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MINIREVIEWS

De novo and recurrence of metabolic dysfunction-associated fatty liver disease after liver transplantation

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new acronym adopted from the consensus of international experts. Given the increasing prevalence of MAFLD in pre-transplant settings, *de novo* and recurrent graft steatosis/MAFLD are common in post-transplant settings. The impact of graft steatosis on long-term outcomes is unclear. The current knowledge of incidence rate, risk factors, diagnosis, long-term outcomes, and management of graft steatosis (both *de novo* and recurrent) is discussed in this review.

Key Words: Metabolic dysfunction-associated fatty liver disease; Metabolic dysfunction-associated steatohepatitis; *De novo*; Recurrent; Graft steatosis; Fibrosis; Survival

Core Tip: Metabolic dysfunction-associated fatty liver disease (MAFLD) is common after liver transplantation. Post transplant metabolic dysfunction, obesity and consequences of immunosuppressant contribute to the development of either *de novo* or recurrent graft steatosis. Post liver transplant MAFLD impact on cardiovascular outcome without significant impact on graft and patient survival. Weight control and tailoring of immunosuppression are the main strategies to prevent post liver transplant MAFLD.

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INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new acronym adopted from the consensus of international experts. MAFLD is defined by the evidence of hepatic steatosis and one of the following criteria: Overweight or obesity, presence of type 2 diabetes mellitus (DM), or evidence of metabolic dysfunction[1,2] Given the increasing prevalence of obesity, nonalcoholic fatty liver disease (NAFLD) has become one of the leading causes of liver transplantation in the United States[3]. The utilization of immunosuppressants in post liver transplant (LT) patients significantly impacts metabolic dysfunction through the development of insulin resistance (IR), DM, hypertension, obesity, and hyperlipidemia[4-7]. Either *de novo* or recurrent graft steatosis can occur after liver transplantation[8]. Most of the studies showed an association between metabolic dysfunction and the occurrence of either *de novo* or recurrent graft steatosis[9-12]. Therefore, the graft steatosis can be referred to as post LT MAFLD. The ongoing injury from graft steatosis can progress to the different stages of hepatic fibrosis and eventually cirrhosis which may develop further complications. In this review, we are going to discuss epidemiology, risk factors or predictors, diagnostic techniques, natural history, outcomes, and management of *de novo* and recurrent graft steatosis.

EPIDEMIOLOGY

Hepatic steatosis has been recognized as the hepatic manifestation of metabolic syndrome (MetS). LT resolves the complications of cirrhosis due to metabolic-associated steatohepatitis (MASH), but the metabolic risks persist and often can get aggravated by exposure to immunosuppressive therapy after LT[13]. Therefore, it is not surprising to expect a higher rate of recurrent graft steatosis after LT compared to that of *de novo* graft steatosis due to the underlying MetS and IR that initially led to cirrhosis[14]. Recurrent or *de novo* graft steatosis after LT poses potential threats to the viability and survival of allografts, and therefore it is critical to characterize and identify the prevalence of recurrent and *de novo* graft steatosis after LT, and identify the risk factors for post-LT MAFLD to improve the overall clinical outcomes in the transplant recipients.

The true incidence of recurrent and *de novo* graft steatosis after LT remains uncertain as previously published studies were from single-center, retrospective studies with heterogeneous definitions of the diseases and methodologies[11,15]. Despite these limitations, we aim to describe the rates of recurrence and occurrence of steatosis in allografts, mainly abstracted from systematic reviews and meta-analyses by Saeed *et al* [11] and Losurdo *et al*[12]. In the review by Saeed *et al*[11] 17 studies representing 2378 patients primarily from North American and Europe were included, and they were categorized into three groups based on the nature of included studies: Recurrent, *de novo*, and combined graft steatosis among LT recipients at 1, 3, and ≥ 5-year follow-ups after LT. The estimated incidence rates of recurrent graft steatosis are 59% (range: 8%-100%), 57% (24%-100%), 82.1% (59%-100%) at 1, 3, and ≥ 5-year after LT respectively while those of recurrent steatohepatitis are 53% (24%-82%), 57.4% (31%-100%), and 38% (4%-71%)[11]. Recurrent graft steatosis was very common after LT, recurring in more than half of the recipients as early as 1 year after LT[11]. The studies assessing both recurrent and *de novo* graft steatosis and steatohepatitis reported 1, 3, and ≥ 5 year incidence rates as 42% (30%-65%), 34% (23%-52%), and 33% (26%-33%) for graft steatosis while 10% (5%-15%), 11% (6%-17%), and 19% (10%-27%) for steatohepatitis [11]. One of the largest studies with 275 subjects assessing recurrent graft steatosis and steatohepatitis has reported the recurrence of graft steatosis in 31% of patients and the recurrence of graft steatohepatitis in 4% of patients after LT[16].

The study by Dumortier *et al*[17] reported *de novo* graft steatosis in 31% and graft steatohepatitis in 3.8% of 421 recipients at 3.3 years after LT. In the systematic review

and meta-analysis by Saeed *et al*[11], incidence rates for *de novo* graft steatosis at 1, 3, and ≥ 5 years after LT were 67%, 40%, and 78% while 13%, 16%, and 17% for *de novo* graft steatohepatitis. These incidence rates were varied depending on the different follow-up periods, but *de novo* graft steatosis was overall very common in post-transplant patients[11]. Also, these incidence rates noted in the review by Saeed *et al* [11] were higher compared to another systematic review and meta-analysis by Losurdo *et al*[12], which reported summarized weighted prevalence of *de novo* graft steatosis as 26% [95% Confidence interval (CI): 20%-31%] and *de novo* graft steatohepatitis as 2% (95%CI: 0-3%). Larger, prospective future studies with clear, consistent inclusion and diagnosis criteria are warranted to better characterize the incidence of recurrent and *de novo* MAFLD and MASH, but existing studies consistently demonstrated very high rates of recurrence and occurrence of graft steatosis among LT recipients.

RISK FACTORS/PREDICTORS

The development of graft steatosis after LT is related to different factors: Recipient, environmental, genetic, and immunosuppressive factors[13]. A retrospective study by El Altrache *et al*[18] reported the association of recurrent graft steatosis with the occurrence of metabolic abnormalities after LT. Similarly, another study by Dureja *et al* [19] described the risk factors for the development of recurrent graft steatosis including an increased body mass index (BMI), post-transplant hypertriglyceridemia, steroid use, MetS, and insulin use. A retrospective study by Galvin *et al*[20], identified risk factors for *de novo* graft steatosis in a post-LT cohort included diabetes, weight gain, BMI, hepatitis C virus (HCV) infection, sirolimus-based immunosuppressant therapy. If none of these factors existed, *de novo* graft steatosis occurred in only 5.4% of patients, but if all 5 factors were present, it would occur in 100% of patients[20]. All these risk factors are associated with IR, and therefore it was suggested that IR might be at the root of the development of *de novo* graft steatosis[20] In a study by Vallin *et al* [10] in comparing recurrent and *de novo* graft steatosis, the prevalence of DM was significantly higher in the recurrent graft steatosis group compared to the *de novo* graft steatosis group (100% *vs* 37.5%, $P < 0.01$)

Among patients with pre-transplant NAFLD, hepatic and peripheral IR leads to insufficient inhibition of hepatic gluconeogenesis, increased lipid accumulation, and reduced glycogen synthesis[21]. Increased circulating free fatty acids from the above-mentioned process further promote inflammation and endoplasmic reticulum stress, which aggravates IR more, leading to a vicious cycle[22]. The immunosuppressive regimen used after LT also plays a critical role in MetS as corticosteroids decrease peripheral glucose absorption, increase hepatic glucose production, and therefore increases the risk of developing post-LT diabetes[13]. Calcineurin inhibitors (CNIs) that are often used as a part of immunosuppressive therapy also are diabetogenic in nature[23]. The chronic use of sirolimus, which inhibits mammalian target of rapamycin (mTOR) multiprotein complexes, has also been shown to lead to hepatic IR [24].

Despite these proposed risk factors for developing graft steatosis after LT, there were inconsistencies among previous studies, likely related to the relatively small sample sizes, and therefore further studies with larger sample sizes are required to better elucidate the heterogeneous findings[25]. In the multivariate analysis with 9 related studies, the most consistent predictors of post-LT graft steatosis and steatohepatitis were post-LT BMI, hyperlipidemia, and history of alcohol use[11]. However, a subsequent meta-analysis showed that post-LT BMI was the only risk factor with a significant impact, a summarized odds ratio of 1.27 (1.19-1.35, $P < 0.001$)[11]. Pre-transplant variables did not have a consistent independent impact on the risk of post-LT graft steatosis and steatohepatitis in the meta-analysis, and immunosuppressive regimens did not show consistent effects[11]. Although post-LT BMI was identified as the consistent predictor, given inconsistent findings of pre-LT variables as a significant risk factor for post-LT graft steatosis and steatohepatitis, immunosuppressive regimen, and hyperlipidemia as risk factors, targeting post-LT obesity may not be sufficient for effective risk factor reduction.

In another meta-analysis assessing *de novo* graft steatosis and steatohepatitis in liver-transplanted patients, alcoholic and cryptogenic cirrhosis was related to the highest prevalence of *de novo* graft steatosis, 37%, and 35% respectively[12]. Ethanol consumption can cause excessive reactive oxygen species, hepatic lipid peroxidation [26], and cryptogenic cirrhosis is often thought to be "burnt-out" steatohepatitis, and

underlying steatohepatitis may be under-recognized. Therefore, such association of the highest prevalence of *de novo* graft steatosis in alcoholic and cryptogenic cirrhosis aligns with existing literature findings[12].

Dumortier *et al*[17] reported steatosis in donors as an important predictor of *de novo* NAFLD, and therefore the interaction between donor and recipient genetics may also affect disease recurrence[13]. Previous genomic studies have reported genetic variation in the patatin-like phospholipase domain as conferring susceptibility for the risk of fibrosis and steatosis[27]. The clinical implication of utilizing steatotic graft is uncertain, and therefore it is not clear if graft steatosis itself is a risk factor for post-LT graft steatosis[28]. Detecting recurrent or *de novo* graft steatosis/steatohepatitis is critical for better clinical outcomes in transplant recipients, and therefore further studies assessing optimal follow-up methodology such as specific diagnostic modalities and timing of follow-ups are warranted to quality care in this vulnerable population. Overall risk factors are summarized in Figure 1.

DIAGNOSIS

Liver biopsy is the gold standard to diagnose hepatic steatosis, hepatic fibrosis, and cirrhosis[29]. Although it has limitations of invasiveness, a small risk of complications, and potential sampling errors[30,31], liver biopsy is shown to be a safe and adequate diagnostic tool in post LT patients. It provides an ability to exclude or detect the presence and/or severity of the coexisting chronic liver disease[29,32]. The approach to diagnose graft steatosis and fibrosis is summarized in Figure 1.

Steatosis

The sensitivity of ultrasound to detect hepatic steatosis is poor when the liver occupies less than 20% of steatosis[33]. Computed tomography-based liver to spleen attenuation ratio can identify only if hepatic macrovesicular steatosis is more than 30%[34]. Biomarker panels such as the fatty liver index and the hepatic steatosis index can enhance the result of ultrasound in identifying hepatic steatosis[35,36]. However, there is limited literature regarding the roles of biomarkers in diagnosing hepatic steatosis in post-transplant settings. Transient elastography (TE) with controlled attenuation parameter (CAP) can predict the degree of hepatic steatosis in pre-transplant settings [37,38]. One study showed detecting graft steatosis with CAP in post LT patients but there is no histologic validation in the study[39]. Magnetic resonance imaging (MRI) based techniques such as MR spectroscopy and MRI-proton density fat fraction (MRI-PDFF) has been shown to accurately detect different degrees of hepatic steatosis[37, 38]. Further studies of MRI-based techniques in diagnosis post-transplant graft steatosis are warranted.

Fibrosis

Both ultrasound and computed tomography are unable to detect different stages of hepatic fibrosis unless the patients have the late stage of cirrhosis with portal hypertension[40]. Ultrasound based shear wave elastography (SWE), using acoustic radiation force impulse (ARFI) techniques, detect fibrosis in fatty liver patients. Studies showed point SWE and two-dimensional SWE accurately detect advanced fibrosis with good sensitivity and specificity in pre-LT setting[38]. Liver stiffness measured by TE also provides good performance in identifying advanced fibrosis. However, obesity, significant ascites, postprandial state, and significant hepatic inflammation or congestion can influence the interpretation. MR elastography (MRE) has also provided a useful and accurate way to identify advanced hepatic fibrosis[37, 38]. Noninvasive serum biomarker especially NAFLD fibrosis score (NFS), aspartate aminotransferase (AST) to platelet ratio index (APRI), and FIB4-score, AST, alanine aminotransferase (ALT) ratio (AAR), BARD, and fibrospect test have been shown to provide good performances in identifying advanced fibrosis in pretransplant NAFLD patients. However, the accuracy of MRE is outperformed compared to that of simple serum biomarkers to predict advanced fibrosis[41]. The major limitations of MRI-based techniques are availability, technical complexity, high cost, and contraindication in claustrophobic patients[37].

In post LT patients, quantifying the degree of liver stiffness or graft fibrosis is challenging. It can be due to preservation injury, fibrosis present before the transplantation. Fibrosis can be heterogeneous across the graft[42]. The acute cellular rejection or any inflammatory conditions overestimates liver stiffness measurement [43]. Given thrombocytopenia persists after liver transplantation despite the resolution

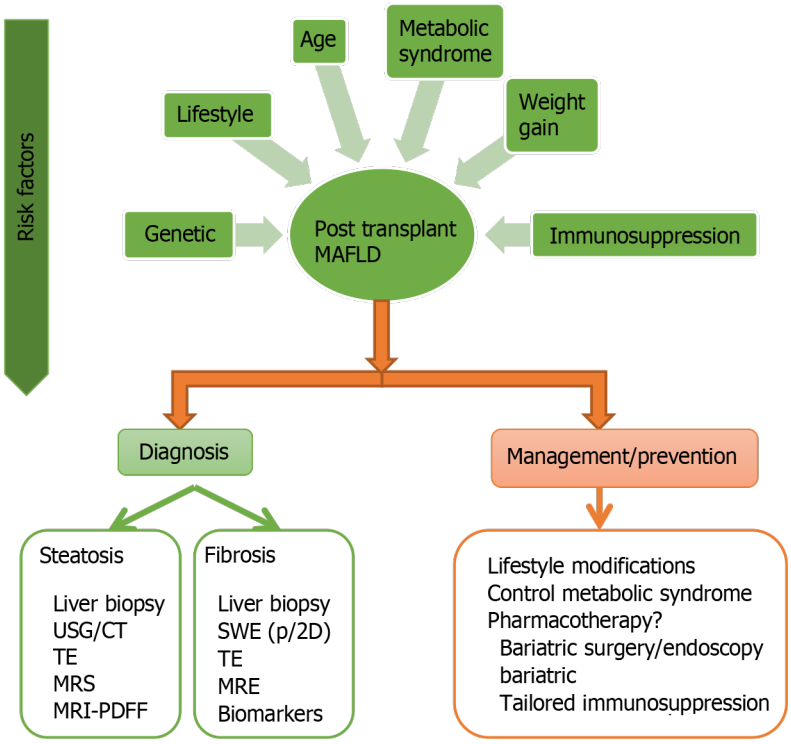

Figure 1 Overview of approach and management of post liver transplant metabolic dysfunction-associated fatty liver disease patients.
USG: Ultrasound; CT: Computed tomography; TE: Transient elastography; MRS: Magnetic resonance spectroscopy; MRI-PDFF: Magnetic resonance imaging-proton density fat fraction; SWE: Shear wave elastography; MRE: Magnetic resonance elastography.

of portal hypertension, serum biomarkers such as APRI or FIB4 that rely on platelet count may overestimate fibrosis[42]. There are a few studies regarding different noninvasive fibrosis tests (NITs) in post LT patients to identify recurrent fibrosis in different types of liver disease conditions. The meta-analysis suggests TE performs better than APRI and FIB4-score to diagnose significant fibrosis. The summary odds ratio was significantly higher for TE (21.27, 95%CI: 14.10-31.77, $P = 1 \times 10^{-30}$) compared to APRI (9.02, 94%CI: 5.79-14.07; $P = 1 \times 10^{-30}$) and FIB-4 (7.08, 95%CI: 4.00-12.55; $P = 1.93 \times 10^{-11}$). However, the majority of the studies are HCV patients[44]. Liver stiffness measured by TE at 3-mo post LT also predicts survival in LT recipients[45]. In a prospective study using ARFI to correlate histologic fibrosis score in 58 post-LT patients of mixed etiologies, the result demonstrated that SWE accurately detect advanced fibrosis (F ≥ 3) and cirrhosis (F4) with AUROC of 93 % and 80%, respectively. However, authors did not provide data on graft steatosis in these populations[46]. In a study of 32 post LT patients, the accuracy of both MRE and fibrospect test is high (AUROC of 0.87 and 0.84, respectively) in detecting fibrosis due to recurrent HCV[47]. In another study of 31 patients who underwent living donor liver transplantation with recurrent HCV infection to compare the accuracy of MRE, TE, and serum biomarkers (APRI and fibro α score to identify advanced fibrosis defined by Metavir stage ≥ 3, it showed MRE and fibro α score can accurately diagnose advanced fibrosis with AUROC of 0.708 and 0.833, respectively. The correlation of TE and APRI was not statistically significant to detect advanced fibrosis[48]. In a pooled analysis of MRE in LT recipients, AUROCs of MRE in detecting advanced fibrosis (stage ≥ 3) using a cut-off of 4.10 kPa and cirrhosis using a cut-off of 5.91 kPa were 0.83 and 0.96 respectively, suggesting high diagnostic accuracy[49].

However, there is limited literature in identifying different stages of hepatic fibrosis with NITs in post LT patients with either *de novo* or recurrent graft steatosis. A study by Galvin *et al*[20] of 430 post LT patients who developed *de novo* graft steatosis showed that the modest accuracy of FIB-4 and NFS to identify advanced fibrosis (F3-4) with AUROCs of 0.75 and 0.74, respectively. AAR with the optimal threshold of > 1.625 was found to have high specificity and accuracy with AUROC of 0.99 to identify cirrhosis (F4). However, only 9 (6%) of patients in the cohort had cirrhosis[20].

More studies are necessary to explore the accuracy of NITs in the diagnosis and assessment of steatosis and fibrosis in the post LT patients with either *de novo* or recurrent MAFLD.

NATURAL HISTORY AND LIVER OUTCOMES

Time-dependent relationships of either *de novo* or recurrent graft steatosis in the post LT patients were found in a few studies. Recurrent graft steatosis was diagnosed by TE in 87.5% of 56 post LT patients at a median time of 75 mo from liver transplantation. Advanced fibrosis was found in 26.8% whereas clinically compensated cirrhosis was found in 5.4% of patients. Recurrent graft steatosis was diagnosed by liver biopsy in 88.2% of 34 post LT patients at a median time of 47 mo from liver transplantation. Recurrent graft steatohepatitis was found in 41.2% of patients and bridging fibrosis was also found in 20.6% of patients who underwent liver biopsy[50]. Another study also showed that a time-dependent increase in the risk of recurrent graft steatosis approached 100% by 5 years compared to approximately 25% incidence of *de novo* graft steatosis in weight-matched controls who were being transplanted for primary biliary cirrhosis/primary sclerosing cholangitis or alcoholic liver cirrhosis[51]. *De novo* graft steatosis was found in 36.11% of 252 post LT patients after 5 years of liver transplantation in a study by Tejedor-Tejada *et al*[52]. Among the patients with *de novo* graft steatosis, significant fibrosis (F ≥ 2) was found in 85.6% with NFS, 81.9% with FIB4, 57.9% with APRI, 61.7% with AAR, and 83% with BARD after 5 years post LT. Similarly, 33.3% of 430 post LT liver biopsies from all causes were found to have *de novo* graft steatosis or steatohepatitis at a median of 3 years after liver transplantation. The significant risk factor for the development of significant fibrosis is age (OR 1.092, 95%CI: 1.02-1.17) on logistic regression analysis. The annual progression of fibrosis in patients with *de novo* graft steatosis was estimated to be 0.4 (interquartile range: 0.2-0.7) per year based on an approximation of fibrosis stage in relation to the number of years after liver transplantation. Insulin use is the only modifiable factor associated with the development of significant fibrosis (F ≥ 2)[20]. In a study by Vallin *et al*[10] that compared the natural history of *de novo* graft steatosis to recurrent graft steatosis, *de novo* graft steatosis was found in 67% and recurrent graft steatosis was found in 100% after 1 year. The prevalence of *de novo* graft steatosis increased to 69% after 3 years and 78% after 5 years. Steatosis disappeared in 22.5% of patients with *de novo* graft steatosis but none of the patients with recurrent graft steatosis disappeared graft steatosis. Recurrent graft steatosis developed advanced fibrosis (stage ≥ 3) in 71.4% of patients whereas *de novo* graft steatosis developed advanced fibrosis in only 12.5% of patients after 5 years post LT. Similarly, more frequent graft steatohepatitis was found in the recurrent graft steatosis group compared to the *de novo* graft steatosis group (71.4% *vs* 17.2%, $P < 0.01$).

Studies have shown worse outcomes in patients being transplanted from steatohepatitis with HCC as well as patients being re-transplanted for graft steatohepatitis[53,54]. *De novo* neoplasms were generally increased in patients with *de novo* graft steatosis compared to controls[52]. However, there is no literature showed an increase in the incidence of recurrent HCC in post LT patients with either *de novo* or recurrent graft steatosis.

PATIENT AND GRAFT SURVIVAL

In a large *de novo* graft steatosis cohort studied by Galvin *et al*[20], there is no significant difference in the short term (1 year) or long-term survival up to 15 years of patients with *de novo* graft steatosis ($n = 143$) compared to those without graft steatosis ($n = 287$) (log-rank 0.54). In another study by Narayanan *et al*[9], neither graft steatosis nor steatohepatitis (regardless of *de novo* or recurrent) was associated with patient mortality at 1 year after adjusting other patient characteristics ($P = 0.25$). De novo steatosis did not statistically significant impact patient survival (time-dependent HR 1.36, 95%CI: 0.99-1.87, $P = 0.057$) or graft survival (time-dependent HR 1.26, 95%CI: 0.92-1.72, $P = 0.15$) after excluding patients with pretransplant hepatic steatosis. Graft survival was not affected by time-dependent graft steatosis nor pre-transplant steatohepatitis. None of the cohorts required re-transplantation due to recurrent steatohepatitis. The study did not show any significant difference in death and fibrosis progression between patients with biopsy-proven *de novo vs* recurrent steatohepatitis [9]. In a study of 252 post LT patients by Tejedor-Tejada *et al*[52], there is no significant difference in the medium and long-term survival between patients with *de novo* graft steatosis and controls[52].

EXTRAHEPATIC OUTCOMES

MAFLD, by definition, is associated with obesity, IR, dyslipidemia, and hypertension, and those conditions have an important impact on transplanted patient outcomes. MAFLD and MetS are intertwined, and this is evident in post-transplant patients that develop MAFLD, either *de novo* or recurrent. In recurrent MAFLD, the MetS risk factors that exist before transplant will persist. In *de novo* MALFD, those risk factors are triggered by immunosuppression (IS) or rapid weight gain after transplant. In both cases, patients carry the same metabolic profile: IR, dyslipidemia, hypertension, and obesity. Indeed, one-third of patients develop DM and obesity in 3 years post-transplant[55]. Another common element between *de novo* and recurrent MAFLD is the use of IS after transplant. Steroids, CNIs are known to cause hypertension, hyperglycemia. mTOR inhibitors often triggers hyperlipidemia in post-transplant patients.

The evidence shows that transplanted patients with recurrent graft steatosis have an increased rate of DM, dyslipidemia, and weight gain[56]. There is reciprocity between MAFLD and MetS. Transplanted patients with *de novo* graft steatosis are five times more likely to be obese and two times more likely to have DM[57]. On the other hand, Sprinzl *et al*[58] reported that almost one-third of patients who underwent a LT in his cohort developed MetS, linked to graft steatosis. Indeed, obesity and dyslipidemia were predictors for the development of *de novo* graft steatosis within one year post LT [58].

The most common cause of death in the population with steatohepatitis are cardiovascular (CV) disease and malignancies[9]. It is easy to extrapolate that the CV and malignancies are also a significant cause of mobility and mortality in post-transplant patients who develop MASH, either *de novo* or recurrent. CV events included myocardial infarction, angina, ischemic stroke, sudden death, and peripheral artery disease. Extrahepatic malignancy included urology, head and neck, skin, lung, hematological, gynecological, gastrointestinal, and brain cancer. Bhati *et al*[50] showed that mortality was attributed to cancer in 25%, infections in 25%, and CV complications in 21% in post LT patients with recurrent graft steatosis[50]. Gitto *et al*[57] demonstrated that post LT patients with *de novo* graft steatosis had an increased risk for CV disease and extrahepatic cancers. Specific factors associated with CV disease in the post-transplant setting are age > 55 years old, male sex, DM, and kidney failure [59]. In a study by Tejedor-Tejada *et al*[52], CV events were found more frequently in patients with post LT *de novo* graft steatosis than controls (23.08% *vs* 19.88%). Similarly, *de novo* malignancies were found more in *de novo* graft steatosis group compared to control (24.18% *vs* 19.25%)[52]

MANAGEMENT

There is very scarce data about post LT *de novo* and recurrent MAFLD management, but recommendations can be drawn from the treatment of MAFLD in the general population. In general, prevention of MetS and gaining weight is the best approach in post-transplant patients. Overall management is summarized in Table 1 and Figure 1.

Lifestyle modifications

Lifestyle modifications are the backbone of the treatment of MAFLD. This approach can target specific components of MetS and is the recommended first treatment for hepatic steatosis[29,60]. Fussner *et al*[61] showed that an increase in BMI was a concrete risk factor for MetS at one-year post-transplant. Hence, avoiding excessive weight gain in the immediate post-transplant setting can help decrease the incidence of MetS. Lifestyle modifications include various and multidisciplinary strategies like physical activity, personalized diet, and behavioral interventions to hold weight gain. Loss of 3%-5% of the body weight showed improved steatosis, and loss of 7%-10% of body weight improved steatohepatitis on a report by Vilar-Gomez *et al*[62]. Evidence shows that decreasing the caloric intake by 750-1000 kcal/d or by 30% resulted in improved IR and hepatic steatosis[63,64]. The literature also shows that high cholesterol diets can trigger steatohepatitis in a mice model[65]. Additionally, the European Association for the Study of the Liver (EASL) recommends avoiding fructose intake since it is associated with hepatic steatosis[60]. The American Association for the Study of Liver Diseases recommends abstinence of heavy alcohol drinking (more than four standard drinks on any day or more than 14 drinks per week in men or more than three drinks on any day or seven drinks per week in women)[29].

Table 1 Summary management strategies

Lifestyle modifications	Dietary modification
	Exercise/ physical activity
	Avoid heavy alcohol consumption
	Benefit with coffee consumption
Pharmacotherapy	No approved drug for MAFLD in post liver transplants patients
Bariatric treatment	Surgery
	Endoscopic
Tailored Immunosuppression	Early taper of steroids
	Decreasing CNIs as possible
	Avoid/cautious use of mTOR inhibitors

CNIs: Calcineurin inhibitors; MAFLD: Metabolic dysfunction-associated fatty liver disease.

In comparison, EASL recommends keeping the alcohol consumption below 30 g in men and 20 g in women since there is evidence of a decrease in the prevalence of hepatic steatosis with moderate alcohol[60]. Interestingly, coffee consumption has been associated with fibrosis risk reduction[66].

In terms of exercise, Kistler *et al*[67] reported that vigorous physical activity held fibrosis progression in hepatic steatosis. The combination of caloric restriction and exercise resulted in weight loss associated with histological improvement of steatohepatitis[62]. However, a trial of dietary counseling and exercise *vs* standard of care after liver transplantation reported only a moderate benefit; still, adhesion to the program was achieved on only 37% of the patients[68]. Therefore, the recommendation for post LT patients with MAFLD is weight loss through diet and exercise.

Pharmacotherapy

It is essential to acknowledge that there is no approved drug for the specific treatment of MAFLD. Nevertheless, there is a significant number of drugs under investigation for hepatic steatosis and steatohepatitis. Pharmacotherapy in patients with hepatic steatosis is used in two ways: to achieve control goals in diabetes, dyslipidemia, and hypertension and to target the progression of the hepatic steatosis. In both cases, caution with drug interaction in post-transplant patients is recommended[69]. MAFLD patients with MetS comorbidities need to have reasonable control of their sugars, lipids, and blood pressure, and they should be referred to a specialist in those areas if necessary. Although not recommended for the treatment of MAFLD *per se*, statins should not be held for those patients meeting lipid profile criteria for statin use[29,70]. The same can be said for diabetic agents; none of them are approved for MALFD treatment but may be used in diabetic patients with steatosis as some have shown some benefits such as pioglitazone and empagliflozin.

In the PIVENS trial, both pioglitazone and vitamin E improved biopsy-proven NASH, although the histological improvement with vitamin E was better[71]. Vitamin E should be used only in diabetic patients. Interestingly, pioglitazone was associated with weight gain. Liraglutide, a glucagon-like peptide-1, was associated in a randomized trial with the resolution of steatohepatitis, minor progression of fibrosis, and weight loss in patients with biopsy-proven NASH[72]. More recently, empagliflozin, a sodium-glucose cotransporter-2 inhibitor, has been shown to reduce steatosis and improve ALT in NAFLD diabetic patients[73]. Orlistat, a medication used for weight loss, has been associated with steatosis improvement, though this effect can be attributed to the weight loss in itself[74].

Metformin, ursodeoxycholic acid, and pentoxifylline have been tried with poor outcomes. Nevertheless, many other drugs as obeticholic acid and elafibranor, are under investigation with promising results. There is no clinical trial of an investigational drug in post LT patients with either *de novo* or recurrent MALFLD.

Bariatric surgery

Maintaining an adequate weight proves to be challenging. Although weight loss of > 7% was associated with improvement in steatohepatitis, only half of the patients

Table 2 Summary of clinical significances and outcomes of *de novo* and recurrent metabolic dysfunction-associated fatty liver disease in post liver transplant patients

	De novo MAFLD	Recurrent MAFLD
Risk factors/Predictors for post LT MAFLD	Post LT weight gain	Post LT weight gain
	HCV	Post-transplant hypertriglyceridemia
	Sirolimus-based immunosuppressant therapy	Steroid
	Insulin resistance/diabetes mellitus	Post LT Metabolic syndrome
		Insulin use
		Insulin resistance/ diabetes mellitus
Progression to steatohepatitis and advanced fibrosis	Less common	More common
Cardiovascular events	Common	Common
Patient and graft survival	No significant impact	No significant impact

LT: Liver transplant; HCV: Hepatitis C virus; MAFLD: Metabolic dysfunction-associated fatty liver disease.

achieved this goal[62]. Bariatric surgery improves long-term mortality from CV disease and cancer in the general population[75]. In a study with steatohepatitis patients who underwent bariatric surgery, 85% had resolution of steatohepatitis with improved fibrosis in 33% of the patients[76]. There are some case reports of bariatric surgery in transplanted patients; Al-Nowaylati *et al*[77] described improvement in weight, glycemia, and HDL in seven patients. Diwan *et al*[78] reported similar findings, but with a high rate of complications and mortality of 20%. Endoscopic bariatric approaches are also on the rise; those techniques demonstrate to be effective weight loss leading to improvement in steatohepatitis[79]. Endoscopy bariatric treatment can be a very feasible option in the post-transplant setting for patients with MAFLD.

Tailored IS

It is known that IS is a contributing factor in the development of MetS after LT. IS can exacerbate preexisting risk factors and contribute to recurrent MAFLD. Similarly, IS can create the conditions to develop *de novo* MAFLD in patients transplanted for other causes requiring higher IS, such as autoimmune hepatitis or rejection. Alas, IS is essential in the post-transplant period. Consequently, a tailored approach looking to reduce the risk factors for MetS and hence MAFLD should be used. Early taper of steroids and decreasing as possible CNIs by adding other agents can add to the glycemic control in transplanted patients with diabetes. Everolimus plus a low dose of tacrolimus has shown a moderate decrease in weight in post-transplant patients[80]; this strategy, along with a rapid decrease in steroids, can be helpful in obese patients. CNIs can also contribute to hypertension and dyslipidemia. Approaches to minimize those side effects can be helpful. mTOR inhibitors are associated with elevated triglycerides; thus, they should be avoided in patients is MAFLD. In summary, protocols with early tapering of steroids and minimal use of CI:N should be considered in post-transplant patients with already risk factors for MAFLD and to minimize the development of those.

CONCLUSION

Given MAFLD is the fastest growing indication for liver transplantation; both *de novo* and recurrent graft steatosis in the context of MetS or MAFLD are common in the post-transplant settings. The role of noninvasive tests in detecting graft steatosis and fibrosis is challenging. Given the performance of image-based techniques is promising, larger cohort studies with histologic validation are necessary. Liver biopsy remains the gold standard for detecting graft steatosis and different degree of graft fibrosis. Although *de novo* and recurrent MAFLD after transplant have common pathways, it appears that recurrent MASH is more severe than *de novo*. Recurrent graft steatosis with the progression of fibrosis is found to be more frequent in patients being transplanted for hepatic steatosis compared to those with *de novo* graft steatosis. Even

though graft steatosis has an impact on CV events and incidence of *de novo* neoplasms, the patient and graft survival seem to be not affected by either *de novo* or recurrent graft steatosis. Management is mainly focused on weight control and tailoring of immunosuppressive therapy. The clinical significances and outcomes of both *de novo* and recurrent MAFLD in post LT population is summarized in Table 2. There are many knowledge gaps in the field of post LT MAFLD and MASH. Further studies are required for long-term outcomes of post LT MAFLD and MASH population and management strategies.

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