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MINIREVIEWS

Metabolic associated fatty liver disease: Addressing a new era in liver transplantation

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Abstract

Metabolic associated fatty liver disease (MAFLD), previously termed non-alcoholic fatty liver disease, is the leading global cause of liver disease and is fast becoming the most common indication for liver transplantation. The recent change in nomenclature to MAFLD refocuses the conceptualisation of this disease entity to its metabolic underpinnings and may help to spur a paradigm shift in the approach to its management, including in the setting of liver transplantation. Patients with MAFLD present significant challenges in the pre-, peri- and post-transplant settings, largely due to the presence of medical comorbidities that include obesity, metabolic syndrome and cardiovascular risk factors. As the community prevalence of MAFLD increases concurrently with the obesity epidemic, donor liver steatosis is also a current and future concern. This review outlines current epidemiology, nomenclature, management issues and outcomes of liver transplantation in patients with MAFLD.

Key Words: Fatty liver; Metabolic associated fatty liver disease; Non-alcoholic fatty liver disease; Liver transplantation; Cirrhosis; Metabolic syndrome

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Core Tip: Metabolic associated fatty liver disease (MAFLD), previously termed non-alcoholic fatty liver disease, is the leading global cause of liver disease and is becoming the most common indication for liver transplantation. Several challenges exist in the pre-, peri-and post-liver transplant setting for patients with MAFLD, which mostly relate to comorbid medical conditions, obesity and cardiovascular risk. Donor

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liver steatosis is also an increasing concern. In this review, we summarise the current literature and provide an approach to address the current challenges of MAFLD and liver transplantation.

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INTRODUCTION

Metabolic associated fatty liver disease (MAFLD), previously termed non-alcoholic fatty liver disease (NAFLD), has emerged as the most common cause of liver disease globally[1]. With the expanding epidemic of obesity worldwide[2], MAFLD is becoming an increasingly burdensome condition, both clinically and economically[3,4]. The global prevalence of MAFLD was estimated at 25% in 2013, rising from 15% in 2005[1]. Obesity and type 2 diabetes mellitus (T2DM) coexist in 51%-60% and up to 76% of individuals with MAFLD, respectively. The peak age group affected is 45-62[1], however it is also a disease of the older patient, with over 40% of people over the age of 60 years affected[5].

The term MAFLD encompasses all fatty liver disease states, which aligns with the traditional view that NAFLD represents a spectrum of liver disease associated with insulin resistance, starting with pure "benign" steatosis (NAFL), through to non-alcoholic steatohepatitis (NASH)[6], which is the inflammatory state that can lead to advanced fibrosis or cirrhosis. The community prevalence of NASH is estimated to be between 1.5% to 6.5%, however, data are sparse due to the reliance on liver biopsy for diagnosis[7]. NASH is more rapidly progressive than benign steatosis, with fibrosis progression occurring at approximately one fibrosis stage every seven years for NASH and every 14 years for NAFL[8]. A subgroup of "rapid progressors" has been proposed in NASH, with 21% of patients in the same study without significant fibrosis progressing to F3/F4 fibrosis over median of 5.9 years. Once cirrhosis is established, time to decompensation is variable but it is estimated that 10%-39% of patients with cirrhosis will decompensate within five years[9-11]. The hepatocellular carcinoma (HCC) risk in MAFLD cirrhosis is estimated to be 6.7% at 5 years, and 15% at 10 years[12]. This variability in the natural history of NAFLD has driven the recent proposition to rename this disease entity as MAFLD, which we have adopted for the majority of this review. There are currently no approved pharmacological therapies that have been proven to effectively halt disease progression in terms of decompensation or HCC development.

Liver transplant (LT) is the major therapeutic intervention in well-selected patients with MAFLD-related advanced liver disease and has a 5-year survival of 85%[13]. The main indications for LT in MAFLD are clinical decompensation or HCC. MAFLD is the fastest rising indication for LT in the United States, the second most common indication for LT overall and the leading indication in female LT recipients[14,15]. Similar trends have also been observed in Europe, Australia and New Zealand[16,17]. The association of MAFLD with obesity, the metabolic syndrome, advancing patient age and cardiovascular morbidity poses several unique challenges in the setting of liver transplantation. This review aims to summarise current data regarding liver transplantation and MAFLD by exploring the pre-, peri- and post-transplant considerations in this patient group.

NOMENCLATURE

While the term NAFLD has been used since the 1980s to describe fatty liver disease in the absence of significant alcohol intake or other causes of steatogenesis[18,19], it does not adequately describe the underlying pathogenic factors that drive the disease process. NAFLD is heterogenous, with a multitude of factors influencing disease severity and natural history, including age, sex, ethnicity, alcohol intake, dietary habits, hormonal status, genetics and epigenetics, microbiota and metabolic status. At an individual level, disease phenotype is shaped by the dynamic interplay between genetics,

metabolic status and environment, and the predominant driver is different between individuals with the same overarching disease. This heterogeneity is clinically important when considering the natural history of disease, non-invasive assessment of fibrosis, applicability of animal modelling and the generalisability of clinical trials. Furthermore, the term NAFLD has derogatory connotations with the use of terms "alcoholic" and "fatty", which may imply blame on the patient for their condition and create stigma. These factors have sparked a revision of the definition and nomenclature of NAFLD, with four aspects cited as main factors in support of a change[20]; that this disease should be diagnosed by inclusion rather than exclusion, that its name should not be directly linked to alcohol, that dichotomous stratification into NASH and non-NASH can be misleading, and that considering disease heterogeneity is vital when approaching management or the design and interpretation of clinical trials.

Recent survey results from an international expert consensus panel reported that the majority panel members believed the terminology should be updated, and that the words "metabolism", "fat", and "liver" should be included in disease nomenclature[21]. Metabolic associated fatty liver +/- disease (MAFL/MAFLD) emerged as the most preferred term, acting as an "umbrella term" for the heterogeneity of disease and reflecting metabolic factors as the major driver of the disease, rather than a lack of alcohol. The proposed criteria for a positive diagnosis of MAFLD are based on histological, imaging or blood biomarker evidence of hepatic steatosis, in addition to the presence of at least one of the following: Obesity, T2DM, or metabolic dysregulation[20]. Hence, this diagnosis can exist regardless of alcohol consumption or other co-existing liver diseases. Renaming fatty liver disease and refocusing the conceptualisation of the disease process to its metabolic underpinning may help to spur a paradigm shift in the approach to its management; in research design and targets, system-wide interventions, funding and public and patient perception[19]. For the purpose of this review, we have used MAFLD in place of NAFLD, particularly as MAFLD is yet to be accepted universally[22] and the term NASH has been removed in the new nomenclature. The term NASH dominates the literature in the setting of LT, reflecting a progressive phenotype of disease and hence we have continued to use NASH as used in the cited studies. We acknowledge and support that this change in nomenclature to MAFLD could be valuable in highlighting the added complexities of managing metabolic disease in pre-, peri- and post-transplant settings (Figure 1).

METABOLIC ASSOCIATED FATTY LIVER DISEASE AND TRENDS IN LIVER TRANSPLANTATION

Chronic Hepatitis C virus (HCV) infection has previously been the leading global indication for LT. However, with the advent of direct acting antivirals (DAAs), this landscape is dramatically changing. It is anticipated that MAFLD related cirrhosis and HCC will become the leading indication for LT within the next decade[23,24]. Even before the widespread use of DAAs for HCV, MAFLD was the most rapidly rising etiology in LT recipients in the United States, increasing four-fold from 2002 to 2012[25]. NASH has now emerged as the second leading etiology of chronic liver disease for LT recipients in the United States. Examination of United Network for Organ Sharing and Organ Procurement and Transplantation (UNOS/OPTN) data from 2004 to 2013 found that new waitlist registrants with NASH increased by 170%, compared with 45% for alcohol related liver disease (ALD) and 14% with HCV[26]. The Australia and New Zealand Liver and Intestinal Transplant Registry reports that the proportion of patients transplanted for MAFLD has increased from 8.0% to 10.2% from 2012 to 2018, compared with a reduction from 33.8% to 13.3% for HCV[13]. European Liver Transplant Registry (ELTR) rates of LT for NASH have increased from 1.2% in 2002 to 8.4% in 2016[27]. UNOS/OPTN data also found that NASH is now the leading indication for LT in females, increasing by 91% from 2004 to 2016[15]. In men, NASH increased by 120% over the same period, second only to alcohol related liver disease[15].

MAFLD has also emerged as the fastest growing cause of HCC in LT candidates. On the basis of Scientific Registry of Transplant Recipients (SRTR) data from 2002-2016, the proportion of NASH in HCC in LT candidates increased sevenfold over that time period, from 2.1% to 16.2%, while the proportion with HCV and ALD remained stable. While HCV remains the leading etiology of HCC in waitlisted candidates at 48% in 2017, NASH is now the second leading etiology at 18%, compared with 2% in 2002[14]. Data from the UNOS/OPTN registry demonstrate similar results, with the number of

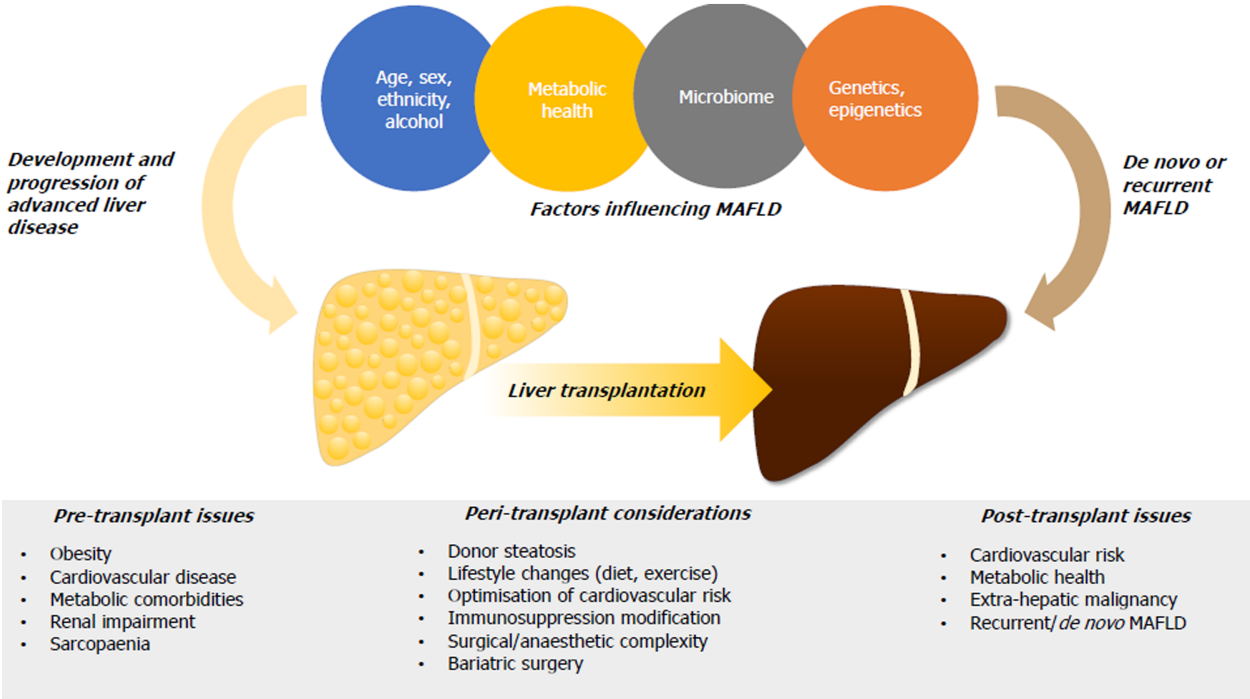

Figure 1 Metabolic associated fatty liver disease and the influence on liver transplantation. MAFLD: Metabolic associated fatty liver disease.

patients undergoing LT for HCC secondary to NASH increasing 4-fold from 2002 to 2012, representing 13.5% of patients in 2012, second only to HCV at 49.9%[25]. In Europe from 2002-2016, 39.1% of patients transplanted for NASH had HCC compared with 28.9% of non-NASH patients[27]. In Australia and New Zealand, similar trends have been observed with NASH associated HCC increasing from 4% of LTs performed in 2004 to 14% in 2017[28].

MAFLD may pose specific challenges on the LT waiting list. A study using UNOS/OPTN data[26] reported that ALD patients were least likely to survive on the waiting list at one year [likely because of higher Model for End Stage Liver Disease (MELD) scores at time of registration]. However, after adjusting for MELD, patients with ALD, HCV or a combination of the two were more likely to survive 90 d on the liver LT waitlist compared with NASH patients. Similar outcomes were also demonstrated at one year.

An important factor in considering longer term data trends in MAFLD and transplantation is the recognition that the majority of patients formerly diagnosed with cryptogenic cirrhosis (CC) likely had "burnt out" NASH[26,29]. Whether the waitlist and post-transplant outcomes for CC can now be considered interchangeable with NASH remains controversial. Golabi *et al*[30] used SRTR data from 1994 to 2016 to compare outcomes of patients listed or transplanted for NASH or CC in the United States. NASH and CC accounted for 12.5% of total listings; the term NASH was not used until 2004 and became more prevalent than CC by 2009. The total CC + NASH rate increased from 8.3% in 2012, to 19.5% in 2016. Interesting, there was almost no pre-transplant diabetes recorded in any liver transplant patients prior to 2004, possibly as LT recipient selection was historically more restrictive in terms of comorbidities. After 2004, diabetes was found at rate of 40%-55% in NASH diagnoses, 30%-35% in CC diagnoses and 14%-18% in other chronic lung disease (CLD) controls. A similar trend was seen for obesity, although unlike diabetes, the rates of obesity in CC were stable pre- and post-2004. As the rates of metabolic syndrome were considerably higher in CC patients *vs* other CLD controls, the authors concluded that a large proportion of CC patients listed for LT have underlying NASH. Post-transplant diabetes was similar in the CC and NASH group, and higher than other CLD controls, inferring that the same metabolic risk underlies liver disease in CC *vs* NASH. Post-transplant outcomes were similar in patients whether CC or NASH was the listing diagnosis. In contrast, in an analysis of Australian registry data from 1994-2017, the phenotypic profiles of NASH and CC were examined, and NASH patients has a significantly higher proportion of diabetes (50% *vs* 16%), hypertension and coronary artery disease, as well as a higher mean body weight at time of LT (93.8 *vs* 68.1 kg), suggesting a low misclassification rate[28]. With the evolution of MAFLD as a diagnosis of inclusion,

future classification of MAFLD patients in these databases could be much clearer.

PRE-TRANSPLANT ASSESSMENT

Several predisposing factors for MAFLD have been identified (Figure 1), however, not all have clinical relevance in the setting of pre-LT assessment. Established genetic polymorphisms associated with MAFLD progression such as *PNPLA3* (patatin-like phospholipase domain-containing protein) and *TM6SF2* (transmembrane 6 superfamily member 2) are not routinely screened for, but may have some influence on post-LT steatosis[31,32]. Similarly, the role of epigenetic factors and the microbiome, beyond traditional metabolic risk factor assessment and modification, are yet to be elucidated in the assessment candidates for LT[21].

As MAFLD often co-exists with metabolic syndrome components and is associated with increased cardiovascular risk, careful evaluation of comorbidities is paramount in pre-LT assessment. Aggressive risk factor modification should be initiated or continued on the waiting list where possible. However, there are scant data to support a specific strategy for the management of comorbidities in MAFLD patients compared to other etiologies. An approach to MAFLD and LT is presented in Table 1.

Cardiovascular disease

The presence of MAFLD carries a significant risk of cardiovascular disease, which is the most common cause of death in this group. Whether MAFLD per se is an independent driver of cardiovascular disease remains contentious[33], the degree of hepatic fibrosis is clearly proportional to cardiovascular risk. A large meta-analysis of 16 studies with over 34000 participants found that the presence of MAFLD was associated with a 64% increased risk of fatal and non-fatal cardiovascular events over a median of seven years follow up, with risk increasing with severity of liver disease, however traditional cardiovascular risk factors were not controlled for[34]. Another large study of European primary care databases found that after adjusting for age, sex, smoking and classic metabolic risk factors (hypertension, T2DM, high cholesterol and statin use), there was no positive association between MAFLD and myocardial infarction or stroke, concluding that cardiovascular risk assessment in adults with MAFLD should be conducted in the same way as for the general population[35]. A single-centre retrospective study of 115 NASH patients undergoing LT, compared to 127 controls with ALD, found that patients with NASH were 4-fold more likely to have a cardiovascular event in the first year after LT, even when controlling for traditional risk factors. The majority (70%) of these events occurred in the post-operative period. There was no difference between patient, graft or cardiovascular mortality between the groups[36].

Whether driven by MAFLD itself or traditional risk factors, patients with advanced liver disease being considered for LT are at great risk of clinically evident or sub-clinical cardiovascular disease. The aim of pre-transplant assessment is to diagnose and manage this pre-LT[37], in particular coronary artery disease, portopulmonary hypertension, and myocardial disease. However, there is currently insufficient evidence to recommend a specific approach to pre-LT cardiovascular assessment in the MAFLD population. A combination of stress-testing, cardiac imaging and invasive angiography may be often required, however the approach to assessment is generally dictated by local protocols and cardiology expertise[38].

Diabetes, hypertension and dyslipidemia

The presence of pre-transplant diabetes has an adverse effect on mortality, with or without MAFLD. An analysis of SRTR data between 1994 and 2013 found that 11.2% of 85194 LT recipients had pre-transplant diabetes. Diabetes pre-LT was found to be an independent predictor of LT recipient mortality with an adjusted hazard ratio of 1.21 (95%CI: 1.12-1.30)[39]. An Australian multicentre cohort study of 617 patients undergoing LT, pre-LT diabetes was associated with reduced post-transplant survival (hazard ratio: 1.89, 95%CI: 1.25–2.86), whereas obesity, hypertension, dyslipidemia, and the metabolic syndrome itself were not. Obese diabetic patients had longer intensive care and hospital stays than non- obese diabetic or obese, non-diabetic patients. The impact of diabetes and obesity was greater in older patients and those with HCC[40]. These results were not specific to patients with NASH as the indication for LT. Optimal glucose control is paramount in the pre- and peri-LT setting, in light of increased postsurgical complications with poor glucose control[41].

While management of the modifiable risks of diabetes, hypertension and

Table 1 Approach to metabolic associated fatty liver disease in the transplant candidate

Management stage	Challenges	Considerations	Approach
Pre-transplant	Cardiovascular disease	Most common cause of death in MAFLD patients; Older patients with multiple comorbidities driving cardiovascular risk, disease may be subclinical; Pharmacologic optimisation of risk factors can be limited by liver dysfunction *e.g.*, statins, beta blockade, anti-platelets agents	Rigorous pre-transplant assessment including stress echocardiography and coronary angiography in high risk patients; Risk factor modification as per general population
	T2DM	Pre-LT diabetes associated with reduced survival post-LT; Poor glycemic control immediately pre-LT and peri- LT increases surgical complications	Tight glycemic control during waitlist period and peri-operative; Multidisciplinary approach to diabetic management
	Renal dysfunction	Multifactorial in MAFLD, with hypertension and T2DM; Even mild disease at time of LT associated with higher risk of all-cause and cardiovascular mortality	Prevent even small deterioration in renal function prior to LT; Consider simultaneous liver kidney transplant where indicated
	Nutrition	Pre-LT nutrition has major influence on post-LT morbidity, mortality and hospital stay; Assessment is difficult in obese patients and those with ascites; Sarcopenic obesity and myosteatosis are common. Risk factors for long term mortality	Specialist nutritional consultation prior to transplant with assessment for sarcopenia; High energy, high protein diet with enteral feeding if required
Peri-operative	Obesity	More common in MAFLD than other etiologies; Peri-operative challenges *e.g.*, surgical technique, wound infection and dehiscence, biliary complications; Balancing healthy weight loss in pre-LT period with muscle loss and sarcopenia; Exercise often limited by frailty and possible transient increases in portal pressure with excessive strain	Controlled weight loss in pre-LT period ensuring protein requirements met. Very low-calorie diets not recommendedBariatric surgery pre-LT or simultaneously with LT in highly selected patients. Sleeve gastrectomy preferred over laparoscopic banding or gastric bypass
	Donor steatosis	Donor steatosis > 30% is a risk factor for primary graft non-function and graft loss; Balancing risk of complications with steatotic donors against organ availability and demand	Assessment of hepatic steatosis at all stages of organ procurement; Future possibilities with machine perfusion and liver reconditioning
	Cardiovascular risk	NASH patients more likely to have cardiovascular events in the post-operative period	Careful pre-operative assessment to predict risk; Close perioperative monitoring
Post-transplant	Recurrent MAFLD	Due to non-dynamic genetic, metabolic and behavioural factors, 50% of MAFLD transplant recipients have recurrent MAFLD post-LT	Choice of less diabetogenic immunosuppression regimen *e.g.*, steroid free protocols, CNI sparing; Lifestyle and behavioural modification and traditional risk factor modifications *e.g.*, hyperlipidemia, hypertension as per general population
	De novo MAFLD	Contributors to new MAFLD post-LT include diabetogenic medications *e.g.*, CNI, steroids, obesity related to steroids, inactivity and return of appetite	As above

MAFLD: Metabolic associated fatty Liver disease; LT: Liver transplant; T2DM: Type 2 diabetes mellitus; CNI: Calcineurin inhibitor.

dyslipidemia in the pre-transplant setting is vital, there is no evidence to suggest that the approach should be different in or specific to the MAFLD patient as opposed other etiologies, although the prevalence of these comorbidities may be higher[38].

Renal dysfunction

Renal dysfunction in MAFLD is often multifactorial, with concomitant hypertension and T2DM as common risk factors for chronic kidney disease in addition to the spectrum of hepatorenal syndrome seen in end stage liver disease. Renal dysfunction is an important risk factor for post-LT cardiovascular disease and mortality, with even mild renal disease at the time of LT being associated with higher risk of all-cause and cardiovascular mortality, independent of measured confounders[42]. This study also showed that each five-unit reduction in estimated glomerular filtration rate was associated with a 2% higher risk of all-cause mortality and 5% higher hazard ratio of cardiovascular mortality. Based on UNOS/OPTN data, NASH is the most rapidly growing indication for simultaneous liver kidney transplant (SLKT)[43,44]. NASH and CC accounted for 22% of all SLKT in 2011, compared with 9% in 2002[43]. While patient and liver graft outcomes are similar in NASH plus CC compared to other etiologies, the risk of kidney graft loss at five years has been reported as over 1.5 fold higher in NASH patients after controlling for recipient characteristics[44]. In the pre-transplant setting, the goal is to prevent small deteriorations in renal function prior to transplant and to consider SLKT where indicated[38].

Obesity

Obesity is a common pre-LT issue in patients with MAFLD and results in added complexities that include managing sarcopenic obesity, the assessment of obesity with fluid overload and considerations regarding bariatric surgery. As well as the correlation of obesity with traditional cardiovascular comorbidities, obesity presents potential peri-operative challenges that include technical surgical issues, wound infection, wound dehiscence and biliary complications[45,46]. However, obesity does not appear to have a clear adverse effect on mortality[47,48]. Between 2002 and 2011, 33% of LT recipients in the United States were classified as obese using body mass index (BMI) compared to 20% in the period between 1988 and 1996[49,50]. The presence of ascites confounds BMI, and when corrected for 11%-20% of patients were reclassified to a lower BMI classification in one study of 1330 LT recipients. This study also showed that patient and graft survival were similar across all BMI categories[47]. Interestingly, overweight and class 1 obese patient had better survival compared to those with normal BMI values, even after adjustment for both ascites and albumin levels. Setting strict BMI cut-offs for LT candidacy remains controversial, and there are limited data to guide this[45]. Class I-III obesity alone does not currently contraindicate LT[38,46]. Similarly, weight loss is a general goal in the Pre-LT setting, however, there are no specific targets or consensus regarding specific diet and exercise regimens. Traditional lifestyle modification used in obesity is generally safe in the pre-LT population[51], however, excessive intrabdominal straining may lead to transient increases in portal pressure[52]. Avoidance of very low-calorie diets (less than 1000 calories per day) is recommended. Specialist nutritionist consultation should be sought to optimise weight loss and balance this with protein and energy requirements for advanced chronic liver disease. Patients with BMI > 35 despite traditional lifestyle modification should be considered for bariatric surgery (BS)[45].

There is ongoing debate regarding patient selection, timing and type of BS in the context of LT. In pre-transplant patients with cirrhosis, malnutrition and sarcopenia following BS can have an adverse effect on delisting and waitlist mortality. In a study of 78 patients with cirrhosis who underwent BS (predominantly Roux-en-Y bypass procedure) with matched controls, NASH was the underlying etiology for liver disease in almost half the patients. The median time from BS to LT was 7 years. Delisting or death on the waiting list was higher in the BS group (33.3% *vs* 10.1%, $P = 0.002$) and the transplantation rate was lower (48.9% *vs* 65.2%, $P = 0.03$). Despite similar BMIs between the two groups, the prevalence of malnutrition was higher in the BS group at the time of LT evaluation with 64% being malnourished *vs* 39% of the control cohort. These outcomes could be affected by selection bias in the study, where patients undergoing inappropriate BS may have decompensated as a result, and only those who went on to LT assessment were included and thus not factoring in a group where BS may have attenuated the need for LT[53]. In a pilot of 6 cirrhotic patients, obesity-associated complications improved or resolved in all patients and nutritional parameters with similar to pre-operative levels[54]. It remains unclear where post-transplant outcomes are improved by obesity intervention pre-transplant.

When choosing the type of BS, LT adds complexity. Gastric bands pose an infection risk in an immunosuppressed patient. Roux-en-Y may be more technically challenging post-transplant, and lack of endoscopic access to the biliary system and gastric remnant may be problematic in the setting of biliary anastomotic strictures or gastrointestinal bleeding[55]. Therefore, sleeve gastrectomy (SG) is generally preferred in this patient population. SG can be done pre-LT, simultaneously during LT or post-LT. SG in cirrhotic patients has only been shown to be safe and efficacious in small retrospective reviews[56] or series in Child-Turcotte-Pugh A patients[54,57]. One small prospective study compared LT alone to simultaneous LT with SG (LT + SG) and demonstrated that patients who underwent LT + SG maintained a significantly higher percentage of total body weight loss after 3 years of follow-up. A lower prevalence of hypertension, insulin resistance, and hepatic steatosis was also demonstrated[58]. This approach can be considered in patients who have significant risk of metabolic or cardiovascular problems post-LT. Bariatric surgery may also be performed post-transplant.

Nutrition and sarcopenia

Pre-LT nutritional status has a major influence on post-LT outcomes, including morbidity, mortality and hospital stay[59]. Malnutrition is common in the pre-LT population and is driven by reduced dietary intake, malabsorption and altered energy metabolism[60]. However, diagnosis can be challenging in the obese patient with decompensated cirrhosis, particularly in the presence of ascites[61,62]. Specialist

nutritionist consultation should be undertaken in pre-LT patients, particularly as BMI and subjective global assessment are unreliable in this patient cohort[63]. Tools such as handgrip strength are emerging as a useful bedside test in stratifying and prognosticating in sarcopenia[64], as well as subcutaneous adipose tissue index in females[65]. Sarcopenia is characterised by a progressive decline of skeletal muscle and strength and is independently associated with mortality in cirrhosis[66]. In a study of 142 patients awaiting LT, 41% were sarcopenic, and this was associated with an over two-fold risk of waiting-list mortality compared to participants without sarcopenia[63]. The coexistence of low muscle mass and increased fat mass is referred to as "sarcopenic obesity" and is estimated to affect up to 35% of patients on the LT waiting list[67]. "Myosteatosis" is defined as pathological fat accumulation in skeletal muscle, either intramyocellular or intermuscular, and has been reported in more than 50% of patients with cirrhosis evaluated for liver transplantation[68]. Both sarcopenia and myosteatosis have been shown to be independent risk factors for long-term mortality in cirrhosis[68]. There are limited data available regarding interventions for sarcopenic obesity in cirrhosis, let alone distinguishing MAFLD patients from other etiologies of chronic liver disease. There is much work to be done to further define these conditions and to develop an evidence base to direct recommendations for nutritional, exercise and pharmacologic therapies in cirrhotic patients and those awaiting liver transplant[67].

Malignancy

It is well established that obesity is associated with increased risk of a number of cancers, including endometrial cancer, esophageal adenocarcinoma, gastric cardia cancer and renal cell carcinoma[69]. Metabolic syndrome has been associated with increased risk of colorectal adenoma and/or cancer[70]. However, an independent association between MAFLD and colorectal malignancy remains contentious[71], with a meta-analysis showing association with adenoma only, not colorectal cancer[72]. All LT patients are evaluated for risk of malignancy and investigated or screened according to local guidelines. There is currently no evidence to support additional screening measures for extra-hepatic malignancy in pre-transplant patients with MAFLD.

POST-TRANSPLANT OUTCOMES

Post-LT survival of patients with MAFLD appears similar to non-MAFLD patients, supported by large registry studies from the United States[24,73,74] and the ELTR[27]. From these studies, 5-year survival was 73%-81% in NASH (+/- CC), compared with 75%-80% in non-NASH non-CC. The 10-year patient survival in NASH was 62% according to ELTR data from 2002-2016 compared with 63% in non-NASH[27]. Survival was lower in patients transplanted for HCC with NASH (47%) compared to HCC without NASH (53%). UNOS data from 1997-2010, 10-year patient survival was 75% in NASH+CC compared with 73% in non-NASH non-CC[73]. In the European cohort, cardiovascular mortality was the second most common cause of death (after infection) with no difference between NASH and non-NASH groups. Increasing age, MELD and extremes of BMI independently predicted death in patients transplanted for NASH without HCC[27]. A limitation of the comparator non-MAFLD groups in large registry studies is that they mostly do not include data after the widespread use of DAAs for HCV, suggesting that more recent outcomes may be different. Small studies have reported increased 30-d and 1-year mortality in NASH LT-recipients, attributed mainly to infection[30,75]. There is no evidence that patients who have undergone LT for MAFLD are at any greater risk of extra-hepatic malignancy post-transplant than other indications and therefore routine post-LT malignancy screening in line with local protocols is recommended.

Given the underlying genetic and environmental factors that drive MAFLD (Figure 1), it is unsurprising that MAFLD may recur post-transplant. It is estimated that 50% of MAFLD transplant recipients have recurrent MAFLD, 75% of which have NASH[76,77], however less than 10% develop advanced fibrosis[76,78]. The true incidence and risk factors for recurrent and *de novo* MAFLD post-transplant is difficult to elucidate due to significant heterogeneity in studies, as reported in a recent systematic review[79]. The 1-, 3-, and ≥ 5-year incidence rates were found to be 59%, 57%, and 82% for recurrent MAFLD and 53%, 57, and 48% for recurrent NASH, however there was low confidence in this result due to significant heterogeneity and high risk of bias in the included studies. Multivariate analysis demonstrated that post-LT body mass index and hyperlipidemia were the most consistent predictors of outcomes[79].

De novo MAFLD after transplant

Many factors contribute to post-LT MAFLD, including post-transplant diabetes, obesity and medication, but the prevention of post-LT MAFLD is similar other indications for LT such as HCV or ALD. From an aforementioned systematic review, the mean 1-, 3-, and ≥ 5-year incidence rates for *de novo* MAFLD were 67%, 40%, and 78% and 13%, 16%, and 17% for *de novo* NASH[79].

Risk factors for both recurrent and *de novo* MAFLD include weight gain, diabetes, hyperlipidemia, hypertension and possibly female sex[79-82]. High dose corticosteroids are associated with hepatic steatosis and metabolic syndrome post-LT[83], as they are in the general population. Possible approaches to risk reduction include early steroid minimisation or steroid-free induction immunosuppression[82,84]. Sirolimus based immunosuppression has been recently associated with *de novo* MAFLD post-LT[85]. Calcineurin inhibitors such as tacrolimus and cyclosporin are also diabetogenic but their effect on *de novo* MAFLD has not been studied. Golabi *et al*[30] noted in their study of SRTR data from 1994 to 2016 that the incidence of post-LT diabetes is declining, likely because of the use of less diabetogenic immunosuppression.

Donor genetic polymorphisms associated with MAFLD (*PNPLA3*, *TM6SF2*) have been implicated in *de novo* steatosis post LT[31,32], however, this is yet to have significant clinical management implications. Similarly, the influence of epigenetics and the microbiome in *de novo* MAFLD after LT requires further research to identify if and how these factors may differ from the pre-LT setting.

Hepatic steatosis and potential liver donors

The degree of steatosis in a potential donor liver graft is an important factor in organ selection and affects liver allograft function. Hepatic steatosis (HS) can be either macro- or microvesicular based on the size of the triglyceride droplets in the hepatocyte; with the former having a greater effect on graft quality. When macrovascular steatosis exceeds 60%, discarding the graft is recommended because of the high rate of primary graft non-function[86,87]. Moderate to severe steatosis (> 30%) is also a risk factor for graft loss and early allograft dysfunction and careful assessment of donor and recipient factors is required if such organs are to be considered for use[88]. Mechanisms associated with poor graft function are not well defined, but include higher susceptibility to ischemia/reperfusion injury[89], toxic cytokine formation, Kupffer cell activation, sinusoidal microcirculatory disorder and injury, which can be compounded in donation after circulatory death donor livers[90]. The degree of HS can be assessed at different stages of organ procurement; with prognostic scores based on donor factors, imaging before harvest and biopsy after procurement. Surgeons mostly rely largely on visual inspection of the liver to assess the degree of HS, which places considerable pressure on the procurement team to make a rapid decision, with significant consequences if inaccurate. With the increasing number of donor organs affected by HS in line with the obesity epidemic, the risk of complications from steatotic donors must be weighed up against organ availability and waitlist mortality while awaiting a subsequent offer. In a recent study of 13362 waitlisted patients who accepted a steatotic donor offer (> 30% macrosteatosis on biopsy), only 53.1% were subsequently transplanted; 23.8% died and 19.4% were removed from the waitlist[91]. In the 759 recipients who received a steatotic graft, peri-operative morality was higher in the first month but the mortality risk was 62% lower beyond this[91]. Candidates with MELD score of 6-21 who accepted a steatotic graft had a 7.88-fold higher mortality risk in the first month posttransplant, whereas MELD 35-40 candidates had a 68% lower mortality risk[91]. In selected patients, the risk of a graft with HS may outweigh the risk of waitlist mortality. Ex-situ machine perfusion is a promising therapy that may recondition steatotic livers for transplantation and nay play a key role in addressing this issue in the future[88,92].

CONCLUSION

MAFLD is likely to become the leading global indication for liver transplantation within the next decade. This changing epidemiology brings the challenges of managing ageing, comorbid patients on the waiting list, through the peri-transplant period and in the long term. However, post-LT outcomes in MAFLD patients appear similar to non-MAFLD indications which implies that with good recipient selection, the outlook for MAFLD patients undergoing LT is optimistic. The rising prevalence of MAFLD has implication for both living and deceased donor livers, and balancing graft quality with organ demand will be an ongoing issue for transplant programs. As the

conceptualisation of MAFLD evolves, so will the ability to better predict disease behaviour and progression, to tailor treatment and to observe patterns of outcomes in liver transplantation across the patient spectrum and therefore address the multiple challenges posed by this disease.

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