Cucco *et al. Metab Target Organ Damage.* 2025;5:16
DOI: 10.20517/mtod.2024.144

Metabolism and Target Organ Damage

Review

Open Access

Challenges in the management of MetALD after liver transplantation

Monica Cucco[1], Chiara Becchetti[1,2], Miki Scaravaglio[1,3], Giulia Dispinzieri[1,3], Francesca Bolis[1,3], Letizia Bagalà[1,3], Marina Strollo[1,3], Michele Orlando[1,3], Giovanni Perricone[1], Chiara Mazzarelli[1], Aldo Airoldi[1], Marcello Vangeli[1], Raffaella Viganò[1], Luca Saverio Belli[1]

[1]Hepatology and Gastroenterology Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan 20162, Italy.
[2]Graduate School for Health Sciences, University of Bern, Bern 3011, Switzerland.
[3]Department of Medicine and Surgery, University of Milano-Bicocca, Milan 20126, Italy.

Correspondence to: Dr. Chiara Becchetti, Hepatology and Gastroenterology Unit, ASST Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore 3, Milan 20162, Italy. E-mail: chiara.becchetti@ospedaleniguarda.it

How to cite this article: Cucco M, Becchetti C, Scaravaglio M, Dispinzieri G, Bolis F, Bagalà L, Strollo M, Orlando M, Perricone G, Mazzarelli C, Airoldi A, Vangeli M, Viganò R, Belli LS. Challenges in the management of MetALD after liver transplantation. *Metab Target Organ Damage.* 2025;5:16. https://dx.doi.org/10.20517/mtod.2024.144

Received: 31 Dec 2024 **First Decision:** 17 Feb 2025 **Revised:** 2 Mar 2025 **Accepted:** 14 Mar 2025 **Published:** 27 Mar 2025

Academic Editor: Amedeo Lonardo **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are among the leading indications for liver transplantation (LT). The definition of metabolic dysfunction- and alcohol-associated liver disease (MetALD) identifies individuals with MASLD who consume moderate levels of alcohol, representing a severe phenotype within the steatotic liver disease (SLD) spectrum. Patients with MetALD face higher risks of post-LT complications, including metabolic syndrome, graft steatosis, and fibrosis. Despite the rising prevalence of MetALD due to increasing obesity and alcohol consumption, data on its recurrence or *de novo* development post-LT remain limited. The management of MetALD post-LT is particularly challenging due to the interplay of metabolic factors and potential alcohol relapse. Current evidence suggests that recurrent or *de novo* MetALD often progresses more rapidly to advanced fibrosis than in native livers, underscoring the importance of early detection and management. Integrated approaches addressing both metabolic syndrome and alcohol-related risks are essential for optimal management. Non-invasive diagnostic modalities, such as transient elastography and specific biomarkers like phosphatidylethanol (Peth), are promising in assessing graft health and alcohol relapse, respectively. Emerging therapies, including glucagon-like peptide-1 receptor agonists (GLP1-RAs) and fibroblast growth factor-21 (FGF21) analogs, offer potential dual-action benefits targeting metabolic dysfunction and alcohol consumption. These innovations, coupled with lifestyle interventions and tailored immunosuppressive regimens,

may improve patient outcomes and reduce graft failure. This review highlights the need for multidisciplinary strategies and further research to optimize the management of MetALD post-LT, aiming to improve survival and quality of life in this high-risk population.

Keywords: MASLD, ALD, liver transplantation, immunosuppression

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are among the leading causes of chronic liver disease and primary indications for liver transplantation (LT)[1,2]. The recently introduced classification "MetALD" identifies individuals with MASLD who had moderate alcohol consumption (up to 20-50 g/day for females, 30-60 g/day for males), refining our understanding of the overlapping spectrum of these conditions. MetALD represents a more severe phenotype within the spectrum of steatotic liver disease (SLD), associated with higher all-cause mortality and poorer clinical outcomes compared to MASLD or ALD alone[3].

The global rise in obesity and alcohol consumption has led to an increasing prevalence of MetALD among LT candidates. These patients experience elevated risks of waitlist mortality, graft failure, and post-LT complications[4]. Risk factors, including alcohol relapse, metabolic syndrome, obesity, and diabetes, may persist or newly develop post-LT, leading to recurrent or *de novo* SLD.

Limited data exist on recurrent or *de novo* MetALD, though emerging evidence suggests that MetALD patients were at high risk of post-LT metabolic syndrome and increased liver graft injury driven more by metabolic features than by alcohol relapse. High BMI at the time of LT and post-LT weight gain have been identified as independent risk factors for recurrent SLD, while severe alcohol relapse remains the predominant cause of graft cirrhosis[5,6].

Effective management of pre- and post-LT metabolic syndrome, particularly obesity, is crucial for MetALD patients. Multidisciplinary approaches targeting metabolic and alcohol-related factors may prevent SLD progression and improve outcomes. Historically, MASLD and ALD have been managed as distinct conditions, focusing on metabolic syndrome and alcohol relapse, respectively. However, MetALD underscores the need for integrating pre- and post-LT strategies addressing both metabolic and alcohol-related factors. Promising therapies, such as glucagon-like peptide-1 receptor agonists (GLP1-RAs) and the fibroblast growth factor-21 (FGF21), offer the potential to concurrently target these overlapping risks. This review examines the diagnostic and therapeutic challenges of MetALD in the post-LT setting, emphasizing the importance of integrated strategies to optimize patient outcomes and guide future research in this evolving field.

THE MAGNITUDE OF THE PROBLEM

Over the past two decades, the prevalence of obesity, type 2 diabetes, and other components of metabolic syndrome has risen significantly, reaching 25%-30% in the general population and 40%-60% in LT recipients[7]. ALD remains the leading indication for LT in Europe, but MASLD has emerged as a prominent indication in the past decade[8,9]. MetALD is also increasingly recognized as it accounts for 10%-20% of LT indications and is associated with worse outcomes compared to ALD or MASLD alone[6]. Post-LT, all three conditions can recur in the graft (recurrent disease) or develop as *de novo* disease.

The impact of SLD of the graft has been extensively characterized, though definitions of MASLD/metabolic dysfunction-associated steatohepatitis (MASH) vary significantly across studies, complicating accurate data interpretation. Recurrence of MASLD has been reported to range from 24.8% to 88.2% and recurrence of MASH occurs in 30%-40% of LT patients[10]. Importantly, the progression to advanced fibrosis or cirrhosis of the graft occurs in one-quarter of these patients and happens more rapidly than in the native liver, usually within 5-10 years[11]. *De novo* MASLD is also significant, with a prevalence ranging from 26% to 56% of LT recipients for non-MASLD causes[10,12]. *De novo* MASH has a prevalence of 2%-10%, suggesting that it seems to be less frequent than recurrent MASH. Similarly, the rates of advanced fibrosis in *de novo* MASLD seem to be lower as compared to recurrent MASLD (0%-17.7% *vs.* 20%-71%)[13,14].

The etiopathogenesis of post-LT MASLD is probably multifactorial. Several studies point out the presence of metabolic risk factors before LT that persist post-LT as possible key drivers[7,15,16]. In addition, immunosuppressive regimens, including corticosteroids (CSs) and calcineurin inhibitors (CNIs), further exacerbate post-LT metabolic syndrome by promoting insulin resistance[17]. Donor factors also seem to play a role in post-LT outcomes, particularly for patients with MASH. The prevalence of donor type 2 diabetes has increased over the past two decades, contributing to lower patient and graft survival due to hepatic steatosis in donor livers, which primes recipients for hepatic and non-hepatic metabolic complications[14,18]. According to the hypothesis regarding the genetic mechanisms of MASLD recurrence following LT, several studies have investigated potential genetic factors contributing to the recurrence of MALSD post-LT in both donors and recipients. The patatin-like phospholipase domain-containing 3 (PNPLA3) rs738409-G variant, or PNPLA3 I148M polymorphism, has emerged as a significant genetic determinant of graft steatosis. This allele, whether present in heterozygosity or homozygosity, increases the risk of post-LT steatosis in a dose-dependent manner, whether inherited from the donor or present in the recipient. When both donor and recipient carry this variant, the risk is significantly amplified, with an odds ratio of up to 29-fold for early post-LT steatosis. Another important genetic factor is the transmembrane 6 superfamily member 2 (TM6SF2) rs58542926-A allele, which is associated with more severe steatosis, inflammation, and fibrosis. Its effects are modulated by recipient adiposity and may interact additively with the PNPLA3 I148M polymorphism. Contrarily, some genetic variants may confer protective effects. The superoxide dismutase-2 (SOD2) rs4880-A variant in recipients and the HSD17B13 rs6834314 variant in donors have been linked to a reduced risk of MASLD recurrence [Figure 1]. The multifactorial nature of post-LT steatosis recurrence underscores the interplay between genetic predisposition and metabolic factors such as recipient obesity and diabetes, highlighting the necessity for personalized management strategies in LT patients[19-21]. The impact of post-LT MASLD on survival remains unclear. While overall survival does not appear significantly affected, higher morbidity has been reported, particularly cardiovascular (CV) events[15,22]. CV events have been found in 15.3% and 30.3% of LT recipients at 3 and 8 years, respectively, especially in recurrent MASLD[23]. Higher rates of extrahepatic cancers, particularly skin (non-melanoma), urological, colorectal, and lung cancers, have also been described[14,15].

Relapse of alcohol use post-LT is another critical concern, with rates of 26.3% to 50.0% depending on alcohol relapse definition, follow-up, and psychosocial support[24]. Relapse increases the risk of graft MASLD, alcoholic hepatitis, advanced fibrosis/cirrhosis, and 10-year mortality three times in relapsed compared to non-relapsed patients[24]. The development of a severe alcohol use disorder (AUD) post-LT is particularly detrimental, with a significant impact on clinical outcomes[25].

A significant challenge in interpreting data on MetALD post-LT arises from variability in diagnostic criteria across studies. The definition of MetALD is relatively recent, and prospective cohort studies specifically designed to investigate its natural history and outcomes post-LT are currently lacking. Instead, most

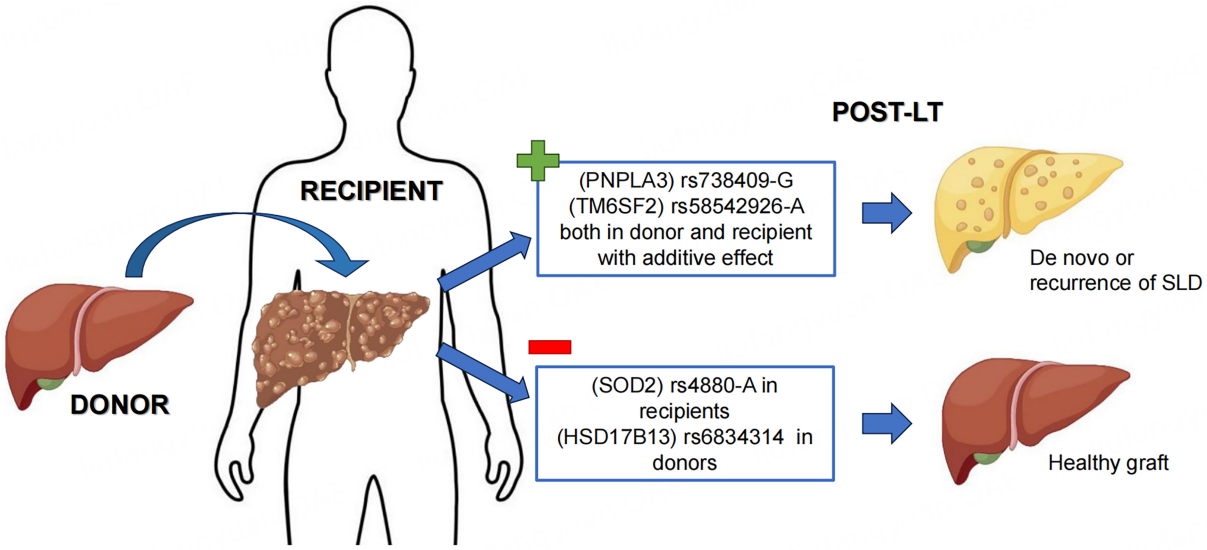

Figure 1. Genetic predisposition for SLD between donor and recipients. SLD: Steatotic liver disease; LT: liver transplantation.

available data come from retrospective analyses that reclassify patients based on prior definitions of alcohol-related and metabolic liver disease, which may not fully capture the unique clinical trajectory of MetALD. A key issue is the distinction between MASLD, MetALD, and ALD. MASLD is defined by the presence of hepatic steatosis in individuals with at least one metabolic risk factor (e.g., obesity, diabetes, dyslipidemia) and minimal alcohol consumption, below 20 g/day for women and 30 g/day for men. MetALD, in contrast, is characterized by both metabolic dysfunction and an average daily alcohol consumption ranging from 20-50 g for females and 30-60 g for males. ALD, on the other hand, is primarily defined by excessive alcohol consumption, and metabolic risk factors were often not systematically assessed in these patients[3]. This approach may have led to misclassification, failing to recognize the combined impact of alcohol and metabolic dysfunction on liver disease progression. The currently available data in the literature indicate that the prevalence of MetALD among LT patients is from 9% to 11%, and it is associated with higher post-LT rates of metabolic syndrome, MASLD, and MASH compared to isolated ALD[26]. A retrospective analysis of 907 LT recipients revealed that MetALD patients were older (median age: 56.3 *vs.* 53.3 years) and exhibited higher rates of obesity (BMI ≥ 30 kg/m^2 in 100%), diabetes (60.6%), and hypertension (75.8%) compared to ALD patients. Post-LT metabolic syndrome prevalence was significantly higher in MetALD (66.7%) than in ALD (42.9%), while alcohol relapse was notably lower (9.1% *vs.* 20.4%), highlighting its unique clinical profile[6]. In addition, the use of protocol biopsies, which is being decreased by the introduction of non-invasive markers, may also have reduced the ability to capture this entity, which can often also be a challenge histologically since some features of MASH and ALD overlap. Therefore, early identification of MetALD in the post-LT setting through an integrated approach addressing both alcohol-related and metabolic issues could not always be easy, but it is essential for developing targeted therapies that optimize patient management and improve graft survival.

HOW TO DETECT METALD POST-LT?

The diagnosis of MetALD hinges on two main aspects: detecting graft steatosis, with a particular emphasis on quantifying fibrosis to provide prognostic insights, and conducting an anamnestic evaluation, complemented by biochemical markers, to assess potentially harmful alcohol consumption in patients with metabolic risk factors.

Liver biopsy is the gold standard for diagnosing steatosis and mostly fibrosis in the post-LT setting and has a pivotal role in ruling out other allograft issues[27]. Despite being generally safe and associated with a low complication rate, liver biopsy is likely not cost-effective given the increasing burden of post-LT steatosis. Consequently, there is a compelling need for effective and reliable non-invasive tests (NITs) in this context. Table 1 summarizes the results of the available studies using NITs in the post-LT era.

In terms of detecting steatosis, ultrasound (US) remains the most commonly used technique, primarily because it is routinely employed, at least annually, for standard surveillance in LT recipients[28]. Steatosis is typically suspected on B-mode imaging when the liver exhibits higher echogenicity compared to the kidney, a difference quantifiable through the hepatorenal index (HRI), which measures the ratio of the echo intensities between the liver parenchyma and renal cortex. Additional indicators include posterior attenuation of the US beam, vessel blurring, difficulty visualizing the diaphragm, and areas of focal sparing[29]. The primary limitation of US in detecting steatosis lies in its poor longitudinal reproducibility. Therefore, quantitative methods are more suitable for longitudinal monitoring. Few studies have investigated the use of CAP in the post-LT period, proposing a cutoff value between 252 dB/m and 270 dB/m for defining steatosis[30,31]. Chayanupatkul *et al.* identified age at LT, post-LT obesity, and ALD as predictors of severe steatosis (CAP >290 dB/m) and noted that most patients with severe steatosis had normal liver tests[32].

Several serum biomarkers, such as the aspartate aminotransferase to platelet ratio index (APRI) and the Fibrosis-4 score (FIB-4), have been investigated for their potential utility in this setting. Additionally, imaging modalities such as transient elastography (TE) and magnetic resonance elastography (MRE) offer promising alternatives. However, the application of these methods remains limited in post-LT patients due to inadequate validation and the paucity of robust studies specifically addressing this population[33]. TE has shown strong diagnostic accuracy in detecting fibrosis in LT recipients in several studies[32,34-39] and outperforms traditional indices like the APRI and FIB-4, which are less reliable in this setting due to persistent thrombocytopenia - a common finding even after resolution of portal hypertension - that diminishes the accuracy of these tests[27]. In multiple prospective studies, TE has demonstrated high sensitivity and specificity for detecting significant fibrosis (≥ F2), with AUROC values ranging from 0.746 to 0.962, with sensitivities and specificities ranging from 51% to 100% and 54% to 100%, respectively, depending on the fibrosis stage and study population [Table 1]. The method appears highly effective in distinguishing early fibrosis from advanced fibrosis. However, its performance may be influenced by factors such as graft stiffness due to inflammation, biliary complications, or early rejection, which can lead to overestimation of fibrosis. Despite these limitations, TE remains the most validated and widely used non-invasive tool for fibrosis assessment in LT recipients, offering a practical alternative to liver biopsy in routine follow-up. MRE is particularly valuable for assessing post-LT fibrosis, providing insights into both liver parenchyma and the biliary tree when integrated with MRI studies[40,41]. A pooled analysis by Singh *et al.* involving 141 transplant recipients reported AUROC values for MRE of 0.73 for any fibrosis (≥ stage 1), 0.69 for significant fibrosis (≥ stage 2), 0.83 for advanced fibrosis (≥ stage 3), and 0.96 for cirrhosis, indicating good to excellent discriminatory ability for detecting advanced fibrosis and cirrhosis[42]. Despite its diagnostic potential, the use of MRE is limited by its availability and excessive costs.

Accurate detection of alcohol use is pivotal for diagnosing alcohol-related liver damage in MetALD, particularly in the post-LT setting, where clinical outcomes rely on sustained abstinence. The initial step involves a detailed history, often complemented by rapid screening tools like AUDIT-C[43], which alone may be sufficient to detect problematic alcohol use. However, given the sensitivity of the post-LT context, where individuals are acutely aware of the harm caused by alcohol, the use of additional markers can provide

Table 1. Studies that have analyzed the use of NITs in post-LT settings

Author	Study design	Study population/ Etiology	*N*	Endpoint	Method of detection	Cutoff for selected endpoints	Accuracy	Limitations
Carrión *et al.*, 2006[80]	Prospective study	LT recipients with HCV	124	Fibrosis CSPH	TE	≥ F2: 8.5 kPa	Se: 90%, Sp: 81%	Only HCV patients
					TE	CSPH: 8.74 kPa	Se. 90%, Sp: 81%	
Toniutto *et al.*, 2007[81]	Prospective study	HCV-infected LT recipients	51	Fibrosis HCV recurrence	APRI	> F2: 1.4	Se: 76%, Sp: 77%	Single-center Only HCV patients
Kamphues *et al.*, 2010[82]	Prospective study	LT recipients for HCV or alcoholic disease	135	Fibrosis	TE	≥ F2 8.5 kPa = F4 10.5 kPa	Se: 72%, Sp: 83% Se: 100%, Sp: 65%	Possibility of diagnostic failures in the examination of the liver biopsy, resulting in wrong estimation of non-invasive measurements of liver fibrosis
					APRI	≥ F2 0.48 = F4 0.48	Se: 70%, Sp: 63% Se: 89%, Sp: 44%	
					FIB-4	≥ F2 2.8 = F4 4.44	Se: 44%, Sp: 87% Se: 44%, Sp: 84%	
Rigamonti *et al.*, 2012[83]	Prospective study	LT recipients	69	Graft disease	TE	Cutoff for exclusion: ≤ 5.3 kPa	Se: 100%, Sp: 54%	
						Cutoff for inclusion: ≥ 7.4 kPa	Se: 54%, Sp: 100%	
Barrault *et al.*, 2013[84]	Prospective study	LT recipients	43	Fibrosis	TE	≥ F2: 7 kPa	Se: 88%, Sp: 68%	
Lutz *et al.*, 2015[85]	Prospective study	LT recipients	48	Fibrosis	HVRI	≥ F2: HVRI < 1.05	Se: 100%, Sp: 91%	Small sample size; the points of measuring the respective values in Doppler ultrasound evaluation; Doppler ultrasound is influenced by stage of respiration and cardiac reflux.
					TE	≥ F2: TE 8.35 kPa	Se: 85%, Sp: 91%	
Mikołajczyk-Korniak *et al.*, 2016[86]	Comparative study	LT recipients for HCV cirrhosis	36	Fibrosis	TE	≥ F2: 4.7 kPa	Se: 93%, Sp: 57%	Small size sample
Crespo *et al.*, 2016[87]	Prospective study	LT recipients who developed biopsy-proven ACR during a 30-month period	27	ACR	TE	Moderate/severe ACR (RAI ≥ 5) *vs.* Mild ACR: TE cutoff 8.5 kPa	Se: 84%, Sp: 100%	Small sample size; patients with post-transplant HCV excluded
Della-Guardia *et al.*, 2017[38]	Prospective study	LT recipients for all etiologies	267	Fibrosis in all etiologies	TE	≥ F1: 8.1 kPa ≥ F2: 12.3 kPa ≥ F3: 15.1 kPa = F4: 16.7 kPa	Se: 51%, Sp: 90% Se: 43%, Sp. 91% Se: 59%, Sp: 90% Se: 100%, Sp: 90%	Reduced number of cases with fibrosis F3-4
		LT recipients with HCV		Fibrosis in HCV-positive	TE	≥ F1: 8.1 kPa ≥ F2: 12.3 kPa ≥ F3: 16.5 kPa = F4: 17.6 kPA	Se: 53%, Sp: 94% Se: 49%, Sp: 91% Se: 55%, Sp: 90% Se: 100%, Sp: 91%	
Siddiqui *et al.*,	Prospective	LT recipients	99	Steatosis	CAP	0 dB/m *vs.* 1-3: 270 dB/m	Se: 74%, Sp: 87%	Limited number of patients

2022[31]	study					0-1 dB/m *vs.* 2-3: 295 dB/m 0-2 dB/m *vs.* 3: 295 dB/m	Se: 100%, Sp: 89% Se: 100%, Sp: 84%	
Siddiqui *et al.*, 2023[35]	Prospective study	LT recipients	132	Fibrosis	TE	0 kPa *vs.* 1-4: 7 kPa 0-1 *vs.* 2-4: 10.50 kPa 0-2 *vs.* 3-4: 12.2 kPa	Se: 81%, Sp: 69% Se: 81%, Sp: 82 Se: 86%, Sp: 89%	Single-center
					APRI	0 kPa *vs.* 1-4: 0.69 kPa 0-1 kPa *vs.* 2-4: 0.75 kPa 0-2 kPa *vs.* 3-4: 0.75 kPa	Se: 42%, Sp: 80% Se: 35%, Sp: 74% Se: 41%, Sp: 73%	
					AAR	0 kPa *vs.* 1-4: 0.89 kPa 0-1 kPa *vs.* 2-4: 0.89 kPa 0-2 kPa *vs.* 3-4: 0.89 kPa	Se: 67%, Sp: 54% Se: 85%, Sp: 51% Se: 86%, Sp: 50%	
					FIB-4	0 kPa *vs.* 1-4: 3.40 kPa 0-1 kPa *vs.* 2-4: 1.73 kPa 0-2 kPa *vs.* 3-4: 2.52 kPa	Se: 33%, Sp: 88% Se: 81%, Sp: 43% Se: 59%, Sp: 66%	
					NFS	0 kPa *vs.* 1-4: 0.77 kPa 0-1 kPa *vs.* 2-4: 0.57 kPa 0-2 kPa *vs.* 3-4: 0.57 kPa	Se: 40%, Sp: 86% Se: 62%, Sp: 73% Se: 59%, Sp: 71%	
Arshad *et al.*, 2023[88]	Prospective study	LT recipients with histological fibrosis assessment	132	Fibrosis	TE	0 kPa *vs.*1-4: 7 kPa 0-1 kPa *vs.* 2-4: 10.50 kPa 0-2 kPa *vs.* 3-4: 12.2 kPa	Se: 81%, Sp: 69% Se: 81%, Sp: 82% Se: 86%, Sp: 89%	
					FIB-4	0 kPa *vs.* 1-4: 3.40 kPa 0-1 kPa *vs.* 2-4: 1.73 kPa 0-2 kPa *vs.* 3-4: 2.52 kPa	Se: 33%, Sp: 88% Se: 81%, Sp: 43% Se: 59%, Sp: 66%	

LT: Liver transplantation; HCV: hepatitis virus C; ACR: acute cellular rejection; ALT: alanine transaminase; AST: aspartate transaminase; TE: transient elastography, HVRI: right hepatic vein resistance index; CSPH: clinically significant portal hypertension; Se: sensitivity; Sp specificity; NITs: non-invasive tests; APRI: aspartate transaminase to platelet ratio index; ACR: acute cellular rejection; AAR: alanine aminotransferase ratio; NFS: NAFLD fibrosis score; LB: liver biopsy.

valuable support. Biomarkers of alcohol use are broadly classified into indirect and direct markers. Indirect markers, such as gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), carbohydrate-deficient transferrin (CDT), and mean corpuscular volume (MCV), reflect the physiological effects of chronic alcohol consumption. However, their reliability post-LT is reduced by confounding factors, including pre-existing graft dysfunction, the iatrogenic effect of immunosuppression, and systemic conditions like bone marrow suppression or vitamin deficiencies. Direct markers, including ethyl glucuronide (EtG) and phosphatidylethanol (PEth), measure alcohol metabolites directly and offer higher specificity. EtG, detectable in urine, blood, and hair, provides insights into recent alcohol use, with hair EtG distinguishing between abstinence, moderate use, and heavy drinking. However, external ethanol exposure (e.g., from hygiene products or medications) can lead to false positives[44-47]. PEth, a phospholipid marker with a detection window of up to 28 days in blood, is both highly sensitive and specific and is not influenced by age, sex, or liver function[48,49]. Lim *et al.* demonstrated PEth's superiority in detecting alcohol use pre- and

post-LT, with a significant increase in relapse detection rates[50]. De La Torre *et al.*'s study further highlighted PEth's role in improving surveillance for alcohol relapse in LT recipients[51]. Extensive evidence confirms that PEth is not endogenously formed without ethanol exposure, underscoring its reliability[52]. Studies reporting these biomarkers in the post-LT setting are reported in Table 2.

The integration of these biomarkers, alongside clinical assessments and NITs, provides a comprehensive approach to screening MetALD in post-LT recipients, while liver biopsy remains the gold standard. Future research should focus on refining biomarker thresholds, understanding their limitations in this unique population, and leveraging point-of-care testing technologies to improve real-time monitoring.

THERAPEUTIC APPROACH

Classical approach to MASLD post-LT

The prevention and management of MASLD post-LT focuses on addressing traditional cardiometabolic risk factors (both pre-existing and *de novo* post-transplant), such as obesity, diabetes, hypertension, and dyslipidemia. Strategies must be adapted to the unique post-LT setting, balancing metabolic health with immunosuppressive therapy requirements. Reducing CS use, lowering CNI doses, and incorporating alternative immunosuppressors such as antimetabolites or mammalian target of rapamycin (mTOR) inhibitors can mitigate metabolic complications while preserving graft function. Thus, the primary approach to managing MASLD after LT remains focused on addressing the individual components of metabolic syndrome[53] [Figure 2].

Obesity

Obesity post-LT contributes to adverse outcomes such as graft steatosis, fibrosis, CV events, and *de novo* SLD. CSs are a well-documented contributor to weight gain, emphasizing the importance of their early tapering. Among CNIs, tacrolimus is associated with less weight gain than cyclosporine in the first year post-transplant. Recent data suggest that everolimus with reduced tacrolimus exposure minimizes weight gain at one and two years post-LT[53,54]. Obesity management begins with supervised physical activity and personalized weight-loss programs tailored to prevent sarcopenia, supported by nutritional assessments[55]. When lifestyle measures are insufficient, pharmacological treatments, like GLP1-RAs, or bariatric surgery, such as sleeve gastrectomy, may be considered, balancing metabolic benefits with potential immunosuppressive drug interactions, although more research is needed to establish their safety post-LT[56]. In the diabetic population, trials evaluating the effects of metformin on weight loss revealed 2.1% weight loss over the first 2 years of therapy[57]. A randomized control trial (RCT) following kidney transplant showed a trend toward less weight gain in the metformin group[58]. Some drawbacks include drug malabsorption related to post-LT bariatric surgery and the need to stabilize transplant outcomes for a congruent time.

Diabetes

Diabetes management post-LT includes addressing both pre-existing diabetes and new-onset diabetes after transplantation (NODAT), which significantly increases morbidity, CV risk, and graft loss. CSs and CNIs, particularly tacrolimus, are primary contributors due to their diabetogenic effects. Definitive diagnosis, based on HbA1c or oral glucose tolerance testing, should occur after three months post-LT, as perioperative hyperglycemia often resolves. Glycemic targets are individualized, aiming for HbA1c levels < 7% for younger or less comorbid patients and < 8% for older patients. Pharmacological therapies must consider hepatic metabolism and potential interactions with immunosuppressants. Metformin, GLP1-RAs, and sodium-glucose cotransporter-2 (SGLT2) inhibitors are promising, with GLP1-RAs offering additional weight-loss benefits. Insulin remains the mainstay for managing severe hyperglycemia. Immunosuppressive regimen adjustments, such as minimizing CSs or using cyclosporine instead of tacrolimus, may also

Table 2. Studies using Peth or EtG to detect alcohol use in the setting of post-LT

Author	Study design	Study population / Etiology	*N*	Follow-up (median)	Endpoint	Method of detection	Cutoff for selected endpoints	Accuracy	Limitations
Staufer *et al.*, 2011[45]	Prospective study	ALD LT-recipients	141	9 months	Alcohol relapse	DRI-EtG-enzyme immunoassay, confirmed by LC-MS-MS	≥ 0,5 mg/L	Se: 89.3%, Sp: 98.9%	FU less than 1 year
						DRI-EtG-enzyme immunoassay, confirmed by LC-MS-MS	≥ 1 mg/L	Se: 75%, Sp: 99.3%	
Piano *et al.*, 2014[89]	Prospective study	ALD LT- recipients	23	Over 1 year	Alcohol relapse	DRI-Etg enzyme immunoassay	≥ 0,5 mg/L	Se: 89,2%, Sp: 98,8%	Lack of confirmation by LC-MS; small population size
Fleming *et al.*[48]	Prospective study	ALD LT-recipients	151	1 year	Alcohol relapse	DBS-Peth extraction, followed by LC-MS-MS	≥ 8 ng/mL	AR (using Peth):29% *vs.* AR (self-reported): 8,6% *P*-value: 0.007	Se/Sp not evaluated; FU of 1 year; 13 ALD-LT-recipients were also transplanted because of LF by HCV
Andersen-Streichert *et al.*, 2017[90]	Prospective study	ALD LT- recipients	61	1 year	Alcohol relapse	Etg hair LC-MS-MS	≥ 7 pg/mL	Se: 84%, Sp: 92%	FU 1 year, small population size
						DBS- Peth extraction, followed by LC-MS-MS	≥ 20 ng/mL	Se: 100%, Sp:96%	
						DRI-Etg enzyme immunoassay, confirmed by LC-MS-MS	≥ 0.5 mg/L	Se: 71%, Sp: 98%	
De La Torre *et al.*, 2024[51]	Single-center retrospective study	ALD LT-recipients before and after using Peth	263	3 years	Alcohol relapse	DBS- Peth extraction, followed by LC-MS-MS	≥ 20 ng/mL	AR (using Peth):17% *vs.* AR (before using Peth): 7% *P*-value: 0,012	Alcohol screening was applied only in case of high clinical suspicion

LT: Liver transplantation; ALD: alcohol-associated liver disease; AR: alcohol relapse; Se: sensitivity; Sp specificity; LC: liquid chromatography; MS: tandem mass spectrometry; DBS: dried blood spot; EtG: Ethyl Glucuronide; HCV: hepatitis virus C; FU: follow-up.

improve glycemic control[18,54,59]. Some concerns exist with respect to the possible increase in immunosuppressed patients with recurrent urinary tract infections with the use of SGLT2 inhibitors[53].

Hypertension

Post-LT hypertension arises from systemic changes, CNI-induced vasoconstriction, and CS use. CNIs promote sodium retention and increase sympathetic activity, while CSs activate the renin-angiotensin-aldosterone system (RAAS). Management strategies include lifestyle changes such as sodium restriction, weight loss, smoking cessation, and exercise, alongside pharmacological interventions. Calcium channel blockers (CCBs), particularly amlodipine, are the

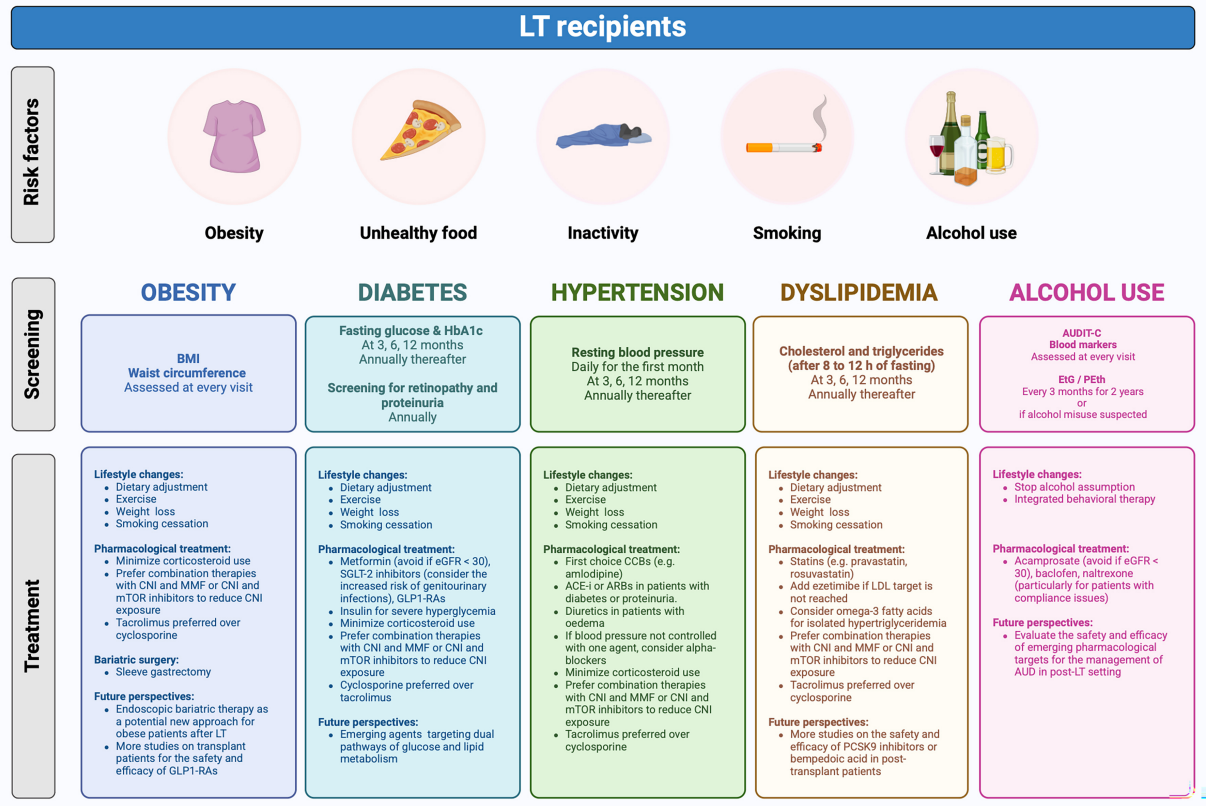

Figure 2. Management workflow of comorbidities in post-LT setting[17,70,91-95]. BMI: Body mass index; GLP1-RAs: glucagon-like peptide-1 receptor agonists; LT: liver transplantation; eGFR: estimated glomerular filtration rate; SGLT2: sodium-glucose cotransporter-2; CCBs: calcium channel blockers; ACE-I: angiotensin converting enzyme-inhibitor; ARBs: angiotensin receptor blockers; mTOR: mammalian target of rapamycin; EtG: ethyl glucuronide; PEth: phosphatidylethanol; AUD: alcohol use disorder.

preferred first-line agents due to their efficacy in counteracting CNI-induced vasoconstriction. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are recommended for patients with proteinuria or diabetes, as they may also provide renal protection and mitigate fibrosis. If edema or rhythm problems are present, diuretics and beta-blockers may be considered, as well as alpha-blockers if arterial pressure is not controlled with a single agent[18,53-55,59].

Dyslipidemia

Multiple factors contribute to dyslipidemia post-LT, including weight gain, poor glycemic control, renal dysfunction, and genetic predisposition. Immunosuppressive medications play a pivotal role: cyclosporine is more commonly associated with hyperlipidemia and hypertriglyceridemia than tacrolimus, due to its inhibition of bile salt synthesis, and mTOR inhibitors promote hypertriglyceridemia by altering insulin signaling and increasing triglyceride production. Combining mTOR inhibitors with tacrolimus or switching to antimetabolites, however, appears to mitigate these effects. Elevated LDL and triglyceride levels contribute to CV morbidity. Management aligns with guidelines for high- or very-high CV risk patients, with statins as the first-line therapy, and pravastatin, rosuvastatin, and fluvastatin preferred due to minimal interaction with CNIs. Ezetimibe may be added when the desired LDL target is not reached with statin monotherapy. Omega-3 fatty acids can be considered for isolated hypertriglyceridemia. Reducing exposure to dyslipidemia-inducing agents such as mTOR inhibitors may also improve outcomes[53-56,60]. Data about the use of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors and bempedoic acid in this group of patients are lacking.

In terms of MASH-specific therapy, lifestyle interventions, including dietary modifications like the Mediterranean diet and structured physical activity, form the foundation of MASLD management[18,27]. As known, many drugs are currently under investigation for the treatment of MASH, showing efficacy in fibrosis regression and MASH resolution in non-transplanted populations, but have yet to be extensively studied in the post-LT context. Among the most advanced agents, resmetirom is an oral, selective thyroid hormone receptor-β agonist developed to target MASH. In March 2024, resmetirom received accelerated approval from the FDA for use in combination with diet and exercise for the treatment of adults with noncirrhotic MASH and moderate (F2) to advanced (F3) liver fibrosis, though its use in cirrhosis remains under evaluation in ongoing phase 3 trials. Resmetirom is also under regulatory review in the European Union for the treatment of MASH[61]. Other agents in phase 3 trials have demonstrated varying degrees of efficacy in fibrosis regression and MASH resolution; these agents include the GLP1-RA semaglutide, the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor co-agonist tirzepatide, the pan-PPAR agonist lanifibranor, the FGF21 analogs efruxifermin and pegozafermin, the fatty acid synthase inhibitor denifanstat, and the dual glucagon and GLP-1 receptor agonist survodutide[62-68].

Classical approach to ALD post-LT

In the post-LT population, patients with metabolic risk factors require heightened awareness regarding alcohol consumption, even at low-to-moderate levels. While the management of AUD is a well-recognized priority, it is equally important to consider the potential for disease progression associated with non-harmful but regular alcohol use in this population. Alcohol consumption, even lower than 20-50 g/day for females and 30-60 g/day for males, can act as an additive risk factor, potentially contributing to hepatic steatosis, graft dysfunction, and CV complications. Therefore, tailored counseling after LT should include education on the potential implications of alcohol intake in the context of their metabolic profile and graft health, to highlight that even non-harmful alcohol consumption might represent incremental risks. By addressing both AUD and the risks of moderate alcohol consumption, we can implement a comprehensive preventative strategy aimed at optimizing long-term outcomes and minimizing the risk of disease progression. The management of AUD and relapse prevention in patients following LT for ALD involves a multidisciplinary approach that combines behavioral, psychosocial, and pharmacological strategies to mitigate the risks of alcohol relapse, graft loss, and associated complications [Figure 2].

Behavioral and psychosocial interventions

The cornerstone of post-LT care for AUD is ongoing psychosocial and behavioral therapy, emphasizing the critical need for long-term monitoring and support. Pre-LT interventions, such as structured psychoeducational and addiction treatment programs, have been shown to reduce the risk of post-LT relapse significantly. Integrating addiction specialists into transplant care teams ensures consistent post-LT engagement, enabling early identification and treatment of high-risk behaviors. Collaborative care models that align addiction specialists, hepatologists, and mental health professionals have demonstrated reduced rates of harmful post-LT alcohol use[69,70]. Socioeconomic factors, such as limited access to healthcare resources, financial constraints, and instability in social support networks, often hamper patients' ability to fully engage in behavioral and psychosocial therapies. These challenges can limit consistent participation in follow-up care, therapy sessions, or lifestyle modifications that are essential to recovery.

Pharmacological therapies

Data on the treatment of AUD in post-LT patients are extremely limited, particularly regarding pharmacologic therapies. The post-LT population has unique characteristics, such as interactions with immunosuppressive drugs, variability in liver and renal function, and a lack of specific clinical studies, which complicates the application of standard pharmacological treatments. As a result, the safety and efficacy of AUD medications in this population remain unclear, making it difficult to formulate definitive

recommendations. This underscores the urgent need for more research to clarify these issues and develop evidence-based strategies specifically designed for post-LT patients. Pharmacotherapy plays an adjunctive role in managing AUD in post-LT settings. Despite limited evidence specific to post-LT populations, several agents used in the general management of AUD are being explored. Further research is necessary to elucidate the effects of both on-label medications (e.g., naltrexone and acamprosate) and off-label options (e.g., gabapentin, baclofen, and topiramate) on alcohol consumption following LT. Baclofen, a gamma-aminobutyric acid (GABA)-B receptor agonist, has shown promise in reducing alcohol cravings and consumption among patients with cirrhosis, including pre-LT populations; its use in post-LT care requires caution due to renal and hepatic adjustments. Naltrexone, an opioid receptor antagonist, is another promising agent, though its use requires careful monitoring for potential interactions with immunosuppressants. Acamprosate, which modulates glutamatergic activity, has also demonstrated effectiveness in AUD but requires further evidence in LT recipients. Importantly, these agents have not shown significant adverse interactions with immunosuppressive therapies when used under careful supervision[70-72].

Comprehensive multidisciplinary models

Optimal post-LT outcomes for ALD patients depend on a seamless integration of interventions addressing AUD within the broader transplant care pathway. Establishing centers of excellence in transplant care, equipped with dedicated addiction management teams, has been advocated. These centers could implement standardized protocols for relapse prevention, provide consistent access to behavioral and pharmacological therapies, and integrate digital tools for remote monitoring and telehealth interventions. Future research should aim to refine definitions of relapse and establish evidence-based guidelines for the management of AUD in LT recipients[70,71].

Dual approach: what is on the horizon? Therapies valid for MetALD as an entity

Post-LT management of MetALD requires addressing metabolic dysfunction and the risk of alcohol relapse[73]. Emerging therapeutic agents, notably GLP-1-RAs and FGF21, offer significant potential by targeting both the metabolic and behavioral aspects of the disease[74].

GLP1-RAs, originally developed for type 2 diabetes and obesity, have shown potential for dual-action benefits in MASLD and in reducing alcohol relapse. Preclinical studies have shown that GLP1-RAs modulate alcohol-induced dopamine release in key brain regions, such as the nucleus accumbens (NAc), while concurrently improving metabolic parameters, including weight reduction and enhanced insulin sensitivity. Semaglutide, a long-acting GLP1-RA, in a phase 2 trial in MASH patients with compensated cirrhosis, did not significantly improve fibrosis or achieve higher rates of MASH resolution compared to placebo. However, semaglutide was associated with significant reductions in liver fat, ALT levels, and metabolic parameters such as weight and glycemic control[62]. On the other hand, semaglutide has exhibited dose-dependent reductions in binge-like and dependence-induced alcohol intake in animal models[75]. The mechanisms underlying the reduction in alcohol consumption observed with semaglutide likely involve a combination of central pathways, including modulation of the dopamine reward system, and peripheral effects, such as delayed gastric emptying and enhanced satiation. Furthermore, the capacity of GLP1-RAs to attenuate the rewarding effects of alcohol while improving cardiometabolic health underscores their potential as dual-action therapies for MetALD[75-77]. In a phase 2 trial, tirzepatide, a dual GLP-1 and GIP receptor agonist, demonstrated significant efficacy, with up to 62% of patients achieving MASH resolution without fibrosis worsening and 55% showing fibrosis improvement[63]. In people with obesity, tirzepatide has been shown to reduce the intake of alcohol; these synergistic benefits warrant further investigation[76,77]. FGF21, a hepatokine induced by ethanol exposure, complements GLP1-RAs by acting through both hepatic and central pathways. It mitigates ethanol-induced toxicity and addresses hepatic injury through its actions

on metabolic regulation and systemic inflammation. FGF21 directly activates noradrenergic neurons in the locus coeruleus (LC), facilitating recovery from ethanol-induced sedation without altering ethanol metabolism. Two FGF21 analogs, pegozafermin and efruxifermin, have been evaluated in clinical phase 2 trials for patients with MASH. Pegozafermin significantly improved fibrosis (up to 27%) and achieved MASH resolution (up to 37%) compared to placebo[66]. Similarly, efruxifermin led to fibrosis improvement in up to 41% of patients and MASH resolution in 33%-36%[65]. In addition, both agents have been shown to reduce metabolic abnormalities, such as elevated triglycerides and LDL cholesterol. These effects establish FGF21 as another therapeutic candidate for MetALD[78,79].

In conclusion, therapies like GLP1-RAs and FGF21 analogs offer innovative approaches to managing MetALD by addressing its metabolic, hepatic, and behavioral dimensions. Their dual efficacy highlights the potential for integrated treatments that improve post-LT outcomes and overall disease management.

Future research should focus on several key areas to optimize the management of MetALD in LT recipients. Early screening protocols for metabolic dysfunction and alcohol relapse, integrated with biomarker-based risk stratification, should be systematically implemented in the post-transplant follow-up phase. Initial interventions should focus on non-pharmacologic approaches, such as structured behavioral and nutritional programs, alongside pharmacotherapy [Figure 2]. A tailored, balanced diet, developed in collaboration with a nutritionist, is essential for preventing both nutritional deficiencies and excessive calorie intake, thereby avoiding weight gain and its associated complications. Regular physical activity and weight management programs are equally important to prevent obesity-related complications and support liver health. Smoking cessation, supported by both behavioral and pharmacological therapies, is critical, as smoking significantly increases the risk of post-transplant complications. Ensuring alcohol abstinence remains a cornerstone of recovery, and tools such as the AUDIT-C questionnaire should be regularly used for risk factor monitoring. This approach facilitates early identification of relapse, enabling timely interventions. In addition to these psychosocial assessments, biomarkers like PEth should be incorporated into the monitoring process to detect ongoing alcohol use. Therapeutic interventions, including cognitive-behavioral therapy and involvement in self-help groups, should be integrated into the care plan to support sustained sobriety and provide additional resources for relapse prevention. A multidisciplinary team, including hepatologists, addiction specialists, nutritionists, and psychologists, must be integrated to provide multidisciplinary care, addressing both physical and psychological aspects of recovery. This collaborative, comprehensive care pathway is essential for optimizing long-term outcomes. Additionally, randomized controlled trials (RCTs) investigating the efficacy of dual-target therapies, such as GLP1-RAs and FGF21 analogs, in LT recipients are crucial to establishing evidence-based treatment guidelines. These trials should assess not only hepatic endpoints (fibrosis regression and steatosis resolution) but also metabolic outcomes (glycemic control, lipid profile) and alcohol consumption patterns, and the long-term impact of GLP1-RAs and FGF21 therapies on graft survival and CV outcomes, as these agents have shown promise in reducing overall morbidity and mortality in metabolic liver disease populations. However, despite the promising therapeutic potential of these agents, there remain unresolved areas in the field of MetALD management in LT recipients. Future clinical trials should explore optimal treatment duration, potential drug-drug interactions with immunosuppressants, side effects, and the most effective combination therapies for addressing both metabolic dysfunction and alcohol-related relapse.

CONCLUSION

MetALD represents a significant and emerging challenge in the management of patients after LT, as it is associated with an accelerated progression of fibrosis and an increased risk of graft failure. This condition underscores the need for a paradigm shift in how post-transplant MASLD and ALD are approached. The

hepatology community is beginning to recognize MetALD as a unique and unified clinical entity, rather than as two distinct pathologies requiring separate treatment strategies. This evolving perspective highlights the importance of adopting a more holistic and integrated approach to diagnosis and patient care. Furthermore, the development of new pharmacological therapies targeting both metabolic dysfunction and alcohol-related liver damage holds promise for improving outcomes in this complex and high-risk population. Tailored interventions addressing these overlapping pathophysiological mechanisms could play a pivotal role in preventing graft dysfunction and enhancing long-term LT outcomes. This requires collaboration among multiple specialists and an integrated approach to managing the patient's complex caries, considering psychological, social, and clinical aspects. The hepatologist can serve as a central coordinator among these specialists and play a key role in promoting prospective studies to better define the role of emerging pharmacological agents in this unique setting.

DECLARATIONS

Authors' contributions

Writing of the manuscript: Cucco M, Becchetti C, Scaravaglio M, Bolis F, Dispinzieri G
Bibliographic search and drafting tables and figures: Bagalà L, Strollo M, Orlando M
Revision for important intellectual content: Perricone G, Mazzarelli C, Airoldi A, Vangeli M, Becchetti C, Belli LS, Viganò R

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014-2019. *JAMA Netw Open*. 2020;3:e1920294. DOI PubMed
2. Younossi ZM, Stepanova M, Al Shabeeb R, et al. The changing epidemiology of adult liver transplantation in the United States in 2013-2022: the dominance of metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease. *Hepatol Commun*. 2024;8:e0352. DOI PubMed PMC
3. Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81:492-542. DOI PubMed
4. Ochoa-Allemant P, Serper M, Wang RX, et al. Waitlisting and liver transplantation for MetALD in the United States: an analysis of the UNOS national registry. *Hepatology*. 2025;81:532-45. DOI PubMed
5. Vanlerberghe BTK, van Malenstein H, Sainz-Bariga M, et al. Utility and prognostic value of diagnosing MAFLD in patients

undergoing liver transplantation for alcohol-related liver disease. *Clin Transplant.* 2023;37:e14965. DOI PubMed
6. Erard D, Villeret F, Chouik Y, et al. Dual alcohol and metabolic-related liver disease: results from a population of liver transplant patients. *Liver Int.* 2024;44:422-32. DOI PubMed
7. Thoefner LB, Rostved AA, Pommergaard HC, Rasmussen A. Risk factors for metabolic syndrome after liver transplantation: a systematic review and meta-analysis. *Transplant Rev.* 2018;32:69-77. DOI PubMed
8. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. *Hepatology.* 2020;72:1605-16. DOI PubMed
9. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 2015;148:547-55. DOI PubMed
10. 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;47:704-14. DOI PubMed
11. Jatana S, Krys D, Verhoeff K, et al. Liver allograft cirrhosis, retransplant, and mortality secondary to recurrent disease after transplant for MASH: a systematic review and meta-analysis. *Transplantation.* 2024;Epub ahead of print. DOI PubMed
12. Sourianarayanane A, Arikapudi S, McCullough AJ, Humar A. Nonalcoholic steatohepatitis recurrence and rate of fibrosis progression following liver transplantation. *Eur J Gastroenterol Hepatol.* 2017;29:481-7. DOI PubMed
13. Vallin M, Guillaud O, Boillot O, Hervieu V, Scoazec JY, Dumortier J. Recurrent or de novo nonalcoholic fatty liver disease after liver transplantation: natural history based on liver biopsy analysis. *Liver Transpl.* 2014;20:1064-71. DOI PubMed
14. Lim WH, Ng CH, Tan DJH, et al. Donor diabetes and steatosis affects recipient survival following liver transplantation based on etiology of liver cirrhosis. *Transplantation.* 2024;108:473-82. DOI PubMed
15. Gitto S, Marra F, De Maria N, et al. Nonalcoholic steatohepatitis before and after liver transplant: keeping up with the times. *Expert Rev Gastroenterol Hepatol.* 2019;13:173-8. DOI PubMed
16. Becchetti C, Ferrarese A, Zeni N, et al. A prospective longitudinal assessment of *de novo* metabolic syndrome after liver transplantation. *Clin Transplant.* 2022;36:e14532. DOI PubMed
17. Charlton M, Levitsky J, Aqel B, et al. International liver transplantation society consensus statement on immunosuppression in liver transplant recipients. *Transplantation.* 2018;102:727-43. DOI PubMed
18. Siddiqui MS, Muthiah M, Satapathy SK, et al. Defining an approach for therapeutic strategies in metabolic dysfunction-associated steatotic liver disease after liver transplantation. *Hepatology.* 2023;Epub ahead of print. DOI PubMed
19. Kim H, Lee KW, Lee K, et al. Effect of PNPLA3 I148M polymorphism on histologically proven non-alcoholic fatty liver disease in liver transplant recipients. *Hepatol Res.* 2018;48:E162-71. DOI PubMed
20. Finkenstedt A, Auer C, Glodny B, et al. Patatin-like phospholipase domain-containing protein 3 rs738409-G in recipients of liver transplants is a risk factor for graft steatosis. *Clin Gastroenterol Hepatol.* 2013;11:1667-72. DOI PubMed
21. Trunečka P, Míková I, Dlouhá D, et al. Donor PNPLA3 rs738409 genotype is a risk factor for graft steatosis. A post-transplant biopsy-based study. *Dig Liver Dis.* 2018;50:490-5. DOI PubMed
22. Villeret F, Dharancy S, Erard D, et al. Liver transplantation for NAFLD cirrhosis: age and recent coronary angioplasty are major determinants of survival. *Liver Int.* 2022;42:2428-41. DOI PubMed PMC
23. Van Herck J, Verbeek J, van Malenstein H, et al. Liver-related and cardiovascular outcome of patients transplanted for nonalcoholic fatty liver disease: a European single-center study. *Transplant Proc.* 2021;53:1674-81. DOI PubMed
24. Kodali S, Kaif M, Tariq R, Singal AK. Alcohol relapse after liver transplantation for alcoholic cirrhosis-impact on liver graft and patient survival: a meta-analysis. *Alcohol Alcohol.* 2018;53:166-72. DOI PubMed
25. Daniel J, Dumortier J, Del Bello A, et al. Integrating an addiction team into the management of patients transplanted for alcohol-associated liver disease reduces the risk of severe relapse. *JHEP Rep.* 2023;5:100832. DOI PubMed PMC
26. Sun K, Ren M, Liu D, Wang C, Yang C, Yan L. Alcohol consumption and risk of metabolic syndrome: a meta-analysis of prospective studies. *Clin Nutr.* 2014;33:596-602. DOI PubMed
27. Germani G, Laryea M, Rubbia-Brandt L, et al. Management of recurrent and de novo NAFLD/NASH after liver transplantation. *Transplantation.* 2019;103:57-67. DOI PubMed
28. Samuel D, De Martin E, Berg T, et al; European Association for the Study of the Liver. EASL clinical practice guidelines on liver transplantation. *J Hepatol.* 2024;81:1040-86. DOI PubMed
29. Ferraioli G, Barr RG, Berzigotti A, et al. WFUMB guidelines/guidance on liver multiparametric ultrasound. part 2: guidance on liver fat quantification. *Ultrasound Med Biol.* 2024;50:1088-98. DOI PubMed
30. Karlas T, Kollmeier J, Böhm S, et al. Noninvasive characterization of graft steatosis after liver transplantation. *Scand J Gastroenterol.* 2015;50:224-32. DOI PubMed
31. Siddiqui MS, Idowu MO, Stromberg K, et al. Diagnostic performance of vibration-controlled transient elastography in liver transplant recipients. *Clin Gastroenterol Hepatol.* 2021;19:367-74. DOI PubMed PMC
32. Chayanupatkul M, Dasani DB, Sogaard K, Schiano TD. The utility of assessing liver allograft fibrosis and steatosis post-liver transplantation using transient elastography with controlled attenuation parameter. *Transplant Proc.* 2021;53:159-65. DOI PubMed
33. Alnimer L, Arellano D, Brombosz E, Noureddin M. Metabolic issues in patients with metabolic dysfunction-associated steatohepatitis (MASH) and their impact on MASH recurrence following liver transplantation: a narrative review. *Liver Transpl.* 2024;Epub ahead of print. DOI PubMed
34. Winters AC, Mittal R, Schiano TD. A review of the use of transient elastography in the assessment of fibrosis and steatosis in the post-

liver transplant patient. *Clin Transplant.* 2019;33:e13700. DOI PubMed

35. Siddiqui MS, Bui AT, Syed T, Tseng M, Hassouneh R, Bhati CS; Liver Transplant Biomarker Group. Performance of vibration-controlled transient elastography and clinical prediction models in liver transplant recipients. *Clin Gastroenterol Hepatol.* 2023;21:1100-2.e2. DOI PubMed PMC
36. Mikolasevic I, Hauser G, Mijic M, et al. Assessment of steatosis and fibrosis in liver transplant recipients using controlled attenuation parameter and liver stiffness measurements. *Can J Gastroenterol Hepatol.* 2021;2021:6657047. DOI PubMed PMC
37. Eshraghian A, Nikeghbalian S, Kazemi K, Shamsaeefar A, Geramizadeh B, Malek-Hosseini SA. Non-alcoholic fatty liver disease after liver transplantation in patients with non-alcoholic steatohepatitis and cryptogenic cirrhosis: the impact of pre-transplant graft steatosis. *HPB.* 2020;22:521-8. DOI PubMed
38. Della-Guardia B, Evangelista AS, Felga GE, Marins LV, Salvalaggio PR, Almeida MD. Diagnostic accuracy of transient elastography for detecting liver fibrosis after liver trannsplantation: a specific cut-off value is really needed? *Dig Dis Sci.* 2017;62:264-72. DOI PubMed
39. Eshraghian A, Fattahi MR, Taghavi A, et al. Metabolic syndrome, hepatic fibrosis, and steatosis diagnosed by liver stiffness measurement and controlled attenuation parameter after liver transplantation: the impact on long-term survival. *Expert Rev Gastroenterol Hepatol.* 2022;16:1003-9. DOI PubMed
40. Navin PJ, Olson MC, Knudsen JM, Venkatesh SK. Elastography in the evaluation of liver allograft. *Abdom Radiol.* 2021;46:96-110. DOI PubMed PMC
41. Mikolasevic I, Stojsavljevic S, Blazic F, et al. Noninvasive markers of liver steatosis and fibrosis after liver transplantation - where do we stand? *World J Transplant.* 2021;11:37-53. DOI PubMed PMC
42. Singh S, Venkatesh SK, Keaveny A, et al. Diagnostic accuracy of magnetic resonance elastography in liver transplant recipients: a pooled analysis. *Ann Hepatol.* 2016;15:363-76. DOI PubMed PMC
43. Arab JP, Díaz LA, Rehm J, et al. Metabolic dysfunction and alcohol-related liver disease (MetALD): position statement by an expert panel on alcohol-related liver disease. *J Hepatol.* 2025;82:744-56. DOI PubMed
44. Agudelo M, Yoo C, Nair MP. Alcohol-induced serotonergic modulation: the role of histone deacetylases. *Alcohol.* 2012;46:635-42. DOI PubMed PMC
45. Staufer K, Andresen H, Vettorazzi E, Tobias N, Nashan B, Sterneck M. Urinary ethyl glucuronide as a novel screening tool in patients pre- and post-liver transplantation improves detection of alcohol consumption. *Hepatology.* 2011;54:1640-9. DOI PubMed
46. Allen JP, Wurst FM, Thon N, Litten RZ. Assessing the drinking status of liver transplant patients with alcoholic liver disease. *Liver Transpl.* 2013;19:369-76. DOI PubMed
47. Favrod-Coune T, Lidsky D, Vionnet J, Magini G, Déglon J, Broers B. A false positive hair ethylglucuronide dosage in an alcohol abstinent patient after liver transplantation: a case report. *Front Med.* 2024;11:1363012. DOI PubMed PMC
48. Fleming MF, Smith MJ, Oslakovic E, et al. Phosphatidylethanol detects moderate-to-heavy alcohol use in liver transplant recipients. *Alcohol Clin Exp Res.* 2017;41:857-62. DOI PubMed PMC
49. Viel G, Boscolo-Berto R, Cecchetto G, Fais P, Nalesso A, Ferrara SD. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. *Int J Mol Sci.* 2012;13:14788-812. DOI PubMed PMC
50. Lim N, Leventhal TM, Thomson MJ, et al. Protocolized screening and detection of occult alcohol use before and after liver transplant: lessons learned from a quality improvement initiative. *Clin Transplant.* 2023;37:e15036. DOI PubMed
51. De La Torre SA, Ibrahim B, Meneses K, Saab S, Shetty A. Impact of phosphatidylethanol in the surveillance for alcohol use in post-liver transplant population: a retrospective study. *Alcohol Clin Exp Res.* 2024;48:2404-11. DOI PubMed PMC
52. Gustavsson L, Alling C. Formation of phosphatidylethanol in rat brain by phospholipase D. *Biochem Biophys Res Commun.* 1987;142:958-63. DOI PubMed
53. Becchetti C, Dirchwolf M, Banz V, Dufour JF. Medical management of metabolic and cardiovascular complications after liver transplantation. *World J Gastroenterol.* 2020;26:2138-54. DOI PubMed PMC
54. Savino A, Loglio A, Neri F, et al. Metabolic-dysfunction-associated steatotic liver disease (MASLD) after liver transplantation: a narrative review of an emerging issue. *J Clin Med.* 2024;13:3871. DOI PubMed PMC
55. Gabrielli F, Golfieri L, Nascimbeni F, Andreone P, Gitto S. Metabolic disorders in liver transplant recipients: the state of the art. *J Clin Med.* 2024;13:1014. DOI PubMed PMC
56. Lonardo A, Mantovani A, Petta S, Carraro A, Byrne CD, Targher G. Metabolic mechanisms for and treatment of NAFLD or NASH occurring after liver transplantation. *Nat Rev Endocrinol.* 2022;18:638-50. DOI PubMed
57. Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the diabetes prevention program outcomes study. *Diabetes Care.* 2012;35:731-7. DOI PubMed PMC
58. Alnasrallah B, Goh TL, Chan LW, Manley P, Pilmore H. Transplantation and diabetes (Transdiab): a pilot randomised controlled trial of metformin in impaired glucose tolerance after kidney transplantation. *BMC Nephrol.* 2019;20:147. DOI PubMed PMC
59. Choudhury A, Singh SP, Desmukh A, Sahoo B, Eslam M. Post-liver transplant metabolic syndrome. *J Clin Exp Hepatol.* 2024;14:101368. DOI PubMed PMC
60. Becchetti C, Dirchwolf M, Schropp J, et al; Swiss Transplant Cohort Study. Use of statins after liver transplantation is associated with improved survival: results of a nationwide study. *Aliment Pharmacol Ther.* 2022;56:1194-204. DOI PubMed PMC
61. Harrison SA, Bedossa P, Guy CD, et al; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med.* 2024;390:497-509. DOI PubMed

62. Loomba R, Abdelmalek MF, Armstrong MJ, et al; NN9931-4492 investigators. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol.* 2023;8:511-22. DOI PubMed PMC
63. Loomba R, Hartman ML, Lawitz EJ, et al; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med.* 2024;391:299-310. DOI PubMed
64. Francque SM, Bedossa P, Ratziu V, et al; NATIVE Study Group. A randomized, controlled trial of the Pan-PPAR agonist lanifibranor in NASH. *N Engl J Med.* 2021;385:1547-58. DOI PubMed
65. Harrison SA, Frias JP, Neff G, et al; HARMONY Study Group. Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol.* 2023;8:1080-93. DOI PubMed
66. Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH. *N Engl J Med.* 2023;389:998-1008. DOI PubMed PMC
67. Loomba R, Bedossa P, Grimmer K, et al. Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: a multicentre, double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol.* 2024;9:1090-100. DOI PubMed
68. Sanyal AJ, Bedossa P, Fraessdorf M, et al; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med.* 2024;391:311-9. DOI PubMed
69. Winder GS, Shenoy A, Dew MA, DiMartini AF. Alcohol and other substance use after liver transplant. *Best Pract Res Clin Gastroenterol.* 2020;46-47:101685. DOI PubMed
70. Arab JP, Izzy M, Leggio L, Bataller R, Shah VH. Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation. *Nat Rev Gastroenterol Hepatol.* 2022;19:45-59. DOI PubMed PMC
71. Sharma P, Shenoy A, Shroff H, et al. Management of alcohol-associated liver disease and alcohol use disorder in liver transplant candidates and recipients: challenges and opportunities. *Liver Transpl.* 2024;30:848-61. DOI PubMed
72. Celik M, Gold MS, Fuehrlein B. A narrative review of current and emerging trends in the treatment of alcohol use disorder. *Brain Sci.* 2024;14:294. DOI PubMed PMC
73. Robinson BL, Ciobanu C, Brown RS Jr, Russo MW. A tale of 2 diseases: ALD and MASLD requirements and monitoring for liver transplantation. *Liver Transpl.* 2025;31:117-21. DOI PubMed
74. Israelsen M, Francque S, Tsochatzis EA, Krag A. Steatotic liver disease. *Lancet.* 2024;404:1761-78. DOI PubMed
75. Chuong V, Farokhnia M, Khom S, et al. The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. *JCI Insight.* 2023;8:e170671. DOI PubMed PMC
76. Jensen EL, Israelsen M, Krag A. Transforming steatotic liver disease management: the emerging role of GLP-1 receptor agonists. *Hepatol Commun.* 2024;8:e0561. DOI PubMed PMC
77. Quddos F, Hubshman Z, Tegge A, et al. Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity. *Sci Rep.* 2023;13:20998. DOI PubMed PMC
78. Stankevic E, Israelsen M, Juel HB, et al. Binge drinking episode causes acute, specific alterations in systemic and hepatic inflammation-related markers. *Liver Int.* 2023;43:2680-91. DOI PubMed
79. Choi M, Schneeberger M, Fan W, et al. FGF21 counteracts alcohol intoxication by activating the noradrenergic nervous system. *Cell Metab.* 2023;35:429-37.e5. DOI PubMed PMC
80. Carrión JA, Navasa M, Bosch J, Bruguera M, Gilabert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. *Liver Transpl.* 2006;12:1791-8. DOI PubMed
81. Toniutto P, Fabris C, Bitetto D, et al. Role of AST to platelet ratio index in the detection of liver fibrosis in patients with recurrent hepatitis C after liver transplantation. *J Gastroenterol Hepatol.* 2007;22:1904-8. DOI PubMed
82. Kamphues C, Lotz K, Röcken C, et al. Chances and limitations of non-invasive tests in the assessment of liver fibrosis in liver transplant patients. *Clin Transplant.* 2010;24:652-9. DOI PubMed
83. Rigamonti C, Fraquelli M, Bastiampillai AJ, et al. Transient elastography identifies liver recipients with nonviral graft disease after transplantation: a guide for liver biopsy. *Liver Transpl.* 2012;18:566-76. DOI PubMed
84. 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;37:347-52. DOI PubMed
85. Lutz HH, Schroeter B, Kroy DC, Neumann U, Trautwein C, Tischendorf JJ. Doppler ultrasound and transient elastography in liver transplant patients for noninvasive evaluation of liver fibrosis in comparison with histology: a prospective observational study. *Dig Dis Sci.* 2015;60:2825-31. DOI PubMed
86. Mikołajczyk-Korniak N, Tronina O, Ślubowska K, et al. Dynamic elastography in diagnostics of liver fibrosis in patients after liver transplantation due to cirrhosis in the course of hepatitis C. *Transplant Proc.* 2016;48:1725-9. DOI PubMed
87. Crespo G, Castro-Narro G, García-Juárez I, et al. Usefulness of liver stiffness measurement during acute cellular rejection in liver transplantation. *Liver Transpl.* 2016;22:298-304. DOI PubMed
88. Arshad T, Bhati CS, Bui AT, et al. Evaluation of liver stiffness measurement-based scores in liver transplantation recipients. *Liver Transpl.* 2023;29:196-205. DOI PubMed PMC
89. Piano S, Marchioro L, Gola E, et al. Assessment of alcohol consumption in liver transplant candidates and recipients: the best combination of the tools available. *Liver Transpl.* 2014;20:815-22. DOI PubMed

90. Andresen-Streichert H, Beres Y, Weinmann W, et al. Improved detection of alcohol consumption using the novel marker phosphatidylethanol in the transplant setting: results of a prospective study. *Transpl Int.* 2017;30:611-20. DOI PubMed
91. Burra P, Becchetti C, Germani G. NAFLD and liver transplantation: disease burden, current management and future challenges. *JHEP Rep.* 2020;2:100192. DOI PubMed PMC
92. American Diabetes Association Professional Practice Committee. 9. pharmacologic approaches to glycemic treatment: standards of care in diabetes-2025. *Diabetes Care.* 2025;48:S181-206. DOI PubMed PMC
93. Mach F, Baigent C, Catapano AL, et al; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41:111-88. DOI PubMed
94. Agarwal A, Prasad GV. Post-transplant dyslipidemia: mechanisms, diagnosis and management. *World J Transplant.* 2016;6:125-34. DOI PubMed PMC
95. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol use disorders identification test. *Arch Intern Med.* 1998;158:1789-95. DOI PubMed