

Review

Open Access



Post-transplant complications in alcohol- and metabolic-associated steatotic liver disease

Shekhar Singh Jadaun , Sanjiv Saigal

Department of Liver Transplant and Hepatology, Centre for Liver and Biliary Sciences, Max Super Speciality Hospital, New Delhi 110017, India.

Correspondence to: Dr. Sanjiv Saigal, Department of Liver Transplant and Hepatology, Centre for Liver and Biliary Sciences, Max Super Speciality Hospital, Street 1, 2 Press Enclave Marg, New Delhi 110017, India. E-mail: sanjivsaigal@hotmail.com

How to cite this article: Jadaun SS, Saigal S. Post-transplant complications in alcohol- and metabolic-associated steatotic liver disease. *Metab Target Organ Damage*. 2025;5:1. <https://dx.doi.org/10.20517/mtod.2024.62>

Received: 18 Jul 2024 **First Decision:** 27 Sep 2024 **Revised:** 14 Nov 2024 **Accepted:** 3 Dec 2024 **Published:** 18 Dec 2024

Academic Editors: Amedeo Lonardo, Ashwani Singal **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Alcohol-associated liver disease (ALD) and metabolic-associated steatotic liver disease (MASLD)/metabolic-associated steatohepatitis (MASH) are severe liver diseases, with liver transplant being the primary curative treatment option. Transplant recipients with ALD suffer from alcohol use disorder (AUD) and poor drug compliance, which can result in graft injury and even graft loss. Relapse of alcohol consumption, lack of drug compliance, and smoking negatively impact the graft and clinical outcome of ALD-related transplantation patients. Furthermore, these patients are at a higher risk of developing non-hepatic complications such as malignancies, cardiovascular diseases, and other metabolic conditions. The management of these conditions requires pharmacological and behavioral strategies to manage complications as soon as they arise. Critical monitoring of these conditions is also advocated. In patients undergoing transplants for MASLD/MASH, early complications arise in obese and diabetic patients. Late post-transplant complications such as cardiovascular diseases, chronic kidney disease, recurring MASLD/MASH, immunosuppression, and arterial hypertension are reported. Integrating behavioral strategies with diet modification and physical activity is crucial to balance underlying metabolic disorders and improve clinical outcomes. Early steroid withdrawal and low calcineurin inhibitor doses can decrease the risk of post-transplant diabetes, hypertension, and dyslipidemia. Lifestyle modifications and tailored immunosuppression are helpful in the prevention and management of post-transplant recurrent MASLD/MASH.

Keywords: Liver transplants, MASLD, ALD, MASH, challenges, complications



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



INTRODUCTION

Alcohol-associated liver disease (ALD), metabolic-associated steatotic liver disease (MASLD) [previously known as non-alcoholic fatty liver disease (NAFLD)], and metabolic-associated steatohepatitis (MASH) [previously known as non-alcohol-associated steatohepatitis (NASH)] are among the most common causes of liver disease globally^[1]. These conditions often translate to liver failure or liver cirrhosis, for which a liver transplant remains the curative treatment.

Currently, alcohol-related liver disease represents the leading cause of liver transplantation^[2]. To mitigate the risk of post-transplant relapse and delisting, individuals with alcohol use disorder (AUD) are typically required to undergo psychosocial and psychiatric interventions to ensure sustained abstinence for a minimum of 6 months prior to transplantation^[3]. However, in cases of acute alcoholic hepatitis unresponsive to pharmacological management, liver transplantation may be considered before the completion of the 6-month abstinence period.

Furthermore, MASH has also emerged as a prominent indication for liver transplantation. MASH is strongly associated with metabolic syndrome and obesity^[4]. Due to the absence of effective pharmacological therapies targeting MASH or hepatic fibrosis, the prevalence of liver transplantation for MASH-related liver disease has significantly increased in recent years^[5]. Therefore, liver transplantation remains the cornerstone of curing severe liver diseases of ALD and MASH/MASLD.

However, liver transplants are associated with various risks [Figure 1]. With advancements in pre-transplant optimization and surgical techniques, clinical outcomes in patients undergoing transplantation in liver cirrhosis due to ALD and MASLD/MASH have improved remarkably over the years^[6]. However, the post-liver transplant period presents a wide spectrum of challenges, necessitating specialized care for this patient population. In ALD patients undergoing transplantation, a history of alcohol abuse, relapse of abnormal drinking behavior, and psychosocial complications need to be addressed. Liver transplant in MASLD/MASH-related cirrhosis can be complicated by post-transplant metabolic syndrome, cardiovascular diseases, and recurrence of MASLD/MASH^[7]. Therefore, the post-transplant period requires meticulous follow-up and comprehensive management approaches to maintain graft function and ensure optimal long-term outcomes.

POST-LIVER TRANSPLANT CHALLENGES ASSOCIATED WITH ALD

Relapse of abnormal drinking behavior

Post-transplant outcomes in ALD are comparable with those of other indications of liver transplantation. While a liver transplant effectively cures the underlying liver disease, it cannot manage the AUD of patients. For such patients, relapse of drinking becomes a crucial concern during the post-transplant period. An abnormal drinking behavior potentially leads to graft injury and progression to alcoholic hepatitis and liver cirrhosis over an extended period. Excessive consumption of alcohol further leads to graft dysfunction or failure [Figure 2]. Therefore, prevention and management of post-transplant alcohol use are important to prevent graft injury and transplant failure^[8].

Clinical evidence

Several factors increase the risk of post-transplant alcohol relapse, including a history of active drinking prior to liver transplantation, psychiatric illness, legal issues related to alcohol use, and inadequate social support. Post-transplant relapse can be quantified as mild, moderate, and severe depending on the amount of alcohol abused. The mild relapse includes occasional drinking, which does not significantly impact survival. Björnsson *et al.* (2005) reported that occasional drinking after a liver transplant did not affect liver

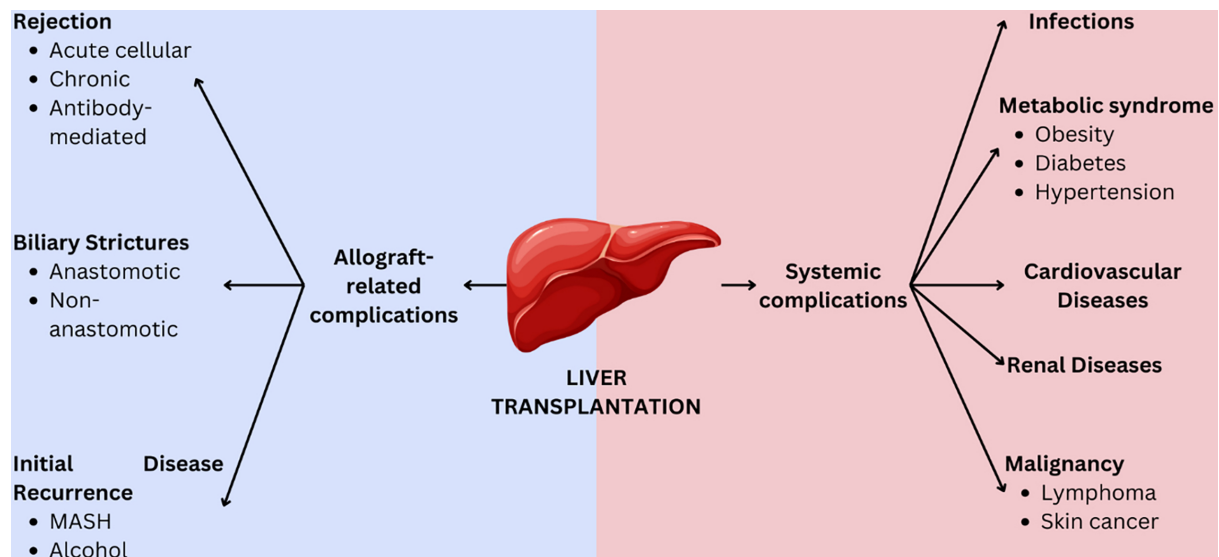


Figure 1. Post-liver transplantation challenges in recipients. The present review describes the post-liver transplant complications and management strategies specific to ALD and MASLD/MASH-related cirrhosis. It aims to elucidate the unique challenges following liver transplant observed in ALD and MASLD/MASH patients. ALD: Alcohol-associated liver disease; MASLD: metabolic-associated steatotic liver disease; MASH: metabolic-associated steatohepatitis.

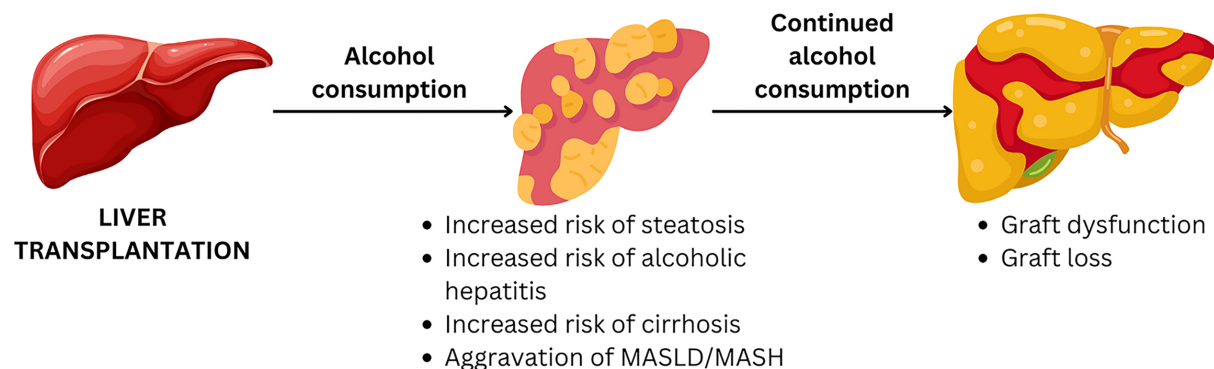


Figure 2. Impact of alcohol use post-transplant on graft health. MASLD: Metabolic-associated steatotic liver disease; MASH: metabolic-associated steatohepatitis.

allograft health^[9]. However, heavy post-liver transplant alcohol consumption potentially results in severe liver diseases such as alcohol-related steatosis, alcohol-related steatohepatitis, and aggravation of MASLD/MASH, contributing to graft dysfunction and progression to graft failure and loss. Heavy alcohol consumption can reduce the 10-year post-transplant survival to 75%-93%, compared to the 45%-71% 10-year survival rate in abstinent recipients^[10-12]. Furthermore, early relapse poses a greater risk of graft dysfunction compared to late relapse, emphasizing the role of early monitoring and management.

The reported rate of recidivism after transplant varies widely across studies, ranging from 10% to 60%^[10,13]. In a systematic review and meta-analysis, Chuncharunee *et al.* (2019) reported a relapse rate of 22% following liver transplantation. Psychiatric comorbidities, smoking, and abstinence of less than 6 months pre-transplant were identified as significant predictors for alcohol relapse^[14]. In another meta-analysis conducted by Dew *et al.* (2008), alcohol relapse varied between 5.6% and 2.5%^[15]. A meta-analysis reported that when comparing AUD patients with those practicing abstinence, alcohol consumption significantly

heightens the risk of liver-related complications, with a 4-fold increase in the incidence of steatosis, a 9-fold rise in alcoholic hepatitis, and an 8-fold elevation in the prevalence of cirrhosis^[12].

Traditionally, 6-month abstinence compliance is suggested before a patient can be placed on a transplant waiting list. This abstinence period reduces the risk of post-transplant relapse, although there is a lack of strong evidence for it, with studies reporting non-definitive results. Recent European and American guidelines do not mandate 6 months of abstinence from alcohol as a prerequisite for listing patients on liver transplant lists^[10,16].

Management

Assessment for the risk of post-transplant relapse

Given the negative effects of alcohol on graft and patient survival, an intensified systematic approach consisting of behavioral interventions and pharmacotherapy is required. Regular monitoring with frequent clinical assessments is essential for the early detection of alcohol use during the post-transplant period. Measures to prevent and manage relapse and addiction behavior should be initiated in the early post-transplant period and be an integral part of post-transplant care^[17]. Potential liver transplant candidates must be thoroughly evaluated for the risk of post-transplant relapse. Risk prediction tools and assessment of key risk factors allow risk stratification and vigilant post-transplant monitoring. Lee *et al.* (2019) developed a tool called SALT score for alcohol relapse prediction after a liver transplant. The score ranges from 0-11, with a score of 5 or higher indicating a 25% positive predictive value for drinking relapse^[18]. Quantification of alcohol intake may also assist in assessing the graft outcomes. Mild relapse, involving occasional drinking, does not affect the graft outcomes. However, consistent drinking behavior called moderate relapse can lead to graft injury and fibrosis, while heavy, dangerous drinking, defined as severe relapse, is associated with early graft loss and poor survival^[19]. Therefore, management strategies should assess the risk factors and the severity of AUD to develop personalized interventions, provide adequate support, and reduce the likelihood of post-transplant relapse.

Behavioral therapy and Pharmacotherapy

Behavioral therapy is the cornerstone of the management of AUDs. Cognitive behavioral therapy, motivational enhancement therapy, psycho-education, and social care and support have proven to be effective in reducing alcohol relapse in ALD patients; however, efficacy in post-liver transplantation settings is lacking. On the other hand, pharmacotherapy involves treatment with several pharmacological agents. Naltrexone is an opioid receptor antagonist shown to reduce drinking relapse and craving^[20]. It is used in liver transplant recipients with relatively no drug interactions, although common side effects include nausea and diarrhea^[19]. However, it should be avoided in patients with significant liver dysfunction^[20]. Acamprosate is also used as an anti-craving agent to reduce the relapse rate in patients with AUD. The drug is administered at a dose of 666 mg three times a day and is generally considered safe in patients with liver dysfunction without any significant drug-to-drug interactions^[21]. However, dose reduction is needed in patients with renal dysfunction. A meta-analysis including 125 randomized control trial (RCT) studies with a total of 22,803 patients showed that both acamprosate and naltrexone were effective in reducing relapse rates in patients with AUD. The findings revealed that both drugs had similar efficacy, but the incidence of adverse events was higher with naltrexone compared to acamprosate^[22].

Topiramate, baclofen, and gabapentin are alternative pharmacological agents used in the management of AUD to reduce relapse rates. These agents may be considered in patients who do not achieve effective abstinence with first-line therapies. However, due to limited exposure to these medications in liver transplant recipients, further investigation is required before the integration into routine practice can be

recommended for transplant recipients^[23].

Combination approaches, including both behavioral and drug therapy, have proved to be more effective than monotherapy^[19,20]. A systematic and integrated multidisciplinary approach involving hepatology and deaddiction teams significantly improves post-transplant outcomes in patients with ALD. Evidence from a study by Magistri *et al.* (2019) demonstrated that multidisciplinary management is associated with earlier relapse detection and reduced mortality rates^[24].

Table 1 presents a comprehensive overview of pharmacological agents used in the management of AUD, along with their recommended dosages and commonly reported adverse effects.

Drug compliance

Post-transplant non-adherence to prescribed medicines potentially results in a greater risk of graft rejection. Transplant recipients who have a relapse of drinking behavior have poor compliance to immunosuppression medications and poor adherence to outpatient visits, leading to an elevated risk of graft rejection. However, studies conducted by Berlakovich *et al.* (2000) and Dew *et al.* (2008) did not find any significant association between alcohol relapse and medication non-adherence^[15,27]. Alcohol consumption alone cannot be considered the sole factor contributing to non-compliance, as other determinants, including medical service-related factors and the psychosocial environment, also play significant roles. However, AUD in the post-transplant period can heighten the risk of graft rejection due to non-adherence to immunosuppressive therapy. This underscores the importance of timely and consistent behavioral follow-up in these patients to mitigate such risks^[8].

Smoking

Smoking often co-occurs with alcohol use and poses a significant health risk for patients with liver disease. This requires a comprehensive evaluation and ongoing follow-up with deaddiction specialists to address both behaviors effectively. Approximately 60% to 90% of ALD patients are active smokers, with many of them continuing to smoke even after receiving a liver transplant^[28,29]. Smoking is correlated with an increased risk of malignancies and cardiovascular disease, which is commonly seen in AUD patients. In a meta-analysis study by Duerinckx *et al.* (2016), smoking was an independent risk factor for post-liver transplant morbidity and mortality^[30]. Pungpapong *et al.* (2002) found that smoking cessation for 2 years before a liver transplant resulted in a significant risk reduction of vascular complications during the post-transplant period^[29]. Therefore, smoking cessation should be part of the management protocol in all transplant centers. Efforts should be made to maintain ongoing abstinence with the use of multidisciplinary efforts and a combination of behavioral and drug therapy^[15].

Non-hepatic complications

Malignancies

Post-transplant malignancies such as oropharyngeal and lung cancer are more common in ALD patients compared to other etiologies of cirrhosis. Smoking is also commonly associated with alcohol use and contributes to the increased incidence of malignancies^[31]. Overall incidence rates of de novo malignancies in ALD transplant recipients are three times higher than in the general population^[32]. Malignancies contribute to a significant proportion of mortality in this patient population^[33]. The risk of aerodigestive cancers is further increased in patients who continue to smoke after transplant^[34]. Higher doses of immunosuppressive therapy elevate the risk of malignancies. However, the use of mammalian targets of rapamycin (mTOR) inhibitors, such as everolimus and sirolimus, has demonstrated a protective effect against the development of certain malignancies^[35]. Given the high risk of cancer in ALD post-transplant patients, regular follow-up involving appropriate screening protocols for early detection of malignancies should be considered^[36].

Table 1. Pharmacotherapy in alcohol abuse disorder

| Drug | Dosing | Adverse effects | Ref. |
|-------------|---|---|---------|
| Naltrexone | Long-acting 380 mg, once every 4 weeks, intramuscular or 50 mg once a day, oral | Nausea, headache, dizziness, and deranged liver functions | [20] |
| Acamprosate | 666 mg once a day, oral | Diarrhea, fatigue | [25] |
| Topiramate | 25-300 mg once a day, oral | Cognitive impairment, paraesthesia, headache | [26] |
| Gabapentin | 300-600 mg 3 times a day, oral | Drowsiness, dizziness, neuropsychiatric effects | [26] |
| Baclofen | 5-10 mg thrice a day | Somnolence, confusion, nausea | [10,26] |
| Varenicline | 0.5-1 mg once a day, oral | Abnormal dreams, nightmares, somnambulism, nausea | [23] |

Smoking cessation, reduction of immunosuppressives, and use of mTOR inhibitors help prevent the development of malignancies post-transplant^[16]. Large-scale randomized control trials (RCTs) are required to establish standardized guidelines aiming for a reduction in the incidence of malignancies.

Cardiovascular and other metabolic diseases

Post-transplant incidence of cardiovascular diseases is higher in ALD-related transplants compared to other etiologies of cirrhosis^[37]. Increased incidence of diabetes mellitus (DM), chronic kidney disease (CKD), and hypertension has also been reported in ALD transplant recipients^[38]. Table 2 shows the post-transplant challenges in ALD.

POST-LIVER TRANSPLANTATION CHALLENGES ASSOCIATED WITH MASH/MASLD

Early postoperative period

The risk of complications immediately following the transplant is higher in specific populations, such as obese and diabetic patients. In obese individuals, post-transplant complications are exacerbated due to technical challenges, leading to prolonged operative times, increased need for blood transfusions, and a higher incidence of vascular complications. Additionally, these patients face an elevated risk of mortality from cardiovascular events within the first month following transplantation^[7,43]. Obese and diabetic patients have a higher risk of surgical site infections, sepsis, renal failure, and the need for prolonged mechanical ventilation, leading to extended periods of hospitalization^[44].

Late postoperative period

Comorbidities associated with metabolic syndromes such as diabetes, hypertension, dyslipidemia, and cardiovascular diseases pose challenges during long-term management and are responsible for significant morbidity and mortality in these patients^[7].

Cardiovascular disease

Cardiovascular risk factors and mortality are frequently present in post-transplant recipients. Pre-existing factors like age, obesity, and metabolic syndrome, as well as new-onset diabetes and obesity after transplant, contribute to cardiovascular morbidity. Medications such as steroids and tacrolimus increase the risk of diabetes, while cyclosporin leads to the progression of metabolic syndrome, hypertension, and dyslipidemia^[45].

MASLD/MASH is a significant risk factor for cardiovascular mortality, attributed to advanced age and the presence of metabolic syndrome. Patients with MASLD/MASH are at an increased risk of major adverse cardiac events (MACE) in the early post-transplant period, which adversely impacts survival outcomes. Comprehensive risk assessment and stringent metabolic control during the post-transplant period are

Table 2. Management of post-liver transplant complications in ALD

| Post-transplant challenges | | Management | Ref. |
|---------------------------------|-------------------------|--|---------|
| Post-transplant alcohol relapse | Behavioral therapy | Cognitive-behavioral therapy Motivational enhancement therapy Contingency management | [19] |
| | Dietary modifications | Low sodium intake High-calorie and protein diet | |
| Smoking | Pharmacotherapy | Acamprosate, baclofen, gabapentin, naltrexone, topiramate, and varenicline | [39] |
| Malignancies | Behavioral therapy | Strong recommendations by hepatologists for smoking cessation | |
| | Behavioral therapy | Smoking cessation and eliminating tobacco intake | [40,41] |
| | Screening | Regular clinical follow-ups and screening with intensified protocols | |
| Cardiovascular disease | Pharmacotherapy | Minimization of immunosuppression (particularly CNIs), and promote the use of everolimus | [42] |
| | Lifestyle modifications | Tobacco and alcohol cessation, weight loss for obese patients, and promote physical activity | |
| | Pharmacotherapy | Minimize CNIs and achieve a blood pressure of less than 140/90 mmHg | |
| Diabetes | Pharmacotherapy | HgA1c less than 7% must be achieved using GLP-1 and SGLT2 inhibitors | [42] |

ALD: Alcohol-associated liver disease; CNIs: calcineurin inhibitors; GLP: glucagon-like peptide; SGLT2: sodium-glucose cotransporter-2.

crucial to mitigating these risks and improving patient outcomes^[46].

CKD

MASLD/MASH is an independent risk factor for CKD leading to renal injury^[47]. In a study by Houlihan *et al.* (2011), MASH patients had a lower estimated glomerular filtration rate (eGFR) compared to non-MASH transplant recipients. Thirty percent of MASH patients developed CKD stage 3 at 2 years compared to 8.3% of non-MASH recipients^[48]. In another investigation conducted by Fussner *et al.* (2014), pre-transplant MASH was an independent predictor of CKD stage 3 or more 5 years post-liver transplant^[49]. Reduction in the dose of calcineurin inhibitors (CNIs) and alternatively using renal-sparing immunosuppression like everolimus and mycophenolate can help preserve renal function in the long term^[50].

Post-transplant MASLD/MASH

Post-liver transplant recurrence of MASLD/MASH is frequently reported, with an incidence rate of 8%-18% within 2 years of transplant^[51,52]. Metabolic risk factors after transplant are illustrated in [Figure 3](#). Long-term follow-up studies exceeding 5 years report graft steatosis in 87.5% of cases^[53]. While fibrosis progression tends to be slower, approximately 26.8% of patients develop advanced fibrosis, and 5.4% progress to cirrhosis. However, recent research indicates that the impact of recurrent MASLD/MASH on post-transplant survival is minimal.

Multiple factors increase the risk of post-transplant MASLD/MASH. The primary risk factors are high body mass index (BMI), dyslipidemia, increased use of steroids, and PNPLA3 polymorphism. Hepatitis C virus (HCV), ALD, and MASLD, as causes of cirrhosis, are commonly associated with post-transplant MASLD/MASH. CNIs, especially tacrolimus, are associated with an increased risk of post-transplant MASLD/MASH, while Everolimus confers a protective effect^[54,55].

Post-liver transplant management of MASLD/MASH relies on the same basic principles as pre-transplant MASLD/MASH. It includes lifestyle modifications such as regular physical activity, calorie restriction, and weight loss. Early tapering of steroids and dose reductions of CNIs are also helpful. Currently, no drug

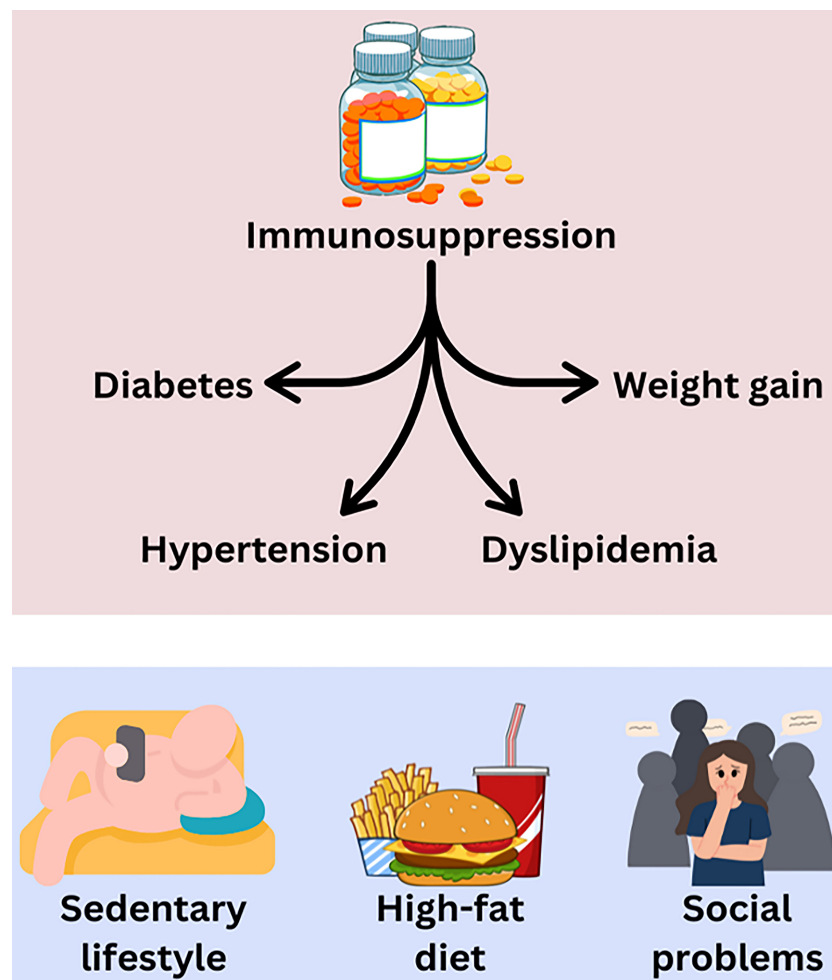


Figure 3. Post-transplant metabolic risk factors.

therapy is approved for use in MASLD/MASH in liver transplant recipients^[50,52].

Management of associated comorbidities such as diabetes, hypertension, dyslipidemia, and cardiovascular disease requires a multidisciplinary approach. In transplant recipients with uncontrolled DM2, immunosuppression modification with steroid withdrawal and reduction in tacrolimus or switch to cyclosporin is advised. Mycophenolate and everolimus do not impact glycemic control and metformin can be safely used in these patients. Newer drugs like GLP (glucagon-like peptide) SGLT2 (sodium-glucose cotransporter-2 inhibitors) can also be used in transplant recipients to promote weight loss and offer benefits such as cardioprotective effects, although data in post-transplant settings remain limited^[7].

Dyslipidemia can be managed effectively through lifestyle modifications and lipid-lowering pharmacotherapy. Hydrophilic statins, such as pravastatin, which are not primarily metabolized by the liver, can be safely used in conjunction with immunosuppressive medications^[56]. A recent study by Rinella *et al.* (2023) demonstrated that statin use following transplantation was associated with improved survival across all patient subgroups, including those undergoing transplantation for MASH-related cirrhosis^[57].

Post-transplant hypertension is associated with major cardiovascular events. VanWagner *et al.* (2020), in a retrospective study, reported that BP control (below 140/90 mmHg) was associated with a significant decrease in mortality compared to transplant recipients with inadequate management of hypertension^[58]. Prevention and early detection of cardiovascular risk factors can reduce major cardiovascular events significantly. A multidisciplinary team including hepatologists, endocrinologists, general physicians, and nurses can play a significant role in decreasing cardiovascular events in post-transplant management.

Immunosuppression

Immunosuppression is paramount for the prevention of rejection and adequate functioning of graft. However, over a long-term period, immunosuppressive drugs lead to renal toxicity, metabolic syndrome including diabetes and hypertension, and increase the risk of cardiovascular events. An approach to tailored immunosuppression is critical in such patients. Gradual tapering and early withdrawal of steroids should be the aim in all MASLD/MASH patients after transplant. The use of mycophenolate with low-dose CNIs has been shown to decrease cardiovascular mortality and improve renal function compared to regimes containing steroids and CNIs^[59]. Everolimus with a reduced dose of CNIs also helps preserve renal function, and provides better control of glycemic and hypertension. Everolimus may also promote weight loss and decrease cardiovascular risk, but it causes dyslipidemia more frequently^[7].

Arterial Hypertension

Arterial hypertension is highly prevalent in the general population, making it one of the most common cardiovascular risk factors. This condition is further amplified in liver transplant recipients, with an incidence reported in approximately 50% to 80% of patients^[60]. According to de Oliveira Lemos *et al.* (2021), arterial hypertension typically develops around 9 months after transplantation^[61]. Before initiating pharmacologic treatment, lifestyle interventions such as weight reduction, regular physical activity, and dietary sodium restriction are strongly recommended to reduce hypertension risk. In some cases, post-transplant hypertension may be transient and resolve spontaneously within a few months, potentially allowing for discontinuation of antihypertensive therapy^[62,63].

Table 3 outlines the incidence rates of post-transplant complications in patients with MASLD/MASH.

FUTURE IMPLICATIONS

Complications specific to ALD and MASLD/MASH require specific attention in liver transplant patients. Early identification and management of such complications can significantly influence both short- and long-term transplant success. Behavioral modifications, including smoking and alcohol cessation, regular physical activity, and dietary interventions, should form the cornerstone of post-transplant care. While pharmacological therapies remain essential, their effectiveness is greatly enhanced when supplemented by sustained lifestyle changes. This integrated approach not only facilitates recovery but also reduces recurrence risks and promotes long-term graft survival. Furthermore, psychological assistance post-transplant for AUD patients may be warranted to promote abstinence. High-quality clinical trials are required to standardize post-transplant care, including pharmacological, psychological, and behavioral treatment.

CONCLUSION

This review highlights the significant global health burden posed by ALD and MASLD/MASH. Both conditions can lead to severe liver damage, necessitating liver transplantation. However, post-transplant complications remain a significant challenge, particularly for patients with ALD and MAFLD.

Table 3. Rate of incidence of post-liver transplant complications in MASLD/MASH

| | Post-transplant issues | Rate of incidence | Ref. |
|-----------------------|---------------------------------|-------------------|---------|
| Mortality | Infection | 15.9%-38% | [64] |
| | Cardiac event | 5.3%-26% | |
| | Graft or multiple organ failure | 6%-41% | |
| | Malignancy | 2.5%-9.3% | |
| Recurrent MASLD | | 8%-100% | [64] |
| Metabolic syndrome | Diabetes | 35.8% | [65] |
| | Hypertension | 61.5% | |
| Cardiovascular events | Overall | 26% | [66,67] |
| | Atrial fibrillation | 13.7% | |
| | Myocardial infarction | 2.8% | |
| | Stroke | 5.5% | |
| | Heart Failure | 6.3% | |
| | Solid-organ malignancy | 4.9% | |
| | Skin cancer | 3.8% | |
| Malignancy | Lymphoproliferative disease | 1.3% | [67] |
| | Bacterial | 36.6% | |
| | Fungal | 5.7% | |
| Infections | Viral | 15.9% | [67-69] |
| | | | |

MASLD: Metabolic-associated steatotic liver disease; MASH: metabolic-associated steatohepatitis.

ALD patients often struggle with AUD and poor medication adherence, increasing the risk of graft injury and loss. Additionally, they are at heightened risk of malignancies and cardiovascular disease. A comprehensive, multidisciplinary approach, combining behavioral interventions and pharmacological therapies, is essential to optimize post-transplant outcomes in these patients. Furthermore, optimizing immunosuppression regimens, including early steroid withdrawal and low-dose CNIs, can help mitigate the risk of post-transplant diabetes, hypertension, and dyslipidemia.

In conclusion, addressing the unique challenges faced by ALD and MAFLD patients post-transplant requires a tailored approach that combines medical interventions, lifestyle modifications, and psychosocial support. By implementing these strategies, we can improve patient outcomes and enhance the long-term success of liver transplantation in these patient populations.

DECLARATIONS

Authors' contributions

Wrote the initial manuscript draft: Jadaun SS

Revised the manuscript: Saigal S

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.

Copyright

© The Author(s) 2024.

REFERENCES

1. Cheemerla S, Balakrishnan M. Global epidemiology of chronic liver disease. *Clin Liver Dis*. 2021;17:365-70. DOI PubMed PMC
2. Cholanteril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol*. 2018;16:1356-8. DOI PubMed PMC
3. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med*. 2011;365:1790-800. DOI PubMed
4. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology*. 2011;141:1249-53. DOI PubMed
5. Ascha MS, Hanounieh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology*. 2010;51:1972-8. DOI PubMed
6. Bittermann T, Mahmud N, Weinberg EM, Reddy KR. Rising trend in waitlisting for alcoholic hepatitis with more favorable outcomes than other high model for end-stage liver disease in the current era. *Transplantation*. 2022;106:1401-10. DOI PubMed PMC
7. Battistella S, D'Arcangelo F, Grasso M, et al. Liver transplantation for non-alcoholic fatty liver disease: indications and post-transplant management. *Clin Mol Hepatol*. 2023;29:S286-301. DOI PubMed PMC
8. Rice JP, Eickhoff J, Agni R, Ghufuran A, Brahmbhatt R, Lucey MR. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. *Liver Transpl*. 2013;19:1377-86. DOI PubMed
9. Björnsson E, Olsson J, Rydell A, et al. Long-term follow-up of patients with alcoholic liver disease after liver transplantation in Sweden: impact of structured management on recidivism. *Scand J Gastroenterol*. 2005;40:206-16. DOI PubMed
10. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: alcoholic liver disease. *Am J Gastroenterol*. 2018;113:175-94. DOI PubMed PMC
11. Erard-Poinsot D, Dharancy S, Hilleret MN, et al. Natural history of recurrent alcohol-related cirrhosis after liver transplantation: fast and furious. *Liver Transpl*. 2020;26:25-33. DOI PubMed
12. 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
13. Ntandja Wandji LC, Ningarhari M, Lassailly G, et al. Liver transplantation in alcohol-related liver disease and alcohol-related hepatitis. *J Clin Exp Hepatol*. 2023;13:127-38. DOI PubMed PMC
14. Chuncharunee L, Yamashiki N, Thakkestian A, Sobhonslidsuk A. Alcohol relapse and its predictors after liver transplantation for alcoholic liver disease: a systematic review and meta-analysis. *BMC Gastroenterol*. 2019;19:150. DOI PubMed PMC
15. Dew MA, DiMartini AF, Steel J, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl*. 2008;14:159-72. DOI PubMed PMC
16. Association for the Study of the Liver. EASL clinical practice guidelines: management of alcohol-related liver disease. *J Hepatol*. 2018;69:154-81. DOI PubMed
17. Asrani SK, Trotter J, Lake J, et al. Meeting report: the dallas consensus conference on liver transplantation for alcohol associated hepatitis. *Liver Transpl*. 2020;26:950-1. DOI PubMed
18. Lee YH, Jung KS, Kim SU, et al. Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008-2011). *J Hepatol*. 2015;63:486-93. DOI PubMed
19. 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
20. Reus VI, Fochtmann LJ, Bukstein O, et al. The American psychiatric association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry*. 2018;175:86-90. DOI PubMed
21. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. *Br J Clin Pharmacol*. 2014;77:315-23. DOI PubMed PMC
22. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014;311:1889-900. DOI PubMed
23. O'Malley SS, Zweben A, Fucito LM, et al. Effect of varenicline combined with medical management on alcohol use disorder with comorbid cigarette smoking: a randomized clinical trial. *JAMA Psychiatry*. 2018;75:129-38. DOI PubMed PMC
24. Magistri P, Marzi L, Guerzoni S, et al. Impact of a multidisciplinary team on alcohol recidivism and survival after liver transplant for alcoholic disease. *Transplant Proc*. 2019;51:187-9. DOI PubMed

25. National Center for Biotechnology Information. LiverTox: clinical and research information on drug-induced liver injury. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK547852/>. [Last accessed on 13 Dec 2024].
26. Morley KC, Baillie A, Fraser I, et al. Baclofen in the treatment of alcohol dependence with or without liver disease: multisite, randomised, double-blind, placebo-controlled trial. *Br J Psychiatry*. 2018;212:362-9. DOI PubMed
27. Berlakovich GA, Langer F, Freundorfer E, et al. General compliance after liver transplantation for alcoholic cirrhosis. *Transpl Int*. 2000;13:129-35. DOI PubMed
28. Ehlers SL, Rodrigue JR, Widows MR, Reed AI, Nelson DR. Tobacco use before and after liver transplantation: a single center survey and implications for clinical practice and research. *Liver Transpl*. 2004;10:412-7. DOI PubMed
29. Pungpapong S, Manzarbeitia C, Ortiz J, et al. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. *Liver Transpl*. 2002;8:582-7. DOI PubMed
30. Duerinckx N, Burkhalter H, Engberg SJ, et al; B-SERIOUS consortium. Correlates and outcomes of posttransplant smoking in solid organ transplant recipients: a systematic literature review and meta-analysis. *Transplantation*. 2016;100:2252-63. DOI PubMed
31. Cheung A, Levitsky J. Follow-up of the post-liver transplantation patient: a primer for the practicing gastroenterologist. *Clin Liver Dis*. 2017;21:793-813. DOI PubMed
32. Saigal S, Norris S, Muiesan P, Rela M, Heaton N, O'Grady J. Evidence of differential risk for posttransplantation malignancy based on pretransplantation cause in patients undergoing liver transplantation. *Liver Transpl*. 2002;8:482-7. DOI PubMed
33. Schrem H, Kurok M, Kaltenborn A, et al. Incidence and long-term risk of de novo malignancies after liver transplantation with implications for prevention and detection. *Liver Transpl*. 2013;19:1252-61. DOI PubMed
34. Coordes A, Albers AE, Lenarz M, et al. Incidence and long-term survival of patients with de novo head and neck carcinoma after liver transplantation. *Head Neck*. 2016;38:707-14. DOI PubMed
35. Zhou J, Hu Z, Zhang Q, et al. Spectrum of de novo cancers and predictors in liver transplantation: analysis of the scientific registry of transplant recipients database. *PLoS One*. 2016;11:e0155179. DOI PubMed PMC
36. Tiwari A, Saigal S, Choudhary NS, et al. De novo malignancy after living donor liver transplantation: a large volume experience. *J Clin Exp Hepatol*. 2020;10:448-52. DOI PubMed PMC
37. Burra P, Senzolo M, Adam R, et al; ELITA, ELTR Liver Transplant Centers. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant*. 2010;10:138-48. DOI PubMed
38. Simo KA, Sereika S, Bitner N, Newton KN, Gerber DA. Medical epidemiology of patients surviving ten years after liver transplantation. *Clin Transplant*. 2011;25:360-7. DOI PubMed
39. Marti-Aguado D, Clemente-Sanchez A, Bataller R. Cigarette smoking and liver diseases. *J Hepatol*. 2022;77:191-205. DOI PubMed
40. Vanlerberghe BTK, van Malenstein H, Sainz-Barriga M, et al. Tacrolimus drug exposure level and smoking are modifiable risk factors for early de novo malignancy after liver transplantation for alcohol-related liver disease. *Transpl Int*. 2024;37:12055. DOI PubMed PMC
41. Singh A, De A, Singh V. Post-transplant malignancies in alcoholic liver disease. *Transl Gastroenterol Hepatol*. 2020;5:30. DOI PubMed PMC
42. Izzy M, Fortune BE, Serper M, et al. Management of cardiac diseases in liver transplant recipients: comprehensive review and multidisciplinary practice-based recommendations. *Am J Transplant*. 2022;22:2740-58. DOI PubMed PMC
43. Spengler EK, O'Leary JG, Te HS, et al. Liver transplantation in the obese cirrhotic patient. *Transplantation*. 2017;101:2288-96. DOI PubMed PMC
44. Dare AJ, Plank LD, Phillips AR, et al. Additive effect of pretransplant obesity, diabetes, and cardiovascular risk factors on outcomes after liver transplantation. *Liver Transpl*. 2014;20:281-90. DOI PubMed
45. D'Avola D, Cuervas-Mons V, Marti J, et al. Cardiovascular morbidity and mortality after liver transplantation: the protective role of mycophenolate mofetil. *Liver Transpl*. 2017;23:498-509. DOI PubMed
46. VanWagner LB, Serper M, Kang R, et al. Factors associated with major adverse cardiovascular events after liver transplantation among a national sample. *Am J Transplant*. 2016;16:2684-94. DOI PubMed PMC
47. Targher G, Bertolini L, Chonchol M, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and retinopathy in type 1 diabetic patients. *Diabetologia*. 2010;53:1341-8. DOI PubMed
48. Houlihan DD, Armstrong MJ, Davidov Y, et al. Renal function in patients undergoing transplantation for nonalcoholic steatohepatitis cirrhosis: time to reconsider immunosuppression regimens? *Liver Transpl*. 2011;17:1292-8. DOI PubMed
49. Fussner LA, Charlton MR, Heimbach JK, et al. The impact of gender and NASH on chronic kidney disease before and after liver transplantation. *Liver Int*. 2014;34:1259-66. DOI PubMed
50. Mehtani R, Saigal S. Long term complications of immunosuppression post liver transplant. *J Clin Exp Hepatol*. 2023;13:1103-15. DOI PubMed PMC
51. Taneja S, Roy A. Nonalcoholic steatohepatitis recurrence after liver transplant. *Transl Gastroenterol Hepatol*. 2020;5:24. DOI PubMed PMC
52. Choudhary NS, Saigal S. Preventive strategies for nonalcoholic fatty liver disease after liver transplantation. *J Clin Exp Hepatol*. 2019;9:619-24. DOI PubMed PMC
53. Bhati C, Idowu MO, Sanyal AJ, et al. Long-term outcomes in patients undergoing liver transplantation for nonalcoholic steatohepatitis-related cirrhosis. *Transplantation*. 2017;101:1867-74. DOI PubMed
54. Shetty A, Giron F, Divatia MK, Ahmad MI, Kodali S, Victor D. Nonalcoholic fatty liver disease after liver transplant. *J Clin Transl*

- Hepatol*. 2021;9:428-35. DOI PubMed PMC
55. Poudel S, Gupta S, Saigal S. Basics and art of immunosuppression in liver transplantation. *J Clin Exp Hepatol*. 2024;14:101345. DOI PubMed PMC
 56. Azhie A, Sheth P, Hammad A, Woo M, Bhat M. Metabolic complications in liver transplantation recipients: how we can optimize long-term survival. *Liver Transpl*. 2021;27:1468-78. DOI PubMed
 57. Rinella ME, Satapathy SK, Brandman D, et al. Factors impacting survival in those transplanted for NASH Cirrhosis: data from the NailNASH consortium. *Clin Gastroenterol Hepatol*. 2023;21:445-455.e2. DOI PubMed
 58. VanWagner LB, Holl JL, Montag S, et al. Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. *Am J Transplant*. 2020;20:797-807. DOI PubMed PMC
 59. Neuberger JM, Mamelok RD, Neuhaus P, et al; ReSpECT Study Group. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. *Am J Transplant*. 2009;9:327-36. DOI PubMed
 60. 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
 61. Lemos BO, Silva RCMA, Silva RFD. Prevalence and time of development of systemic arterial hypertension in patients after liver transplantation. *Arq Gastroenterol*. 2021;58:77-81. DOI PubMed
 62. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American association for the study of liver diseases and the american society of transplantation. *Liver Transpl*. 2013;19:3-26. DOI PubMed
 63. Di Stefano C, Vanni E, Mirabella S, et al. Risk factors for arterial hypertension after liver transplantation. *J Am Soc Hypertens*. 2018;12:220-9. DOI PubMed
 64. Paklar N, Mijic M, Filipec-Kanizaj T. The outcomes of liver transplantation in severe metabolic dysfunction-associated steatotic liver disease patients. *Biomedicines*. 2023;11:3096. DOI PubMed PMC
 65. Yalamanchili K, Saadeh S, Klintmalm GB, Jennings LW, Davis GL. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. *Liver Transpl*. 2010;16:431-9. DOI PubMed
 66. Narayanan P, Mara K, Izzy M, et al. Recurrent or de novo allograft steatosis and long-term outcomes after liver transplantation. *Transplantation*. 2019;103:e14-21. DOI PubMed
 67. Kwong AJ, Devuni D, Wang C, et al; Re-Evaluating Age Limits in Transplantation (REALT) Consortium. Outcomes of liver transplantation among older recipients with nonalcoholic steatohepatitis in a large multicenter US cohort: the re-evaluating age limits in transplantation consortium. *Liver Transpl*. 2020;26:1492-503. DOI PubMed PMC
 68. Gitto S, Golfieri L, Gabrielli F, et al; MEDITRA Research Group. Physical activity in liver transplant recipients: a large multicenter study. *Intern Emerg Med*. 2024;19:343-52. DOI PubMed PMC
 69. Anastácio LR, Davisson Correia MI. Nutrition therapy: integral part of liver transplant care. *World J Gastroenterol*. 2016;22:1513-22. DOI PubMed PMC