*transplantology*

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*Review*

# Liver Transplantation in the Era of Metabolic Dysfunction–Associated Fatty Liver Disease: Challenges, Ethical Dilemmas, and Future Directions

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## Abstract

Metabolic dysfunction–associated fatty liver disease (MAFLD) is now the leading indication for liver transplantation (LT), reshaping the landscape of transplant hepatology. Its close association with obesity, type 2 diabetes, cardiovascular disease, and extrahepatic malignancies poses unique challenges throughout the transplant continuum. This narrative review synthesizes current evidence across the pre-, peri-, and post-transplant spectrum, with a focus on practical implications for clinical management. We explore pre-transplant evaluation, focusing on how metabolic comorbidities, frailty, and organ allocation disparities intersect with emerging interventions such as GLP-1 receptor agonists, bariatric surgery, and structured weight loss programs. The increase in pediatric MAFLD, especially its early-onset aggressive form, indicates an evolving and concerning future burden on transplant programs. In the peri-operative and post-transplant periods, we address MAFLD recurrence, cardiometabolic complications, and the rising incidence of new cancers, particularly in relation to calcineurin inhibitor (CNI) exposure. Customized immunosuppression strategies, using mTOR inhibitors and mycophenolate mofetil, are discussed for their role in balancing graft protection with reducing cancer risk. We also review the application of machine perfusion technologies to optimize and expand the pool of steatotic donor livers. Future directions include the development of non-invasive diagnostic biomarkers, precision immunosuppression, and genomics-based risk stratification. Collectively, these insights emphasize the urgent need for multidisciplinary, patient-specific approaches and prospective, multicenter studies to optimize outcomes and equity in the era of MAFLD-driven liver transplantation.

**Keywords:** metabolic dysfunction–associated fatty liver disease (MAFLD); liver transplantation; metabolic comorbidities; obesity and diabetes; immunosuppression management; organ allocation; machine perfusion; precision medicine



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## 1. Introduction

### *1.1. From NAFLD to MAFLD/MASLD: Evolving Nomenclature and Diagnostic Criteria*

The transition from non-alcoholic fatty liver disease (NAFLD) to metabolic-dysfunction-associated fatty liver disease (MAFLD) and, most recently, metabolic-dysfunction-associated steatotic liver disease (MASLD) marks a paradigm shift toward terminology

that is pathophysiologically precise and clinically inclusive. NAFLD, first defined in 1980 as hepatic steatosis in the absence of significant alcohol consumption, became the most common liver disorder globally, particularly among individuals with obesity and type 2 diabetes mellitus (T2DM) [1]. However, its exclusion-based definition, requiring the elimination of other causes such as alcohol and viral hepatitis, failed to acknowledge the disease's metabolic underpinnings, risked stigmatization, and complicated communication in both clinical and research contexts [2–4].

As summarized in Table 1, the comparative diagnostic criteria highlight the progression from exclusion-based definitions (NAFLD) to metabolically driven frameworks (MAFLD/MASLD), underscoring their clinical and research implications.

In 2020, MAFLD was proposed as a replacement for NAFLD, introducing positive diagnostic criteria that directly linked hepatic steatosis to metabolic dysfunction, specifically overweight/obesity, T2DM, or ≥2 metabolic risk factors, regardless of alcohol intake. This change aimed to improve disease recognition, align diagnosis with underlying pathophysiology, and facilitate targeted management [5–7].

Compared to historical NAFLD data, the MAFLD framework has increased awareness and improved diagnostic accuracy, enabling more consistent identification of patients with underlying metabolic dysfunction [8]. Although overall prevalence patterns are similar to those of NAFLD, the updated criteria have strengthened the understanding of metabolic associations and enhanced risk stratification.

Further refinement occurred in 2023, when an international consensus group introduced MASLD as a subcategory of steatotic liver disease (SLD). MASLD requires hepatic steatosis plus at least one cardiometabolic risk factor, and the related category, metabolic dysfunction- and alcohol-associated liver disease (MetALD), accounts for patients with moderate alcohol intake alongside metabolic dysfunction [9,10]. Table 1 illustrates these evolving definitions, contrasting their diagnostic approaches, alcohol thresholds, and criticisms, while also emphasizing how each term reflects different perspectives on disease pathogenesis.

While MASLD aims to balance diagnostic precision with inclusivity and reduce stigma, many experts continue to favor MAFLD due to its closer alignment with disease pathogenesis and its proven superior utility in identifying both hepatic and extra-hepatic outcomes compared to both NAFLD and MASLD [11].

Importantly, these nomenclature changes have significant clinical and research implications. The focus on metabolic risk improves identification of at-risk patients and highlights cardiovascular comorbidity, while creating new opportunities to study the interplay between alcohol use and metabolic dysfunction [8,12]. Despite these benefits, overlap remains high, over 99% of NAFLD cases meet MASLD criteria, and the pace of change has generated uncertainty in some settings [1,3].

**Table 1.** Evolution of Diagnostic Criteria for NAFLD, MAFLD, MASLD, and MetALD.

| Feature | NAFLD (1980–2020) | MAFLD (2020–Present) | MASLD (2023–Present) | MetALD (2023–Present) |
|---|---|---|---|---|
| **Definition** [13,14] | Hepatic steatosis, excluding significant alcohol use and other causes | Hepatic steatosis plus ≥1 of: overweight/obesity, T2DM, or ≥2 metabolic risk factors † | Hepatic steatosis plus ≥1 cardiometabolic risk factor ‡ | MASLD criteria plus moderate alcohol intake |

**Table 1.** *Cont.*

| Feature | NAFLD (1980–2020) | MAFLD (2020–Present) | MASLD (2023–Present) | MetALD (2023–Present) |
|---|---|---|---|---|
| **Alcohol Threshold** * [7,13,15] | <30 g/day (men), <20 g/day (women) | No restriction if metabolic criteria met | ≤140 g/week (women), ≤210 g/week (men) | >140–350 g/week (women), >210–420 g/week (men) |
| **Diagnostic Approach** [7,13,15] | Diagnosis of exclusion | Positive criteria emphasizing metabolic dysfunction | Positive criteria with broader inclusion | Positive criteria plus specified alcohol intake |
| **Key Criticisms** [7,13,15–17] | Excludes metabolic pathogenesis; stigmatizing term; exclusionary | May underplay role of alcohol | New term may cause confusion; limited criteria for lean individuals | May underestimate alcohol-related liver injury |

Summary: This table illustrates the progressive transition from exclusion-based terminology (NAFLD) to metabolically inclusive frameworks (MAFLD, MASLD, MetALD). The evolution highlights the recognition of metabolic dysfunction as the central driver of disease while incorporating alcohol use more systematically. Footnotes: * Alcohol intake thresholds are based on consensus guidelines and differ by sex. † "Metabolic risk factors" include hypertension, dyslipidemia, insulin resistance, or elevated waist circumference. ‡ "Cardiometabolic risk factor" refers to conditions increasing both metabolic and cardiovascular disease risk. Abbreviations: NAFLD: Non-Alcoholic Fatty Liver Disease; MAFLD: Metabolic Dysfunction–Associated Fatty Liver Disease; MASLD: Metabolic Dysfunction–Associated Steatotic Liver Disease; MetALD: Metabolic Dysfunction- and Alcohol-Associated Liver Disease; T2DM: Type 2 Diabetes Mellitus.

### *1.2. Global Epidemiological Trends*

MAFLD is a growing global health concern, with current estimates indicating that MAFLD affects approximately 38% of adults worldwide, with projections exceeding 55% by 2040 [18]. The annual incidence is approximately 4.6 cases per 100 patient-years, although rates vary significantly across regions [19]. Among individuals with T2DM, prevalence reaches 65.33% globally, underscoring the disease's deep entrenchment within the spectrum of metabolic disorders. Geographic variation remains striking: prevalence in T2DM populations peaks in Eastern Europe (80.62%) and the Middle East (71.24%) but falls to 53.10% in Africa [18].

Equally concerning is the growing impact of MAFLD among children and adolescents. The rise in pediatric obesity and insulin resistance has driven a notable increase in MAFLD diagnoses in younger populations. Early-onset MAFLD often displays more severe histological patterns and carries a heightened risk of progression to advanced fibrosis or cirrhosis in adulthood [20]. In pediatric populations, MAFLD already affects 7–14% of children and adolescents, signaling an upcoming public health challenge [17]. This evolving epidemiology underscores the need for early identification, routine surveillance, and targeted interventions in pediatric patients to reduce long-term liver-related morbidity and transplantation demand [20].

The primary risk factors—obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia—are compounded by associations with hepatocellular carcinoma (HCC), other gastrointestinal and extrahepatic malignancies, cardiovascular disease (CVD), chronic kidney disease (CKD), and reduced quality of life [18,19,21]. MAFLD is now a leading cause of liver-related morbidity and mortality and an emerging driver of liver transplantation (LT) demand [22]. Its economic impact on healthcare systems is substantial, necessitating the development of coordinated international strategies for early detection, prevention, and management [23]. Without robust intervention, the prevalence and clinical burden of MAFLD will continue to climb, further straining transplant services and widening its footprint on global health.

While the transition from NAFLD to MAFLD offers a more pathophysiologically coherent framework, it also poses challenges, including difficulties in interpreting historical data and aligning therapeutic development. The exceptionally high prevalence among patients with T2DM underscores the need for integrated care models that address both metabolic and hepatic health. As the epidemic spreads, comprehensive public health policies that combine lifestyle interventions, population screening, and regulatory measures will be essential to curb its trajectory and mitigate downstream consequences for LT.

As illustrated in Figure 1, the trajectory of fatty liver disease and its role in LT can be divided into four phases. The field began with the initial definition of NAFLD in 1980 and early recognition of NASH (Phase 1) [12,13]. By the early 2000s, NAFLD was widely recognized as a metabolic disorder, prompting the development of guidelines by major liver societies (Phase 2) [12,24]. During the 2010s, NAFLD and NASH rose sharply as leading causes of cirrhosis and LT, culminating in the proposal of MAFLD as a pathophysiologically aligned term (Phase 3) [6,15,25,26]. Most recently, the introduction of MASLD and MetALD, along with advances in precision medicine and transplant technologies, has defined the current era (Phase 4) [4,9,11,22,27]. This evolution underscores the shift from exclusion-based definitions to inclusive, metabolically focused approaches with direct implications for transplantation.

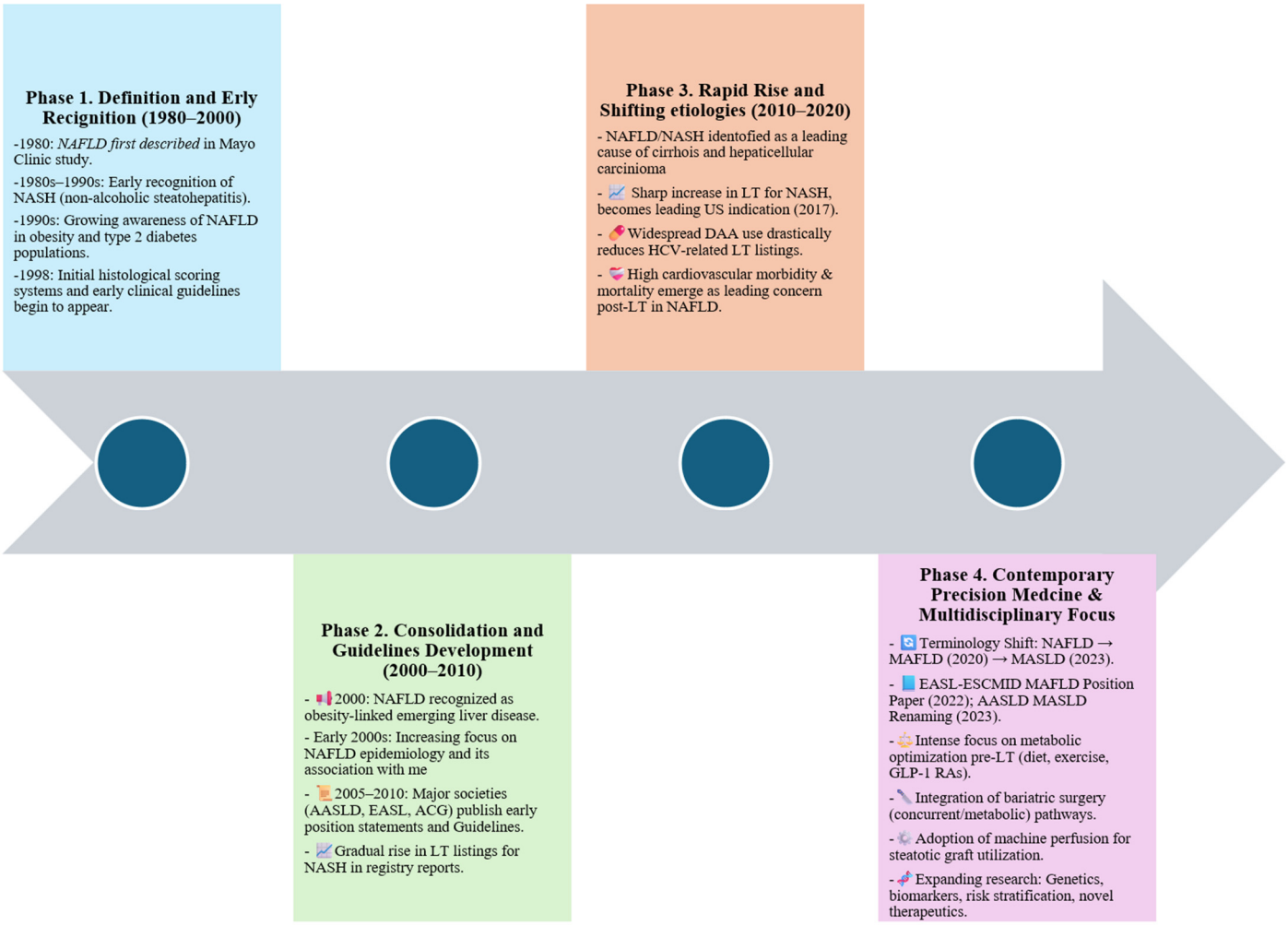


**Figure 1.** Timeline of evolving trends in MAFLD and liver transplantation. This figure illustrates four major phases in the recognition and management of fatty liver disease leading up to its role in liver transplantation. Phase 1 (1980–2000) covers the definition of NAFLD, the identification of NASH, and early histological and clinical studies. Phase 2 (2000–2010) marked the development of guidelines and

the recognition of NAFLD as a significant liver disease associated with metabolic syndrome. Phase 3 (2010–2020) marks the rapid rise in NAFLD/NASH as a leading indication for liver transplantation, as well as the introduction of the MAFLD definition. Phase 4 (2020–present) represents the contemporary era, defined by new nomenclature (MASLD, MetALD), cardiometabolic integration, precision medicine, and innovative transplant technologies. Together, these phases demonstrate the evolution from descriptive definitions to pathophysiologically grounded frameworks that guide current transplant practice. Abbreviations: LT: Liver Transplantation; NAFLD: Non-alcoholic fatty liver disease; MASLD: Metabolic Dysfunction-associated Steatotic Liver Disease; NASH: Non-alcoholic Steatohepatitis; AASLD: American Association for the Study of Liver Diseases; ACG: American College of Gastroenterology; EASL: European Association for the Study of the Liver; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; US: United States; DAA: Direct-Acting Antivirals; GLP-1 RA: Glucagon-like peptide-1 receptor agonist.

### *1.3. Rationale for Review: Increasing Burden of MAFLD-Related Liver Failure and Transplantation Needs*

The growing prevalence of MAFLD is reshaping the landscape of LT. Whereas viral hepatitis and alcohol-related liver disease once dominated transplant indications, waiting lists are now increasingly filled with patients suffering from MAFLD-related cirrhosis and HCC, both downstream consequences of metabolic liver disease [24–26]. Projections suggest that within the next decade, MAFLD-related cirrhosis will become the leading indication for LT in many high-income countries [24].

This shift is primarily driven by the global obesity epidemic, rising prevalence of T2DM, and the widespread burden of metabolic syndrome, each of which accelerates disease progression and worsens transplant outcomes [4,24,28,29]. The multisystem nature of MAFLD further compounds these challenges. CVD, CKD, and oncologic comorbidities are highly prevalent in this population, complicating candidate selection, perioperative risk stratification, and long-term post-transplant care [23,30,31]. Standard transplant protocols often fail to fully address these complexities, underscoring the need for tailored, multidisciplinary approaches that integrate expertise in hepatology, cardiology, endocrinology, and oncology [25].

This review synthesizes current evidence on the epidemiology, evolving nomenclature, and clinical challenges of MAFLD in the context of LT. The aim is to highlight shifting disease patterns, identify gaps in existing practice, and propose strategies for prevention, early detection, and optimized post-transplant care. By addressing both hepatic and extrahepatic dimensions, we aim to inform policy, guide clinical decision-making, and support public health strategies that mitigate the mounting transplantation burden.

### *1.4. Literature Search and Selection*

A structured literature search was conducted to support the development of this narrative review. Searches were conducted in PubMed, Embase, Scopus, and Web of Science from the database's inception through August 2025. The search strategy included combinations of the following keywords and MeSH terms: "MAFLD," "MASLD," "NAFLD," "NASH," "liver transplantation," "metabolic syndrome," "immunosuppression," "cardiovascular disease," "hepatocellular carcinoma," "pediatric," "recurrence," "post-transplant outcomes," and "malignancy."

Reference selection focused on original research articles, clinical trials, observational studies, and relevant systematic or narrative reviews published in English. Articles were included if they addressed MAFLD or MASLD in the context of liver transplantation or its pre- and post-transplant complications. Preference was given to recent publications (within the last 5–10 years), landmark studies, and high-impact data from registries such as UNOS and SRTR.

Additional sources were identified by reviewing the bibliographies of key papers. Final reference selection was made based on relevance, recency, quality of evidence, and contribution to thematic sections of the manuscript. This approach enabled a comprehensive and balanced synthesis of current knowledge while retaining the flexibility of a narrative review format.

## 2. Epidemiology and Burden of MAFLD in the Transplant Setting

### *2.1. Rising Impact of MAFLD in Cirrhosis and End-Stage Liver Disease*

MAFLD has emerged as a major contributor to cirrhosis and end-stage liver disease (ESLD), increasingly displacing viral and alcohol-related liver disease as a primary cause of hepatic decompensation. This trend correlates strongly with the global surge in obesity, T2DM, and metabolic syndrome, key drivers of liver fibrosis and disease progression [32,33].

In particular, longitudinal data from the United States show that the prevalence of MAFLD-related cirrhosis increased markedly, rising from 3.34% between 1992 and 2011 to 6.16% in the period between 2014 and 2019 [34]. Importantly, broader recognition of metabolic risk factors has helped explain previously cryptogenic cases of cirrhosis, especially in lean individuals who meet the criteria for metabolic dysfunction, thereby enhancing diagnostic accuracy and clinical awareness.

Progression to cirrhosis is most likely in patients with advanced fibrosis or severe steatohepatitis. Among these individuals, liver-related outcomes, including HCC, hepatic decompensation, and death, are increasingly common [33,35]. Mortality remains significant, with MAFLD-related cirrhosis estimated to result in 7.46 deaths per 100 person-years [34].

Beyond hepatic failure, MAFLD is linked to broader systemic complications. Cardiovascular disease (CVD), chronic kidney disease (CKD), and extrahepatic malignancies are frequent comorbidities, underscoring the multi-organ burden of this condition [36,37]. In particular, the gut–liver–kidney axis has been implicated in disease pathogenesis, with intestinal dysbiosis contributing to systemic inflammation and renal injury [36]. As cardiovascular events remain the leading cause of mortality in these patients, the transplant setting must increasingly account for both hepatic and cardiometabolic risks in evaluation and post-operative care [4].

### *2.2. MAFLD as an Emerging Indication for LT*

The rise in MAFLD as a primary indication for LT represents a significant shift in the transplant landscape. Analyses from major transplant registries, including the United Network for Organ Sharing (UNOS) and the European Liver Transplant Registry (ELTR), confirm a consistent upward trend in LTs performed for MAFLD, underscoring its growing importance as a leading indication for transplantation [22,38,39]. Large cohort studies further support this observation, reporting a marked increase in the number of patients with MAFLD added to transplant waiting lists over the past twenty years [22,26].

This pattern is further detailed in Table 2, which compares MAFLD with other major indications for transplantation. The table highlights MAFLD's rapid increase in prevalence, distinct comorbidity burden, and unique post-transplant challenges.

The contrast with other liver diseases further emphasizes this shift. Hepatitis C virus (HCV)- related liver disease has sharply declined as an LT indication due to the transformative impact of direct-acting antivirals (DAAs), which have drastically reduced the need for transplantation in this population [39]. Alcohol-related liver disease (ALD) remains a major indication, yet the growth of MAFLD cases now outpaces ALD, largely driven by sedentary lifestyles, unhealthy dietary habits, and rising global obesity rates [26,38,39].

MAFLD is also increasingly recognized as a major contributor to HCC. Its incidence has risen in parallel with the global increase in metabolic dysfunction, and a significant proportion of HCC cases on transplant waiting lists are now attributable to MAFLD [21,58]. This reinforces the expanding role of metabolic liver disease in liver cancer etiology and transplantation demand [59].

**Table 2.** Comparative Profiles of Liver Transplant Indications Across Major Etiologies (MAFLD, ALD, HCV, and Other Causes).

| Parameter | MAFLD | Alcohol-Related Liver Disease (ALD) | Hepatitis C Virus (HCV) | Other (e.g., Autoimmune, Cholestatic) |
|---|---|---|---|---|
| **Primary Risk Factors** | Obesity, T2DM, dyslipidemia, metabolic syndrome [12,13] | Chronic alcohol use [40] | Chronic HCV infection [41] | Autoimmune or genetic cholestatic disorders [42] |
| Demographics | Predominantly middle-aged to older adults; higher prevalence in women [17,24] | Younger to middle-aged males [40] | Middle-aged, historically more male-predominant [41] | Variable depending on etiology [43] |
| Trend in LT Listing (2000–2020) ‡ | Rapid increase; leading indication in the US by 2017 [15,44] | Stable to slightly increasing [45] | Sharp decline after DAA * introduction [46,47] | Stable or slowly declining |
| Comorbidities | High burden of cardiovascular disease, obesity, T2DM, metabolic syndrome [25,48] | Alcohol use disorder, malnutrition, and psychiatric comorbidities [49] | Hepatic decompensation; antiviral treatment failure [50] | Disease-specific comorbidities [51] |
| Waitlist Mortality | Higher due to CVD, metabolic syndrome, sarcopenia; often underestimated by MELD [52] | Variable; high risk of decompensation and relapse [53] | Lower in DAA era [50] | Variable by disease |
| MELD at Listing (Median) | Often lower MELD despite significant morbidity; underestimates risk [52] | Moderate MELD; matches severity [49] | Historically higher MELD pre-DAAs; now lower [46] | Variable |
| 1-Year Graft Survival # | 85–90%; comparable to ALD, slightly lower than HCV [54] | ~85%; relapse risk affects outcomes [45] | >90% with viral clearance [46] | ~85–90%, depending on etiology [51] |
| 5-Year Graft Survival # | ~70–75%; limited by cardiovascular mortality and metabolic complications [55] | ~70%; relapse reduces survival [45] | ~80–85% with DAAs [46] | ~75–80%, variable [43] |
| Post-LT Challenges | High recurrence of steatosis, MASH †; increased cardiovascular mortality [56] | Risk of alcohol relapse; infections [45] | Recurrence risk (now low with DAAs) [46] | Variable, depending on underlying disease [51] |

**Table 2.** *Cont.*

| Parameter | MAFLD | Alcohol-Related Liver Disease (ALD) | Hepatitis C Virus (HCV) | Other (e.g., Autoimmune, Cholestatic) |
|---|---|---|---|---|
| Special Considerations | Pre-LT metabolic optimization; aggressive cardiovascular risk assessment [57] | Addiction counseling, relapse prevention [40] | Antiviral therapy pre/post-LT [41] | Disease-specific treatments |

Footnotes: * "DAA" refers to direct-acting antivirals, which have reduced the need for transplantation in HCV. † "MASH" = metabolic dysfunction-associated steatohepatitis, formerly "NASH." ‡ US listing data based on national transplant registry analyses. # Graft survival rates are approximate pooled values from large registry and cohort studies. Abbreviations: LT: Liver Transplantation; MAFLD: Metabolic Dysfunction–Associated Fatty Liver Disease; MASH: Metabolic Dysfunction–Associated Steatohepatitis; ALD: Alcohol-Related Liver Disease; HCV: Hepatitis C Virus; T2DM: Type 2 Diabetes Mellitus; DAA: Direct-Acting Antiviral; MELD: Model for End-Stage Liver Disease.

Patients with MAFLD awaiting transplantation face distinct clinical challenges. They are more likely to present with comorbidities such as T2DM, hypertension, and CVD, which complicate both waitlist management and perioperative care [26,38]. These comorbidities contribute to higher waitlist mortality and necessitate thorough pre-transplant evaluation to optimize patient outcomes [60].

The shift from NAFLD to MAFLD/MASLD terminology has improved awareness and may facilitate more precise interventions. However, the growing burden of MAFLD as a transplant indication highlights the urgent need for tailored strategies—spanning medical optimization, surgical risk reduction, and long-term post-transplant care [20].

### *2.3. Comparison with Other Etiologies (HCV, ALD)*

LT candidates and recipients with MAFLD differ significantly from those with alcohol-related liver disease (ALD) and hepatitis C virus (HCV) infection. These differences span demographics, comorbidities, disease progression, transplant indications, and outcomes—factors that influence listing, surgical risk, and prognosis.

MAFLD patients are typically older and more often female compared to ALD and HCV cohorts. Ethnic variation also plays a role; MAFLD prevalence is highest among Hispanic populations, while ALD is more common in Caucasians [1].

Clinically, MAFLD is frequently accompanied by obesity, T2DM, and cardiovascular disease (CVD), unlike ALD and HCV, where such comorbidities are less pronounced. These conditions increase perioperative risk and contribute to long-term complications [29,61]. The disease course also differs. MAFLD progresses from simple steatosis to steatohepatitis (MASH), followed by fibrosis and cirrhosis. Importantly, HCC can develop even in the absence of cirrhosis [1,62]. In contrast, ALD and HCV tend to follow a more linear trajectory toward cirrhosis.

Transplant indications reflect these differences. While decompensated cirrhosis is common to all etiologies, MAFLD contributes disproportionately to HCC, largely driven by obesity and metabolic dysfunction [24,63]. Acute-on-chronic liver failure (ACLF) is more often seen in ALD and HCV, where systemic inflammation and rapid deterioration are typical. Although ACLF is less common in MAFLD, its management is complicated by a higher burden of metabolic comorbidities [64].

Differences also extend to post-transplant outcomes. One-year graft survival is generally favorable in patients with MAFLD; however, the comorbidity burden significantly influences long-term outcomes. HCV patients have historically had poorer outcomes; however, the introduction of direct-acting antivirals (DAAs) has significantly improved post-transplant survival [63,65,66]. These divergent trajectories emphasize the impor-

tance of etiology-specific transplant strategies, particularly in MAFLD, where metabolic complexities necessitate tailored pre- and post-transplant care.

### *2.4. Global and Regional Disparities in the Prevalence and Burden of MAFLD*

MAFLD prevalence and its clinical burden vary widely worldwide, shaped by geographic, socioeconomic, genetic, lifestyle, and healthcare access factors.

The Western Pacific region exhibits some of the highest age-standardized prevalence rates (ASPR), with Palau experiencing a steep increase between 1990 and 2019, while Brunei Darussalam has reported some of the lowest rates [67]. In the United States, prevalence is highest among Hispanics, followed by non-Hispanic Whites and non-Hispanic Blacks [68]. Globally, regions with lower sociodemographic index (SDI) scores tend to bear a greater burden, reflecting broader inequities in healthcare and prevention [69,70].

Socioeconomic status (SES) is a major determinant of MAFLD risk. Individuals with lower SES often face limited access to healthcare, poor diet, and a higher prevalence of obesity and T2DM—factors that drive the disease [71,72]. Urbanization, particularly in South Asia, has accelerated the shift toward sedentary lifestyles and increased consumption of processed foods, further fueling the rise in MAFLD [72,73].

Genetic and ethnic predisposition also contribute to disparities. Variants such as **PNPLA3 rs738409 (I148M)**, **TM6SF2 rs58542926**, and **MBOAT7 rs8736** are linked to hepatic fat accumulation and inflammation. PNPLA3 is particularly common in Hispanic populations, correlating with their elevated disease risk [74,75]. Conversely, African Americans appear to carry protective genetic variants, although these have not yet been fully characterized [74]. In Chinese populations, the combined presence of PNPLA3 and TM6SF2 variants has an additive effect, whereas in Latinos, genetic risk scores have shown promise in identifying individuals at higher risk [76,77]. **MBOAT7** has also been implicated in regulating Toll-like receptors and promoting inflammation in steatohepatitis [78], while **MERTK** has been linked to fibrosis in both hepatic and extrahepatic tissues [79].

Healthcare inequities compound these risks. Ethnic minorities often face delayed diagnosis, limited access to specialty care, insufficient insurance coverage, and systemic barriers in referral pathways [68]. These challenges contribute to worse outcomes and underrepresentation in clinical trials, further widening the evidence gap in prevention and treatment.

Efforts to reduce these disparities must include region-specific public health strategies, early screening of high-risk groups, culturally tailored lifestyle interventions, and policy measures to ensure equitable access to liver transplantation and advanced care.

## 3. Indications and Timing for Liver Transplant in MAFLD

LT in patients with MAFLD presents unique challenges due to complex comorbidities, variable disease progression, and limitations of current assessment tools. The primary indications include decompensated cirrhosis, HCC, and ACLF. However, a high comorbidity burden and suboptimal risk-stratification models complicate listing and timing decisions.

### *3.1. Indications: Decompensated Cirrhosis, HCC, and ACLF*

Decompensated cirrhosis remains the most common indication for LT in MAFLD, presenting with complications such as jaundice, ascites, hepatic encephalopathy, and variceal bleeding [26]. The MELD score is the standard tool for prioritizing these patients based on short-term mortality risk [39].

HCC represents another major indication. In MAFLD, its presentation may deviate from traditional patterns, with tumors sometimes arising in the absence of cirrhosis or advanced fibrosis. This can complicate early detection, particularly in patients with obesity

or metabolic syndrome, where imaging sensitivity may be reduced [21,80]. While the Milan criteria remain the standard for determining LT eligibility in HCC, their restrictive nature may exclude some patients who could benefit from transplantation [21]. Expanded selection criteria that incorporate tumor biology and response to locoregional therapy are under investigation [20].

### *3.2. Pathogenesis of HCC in MAFLD and Its Implications for Liver Transplantation*

Emerging data reveal a rising incidence of HCC in MAFLD, including cases in non-cirrhotic livers. This is particularly evident in individuals with obesity, T2DM, and insulin resistance—independent risk factors for liver carcinogenesis [81–83]. Pathophysiologic mechanisms include lipotoxicity-induced mitochondrial dysfunction, oxidative stress leading to DNA damage, chronic inflammation mediated by cytokines (e.g., TNF-α, IL-6), and dysregulated insulin–IGF-1 signaling, which promotes cellular proliferation and inhibits apoptosis [84,85]. Alterations in gut microbiota and adipokine signaling may further drive hepatic inflammation and tumorigenesis.

These developments pose several challenges for transplantation. Patients without cirrhosis are often excluded from routine HCC surveillance, increasing the risk of late-stage detection. Additionally, their lower MELD scores can delay listing, despite significant oncologic risk. Conventional criteria, such as the Milan classification, may inadequately reflect tumor biology, limiting access to LT for candidates with otherwise favorable prognoses. These trends underscore the need for more inclusive surveillance strategies, better risk stratification tools, and broader transplant eligibility criteria based on biological behavior rather than tumor size alone [82,86,87].

### *3.3. ACLF as an Emerging Indication*

ACLF in the context of MAFLD is increasingly recognized as a distinct clinical entity [38,64]. Its growing prevalence reflects both the global burden of metabolic dysfunction and the cumulative effect of multisystem comorbidities [26]. ACLF is characterized by rapid deterioration in liver function accompanied by extrahepatic organ failure, often progressing despite optimal medical management. Common triggers include bacterial infections and acute cardiovascular events [38]. Given its aggressive course and poor prognosis, early transplantation is essential. However, cardiovascular and metabolic comorbidities complicate risk assessment, underscoring the need for multidisciplinary evaluation [29].

### *3.4. Challenges in Timing Due to Multi-System Comorbidities*

Determining the optimal timing for LT in MAFLD is complicated by the high prevalence of comorbidities, including CVD, T2DM, CKD, frailty, and sarcopenia [29,62]. T2DM affects up to 80% of patients [26], and CKD is a strong predictor of poorer post-transplant survival [38]. CVD, including coronary artery disease (CAD) and heart failure, remains one of the most significant perioperative risks [29]. These comorbidities are not fully accounted for by MELD-based allocation, yet they contribute substantially to waitlist mortality [60].

Pre-transplant optimization is therefore critical. Interventions may include comprehensive cardiac evaluation, structured physical rehabilitation, aggressive management of obesity and metabolic risk factors, and nutritional support [26].

### *3.5. Role and Limitations of the MELD Score in MAFLD*

Since its introduction, the MELD score has significantly reduced waitlist mortality by providing an objective, laboratory-based assessment of liver disease severity [39]. However, in MAFLD patients, MELD often underestimates mortality risk because it does not incorporate extrahepatic complications such as CVD, obesity-related respiratory dysfunction, or metabolic instability [62]. Additionally, complications that are common in MAFLD, such

as refractory ascites, recurrent hepatic encephalopathy, and portal hypertension–related bleeding, are not directly captured by MELD [26], which may delay timely transplantation for patients with severe clinical impairment [38].

Modified scoring systems such as MELD-Na and MELD 3.0, which incorporate additional variables, including serum sodium, sex, and albumin, have shown improved predictive accuracy [88]. While these models may better reflect the complexity of MAFLD/MASLD, further validation is required to ensure fair organ allocation.

## 4. Pre-Transplant Evaluation: Unique Considerations in MAFLD

The pre-transplant evaluation of patients with MAFLD requires particular attention due to the interplay of metabolic, cardiovascular, respiratory, nutritional, and psychosocial factors (Figure 2). Compared with other liver disease populations, MAFLD patients frequently present with a greater burden of comorbidities, necessitating a comprehensive, multidisciplinary approach to optimize perioperative safety and long-term outcomes.

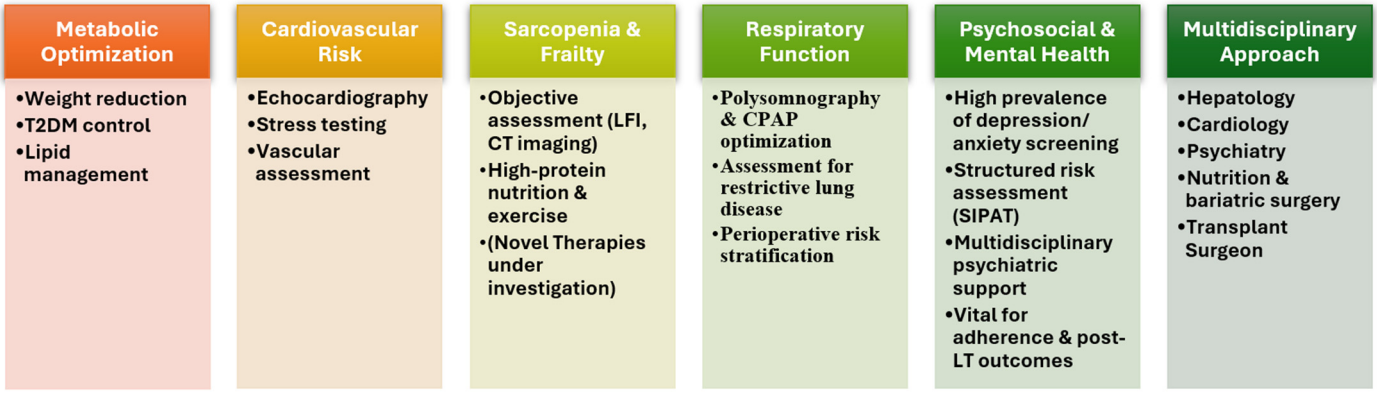


**Figure 2.** Structured pre-transplant evaluation framework tailored to MAFLD patients, emphasizing metabolic, cardiovascular, respiratory, and psychosocial domains. Footnotes: T2DM: Type 2 Diabetes Mellitus. Optimal glycemic control (e.g., HbA1c < 7–7.5%) is a primary goal to mitigate perioperative risk. Sarcopenia & Frailty: The assessment of muscle mass and physiological reserve is critical, as both are independent predictors of waitlist mortality and post-transplant survival in MAFLD. LFI: The Liver Frailty Index is a validated, performance-based tool for objective frailty assessment in liver disease cohorts. SIPAT: Stanford Integrated Psychosocial Assessment for Transplantation. A validated tool for evaluating psychosocial readiness and predicting post-transplant outcomes. Formal sleep study (polysomnography) is indicated if obstructive sleep apnea is suspected due to its high prevalence in MAFLD and its impact on cardiovascular risk. Evaluation necessitates a formal, collaborative meeting of all disciplines to synthesize findings and determine candidacy. Abbreviations: MAFLD: Metabolic dysfunction-associated fatty liver disease; CPAP: Continuous Positive Airway Pressure; SIPAT: Stanford Integrated Psychosocial Assessment for Transplantation; T2DM: Type 2 Diabetes Mellitus.

### *4.1. Diabetes and Metabolic Syndrome*

Diabetes and metabolic syndrome are strongly linked to accelerated liver fibrosis, increased risk of hepatocellular carcinoma, and worsened metabolic complications in MAFLD [89–91]. Pre-transplant diabetes is associated with higher cardiovascular mortality, increased post-transplant metabolic syndrome, and elevated risk of end-stage renal disease [38,92].

Effective management requires an integrated approach that combines lifestyle modification and pharmacological therapy [93]. Bariatric surgery—particularly sleeve gastrectomy and gastric bypass—has demonstrated substantial, sustained weight loss, improved liver histology, and reduced comorbidities in transplant candidates [94–96]. While these proce-

dures offer significant benefits, surgical risk and eligibility limitations may restrict their widespread use [95].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as liraglutide and semaglutide, have emerged as effective non-surgical options for weight and metabolic management. They reduce hepatic steatosis, inflammation, and fibrosis—even in non-diabetic patients—and are increasingly integrated into structured pre-transplant weight loss programs [97–99]. However, side effects, cost, and long-term adherence can limit their utility [100].

Achieving optimal metabolic status often requires a multidisciplinary approach involving hepatologists, diabetologists, nutritionists, and transplant surgeons (Figure 2). A coordinated strategy—combining pharmacologic, surgical, and behavioral interventions—can enhance transplant candidacy and improve both short- and long-term outcomes [22,96].

### *4.2. Cardiovascular Risk Assessment*

CVD remains a leading cause of morbidity and mortality in MAFLD patients before and after transplantation [4,37,101,102]. These patients frequently present with subclinical atherosclerosis and coronary artery disease (CAD), necessitating a thorough cardiovascular evaluation.

Non-invasive assessments such as stress echocardiography and coronary computed tomography angiography (CCTA) are commonly used to detect CAD and structural abnormalities [103]. Invasive coronary angiography is reserved for high-risk patients due to procedural risks [104]. As shown in Figure 2, accurate risk stratification informs the need for pre-transplant interventions, such as coronary revascularization, which may reduce perioperative complications [105,106].

The presence of pre-existing CVD is associated with higher rates of major adverse cardiovascular events (MACE) and lower graft and patient survival, particularly in the first year post-transplant [107]. These risks highlight the importance of close collaboration between transplant hepatology and cardiology teams throughout the evaluation process.

### *4.3. Sarcopenia and Frailty*

Sarcopenia, the loss of skeletal muscle mass and function, and frailty, defined as reduced physiological reserve, are common in ESLD and carry significant prognostic implications for MAFLD patients awaiting transplantation [108–110]. Chronic inflammation, insulin resistance, hormonal imbalances, and high comorbidity exacerbate these conditions, which are linked to higher waitlist mortality, prolonged hospitalization, and reduced post-transplant survival [111,112]. Assessment tools such as the Liver Frailty Index, CT-based muscle mass measurement, and physical performance tests help identify at-risk patients [113]. Management includes high-protein nutritional support (>1.5 g/kg/day), branched-chain amino acid supplementation, and combined resistance and aerobic exercise regimens [114]. Pharmacologic therapies such as myostatin inhibitors and testosterone replacement are under investigation as potential adjuncts (Figure 2).

### *4.4. Obstructive Sleep Apnea and Pulmonary Complications*

Obstructive sleep apnea (OSA) is highly prevalent in MAFLD due to shared risk factors such as obesity, insulin resistance, and dyslipidemia [115,116]. Intermittent hypoxia, a hallmark of OSA, may exacerbate liver injury through oxidative stress, systemic inflammation, and metabolic dysregulation [117]. The severity of OSA correlates with the degree of fibrosis and steatohepatitis, even independent of obesity [118]. Polysomnography remains the gold standard for diagnosis, and continuous positive airway pressure (CPAP) therapy has been shown to improve liver enzyme levels and metabolic parameters (Figure 2) [119]. Optimizing OSA before transplantation reduces perioperative hypoxia-

related complications. Additionally, restrictive lung disease and other pulmonary impairments may increase anesthetic risk and postoperative respiratory failure, warranting thorough respiratory evaluation [118,120].

### *4.5. Psychosocial and Mental Health Evaluation*

Psychosocial and mental health assessment is a critical component of pre-transplant evaluation in MAFLD. These patients have high rates of psychiatric comorbidities that can significantly affect candidacy and outcomes. A bidirectional Mendelian randomization study suggests MAFLD increases the risk of anxiety disorders, while major depressive disorder may predispose to MAFLD, highlighting shared causality [121]. A meta-analysis reported high prevalence of depression (26.3%), anxiety (37.2%), and stress (51.4%) among adults with NAFLD [122]. Disease severity appears to be inversely correlated with quality of life, with patients frequently experiencing fatigue, cognitive dysfunction, and psychological distress [123]. Biological links between psychiatric morbidity and MAFLD include dysregulation of the PI3K/AKT/mTOR signaling pathway, which affects both immune balance and liver disease progression [124]. In transplantation, early identification of psychosocial risk factors is vital, as depression, anxiety, poor social support, low health literacy, and substance use disorders negatively impact adherence and outcomes [125–128]. Poor psychosocial profiles are associated with higher rates of medication non-adherence, relapse, and reduced post-transplant quality of life [125,128]. Standardized tools such as the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) enable structured risk stratification (Figure 2) [129–131]. Multidisciplinary care, involving psychiatrists, psychologists, social workers, and coordinators, provides targeted interventions, including cognitive-behavioral therapy, stress management, adherence support, and tailored counseling [132,133]. Integrating psychosocial care into the pre-transplant pathway improves perioperative preparedness, adherence, and long-term outcomes. Addressing mental health early may not only optimize quality of life post-transplant but also slow disease progression prior to surgery.

### *4.6. Extrahepatic Malignancy Risk in MAFLD and Implications for Transplant Evaluation*

In addition to HCC, MAFLD is associated with an increased risk of extrahepatic malignancies, particularly gastrointestinal cancers (e.g., esophageal, gastric, colorectal, and pancreatic), as well as breast and lung cancer. Shared metabolic and inflammatory mechanisms, including insulin resistance, chronic hyperinsulinemia, systemic inflammation, adipokine dysregulation, and gut microbiota imbalance, drive this elevated oncologic risk [134,135]. Genetic and epigenetic alterations, such as activation of the PI3K/AKT/mTOR pathway, further promote carcinogenesis in this population [136]. These malignancies can influence transplant eligibility, as active or recent cancer may contraindicate listing, and even occult malignancy may impact long-term post-transplant outcomes. Consequently, expanded cancer screening, particularly for colorectal and breast cancer, may be warranted in high-risk MAFLD patients being evaluated for LT.

Importantly, recent large-scale cohort studies suggest that statin therapy may reduce the incidence of both hepatic and extrahepatic cancers in patients with MAFLD, possibly through anti-inflammatory, pro-apoptotic, and immunomodulatory effects [137]. Given their established cardiovascular benefits and emerging antineoplastic potential, statins may serve a dual protective role and should be considered as part of the comprehensive metabolic optimization of LT candidates with MAFLD.

## 5. Intraoperative and Perioperative Challenges

LT in patients with MAFLD presents distinctive intraoperative and perioperative challenges, many of which are amplified by obesity and metabolic comorbidities. These challenges include surgical technical difficulties, anesthetic and ventilatory risks, implications for graft function, early complications, and the application of novel surgical techniques designed to improve outcomes.

### *5.1. Technical Surgical Considerations Due to Obesity*

Obesity in MAFLD patients introduces significant technical hurdles during LT. A thickened abdominal wall can complicate surgical exposure and incision planning, often requiring larger incisions that increase the risk of wound-related complications [138,139]. A large, fatty liver further limits surgical manipulation and heightens the risk of parenchymal injury [38]. These anatomical difficulties contribute to higher rates of wound infection and incisional hernia, exacerbated by increased tissue tension and impaired wound healing associated with obesity [140,141]. Surgical site infections are particularly common, prolonging hospitalization and escalating healthcare costs [142,143]. In addition, fatty infiltration of perihepatic tissues may distort vascular anatomy, obscure surgical landmarks, and complicate vascular anastomoses, thereby increasing the risk of thrombosis or bleeding [141,144]. Consequently, obese recipients typically experience longer operative times and greater intraoperative blood loss compared with non-obese recipients [22,38,139,143]. Strategies such as preoperative weight optimization, meticulous operative planning, and vigilant postoperative wound management are essential to reduce these risks.

### *5.2. Anesthetic Risk and Ventilation Difficulties*

Anesthetic management in MAFLD is complicated by obesity-related anatomical challenges, cardiovascular comorbidities, and respiratory compromise. CVDs, including CAD, hypertension, and pulmonary hypertension, are highly prevalent in this population [103,144]. OSA, also common, further aggravates perioperative respiratory instability [38]. Preoperative evaluation with CAD screening, such as coronary artery calcium scoring or coronary angiography, is critical for risk stratification [103]. Intraoperatively, airway management can be challenging due to the short neck anatomy and excessive pharyngeal tissue, necessitating the availability of advanced airway devices [145]. Ventilation is further challenged by reduced chest wall compliance and increased intra-abdominal pressure, particularly during the anhepatic phase [145,146]. Protective ventilation strategies, including low tidal volumes, appropriate positive end-expiratory pressure (PEEP), and intraoperative monitoring with tools such as transesophageal echocardiography (TEE) and arterial pulse contour analysis, are recommended to maintain oxygenation and prevent barotrauma [145].

### *5.3. Impact on Graft Function and Early Complications*

MAFLD is associated with a heightened risk of early allograft dysfunction (EAD), primarily due to metabolic stress, ischemia–reperfusion injury, and the frequent presence of steatosis in donor livers [22,26]. Reported EAD incidence ranges from 10.8% to 41.3% in LT populations, with higher rates observed in patients with metabolic syndrome, high visceral adiposity, and prolonged cold ischemia times [147].

In the immediate postoperative period, patients with MAFLD are at increased risk of surgical site and opportunistic infections, reflecting impaired wound healing and an immunosuppressive state [26]. Cardiovascular events, such as myocardial infarction and arrhythmias, are also common during this period due to persistent underlying risk factors [60]. Additionally, acute kidney injury (AKI) frequently occurs, especially in patients

who develop EAD. Management strategies for AKI include careful fluid balance, avoidance of nephrotoxic medications, and, when necessary, early initiation of renal replacement therapy [148].

### *5.4. Role of Novel Surgical Techniques and Technologies*

Emerging surgical and preservation technologies offer potential benefits in the management of MAFLD LT. Minimally invasive and robotic approaches may improve surgical ergonomics and precision, especially in obese patients, while also reducing operative trauma and recovery times [149,150]. Intraoperative imaging tools, such as near-infrared fluorescence with indocyanine green (ICG), can facilitate identification of vascular and biliary structures, aiding dissection of complex anatomy [149]. Machine perfusion (MP), encompassing both hypothermic and normothermic techniques, is being explored as a strategy to optimize and recondition steatotic donor grafts, prolong preservation, and improve post-transplant graft function [151,152]. While promising, these technologies remain underutilized, and further prospective trials are needed to establish their role in the MAFLD transplant setting.

## 6. Post-Transplant Outcomes in MAFLD Patients

Metabolic comorbidities, cardiovascular risk, graft health, and long-term quality of life shape post-transplant outcomes in MAFLD recipients. Although overall survival rates are generally favorable and often comparable to other transplant indications, this population faces unique challenges, particularly regarding recurrence of disease, cardiovascular events, and metabolic complications.

### *6.1. Patient and Graft Survival Data*

MAFLD is now a leading indication for LT, reflecting the global increase in obesity and metabolic syndrome. Short-term survival outcomes are encouraging. Analyses of the SRTR database indicate that patients transplanted for MASH, a subset of MAFLD, achieve the highest 1-year graft survival compared with alcoholic cirrhosis (AC) and HCV-related liver disease [65]. As outlined in Table 3, short-term (1-year) outcomes are consistently favorable, in some studies surpassing those of other etiologies.

Intermediate survival (3–5 years) is generally comparable to, or slightly better than, that of AC and HCV, although cardiovascular mortality remains a significant concern [38,153]. Beyond five years, survival is most often limited not by graft failure but by systemic complications such as CVD, infections, and new-onset diabetes after transplant (NODAT) [154,155]. Some cohorts suggest that while MAFLD recipients outperform HCV and AC patients early after LT, HCV patients may achieve superior graft survival at longer follow-up intervals [65].

Cardiovascular events, infections, multiorgan failure, and recurrent disease are leading causes of late mortality, with recurrent steatosis being particularly common [22,60,154,155].

### *6.2. Cancers as Post-Transplant Outcomes*

The risk of developing de novo malignancies post-transplantation is notably high among MAFLD transplant recipients, primarily due to metabolic dysregulation and the necessity for long-term immunosuppressive therapy. CNIs, such as tacrolimus, are commonly used in post-transplant care but have been associated with an increased risk of malignancies, particularly non-melanoma skin cancers and upper aerodigestive cancers, due to their potential oncogenic effects and their suppression of immune surveillance [156–158]. Strategies to mitigate this risk include minimizing CNI exposure and incorporating mTOR inhibitors, such as sirolimus and everolimus, which have demonstrated antitumor properties and are associated with a reduced incidence of post-transplant malignancies [157–159].

Studies have shown that mTOR inhibitors can reduce the incidence of malignancies when used in combination with mycophenolate mofetil (MMF) or as part of a CNI-free regimen, with significant reductions in cancer rates observed in patients switched to sirolimus-based therapies [158–160]. Additionally, modifiable lifestyle factors play a crucial role in cancer prevention post-transplant. Smoking cessation, alcohol abstinence, and the management of obesity and insulin resistance are vital components of survivorship care, as these factors are linked to an increased risk of malignancy [161]. Adopting a Mediterranean-style diet and engaging in regular physical activity are recommended to optimize metabolic health, reduce cancer risk, and improve cardiovascular and graft-related outcomes [162]. Personalized immunosuppression approaches, tailored to individual risk profiles, are essential to balance graft rejection prevention with long-term oncological safety, underscoring the need for further research to optimize these regimens [156,157].

**Table 3.** Post-Transplant Outcomes in MAFLD Recipients: Survival *, Recurrence †, and Long-Term Complications.

| Outcome | Summary Findings | Key References |
| --- | --- | --- |
| **Short-Term Survival (1-Year)** * | Generally favorable; some studies report highest 1-year graft survival rates among NASH/MAFLD recipients compared to ALD and HCV | [65] |
| Intermediate-Term Survival (3–5 Years) * | Comparable or slightly better than ALD and HCV; cardiovascular mortality remains a major concern | [38,153] |
| Long-Term Survival (>5 Years) * | Outcomes often limited by cardiovascular events and metabolic complications rather than graft failure | [154,155] |
| Recurrence of MAFLD/MASLD † | High rates: steatosis ~80% at 5 years; steatohepatitis ~60.3%; progression to advanced fibrosis in ~20% | [163] |
| Major Adverse Cardiovascular Events (MACE) | Significant contributor to late mortality; strongly associated with pre- and post-transplant metabolic syndrome | [164,165] |
| New-Onset Diabetes (NODAT) ‡ | Common, driven by pre-existing insulin resistance and immunosuppressive therapy | [166,167] |
| De Novo Malignancies | Increased incidence of gastrointestinal and hormone-related cancers; linked to metabolic dysregulation and immunosuppression; mTOR/MMF-based regimens and lifestyle changes may reduce risk | [135,156–162] |
| Quality of Life | Significant improvement post-LT, but physical function may remain lower than general population; comorbidities impact outcomes | [168,169] |

Footnotes * Survival percentages are approximate pooled estimates from registry and cohort studies; exact rates vary by cohort size and geography. † Recurrence of steatosis and fibrosis assessed primarily by biopsy and imaging. ‡ NODAT = new-onset diabetes after transplant, typically defined as diabetes requiring treatment after LT in a non-diabetic recipient. Abbreviations: MAFLD: Metabolic Dysfunction–Associated Fatty Liver Disease; MASLD: Metabolic Dysfunction–Associated Steatotic Liver Disease; ALD: Alcohol-Related Liver Disease; HCV: Hepatitis C Virus; LT: Liver Transplantation; MACE: Major Adverse Cardiovascular Events; NODAT: New-Onset Diabetes After Transplant.

### *6.3. Recurrence of MAFLD Post-Transplant*

Recurrence of MAFLD after LT is frequent and clinically significant. Steatosis recurs in up to 80% of recipients within five years, with steatohepatitis recurrence rates near 60% and approximately 20% progressing to advanced fibrosis [163]. Recurrence can occur as early as the first post-transplant year.

Emerging data indicate that recurrent and de novo MAFLD affect a substantial proportion of LT recipients, with de novo disease occurring in 18% to 78% of cases [170,171]. This recurrence may follow a more aggressive course than in non-transplant patients, leading to accelerated fibrosis, cirrhosis, and eventual graft dysfunction. It also increases long-term risks of CVD and malignancy [170,171].

The pathogenesis of recurrence is multifactorial. It involves both modifiable and non-modifiable factors, including pre-transplant obesity, T2DM, dyslipidemia, post-transplant metabolic syndrome, high BMI, immunosuppressive agents (especially cyclosporine), donor liver steatosis, and systemic inflammation [38,60,170,171]. Lifestyle behaviors, particularly sedentary activity and poor diet, further contribute to disease recurrence [60]. Histologically, recurrence typically begins with simple steatosis and can progress to MASH and fibrosis [172,173].

Although some studies suggest that recurrent steatosis alone does not significantly impair long-term graft survival [165,174], progression to advanced fibrosis clearly does. This underscores the importance of early detection, risk stratification, and aggressive metabolic management. Non-invasive diagnostic tools, such as elastography and imaging-based fibrosis assessment, are increasingly used for follow-up. However, liver biopsy remains the gold standard for confirming recurrence and assessing the fibrosis stage [60].

Management strategies emphasize comprehensive metabolic control. These include lifestyle interventions (such as diet, exercise, and weight loss), individualized immunosuppressive regimens to minimize metabolic toxicity, and adjunctive pharmacologic therapies. GLP-1RAs, such as liraglutide and semaglutide, have shown promise in reducing hepatic steatosis, improving metabolic profiles, and potentially preventing MAFLD recurrence after LT [170,171]. Despite these developments, there is still no standardized, transplant-specific guideline for MAFLD recurrence prevention and treatment [170].

Given the rising prevalence of MAFLD as a primary indication for LT, the increasing recurrence rates emphasize the need for coordinated long-term follow-up strategies, multidisciplinary management, and ongoing research to enhance patient and graft outcomes [38,66].

### *6.4. Long-Term Metabolic Complications*

Long-term metabolic issues greatly affect outcomes in patients with MAFLD. CVD remains the primary cause of late mortality, with major adverse cardiovascular events closely linked to obesity, hypertension, T2DM, and metabolic problems [164,165,167]. Immunosuppressive treatments, especially CNIs and corticosteroids, worsen these risks [37].

NODAT is common, reflecting pre-existing insulin resistance, immunosuppression, and post-transplant weight gain [166,175]. Recurrent MASH also threatens graft health and may require retransplantation; risk factors include metabolic derangements, genetic predisposition, and immunosuppressive regimens [22,60,166,176]. Management strategies emphasize weight control, diet modification, physical activity, and optimization of immunosuppressive therapy to reduce metabolic side effects, as well as emerging pharmacotherapies targeting steatohepatitis and fibrosis [164,166].

### *6.5. Quality of Life (QoL) and Functional Status*

LT consistently enhances quality of life (QoL) and functional status in MAFLD recipients. Tools such as the SF-36, CLDQ, and EORTC QLQ-C30 show significant improvements compared to pre-transplant baselines, especially in physical health areas [169,177,178]. These improvements usually stabilize after the first year post-transplant, with some studies observing slight declines over longer follow-up periods [168].

Persistent comorbidities, especially obesity, T2DM, and CVD, continue to impact physical and mental health [179]. While most recipients regain independence in daily activities, fewer than half return to work, and workforce participation often declines within five years [169,180]. Structured exercise and rehabilitation programs have been proven to improve both physical function and QoL [169]. Outcomes are generally similar to those of patients transplanted for other liver disease causes, although ongoing metabolic and cardiovascular risks require ongoing intervention.

## 7. Immunosuppression Management and MAFLD

Immunosuppressive therapy is essential for preventing graft rejection in liver transplant patients, but it presents significant challenges in patients with MAFLD. These individuals commonly have pre-existing metabolic conditions such as obesity, T2DM, dyslipidemia, and hypertension. The metabolic side effects of immunosuppressants can worsen these comorbidities, increase cardiovascular risk, and accelerate disease recurrence. The primary challenge lies in achieving effective graft protection while minimizing metabolic toxicity.

### *7.1. Metabolic Consequences of Immunosuppressants*

Different immunosuppressant classes exert distinct metabolic effects that can worsen MAFLD-related comorbidities (Table 4):

- Corticosteroids are highly effective but strongly associated with post-transplant weight gain, insulin resistance, hypertension, and dyslipidemia [181–184]. Early withdrawal or maintenance at low doses reduces these complications while preserving graft integrity, especially in tacrolimus-based regimens [185,186].
- Calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporine remain the backbone of most protocols. Tacrolimus is more diabetogenic, increasing the risk of NODAT, whereas cyclosporine more prominently disrupts lipid metabolism [166,181,187,188]. Both agents contribute to hypertension and nephrotoxicity.
- mTOR inhibitors (sirolimus, everolimus) are often used as CNI-sparing agents. They may reduce the recurrence of steatohepatitis and delay fibrosis progression but can also worsen lipid profiles, induce insulin resistance, and impair wound healing [60,167,183,188].
- Antimetabolites (mycophenolate mofetil, azathioprine) are largely metabolically neutral, making them valuable adjuncts to reduce exposure to more toxic agents [188,189].

**Table 4.** Metabolic effects of immunosuppressants in liver transplant recipients with MAFLD and strategies to mitigate risk.

| Immunosuppressant Class | Key Metabolic Effects | Management Strategies † |
|---|---|---|
| Corticosteroids | Weight gain, insulin resistance, hypertension, dyslipidemia | Early withdrawal or taper to low dose; use steroid-minimization protocols |
| Calcineurin Inhibitors (Tacrolimus, Cyclosporine) | Hypertension, nephrotoxicity, hyperglycemia; tacrolimus → higher risk of NODAT, cyclosporine → greater dyslipidemia; increased risk of de novo malignancies, especially in metabolically at-risk recipients | CNI minimization strategies (dose reduction, combination with antimetabolites or mTOR inhibitors); careful monitoring of glucose and renal function; consider mTOR/MMF-based regimens to reduce long-term oncologic risk |

**Table 4.** *Cont.*

| Immunosuppressant Class | Key Metabolic Effects | Management Strategies † |
| --- | --- | --- |
| mTOR Inhibitors (Sirolimus, Everolimus) | Hyperlipidemia, insulin resistance, proteinuria, impaired wound healing | Use as CNI-sparing agents; monitor lipid profile and renal function; consider benefits for fibrosis delay and reduced HCC recurrence |
| Antimetabolites (Mycophenolate mofetil, Azathioprine) | Largely metabolically neutral * | Adjunct therapy to reduce CNI/corticosteroid exposure; valuable in high-risk metabolic profiles |

**Footnotes:** * "Metabolically neutral" indicates minimal direct impact on weight, glucose, lipids, or blood pressure but does not exclude other systemic side effects. † Management strategies should be individualized based on comorbidities, cardiovascular risk, and graft function. Abbreviations: CNI: calcineurin inhibitor; mTOR: mechanistic target of rapamycin; MAFLD: metabolic dysfunction–associated fatty liver disease; NODAT: new-onset diabetes after transplantation; HCC: hepatocellular carcinoma.

A particularly important complication is NODAT, which affects about 13% of recipients within the first year after transplant [181]. Its development involves both beta-cell toxicity and insulin resistance, most strongly associated with tacrolimus, cyclosporine, and corticosteroids [166,190]. Since CVD is already a leading cause of non-graft mortality in MAFLD, the pro-atherogenic effects of these drugs call for close monitoring and early intervention [164,182].

### *7.2. Tailored Immunosuppression Strategies*

Personalized immunosuppressive regimens are increasingly acknowledged as vital in MAFLD recipients, who frequently have significant metabolic comorbidities. Standardized protocols might expose these patients to unnecessary risks of nephrotoxicity, CVD, and recurrent graft steatosis [191–193].

Beyond metabolic risks, immunosuppressive strategies should also consider oncologic concerns. CNIs, especially tacrolimus, have been linked to a higher risk of de novo malignancies, particularly in individuals with underlying metabolic dysfunction. Including mTOR inhibitors and MMF in immunosuppressive regimens can help reduce CNI exposure and potentially lower post-transplant cancer rates [158–161]. Therefore, immunosuppressive therapy should be tailored to each patient's risk profile (Table 4):

- Steroid minimization or withdrawal protocols improve weight control and lower the incidence of NODAT, while maintaining low rejection rates [185]. These regimens also decrease the risk of cytomegalovirus infection, providing an additional benefit in metabolically fragile patients [192].
- CNI minimization strategies, often achieved by lowering tacrolimus or cyclosporine exposure in combination with anti-CD25 monoclonal antibodies, antimetabolites, or mTOR inhibitors, reduce nephrotoxicity and improve metabolic outcomes [193,194].
- Incorporation of mTOR inhibitors into CNI-based regimens may allow lower CNI exposure, potentially improving blood pressure and kidney function [194]. Their antiproliferative properties may also lower HCC recurrence and slow fibrosis, though careful monitoring for hyperlipidemia and wound complications is essential [193,194]. However, this combination is not without drawbacks. Co-administration of CNIs and mTOR inhibitors has been associated with an increased risk of adverse events, including delayed wound healing, proteinuria, oral ulcers, and dyslipidemia. Furthermore, some studies suggest a potential rise in acute rejection rates and nephrotoxicity when dosing is not properly balanced [195,196]. These limitations underscore the need for careful monitoring and individualized risk-benefit assessment when implementing dual immunosuppressive regimens.

Overall, tailoring immunosuppression in MAFLD should aim to limit drug-induced metabolic injury, prevent cardiovascular events, and reduce the likelihood of recurrent graft steatosis or progression to steatohepatitis, while maintaining effective protection against rejection.

## 8. Allocation and Ethical Considerations

The allocation of donor livers for patients with MAFLD raises complex ethical and clinical challenges. Obesity, advanced age, and cardiometabolic comorbidities not only complicate perioperative and post-transplant management but also intersect with broader debates on equity, resource allocation, and policy development in LT.

### *8.1. Equity in Access: Impact of Obesity, Age, and Comorbidities*

Obesity remains a major barrier to LT listing, with many centers applying strict BMI cutoffs due to increased perioperative risk, including longer operative times, higher rates of wound infections, biliary complications, and post-transplant metabolic syndrome [197]. These policies are supported by evidence of higher complication rates and reduced long-term survival among obese recipients [143]. Advanced age and comorbidities, particularly CVD and T2DM, further limit transplant eligibility, even in patients with high MELD scores [26,38]. Collectively, these risk factors often result in exclusion from waitlists, highlighting the need for comprehensive pre-transplant metabolic and cardiovascular optimization [153].

### *8.2. Allocation Policy Debates: BMI and Transplant Eligibility*

The Lack of a standardized, evidence-based consensus on BMI thresholds for LT eligibility has resulted in considerable variation in clinical practice. Cutoffs typically range from 35 to 40 $kg/m^2$, although these are not universally applied and may differ between transplant centers and countries [198,199]. Advocates of BMI restrictions point to increased perioperative morbidity, longer hospital stays, and higher healthcare costs [143], as well as reduced long-term graft survival [38]. Conversely, emerging data suggest that carefully selected obese recipients with controlled metabolic profiles can achieve outcomes comparable to non-obese patients [200]. Alternative metrics such as waist circumference, body composition analysis, and frailty assessment may better predict perioperative risk and long-term outcomes [138,201]. Incorporating these parameters could foster more individualized and equitable selection processes.

### *8.3. Disparities in Access and Outcomes*

Transplant disparities in MAFLD extend beyond BMI and comorbidity thresholds, with race, ethnicity, and SES significantly influencing access and outcomes. Black patients continue to experience lower listing-to-ESLD death ratios compared with White patients, while Hispanic patients paradoxically exhibit superior post-transplant survival despite socioeconomic disadvantage—a phenomenon termed the "Hispanic Paradox" [202,203]. Lower SES is strongly associated with reduced access to pre-transplant evaluation, higher waitlist mortality, and poorer long-term survival due to challenges with medication adherence and higher rates of hospital readmission [204]. Additionally, patients from disadvantaged communities exhibit poorer long-term survival, partly due to difficulties adhering to complex post-transplant regimens and higher rates of readmission [205]. Addressing these disparities requires culturally tailored care models, patient education programs, and financial support initiatives to reduce systemic inequities [206].

*8.4. Role of Pre-Transplant Interventions in Shaping Allocation Decisions*

Pre-transplant interventions, particularly bariatric surgery and structured lifestyle programs, are increasingly recognized as strategies to expand transplant eligibility in obese MAFLD patients. Bariatric procedures, such as laparoscopic sleeve gastrectomy, can induce sustained weight loss, improve obesity-related comorbidities, and reduce cardiovascular risk, with evidence supporting lower postoperative complications and improved survival in cirrhotic patients [207–209]. Similarly, multidisciplinary programs integrating diet, exercise, and pharmacotherapy (e.g., GLP-1 receptor agonists) have facilitated significant weight reduction and enabled listing eligibility in previously excluded patients [210]. While these interventions improve outcomes, ethical concerns persist regarding access inequities, as patients with limited healthcare resources may be disproportionately disadvantaged by requirements for pre-transplant weight loss [197]. Nonetheless, accumulating evidence supports their role in improving post-transplant prognosis, making them an important consideration for future allocation frameworks [210,211].

Thus, allocation policies for MAFLD must strike a balance between risk reduction and equitable access, moving beyond rigid BMI thresholds, addressing socioeconomic disparities, and incorporating structured pre-transplant interventions into future frameworks.

## 9. Future Directions and Emerging Research

The growing prevalence of MAFLD has intensified the demand for LT. However, donor organ availability remains limited, and a substantial proportion of potential grafts, particularly steatotic livers, are discarded due to concerns over primary non-function and poor post-transplant outcomes. These challenges have driven advances in several key areas, including biomarker development, novel weight-loss interventions, machine perfusion technologies for marginal graft utilization, and the integration of genetics and precision medicine into patient selection and management (Figure 3).

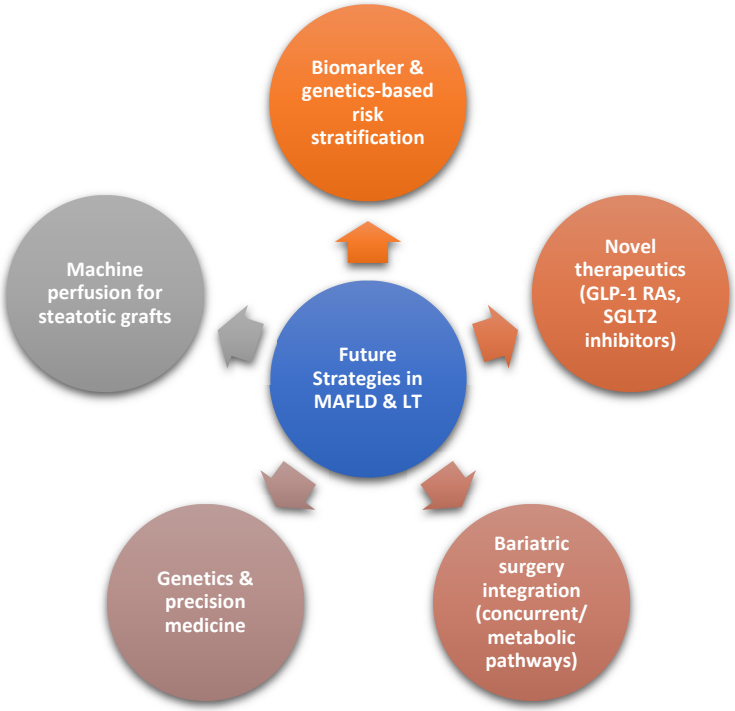


**Figure 3.** Emerging strategies to optimize outcomes in MAFLD-related transplantation, reflecting a shift toward precision medicine and integrated metabolic care. **Footnotes: GLP-1 RAs:** Glucagon-like peptide-1 receptor agonists (e.g., semaglutide, liraglutide). SGLT2 inhibitors: Sodium-glucose

cotransporter-2 inhibitors (e.g., empagliflozin, dapagliflozin). Steatotic graft assessment and resuscitation techniques, such as normothermic regional perfusion (NRP) and hypothermic oxygenated perfusion (HOPE), are key applications. Abbreviations: GLP-1 RA: Glucagon-like peptide-1 receptor agonist; LT: Liver Transplantation; MAFLD: Metabolic dysfunction-associated fatty liver disease; SGLT2i: Sodium-glucose cotransporter-2 inhibitor.

### *9.1. Role of Biomarkers and Non-Invasive Testing Pre- and Post-Transplant*

Non-invasive diagnostic and prognostic tools are increasingly shaping the management of MAFLD in LT candidates and recipients. Imaging techniques, such as transient elastography (FibroScan) and magnetic resonance elastography (MRE), enable an accurate, non-invasive assessment of liver fibrosis, thereby reducing the reliance on liver biopsy. FibroScan provides a rapid, bedside evaluation; however, its accuracy may be reduced in obese patients. In contrast, MRE provides greater precision but is limited by cost and availability [212,213].

Biomarker-based panels, including the Fibrosis-4 (FIB-4) index, NAFLD Fibrosis Score (NFS), and Enhanced Liver Fibrosis (ELF) test, have been validated for fibrosis staging and longitudinal monitoring [214,215]. Post-transplant, these tools support the detection of recurrent steatosis and steatohepatitis, reducing the need for repeat biopsies [22,60]. Emerging biomarkers, such as specific microRNAs and inflammatory mediators, hold promise for early detection of graft steatosis and for tailored post-LT immunometabolic management [216]. Combining imaging and biomarker data may improve risk stratification, guide therapeutic interventions, and enhance both graft and patient survival [217].

### *9.2. Weight Loss Therapies and Metabolic Interventions Pre-Transplant*

Pre-transplant metabolic optimization is an evolving focus, with promising results from both pharmacological and surgical interventions. GLP-1 receptor agonists such as semaglutide and liraglutide have demonstrated significant weight loss and metabolic improvements in patients with MAFLD, including reductions in BMI, waist circumference, hepatic inflammation, and cardiovascular risk markers [218,219]. Tirzepatide, a dual GLP-1/GIP agonist, has shown even greater efficacy for weight loss [220]. Although SGLT2 inhibitors are less studied in this context, early data suggest potential benefits for glycemic control and weight reduction. Bariatric surgery, particularly laparoscopic sleeve gastrectomy, has proven effective for achieving sustained weight loss, improving obesity-related comorbidities, and enhancing transplant eligibility [207,208]. In MAFLD-related cirrhosis, pre-LT bariatric surgery has been associated with fewer postoperative complications and better survival [209]. Multidisciplinary lifestyle modification programs, sometimes combined with pharmacotherapy, have facilitated clinically significant weight loss in high-BMI candidates, enabling transplant listing in a substantial proportion [100]. While the development of novel pharmacotherapies such as incretin-based and thyroid hormone receptor agonists represents an exciting advancement in MAFLD management, their detailed discussion is beyond the scope of this transplantation-focused review, which centers on pre- and post-transplant challenges.

While these strategies are effective, their integration into standard LT protocols remains inconsistent, and further multicenter research is needed to confirm generalizability and long-term benefits.

### *9.3. Machine Perfusion and Marginal Grafts in MAFLD Patients*

The shortage of suitable donor livers has been exacerbated by the increasing prevalence of steatotic grafts, particularly in the era of rising obesity and MAFLD [221]. Traditionally, grafts with significant macrovesicular steatosis are discarded due to higher rates of early graft dysfunction and failure [22]. Machine perfusion technologies, both normothermic

(NMP) and hypothermic (HMP), are emerging as viable solutions for reconditioning these marginal organs. NMP maintains the liver at physiological temperature while delivering oxygen and nutrients, thereby reducing ischemia–reperfusion injury, extending preservation time, and enabling real-time functional assessment [222,223]. HMP, performed at low temperatures, offers preservation benefits, though its capacity for reconditioning steatotic livers is more limited [151]. Clinical studies have shown that NMP increases the utilization of macrosteatotic grafts from 56.4% to 86.1% without compromising survival [224] and can reduce early allograft dysfunction and biliary complications [225]. Experimental work suggests that prolonged NMP may even reduce hepatic fat content, or "defatting," potentially converting previously unusable grafts into viable ones [226]. While these technologies hold great promise, widespread adoption is limited by cost, technical complexity, and the need for standardized protocols.

### *9.4. Genetics and Precision Medicine Approaches*

Genomics is poised to transform the management of MAFLD in LT candidates and recipients by enabling more accurate risk prediction and personalized therapy. Polygenic risk scores (PRS), which aggregate the effects of multiple genetic variants, have been shown to stratify risk for liver disease progression [227,228]. Variants in PNPLA3 and TM6SF2, among others, are strongly associated with hepatic fat accumulation, fibrosis, cirrhosis, and HCC, and are increasingly incorporated into predictive models [229]. Integrating genetic data with clinical and biochemical markers may enhance the selection of pre-transplant interventions and inform post-transplant surveillance [230,231]. Genetic-based algorithms are also being explored for non-invasive diagnostics, potentially allowing earlier and more targeted management of high-risk patients [232]. In the realm of pharmacogenomics, tailoring immunosuppressive regimens to a patient's genetic profile could minimize adverse effects and optimize graft outcomes [233]. Experimental therapies, such as gene silencing for PNPLA3, represent an emerging frontier in targeted treatment for MAFLD [234]. Although these advances are promising, challenges include robust validation of genetic tools, integration into routine clinical workflows, and ensuring equitable access to precision medicine.

Overall, future research in MAFLD and LT will likely focus on refining non-invasive diagnostics, expanding the therapeutic toolbox for pre-transplant optimization, leveraging machine perfusion to utilize marginal grafts, and integrating precision genomics into patient care. The convergence of these innovations holds the potential to address both the clinical and ethical challenges of transplantation in this rapidly growing patient population.

## 10. Conclusions

MAFLD has firmly established itself as a leading driver of LT, introducing a complex clinical landscape that spans the entire transplant continuum. The rising prevalence of obesity, T2DM, and metabolic syndrome, now affecting both adult and pediatric populations, has amplified the demand for LT, while simultaneously introducing new perioperative risks, allocation dilemmas, and long-term complications, including CVD and de novo malignancies.

Despite these multifactorial challenges, the transplant community has made significant strides in developing pre-transplant weight management strategies (e.g., GLP-1 receptor agonists and bariatric surgery), refining risk stratification, and individualizing immunosuppressive regimens to reduce oncologic and metabolic burden. Machine perfusion has further improved the utility of steatotic donor livers, offering a solution to the widening gap between organ supply and demand.

Multidisciplinary collaboration remains essential—not only among hepatologists and transplant surgeons but also involving endocrinologists, oncologists, cardiologists, and nutrition experts—to ensure comprehensive care across the lifespan. Special attention must be given to the early onset and aggressive progression of MAFLD in children and adolescents, which will shape future transplant trends and long-term outcomes.

Moving forward, innovation in both clinical practice and policy is critical. This includes integrating non-invasive diagnostics, expanding access to metabolic optimization protocols, and applying genomic and biomarker-driven tools to tailor immunosuppression and surveillance. At the same time, robust, prospective, multicenter studies are urgently needed to validate emerging therapies, optimize long-term outcomes, and address persistent evidence gaps.

By embracing these strategies, the transplant field can evolve to meet the growing demands of MAFLD with precision, equity, and improved patient-centered outcomes.

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