US as mild, moderate or severe is quite dependent on the experience of the sonographist and the image quality, which can be impaired in many circumstances; thus, it amounts to a quite subjective analysis

without proper quantification of liver steatosis. Therefore, to adequately address steatosis by ultrasound and minimize operator and image-dependent bias, several computer-aided approaches have been proposed to quantify the level of liver steatosis[38,42,43]. Studies by Webb *et al*[38] and Mancini *et al*[43] reported that computer-aided measurement of the ultrasound hepatic/renal echo-intensity ratio (H/R) was highly correlated with the liver fat content determined by histology and [1H]-magnetic resonance spectroscopy, respectively. Xia *et al*[42] confirmed those conclusions in their study and added the hepatic/renal intensity ratio and ultrasound hepatic echo-intensity attenuation rate measurement and a tissue-mimicking phantom for standardization to make the results more comparable among different US machines. The optimal cut-off value for liver fat content that is sufficient to diagnose hepatic steatosis by ultrasound was 9.15%, and by using this cutoff, the sensitivity and specificity for quantitative computer-assisted ultrasound to diagnose hepatic steatosis were 95.1% and 100%, respectively, which were better than those of qualitative US, whose sensitivity and specificity were 82.5% and 83.3%, respectively[42].

Several other methods have been proposed to ameliorate the quantitative detection of liver steatosis with US, such as texture analysis by a gray-level co/occurrence matrix algorithm and the implementation of artificial intelligence of convolutional neural networks, which do not require the selection of the region of interest by the sonographer and thus minimize the subjectivity of the procedure[44-46]. Although there are unquestionable advancements in the quantification of liver steatosis by US, the diversity of the mechanisms used and the algorithms as well as the lack of appropriate cut-off levels and implementation of such methods in the post-LT liver graft, the conclusion is that US can be used as a screening modality for detecting hepatic steatosis but not as a quantitative assessment in the LT setting[47].

Since the introduction of fibroelastography in the evaluation of liver fibrosis, basic US has had little or almost a peripheral role. With the introduction of contrast-enhanced US and liver-specific contrasts, there is still hope for US. A recent study on 409 patients with hepatitis C used a liver-specific contrast agent to investigate the associations between the collapse of microbubbles and the progression of liver disease, and the range of bubble destruction was significantly increased according to the progression of fibrosis staging[48].

TRANSIENT ELASTOGRAPHY

In the last decade, clinical attention has been focused on one-dimensional transient elastography (TE), which is an US-based method that uses shear wave velocity to assess tissue (*e.g.*, liver) stiffness[49]. Since 2001, TE has been applied in medical practice under the name FibroScan®[49]. Liver stiffness measurements (LSM) as assessed by TE have been validated in pre-LT patients with various CLDs[50,51]. Initially, TE was developed for the assessment of liver stiffness as a surrogate marker of liver fibrosis; thus, LSM has been present in TE devices from its beginning. LSM values range from 1.5 to 75 kPa, where lower values indicate a more elastic liver[49]. Later, in 2011, a new parameter called the controlled attenuation parameter (CAP) was developed and incorporated into the TE device. CAP has allowed the detection and grading of steatosis by assessing the degree of US attenuation due to liver fat using the TE probe simultaneously with LSM. With this improvement, by use of TE with CAP, we can simultaneously assess both steatosis and fibrosis. The lowest CAP value is 100 and the highest 400 dB/m, where higher numbers indicate more pronounced steatosis[24,49].

Comparison of transient elastography and liver biopsy

In comparison to the LB, TE measures a much larger region of interest. With the help of TE, we can measure a cylindrical liver segment 1 cm wide and 4 cm long at a medium depth of 4.5 cm. This region of the liver parenchyma is approximately 100 times larger than the volume of the liver cylinder obtained by LB. The result of the TE exam is obtained as a median of at least 10 measurements. The drawback is that the information (LSM and CAP) cannot be obtained by a single measurement[24,49].

Effects of probe choice on transient elastography results

Earlier data reported the limitations of the M probe in obese patients in those with an increased skin-to-liver capsular distance. In those patients, if we use the M probe, there is a much higher failure rate. This led to the development of the XL probe that is specially designed for obese people[52]. Additionally, there were some uncertain data regarding the impact of other histological features on LSM; for example, there are

some data that reported that steatosis can influence LSM readings. Similarly, some studies suggested that cut-off values differ according to probe choice, M or XL[52-54]. However, recently, Eddowes *et al*[52] published the largest study about the accuracy of CAP and LSM obtained with the M or XL probe only in a population of patients with NAFLD. An automatic probe selection tool was set in the TE software that recommends the adequate probe depending on the skin-to-liver capsule distance of each patient. According to this study, CAP and LSM are accurate noninvasive tools for assessing liver steatosis and fibrosis in patients with NAFLD. In contrast to some conflicting earlier data, the authors have found that probe type and steatosis did not affect the LSM values, and the only parameter that affects LSM was the histological fibrosis grade[52].

Transient elastography in different liver diseases

The first purpose of TE devices was to assess the fibrosis stage in patients with viral hepatitis to reduce the need for LB. Those studies showed a good association of LSM with liver histology[49,55-59]. According to earlier data, the AUROC for the detection of significant fibrosis in patients with chronic HBV ranges from 0.86 to 0.97, with cut-off values from 5.2 to 8.0 kPa, while chronic HCV ranges from 0.73 to 0.91, with cut-off values from 5.2 to 9.5 kPa. In the case of patients with cirrhosis, the AUROC for identification in HBV ranges from 0.80 to 0.97, with cut-off values from 9.7 to 14.0 kPa, and in chronic HCV, the AUROC for cirrhosis ranges from 0.87 to 0.98, with cut-off values from 11.9 to 14.8 kPa[49,55-59]. Later, few studies investigated the accuracy of LSM in patients with NAFLD. According to these studies, the LSM cut-off value for significant fibrosis (F ≥ 2) ranges from 6.2 to 11 kPa; for F ≥ 3, from 8 to 12 kPa; and for F4, the LSM cut-off values range from 9.5 to 20 kPa[60-65]. The largest study that investigated the accuracy of LSM only in the NAFLD population reported that LSM identified patients with fibrosis with AUROCs of 0.77 (95%CI: 0.72-0.82) for F ≥ F2; 0.80 (95%CI: 0.75-0.84) for F ≥ F3; and 0.89 (95%CI: 0.84-0.93) for F = F4[52]. Furthermore, Youden cut-off values for F ≥ F2, F ≥ F3, and F4 were 8.2 kPa, 9.7 kPa, and 13.6 kPa, respectively[52].

Challenges in transient elastography performance

Taken together, TE with CAP is an adjunctive modality that can replace the gold standard, LB, when clinically warranted[24]. However, it should be mentioned that LSM is not an absolute measure of fibrosis but is instead a component of liver assessment and should be interpreted together with other clinical results, such as underlying liver disease, comorbidity, physical examination, laboratory tests, and other imaging methods[49]. Additionally, we must keep in mind that TE has some limitations. For example, it has been shown that food intake affects LSM values, and it is suggested that a minimum two-hour fast is currently recommended prior to the exam[49,66]. Bardou-Jacquet *et al*[67] reported that active alcohol consumption led to an overestimation of the LSM[67]. In cases of liver inflammation, such as chronic hepatitis with transaminase flare, LSM can also be overestimated. Thus, it is suggested that LSM interpretations in patients with high alanine-aminotraspherase (ALT) levels must be made with caution. Acute hepatitis and extrahepatic cholestasis also increase LSM, as does the case of heart failure in which LSM may be increased due to increased blood volume in the liver. In patients with ascites, TE is not possible because elastic waves do not travel through liquids, and in patients with narrow intercostal spaces, the success rate of TE examination is low (Table 3)[49].

In the post-LT population, data regarding the use of TE with CAP are sparse, especially in the context of *de novo* or recurrent NAFLD.

Usefulness of transient elastography in the post-LT setting

Interesting data regarding the use of TE with CAP in the context of LT were reported for the donor selection process and acute cellular rejection (ACR). One of the key points in successful LT is the determination of graft steatosis. There are differences in the mean of liver graft evaluation for the presence of steatosis between transplant centers, and there is no consensus regarding the need for LB[68]. Mancia *et al*[69] investigated the usefulness of CAP and LSM in the assessment of steatosis and fibrosis in 23 brain-dead potential donors. The authors concluded that CAP and LSM had good prediction of the histological status of steatosis of a potential liver graft[69]. Furthermore, the usefulness of LSM was investigated in the context of ACR because the inflammatory cascade driving ACR could be a cause of increased LSM. Crespo *et al*[70] investigated the usefulness of LSM in the detection and grading of ACR in liver transplant patients. The authors concluded that LSM has good diagnostic accuracy for

Table 3 Factors that influence liver stiffness measurement measurements

Factors	Influence
Food intake	Increase LSM
Active alcohol consumption	Increase LSM
Liver inflammation	Increase LSM
Cholestasis	Increase LSM
Right heart failure	Increase LSM
Ascites	Unreliable measurements
Operator inexperience	High rate of unsuccessful measurements and examinations

LSM: Liver stiffness measurement.

discriminating mild from moderate/severe ACR with an AUROC of 0.924[70]. A cut-off value of 8.5 kPa had a positive predictive value of 100% to diagnose moderate/severe ACR[70]. Before routine performance in this setting, further studies are needed to better define the cut-off points and TE applicability in decision and treatment algorithms.

Data from a previous meta-analysis comparing noninvasive methods for assessment of post-LT graft fibrosis shows that TE performs better than the serum-based biomarkers APRI and FIB 4 TE odds ratio 21.17 (95%CI: 14.10-31.77, APRI: 9.02, 95%CI: 5.79-14.07; and FIB-4 7.08, 95%CI: 4.00-12.55)[25].

In contrast to the investigation of the usefulness of TE with CAP in the pre-LT setting, its rate of investigation and accuracy in the post-LT setting was defined by underlying disease. Numerous studies have confirmed the TE accuracy post-LT in diagnosing patients with significant and advanced fibrosis, but mostly in HCV-positive recipients, even though data for various other etiologies are emerging[71-74]. Studies on the HCV population were performed to discriminate between slow and rapid progressors of graft fibrosis and response to therapy[71]. A study by Rinaldi *et al*[75] revealed that significant changes in LSM are related to the development of clinically significant graft disease (*e.g.*, all cases with a 20% increase in LSM in at least 3 measurements 3 mo apart developed biopsy proven significant graft injury or even cirrhosis).

To the best of our knowledge, only two studies have investigated the accuracy of TE with CAP in diagnosing fatty liver disease in post-LT patients. The first one was published five years ago by Karlas *et al*[76]. The authors evaluated post-LT steatosis by TE with CAP in 204 Liver transplant recipients[76]. Of 204 patients, 50% were transplanted due to alcoholic cirrhosis, and 2% were transplanted due to ESLD because of NAFLD. Since this study was published in 2015, at the time of study, the XL probe was not available, which is probably the reason why only 157 of the cases were able to achieve valid results. According to this study, 44% of recipients had steatosis, with 24% having advanced steatosis[76]. Given that the authors did not have the XL probe, the incidence of steatosis could be even higher. According to LSM, there was a high prevalence of transplant fibrosis (31%, defined by LSM > 7.9 kPa) and cirrhosis (13%, defined by LSM > 12 kPa). Advanced fibrosis (TE > 7.9 kPa) was associated with increased CAP results[76]. The relatively high prevalence of fibrosis and cirrhosis defined by LSM could be a consequence of a higher rate of obese recipients and a longer follow-up interval since LT[76]. The authors did not compare the results of TE with CAP measurements with the LB. However, the authors have shown that the same risk factors for fatty liver disease in the general population were associated with increased CAP; increased BMI and diabetes mellitus, which are specific components of MetS, were associated with an increased risk of advanced steatosis and fibrosis[76]. Interestingly, the authors found a correlation between CAP values and the liver recipient PNPLA3 status[76]. Furthermore, this year, Chayanupatkul *et al*[77] published the second study about the usefulness of TE with CAP in a post-LT setting. They analyzed 150 LT recipients. The presence of steatosis was defined by CAP values of ≥ 222 dB/m, and severe steatosis was defined as ≥ 290 dB/m. Of the 150 analyzed recipients in this study, 70% had steatosis, while 40% of these had severe steatosis. Interestingly, 81.0% of recipients with severe steatosis had normal ALT at the time of TE. In multivariable analyses, age at LT, post-LT obesity and alcoholic liver disease were significant predictors of severe steatosis[77]. Additionally, in this study also, the results of TE with CAP were not investigated in comparison to the LB. In this study,

there was a much higher prevalence of steatosis defined by TE than that in the study published by Karlas *et al*[76]. The authors did not find that steatosis defined by increased CAP values is a risk factor for morbidity and mortality after LT. The median follow-up period after LT was 66.1 mo. There was no difference with respect to the overall death rates and the percentage of recipients with cirrhosis between the severe steatosis and non-severe steatosis groups[77]. As mentioned, it was shown that most recipients with severe steatosis and, more importantly, those with cirrhosis had normal ALT (< 40 U/L). These results are in line with the results of Dumortier *et al*[14], who showed that there was no significant difference in ALT levels between those with and without fibrosis. Moreover, 31% of recipients with LB-proven NASH post-LT had normal ALT. From the data in the pre-LT setting, we know that approximately 50% of patients with NAFLD have normal transaminase levels; thus, ALT is not a good method of NAFLD screening in the post-LT setting[77].

Taken together, the clinical consequences of nonalcoholic fatty liver (NAFL) in the context of the post-LT setting have not yet been completely elucidated. Currently, we know that graft steatosis occurs in a considerable proportion of LT recipients, but there are currently no data about graft steatosis as a risk factor for advanced fibrosis, graft loss or impaired survival after LT. Thus, further imaging-based steatosis and fibrosis investigations are needed using LB comparison in the LT population[16].

OTHER IMAGING METHODS

pSWE/ARFI techniques

Published concordance between TE and SWE findings in the general population ranges from moderate to excellent depending on the study. Studies on the LT population are limited. In a study of Dubois *et al*[78], mean SWE value for patients without significant fibrosis (≤ F1) was 15.90 ± 9.2 kPa *vs* 19.27 ± 7.7 kPa for patients with fibrosis and did not reach statistical significance (P = 0.185). 2D-SWE values were higher in patients with cirrhosis when compared with those without, but there was also no significant difference (24.5 ± 7.3 kPa *vs* 16.0 ± 9 kPa, P = 0.119). The possible explanation of this lack of significant association could be underpowering. Also, it is important to stress out the high rate of liver stiffness of patients with no significant fibrosis, that was significantly higher than those reported in native livers, and possibly influenced by other post-LT specific factors influencing the liver stiffness (*e.g.*, inflammation, congestion, steatosis). A 2D-SWE cutoff value ≥ 17.05 kPa was found optimal for the detection of any grade of significant fibrosis, with an AUROC of 0.657 ± 0.13 (95%CI: 41%-91%), a sensitivity of 71.4% (95%CI: 35%-92%), a specificity of 59.2% (95%CI: 45%-72%), and PPV and NPV of 20% and 94%, respectively. Overall, this cutoff value correctly classified 60.7% patients. A 2D-SWE value below 7.85 kPa rules out the presence of significant fibrosis, resulting in a 100% NPV. A 2D-SWE value above 26.35 kPa ruled in significant fibrosis, with a 33.3% PPV[78].

A study by Perry *et al*[79], revealed no significant difference in mean PSWE measurements in patients with native livers and those with transplanted livers compared to finding of LB. pSWE accurately differentiate between patients with no-to-mild hepatic fibrosis (F0-F1) and moderate-to-severe hepatic fibrosis (≥ F2) with sensitivity of 72% and specificity of 69%.

To conclude the position of pSWE/ARFI in routine practice and evaluation of disease outcome, this method should be fully investigated[79].

MR elastography

MR elastography (MRE) is established as an accurate current non-invasive method for assessment of liver fibrosis. MRI has been found to perform better than US or computed tomography with sensitivity and specificity of 90% and 91% respectively, however still needs further validation[80-83]. Interestingly, and contrary to TE, studies have reported the excellent diagnostic accuracy of MRE in the diagnosis of cirrhosis and fibrosis even in patients with higher BMI or in those with ascites[81-83]. In the general population, comparisons between the accuracy of TE and MR elastography provide conflicting results. In a LT setting MRE can be use alone for fibrosis assessment or combined with standard liver magnetic resonance cholangio-pancreatography protocol to evaluate the graft and biliary tree[83]. The study by Singh *et al*[84] revealed a mean AUROC for significant fibrosis and cirrhosis between 0.69 and 0.96 in LT-setting. A Kamphues *et al*[85] analyzed 25 patients, who had received a liver graft due to HCV. All patients underwent both liver biopsy and MR elastography. They have found that AUROC of MR elastography based on μ for diagnosis of severe

fibrosis (F ≥ 3) was 0.87 and 0.65 for diagnosis of significant fibrosis (F ≥ 2)[85]. Thus authors had found that MR elastography is a good diagnostic tool for the assessment of higher grades of fibrosis in HCV patients after LT[85]. On the other hand, the poor correlation for lower grades of fibrosis was reported[85]. According to available data, MRE appears to demonstrate good diagnostic accuracy in the diagnosis of advanced fibrosis in post-LT setting. We can combine MRE with standard liver MRI/magnetic resonance cholangiopancreatography in order to evaluate liver parenchyma as well as focal graft lesions and finally biliary obstruction. However, its applicability is influenced by availability, cost, and time-related concerns. Before final conclusions about its routine applicability, further studies specifically on LT recipients, are needed[83].

CONCLUSION

Until further data arrive, LB remains the gold standard for establishing a conclusive diagnosis of recurrent NAFLD as well as to rule out competing etiologies. Management of LT recipients is focused on prevention and treatment of any graft diseases. Except for possible acute and chronic rejections, infections, biliary or vascular complications, recipient and graft morbidity and mortality are closely related to the development of various causes of liver fibrosis. Many regular laboratory and morphological evaluations are performed as early as possible to recognize any graft damage, and LB plays a central role in the diagnosis and exclusion of various graft diseases and the detection of fibrosis. TE with CAP in LT recipients has not yet been fully investigated. We strongly believe that this method could be very useful in post-LT settings. An important advantage of noninvasive methods, especially TE with CAP, in the evaluation of liver fibrosis are their noninvasiveness and repeatability, offering insight into dynamic changes in graft disease and the development of fibrosis. As shown in earlier data, fibrosis of liver allografts often occurs with normal transaminase levels. Thus, ALT is not a good marker for the prediction of fibrosis. Per protocol biopsies are not performed in many transplant centers, and as mentioned, many transplant recipients with advanced fibrosis have normal or mildly elevated ALT; therefore, LSM could be a good method for the selection of those who need LB. Given that TE with CAP is a noninvasive and easily obtained method, it is risk free, objective and operator-independent and requires only 5-10 min for the examination, and it is a great method for the follow-up of fibrosis progression in every-day clinical practice. In our opinion, patients with permanently elevated and increasing LSM findings should be scheduled for LB to identify the cause and stage of liver graft disease. Previous meta-analysis shows that TE performs better than the serum-based biomarkers APRI and FIB 4[25]. Still, considering their performance and invasiveness, LB and various noninvasive methods are not exclusive and should be used as complementary procedures.

There is little published experience so far using TE with CAP, especially in the context of *de novo* or recurrent NAFLD. Therefore, prospective, well-designed studies with per protocol biopsies should investigate the usefulness of TE with CAP in the post-LT setting. Additionally, these studies should answer the most important question of the optimal cut-off values of graft fibrosis in comparison to LSM in the post-LT population.

Second, post-LT graft steatosis is becoming an increasingly important issue in the transplant population. Both recurrent and *de novo* NAFLD are common after LT. By longitudinal use of CAP, we could recognize those two conditions. The question arises as to whether TE with CAP can be used to detect and monitor *de novo* NAFLD and recurrent NAFLD. Additionally, the progression of LSM values may be used as a determinant of liver allograft fibrosis severity. To date, there are still no efficient drugs for NAFLD, and the only treatment options for NAFLD generally include lifestyle changes and treatment of obesity, diabetes, hypertension and dyslipidemia. Therefore, the question arises as to whether monitoring the changes in the CAP and LSM could be useful for evaluating the treatment of those MetS components and the effect of treatment of MetS and its components on *de novo* and recurrent NAFLD. Additionally, this could motivate clinicians who manage LT recipients to treat MetS more aggressively and its components. We still do not know much about *de novo* and recurrent NAFLD; some data are connecting them with the poor survival and with a higher incidence of cardiovascular events[86]. These data are not surprising given the data in the pre-LT setting, where it has been shown that NAFLD is not only a liver disease but also a multisystem disease that is mainly connected to diabetes mellitus,

cardiovascular diseases and chronic kidney disease but also to some other chronic diseases, such as colorectal cancer[87]. CAP, as a surrogate marker of NAFLD in the pre-LT setting, showed a correlation with cardiovascular risk[88,89] and CKD[90]. Given this association, the question is whether patients with *de novo* or recurrent NAFLD with both increased CAP and specifically an increased LSM could benefit from much earlier and much stronger screening for CVD and CKD. This is important because CKD and CVD are the main determinants of patient and allograft survival. We are asking whether CAP and LSM could be surrogate markers of subclinical atherosclerosis and consequently markers of increased CVD risk in the post-LT setting.

Finally, cost-effective studies are needed to investigate the usefulness of TE with CAP in the post-LT setting.

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