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ABOUT COVER

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REVIEW

Clinical considerations in the management of non-alcoholic steatohepatitis cirrhosis pre- and post-transplant: A multi-system challenge

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Abstract

Non-alcoholic steatohepatitis (NASH) is the most common chronic liver disease worldwide, and the fastest growing indication for liver transplantation in the United States. NASH is now the leading etiology for liver transplantation in women, the second leading indication for men, and the most common cause amongst recipients aged 65 years and older. Patients with end-stage liver disease related to NASH represent a unique and challenging patient population due the high incidence of associated comorbid diseases, including obesity, type 2 diabetes (T2D), and hypertension. These challenges manifest in the pre-liver transplantation period with increased waitlist times and waitlist mortality. Furthermore, these patients carry considerable risk of morbidity and mortality both before after liver transplantation, with high rates of T2D, cardiovascular disease, chronic kidney disease, poor nutrition, and disease recurrence. Successful transplantation for these patients requires identification and management of their comorbidities in the face of liver failure. Multidisciplinary evaluations include a thorough pre-transplant workup with a complete cardiac evaluation, control of diabetes, nutritional support, and even, potentially, consultation with a bariatric surgeon. This article provides a comprehensive review of the conditions and challenges facing patients with NASH cirrhosis undergoing liver transplantation and provides recommendations for evaluation and management to optimize them before liver transplantation to produce successful outcomes.

Key words: Liver transplantation; Non-alcoholic fatty liver disease; Obesity; Metabolic syndrome

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Core tip: Non-alcoholic steatohepatitis (NASH) is the most common chronic liver disease worldwide, and the fastest growing indication for liver transplantation (LT) in the United States. Patients with NASH represent a unique and challenging population due the high incidence of associated conditions (*i.e.* obesity, diabetes, and hypertension), which carry considerable risk of morbidity and mortality before and after LT due to cardiovascular disease and kidney disease. This article provides a comprehensive review of the conditions and challenges facing patients with NASH and provides recommendations for evaluation and management to optimize them before LT.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a global epidemic and the most common cause of chronic liver disease worldwide[1]. NAFLD represents a spectrum of liver disease, starting with simple steatosis (NAFL) and progressing to non-alcoholic steatohepatitis (NASH) with inflammation and cellular injury in addition to fat accumulation[2]. Livers affected by NASH may ultimately develop fibrosis and progress to cirrhosis and liver failure requiring liver transplantation (LT)[3]. While chronic infection with hepatitis C virus (HCV) has long-been the leading indication for liver transplantation, the recent advent of direct antiviral agents has resulted in increased rates of disease resolution and decreased the need for LT[4-6]. Simultaneously, the increasing prevalence of obesity throughout the world has led to an increased incidence of NASH and NASH-related cirrhosis[1]. Importantly, NASH is now the leading indication for LT in women, the second leading indication for men, and the most common non-malignant indication amongst recipients aged 65 years and older[7,8].

NASH cirrhosis represents a growing challenge in transplantation with no effective treatment. Strongly associated with the metabolic syndrome, patients with NASH often have the associated comorbidities of obesity, type 2 diabetes (T2D), cardiovascular disease, and chronic kidney disease, amongst others[9-12]. This constellation of diseases, along with end-stage liver disease (ESLD), makes treating patients with NASH cirrhosis a challenging clinical endeavor. Furthermore, these conditions increase the risk of transplantation and may complicate post-LT immunosuppression and care.

To address this unique clinical challenge, here we present a comprehensive review article in which we discuss the difficulties in managing patients with NASH before and after LT, with consideration given to the interplay of disease physiologies and potential treatments where available.

PRE-TRANSPLANT CONSIDERATIONS FOR PATIENTS WITH NASH

NASH is the fastest rising cause of ESLD amongst registrants on LT waitlists in the United States, with a 170% increase from 2004 to 2013[13]. The number of LT performed for NAFLD increased fourfold between 2002 and 2012[6]. During nearly the same time, the mean age of all LT recipients increased, and the increase in age amongst HCV-negative patients was associated with an increase in NASH cirrhosis[14]. NASH has become the most common indication for LT amongst patients ≥ 65 years old[8]. Recently, Parikh *et al*[15]. using national data to model the rise of NASH in LT in the United States, predicted a 55.4% increase in NASH-related waitlist additions by 2030. In concert with decreasing prevalence of HCV[16]. NASH will likely become the most common indication for both waitlisting and receipt of LT in the next 15 years[15,17]. In addition to aging, NASH has a predilection for the female gender. Our group recently

showed that NASH is the leading indication for LT waitlist registration and transplantation for women[7].

NASH and obesity

NASH patients are a unique and complex population, with multiple comorbidities complicating their underlying liver disease (Figure 1). Obesity is a growing epidemic in the United States, with an estimated 38% of adults having a body mass index (BMI) > 30 kg/m^2[18]. Obesity alone has been a point of contention in LT[19]. In the pre-model for end-stage liver disease (MELD) era, Nair *et al*[20] considered morbid obesity (BMI ≥40 kg/m^2) an independent predictor of mortality in LT recipients. In contrast, Leonard *et al*[21] evaluated LT outcomes by recipient BMI after removing ascites and found no difference in survival. Nonetheless, obesity has been associated with increased rates of early graft dysfunction, longer hospital stays, and increased rates of infection in the United States and the United Kingdom[20,22,23]. In the pre-LT setting, Segev *et al*[24] found that obese patients were more likely to be turned down for organ offers and to receive fewer MELD exception points than were leaner individuals. There is a trend towards worse outcomes when BMI is > 40 kg/m^2 and with concomitant diabetes[25,26]. Overall, the International Liver Transplantation Consensus Statement on ESLD due to NASH does not recommend against LT on the basis of obesity alone but supports careful patient selection in the presence of comorbidities[27].

NASH is the result of progression from NAFL and is often considered the hepatic manifestation of the metabolic syndrome[2]. The syndrome has been defined in a joint publication of the International Diabetes Foundation and the National Heart, Lung, and Blood Institute in the United States (Table 1). In addition to being associated with older aged and female patients, NASH is also commonly seen with obesity, hypertension, diabetes, renal disease and cardiovascular disease[28].

Insulin resistance, metabolic syndrome and NASH

Insulin resistance likely is the primary pathogenetic factor that ties metabolic syndrome and NAFLD/NASH together. In the liver, elevated serum glucose and insulin values increase the activity of carbohydrate response element binding protein and sterol regulatory-element binding protein 1c, which leads to impaired metabolism of liver lipid, increased lipid deposition, and further inhibition of insulin signaling within the liver[29-31]. Hepatic insulin resistance and steatosis may be the "first hit" in the development of NAFLD, sensitizing the liver to "second hits," which lead to the development of inflammation, fibrosis, and necrosis that are characteristics of NASH[32,33]. The second hits are multifactorial—inflammatory cytokines, adipokines, mitochondrial dysfunction, oxidative stress, breakdown of the gut mucosal barrier with endotoxemia, and activation of Kuppfer cells and hepatic stellate cells[34-38].

Not surprisingly, diabetes is common amongst LT candidates with NASH. The incidence of diabetes amongst patients awaiting LT with NASH is more than 2-fold higher than any other causes, ranging from 46%-55%[13,39]. Hoehn *et al*[40] reported that NASH was the most common cause of ESLD amongst patients undergoing LT with diabetes. Furthermore, the severity of liver disease in NAFLD/NASH may be related to T2D. In a 2006 study examining the association between NAFLD and diabetes, 71% of patients with biopsy- proven NASH had diabetes, whereas only 46% of patients with simple steatosis had the disorder[41]. Importantly, pre-LT diabetes is associated with early postoperative complications, such as infection and adverse cardiovascular events[42].

Hypertension is another component of the metabolic syndrome seen commonly in LT candidates with NASH[43]. In an evaluation of listed patients, hypertension was present in 46% of those with NASH compared with 28% of those with HCV[39]. An independent association between NAFLD/NASH and hypertension has been reported[44,45]. While hypertension is not prevalent amongst individuals awaiting LT, pathogenetic mechanisms associated with arteriolar hypertension may contribute to the increased incidence of renal dysfunction and cardiovascular risk in patients with NASH[46].

Renal dysfunction with NASH

Patients with NASH commonly have multiple risk factors for chronic kidney disease (CKD). CKD, defined as decreased estimated glomerular filtration rate (eGFR) and/or overt proteinuria and/or abnormal albuminuria, is common in patients with NAFLD and NASH, with a prevalence of 20%-55%[47]. While the development of CKD in these patients is likely related in part to the end-organ effects of diabetes, hypertension, and insulin resistance, distinct pathogenetic mechanisms due to NASH per se are

Table 1 Metabolic syndrome criteria

Metabolic syndrome criteria	
Characteristic	**Description**
Waist circumference	≥ 88 cm in females
	≥ 102 cm in males
Triglycerides	≥ 150 mg/dL
	On drug treatment for elevated triglycerides
HDL	≤ 40 mg/dL for men
	≤ 50 mg/dL for women
	On drug treatment for low HDL
Hypertension	Systolic blood pressure ≥ 130 mmHg
	Diastolic blood pressure ≥ 85 mmHg
	On anti-hypertensive drug treatment for history of hypertension
Diabetes	Elevated fasting glucose ≥ 100 mg/dL
	On drug treatment for elevated glucose

Patients must exhibit 3 of the 5 components to have the diagnosis with metabolic syndrome. Based on consensus statement from International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity[182]. HDL: High-density lipoprotein.

possible[48-51], as NAFLD and NASH have been independently associated with both the prevalence and incident of CKD[52-54], where the risk of developing CKD has hazard ratios (HR) of 1.49-1.85.

The severity of CKD has been related also to the severity of liver disease. Yasui *et al*[55] examined 174 Japanese patients with NAFLD and found a higher rate of CKD with NASH than with simple steatosis (21% *vs* 6%, $P = 0.007$). Another study evaluated 80 patients with biopsy-proven NASH and found that eGFR decreased with increasing degrees of hepatic fibrosis[56]. Musso *et al*[57] presented the most comprehensive evaluation of NAFLD/NASH and CKD in a meta-analysis, which included 63902 patients and 33 studies; that study found both an independent association between NAFLD and CKD in both diabetic and non-diabetic patients, and higher prevalence and incidence of CKD with NASH than with simple steatosis.

CKD may affect all patients with NAFLD and NASH, but it is especially problematic for patients awaiting LT. Park *et al*[43] evaluated waitlisted patients and found higher serum creatinine values and prothrombin times in patients with NASH than in those with other causes of ESLD and the same MELD score; this observation was confirmed by Wong *et al*[13], who found a lower eGFR amongst waitlisted patients with NASH than amongst those with other causes of ESLD. The presence of renal dysfunction and CKD prior to LT is a risk factor for post-LT CKD and is associated with worse graft and patient survival[58-60]. Fussner *et al*[58] reported that NASH and female gender were independently associated with CKD at 1 year after LT. Houlihan *et al*[61] reported similarly higher rates of stage III CKD in patients with NASH than in those with liver disease of other causes (31.2% *vs* 8.3%, $P < 0.001$) at 2 years after LT; however, they found no difference in 1-year or 5-year patient or graft survival. Importantly, however, patients with NASH are more likely than those with ESLD from other etiologies to require renal replacement therapy prior to transplantation, which carries a 150% increased risk of mortality before transplantation[62,63].

Simultaneous liver and kidney transplantation (SLKT) is an option for patients with NASH cirrhosis and CKD. NASH is the fastest rising indication for SLKT in the United States, increasing from 6.3% of SLKT in 2002 to 19.2% in 2011[64]. In a comparison with patients undergoing SLKT for alcoholic cirrhosis, NASH, and HCV, Singal *et al*[65] found similar 5-year liver allograft survival but significantly worse renal allograft survival and a 1.5-fold increased risk of renal graft loss. Molnar *et al*[66] compared pre-LT eGFR and post-LT renal recovery in 4,088 NASH LT recipients from the United Network for Organ Sharing database. Over a median follow-up of 5 years, NASH patients with preserved renal function had a lower risk of death than did those with eGFR < 30 mL/min; however, similar rates of death and graft loss were seen for

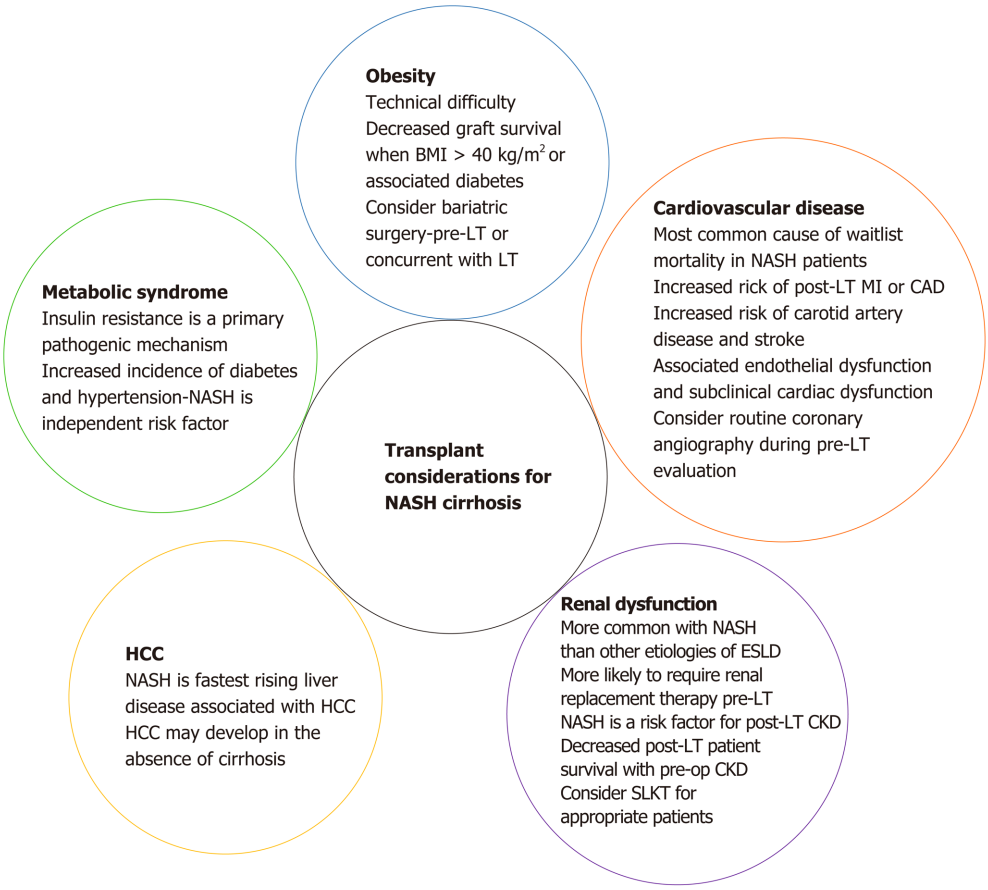

Figure 1 Optimizing patients with non-alcoholic steatohepatitis cirrhosis for liver transplantation. Patients with non-alcoholic steatohepatitis cirrhosis represent a unique and challenging population. Comorbid conditions which may complicate pre- and post-transplant care are presented along with considerations for optimization. BMI: Body mass index; LT: Liver transplantation; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma; ESLD: End-stage liver disease; CKD: Chronic kidney disease; SLKT: Simultaneous liver and kidney transplantation.

NASH patients with SLKT and as those with reduced renal function[66].

Cardiovascular disease and NASH

Increasing literature supports an increased risk of cardiovascular events in patients with NASH. Cardiovascular disease (CVD) is a leading cause of mortality in LT patients, accounting for 19%-42% of non-graft-related mortality[67,68]. In LT patients, CVD is associated with typical risk factors: Diabetes, hypertension and renal dysfunction[67]. Additionally, recent research supports NAFLD and NASH as independent risk factors for the development of CVD[69,70].

The pathogenetic mechanisms for CVD in patients with NAFLD are multifactorial and incompletely understood. In addition to the typical risk factors—hyperlipidemia, hypertension and impaired glucose tolerance—characteristics unique to NAFLD, have been found independently associated with endothelial dysfunction[71-73]. Arterial stiffness may play a role and has also been associated with NAFLD[74-78]. Endothelial dysfunction is a separate but inter-related mechanism that is common with atherosclerosis and is regulated by multiple mechanisms[79]. As both a result and mediator of arterial changes, NAFLD has been associated with increased expression of biomarkers of endothelial dysfunction, such as sICAM-1 and plasminogen activator inhibitor-1 (PAI-1)[80,81]. PAI-1 is not just a marker of endothelial dysfunction, but is also prothrombotic and associated with increased risk of myocardial infarction[82,83]. Changes in cardiac function also are present in patients with NAFLD: Kim *et al*[78] showed that NAFLD was independently associated with left ventricular diastolic dysfunction. Insulin resistance is a primary contributor to cardiac dysfunction, being associated with myocyte growth, interstitial fibrosis, sodium retention and changes in sympathetic nervous system activation[84,85].

Unfortunately, much of the cardiac dysfunction in NAFLD is subclinical and difficult to diagnose. NAFLD has been associated with decreased myocardial

perfusion reserve, which may make patients with NAFLD prone to subendocardial ischemia in the presence of hemodynamic compromise[86]. LT screening guidelines recommend that dobutamine stress echocardiography be performed, and, if abnormal, be followed with coronary angiography[87,88]. In a study of patients with NAFLD undergoing LT evaluation, 37% did not reach target heart rate during stress echocardiography[89]. Tests of cardiac function in NAFLD patients may not reveal the severity of disease: A meta-analysis of cardiac stress test results during LT evaluation revealed a pooled sensitivity of 21-28% and specificity of 82-91% for coronary artery disease[90]. Dobutamine stress echocardiography has poor predictive value for post-operative cardiovascular events, with a reported positive predictive value of 6.7% and negative predictive value of 83.5%[91]. Prolonged QT segment may be a marker for cardiac dysfunction in NAFLD, and changes in cardiac morphology may lead to the development of atrial fibrillation, which has been independently associated with NAFLD[92,93]. Importantly, atrial fibrillation is a risk factor for both intra-operative and post-operative cardiac events in LT[94].

An early study by Kadayifci *et al*[95] reported an increased prevalence of coronary artery disease associated with NASH-related cirrhosis compared other causes of liver disease (21.6% *vs* 5%, $P = 0.005$ respectively). Similarly, Patel *et al*[96] found an increased risk of severe coronary artery stenosis, defined as stenosis > 70% on angiography, in patients with non-alcohol related ESLD. Carotid artery disease also is increased in patients with NASH[97]. Carotid intima-media thickness, a marker of atherosclerosis, is associated with increased risk for myocardial infarction, cerebrovascular accidents and peripheral vascular disease[98]. Two studies have found increased carotid intima-media thickness in patients with NAFLD[99,100].

An increased risk of CVD events with NAFLD before and after LT has been reported[101-105]. CVD has been found the reason for waitlist mortality more often in patients with NASH than in those with other kinds of ESLD[13], and Vanwagner *et al*[89] have reported that patients who underwent LT for NASH were more likely to die of a cardiovascular event within 1 year post-LT than were those who had LT for alcoholic cirrhosis (adjusted OR = 4.12, 95%CI: 1.91-8.90). The same group later reported a higher incidence of sudden cardiac death or acute heart failure in patients transplanted for NASH than in those transplanted for other causes of ESLD[106]. A systematic review and meta-analysis comparing patients with LT for NASH with those without NASH supported these findings, showing that the recipients who had NASH had higher rates of death due to CVD[107].

Bariatric surgery and NASH

Patients with NAFLD and obesity should pursue exercise and nutrition counseling. However, dieting, exercise, and behavioral therapy are poorly tolerated by those patients who have severe liver disease[108]. As obesity in patients with NASH cirrhosis might prohibit LT, bariatric surgery has been proposed as an option[109]. Weight loss surgery can reduce the burden of comorbidities in patients with NASH, resulting in weight loss and improvement in T2D, hypertension, and insulin resistance[110,111]. Bariatric surgery in this population should be sleeve gastrectomy rather than gastric banding or gastric bypass, as the latter procedures might make the anatomy difficult for LT. Sleeve gastrectomy results in excellent weight loss and additionally has the benefit of not being a malabsorptive procedure, which may otherwise impact absorption of immunosuppressive medications post-LT.

Optimal timing of bariatric surgery for patients with NASH has not been determined; various groups have reported successful outcomes when the surgery is performed prior to, concurrent with, or after LT[112]. Shimizu *et al*[113] performed bariatric surgery in 23 patients with cirrhosis (22 with Child's A cirrhosis); 14 patients underwent laparoscopic roux-en-y gastric bypass and 8 underwent laparoscopic sleeve gastrectomy. Overall, mean weight loss was approximately 35 kg, diabetes resolved or improved in 87%, and hypertension resolved or improved in 69%. The rates of complication were similar between the 2 procedures (28.6% for bypass *vs* 37.5% for sleeve gastrectomy; $P > 0.05$). A case series from France of 109 patients with NASH who underwent bariatric surgery had similar improvement in BMI, but, more important, had improvement in features of NASH: Less hepatocellular ballooning in 84.2% and reduction in lobular inflammation in 67.1%[114]. However, this study included mostly NASH patients without cirrhosis.

The presence of decompensated cirrhosis, however, may prohibit elective weight-loss surgery. For these patients, bariatric surgery at time of transplantation may be an option. Heimbach *et al*[115] published one of the first case series with this approach, on patients listed for LT with BMI > 35 kg/m^2. Seven patients were unsuccessful in pre-LT weight loss and ultimately underwent simultaneous LT and sleeve gastrectomy,

with a median MELD score of 32 and BMI at transplantation of 48 kg/m^2. Post-LT, all 7 patients had resolution of diabetes and hypertension and achieved a BMI below 35 kg/m^2. Only 1 patient had a complication related to the bariatric surgery procedure, a leak at the gastric staple line. Since this initial report, a few more small case series have been published with similar findings[116,117]. Zamora-Valdes *et al*[118] recently updated the long-term results from the initial study, reporting that patients who underwent combined transplantation and sleeve gastrectomy maintained weight loss and had a lower incidence of diabetes, hypertension, and hepatic steatosis at 3 years after LT than did those who had pre-LT weight loss without bariatric surgery. Bariatric surgery after transplantation remains an option for obese patients; however, this approach is more technically complicated because of adhesions and increased risk of immunosuppression-related complications[119-121].

Other issues for LT in patients with NASH

Over the past 5 years, the nutritional status of patients with ESLD has become increasingly recognized as an important factor in outcomes. Despite increased weight and BMI, many obese individuals are nutritionally depleted, with muscle wasting and fatty muscle infiltration, which can lead to sarcopenic obesity[122-124]. Carey *et al*[125] performed a multicenter study to better define sarcopenia in LT, finding that skeletal mass index was independently associated with waitlist mortality and identifying cutoffs to define sarcopenia (< 50 cm^2/m^2 for men and < 39 cm^2/m^2 for women). Carias *et al*[126] identified NASH as an independent predictor of sarcopenic obesity.

Portal vein thrombosis (PVT) is a common complication of chronic liver disease and is a risk factor for graft loss in patients with cirrhosis[127-131]. Patients with NAFLD have been found at higher risk for venous thromboembolism, such as pulmonary embolus or deep vein thrombosis[132]. Patients with NASH cirrhosis are at increased risk also for pre-LT PVT[133]. Stine *et al*[134] reported that, amongst patients with NASH, those who are older than 60 years and have a BMI > 30 kg/m^2, hypertension and diabetes, have an even higher risk of pre-LT PVT. Agbim *et al*[135] recently reported a 37% increased risk of graft loss and a 31% increased risk of death amongst patients who underwent LT for NASH cirrhosis with pre-LT PVT compared to those without PVT.

Hepatocellular carcinoma with NASH

In addition to cirrhosis, NASH is associated also with the development of hepatocellular carcinoma (HCC), with an estimated incidence of 2.6% per year[136]. NASH is the fastest rising cause of HCC in LT[137]. Data from two North American centers reveal that the proportion of LT for NASH-related HCC rose from 4% to 9% between 2004 and 2014[138]. In a separate evaluation of data on Scientific Registry of Transplant Recipients, Younossi *et al*[137] found that the proportion of LT candidates who had NASH-related HCC increased 7.7-fold between 2002 and 2016 (2.1% to 16.2%, P < 0.0001), while the proportions of HCC related to HCV and alcohol-related liver disease remained stable. Moreover, up to 38% of patients with NASH and NAFLD may develop HCC, even in the absence of cirrhosis[139,140]. Survival outcomes for patients transplanted with HCC due to NASH do not seem to differ from outcomes with transplantation for other causes of HCC[137].

Like other comorbidities associated with NASH, insulin resistance, oxidative stress, and an inflammatory environment contribute to the development of HCC[141,142]. Furthermore, over 28000 somatic mutations have been identified in HCC[143]. Grohmann *et al*[144] have described an independent mechanism in which obesity contributes to development of HCC through activation of signal transducer and activators of transcription (STAT)-1 and STAT-3 signaling. Together, STAT-1 and STAT-3 create a pro-inflammatory environment and drive oncogenesis, respectively[145,146]. Undoubtedly, as obesity and NAFLD become more prevalent, more mechanisms contributing to the pathogenesis of NASH and HCC will be identified.

NASH and the waitlist

The combined effects of comorbidities yield a NASH population with complex systemic diseases. Unfortunately, this complexity compounds patients' pre-transplant management. O'Leary *et al*[39] reported that NASH patients presenting for LT evaluation were more likely than others to be denied listing because of their comorbidities (72%). They also were more likely than patients with HCV to be removed from listing due to death or being "too ill" for transplantation (22% *vs* 16%, P = 0.006) and were less likely to receive a transplant (27% *vs* 46%, P < 0.001). Notably, when patients had MELD scores > 15, there was no difference in rate of transplantation, removal from waitlist, or progression of MELD score. Wong *et al*[13]

found that NASH patients, compared with patients with alcoholic liver disease, had a lower rate of transplantation and increased mortality rate at 90-days from listing, but this discrepancy disappeared at 1-year after listing. More recently, in an examination of patients on the United Network for Organ Sharing waitlist from 2002 to 2016, Thuluvath *et al*[147] found that NASH patients also had a slightly higher unadjusted incidence of death or deterioration (29%) than did those with alcoholic liver disease (28%, $P > 0.05$); however, multivariable analysis showed that much of the difference could be attributed to factors associated with NASH (*i.e.*, older age and diabetes) and not to NASH independently. In light of these findings, no scoring system for pre-transplant mortality has been developed specifically for patients with NASH cirrhosis. To date, the MELD score is the most validated predictor of pre-transplant mortality regardless of etiology. Because of their older age, obesity, and multiple comorbidities, waitlisted NASH patients face numerous challenges: As waitlists for transplantation grow longer and the median MELD score at transplantation continues to rise, patients with NASH are at an ever-increasing risk for poor outcomes before reaching LT.

Older age and multiple comorbidities make patients with NASH who are undergoing LT evaluation a highly complex population. Proper pre-transplant evaluation includes a thorough assessment for diabetes, hypertension, renal dysfunction, and cardiovascular risk factors. Table 2 highlights our recommendations for each of these conditions. As with all patients undergoing LT, optimization of medical comorbidities is a necessity to achieve successful outcomes. We also recommend that obese patients undergo consultation with a nutritionist, an exercise therapist, and, if felt indicated, a bariatric surgeon. For obese patients with diabetes and/or hypertension who are not candidates for elective bariatric surgery, we recommend consideration of performing sleeve gastrectomy at the time of transplantation, but this consideration deserves scrutiny.

OUTCOMES FOR LT IN NASH RECIPIENTS

Overall survival

Prognosis after LT for NASH is generally acceptable. A recent large-volume ten-year review from the Scientific Registry of Transplant Recipients (SRTR) found 1- and 3-year patient survival rates of 84% and 78% after LT for NASH compared with 87% and 78% for other indications[148]. No significant difference in 5-year graft loss or mortality was observed, suggesting that NASH itself is not an independent risk factor for mortality. In a meta-analysis of 16 studies on post-LT survival with NASH, most studies found no significant survival difference was found between NASH and other etiologies of liver disease[149]. Another study documented superior survival in NASH patients compared with LT recipients for other causes for transplantation, such as HCC, hepatitis C or alcoholic liver disease[150].

Mortality after LT for NASH patients is most common within the first few years after transplantation, with cardiovascular events being the primary cause[151-153]. Furthermore, the incidence of mortality from cardiovascular causes is 15% higher in NASH patients in the first year, but this difference is not sustained beyond the first postoperative year. Kennedy *et al*[154] reported long-term mortality in NASH patients after LT is primarily associated with malignancy (recurrent HCC and extrahepatic malignancy), cardiovascular complications, and infectious complications. A study by Bhati *et al*[155] also identified pre-transplant obesity (BMI > 30 kg/m^2) and age of 60 years at the time of transplantation as predictors of post-LT mortality.

Complications

Despite lack of non-inferior survival data, the overall incidence of morbidity after LT appears to be higher for NASH recipients than others[156]. Metabolic syndrome develops in up to 50% of patients after LT for NASH; however, no significant difference between NASH and other etiologies of liver disease has been shown[149]. Nonetheless, it is postulated that LT recipients with NASH have a predisposing metabolic milieu that persists despite transplantation, and it may be further modulated by steroid-based immunosuppressive regimens. A strong correlation between metabolic syndrome and insulin resistance has been suggested, but this relationship has been poorly studied in the LT population.

Pre-existing diabetes is often cited as the leading cause of post-transplant morbidity, owing to impaired neutrophil function and increased susceptibility to infection with post-transplant hyperglycemia[156-158]. New onset diabetes after LT is associated with pre-transplant glucose intolerance, obesity, and family history, but the toxic effects of

Table 2 Recommendations for pre-transplant evaluation in patients with non-alcoholic steatohepatitis cirrhosis

Evaluation and therapy for liver transplant candidates with non-alcoholic steatohepatitis	
Hypertension	Target blood pressure 130/80
	Initiate anti-hypertensive medical therapy
Diabetes	Blood glucose control
	Monitor insulin resistance
	Hemoglobin A1c optimization
Hyperlipidemia	Initiate statin therapy as appropriate
Renal dysfunction	Renal ultrasound
	Measure GFR by quantitative method
	Consider simultaneous liver/kidney transplantation
Cardiovascular disease	Identify cardiovascular risk factors—hypertension, diabetes, hyperlipidemia
	Comprehensive cardiac evaluation to include EKG, DSE
	Strong consideration for coronary angiography, in addition to OR in place of DSE
	Carotid artery duplex
Obesity	Consultation with nutritionist or dietician and exercise therapist
	Consider consultation with bariatric surgeon
	Consider pre-transplant or simultaneous LT + bariatric surgery if fail weight loss strategies with concurrent comorbid conditions

GFR: Glomerular filtration rate; EKG: Electrocardiography; DSE: Dobutamine stress echocardiogram; LT: Liver transplantation.

immunosuppressants on pancreatic B cells (particularly by calcineurin inhibitors) may play a role in its etiology[159,160]. Likewise, new onset obesity post-transplant occurs more often in NASH patients than in those with liver disease of other causes, and is closely linked to post-LT diabetes and *de novo* NASH[161,162]. In a study examining BMI change after LT, 22% of 320 recipients who were not obese pre-transplant became obese within 2 years after transplantation[163].

Several studies have reported a higher frequency of hypertension and dyslipidemia in post-LT patients with NASH than with other liver diseases and is often related to immunosuppression[164,165]. Among immunosuppressants, calcineurin-inhibitor based regimens were found closely linked with the development of these morbidities. Cyclosporine use was a risk factor for dyslipidemia and hypertension, whereas tacrolimus use was linked to post-LT diabetes by impairing insulin secretion, as discussed earlier[166,167].

In an examination of all post-operative morbidity, Dare *et al*[157] found similar rates of modified Clavien–Dindo grade 1 and 2 complications between NASH and non-NASH transplant recipients; however, NASH transplant recipients had increased rates of wound infections, bacteremia and pneumonia. Donor factors such as demographics, donation type (*e.g.*, donation after brain death or donation after circulatory death), BMI, cause of death, blood loss and transfusion requirement have not been found to be related to morbidity and mortality after transplantation amongst NASH recipients[168,169]. Reported early reoperation rates for bleeding or biliary complications are around 15%, and re-transplantation rates are under 10%[169,170].

NASH recurrence and post-transplant de novo NASH

The development of histologic NAFLD after LT has been well documented[171]. Metabolic syndrome after LT predisposes recipients to recurrent and/or *de novo* NAFLD and NASH[172]. The use of corticosteroids has also been implicated in the recurrence of NAFLD post-LT[173]. At 2 years post-LT, around 60%-80% of recipients develop NAFLD, with at least grade 2 steatosis or above (34%-66% by biopsy). More extensive liver disease, such as NASH with progressive fibrosis (METAVIR stage ≥ 2, defined as "more than septal formation", including bridging fibrosis and cirrhosis), is rare however, occurring in only around 5% of recipients at 5 years post-LT[162,171]. In a review of LT in 227 patients with NASH-related or cryptogenic cirrhosis, the probability of developing histologic hepatic steatosis after LT was 8.2%, 24.9% and

32.9% at 1, 5 and 10 years, respectively, but with only 6% developing recurrent NASH during the study period[174].

Few studies have shown evidence of fibrosis beyond simple steatosis and early-stage NAFLD developing in the recipient allograft post-LT for NASH. In a recent single-center study, 88.2% of the 34 NASH recipients who had a liver biopsy post-LT had recurrent NAFLD, with 41.2% having evidence of recurrent NASH (median time from transplant of 47 mo)[155]. Subgroup analysis demonstrated that patients with NAFLD/NASH had a significantly higher rate of impaired fasting glucose and hypertriglyceridemia than did recipients without recurrent NAFLD. In the same study, 87.5% of 56 recipients being evaluated with transient elastography had NAFLD (median time 75 mo). In this cohort, 81% of those with NAFLD recurrence had diabetes, compared with 51% of those without recurrence.

Histologic NASH has been shown to develop in the transplanted livers of NASH patients and has been documented as early as 6 mo post-LT[175]. A major risk factor for the development of NASH is metabolic syndrome; one large series found NASH in 34% of recipient livers in patients who had metabolic syndrome compared with 13% in recipient livers of patients who did not exhibit metabolic syndrome[120]. In the same study, hypertension and diabetes requiring insulin use were found to be significant risk factors for NASH recurrence—32% of hypertensive LT recipients developed NASH recurrence as opposed to 12% of those without hypertension; 37% of insulin users developed recurrence compared to 6% of non-users[120]. Notably, the mean time from transplantation to documented NASH recurrence in this study was 18.2 mo[120]. A separate study showed of NASH recipients showed 11% of allografts had progression from steatosis to steatohepatitis on serial biopsies post-LT with cumulative steroid exposure as a significant contributing factor to this progression[173].

More recently, the unique entities of *de novo* NAFLD and NASH developing in transplanted livers have been recognized. A retrospective series of 68 LT recipients (84% transplanted for hepatitis C) reported development of *de novo* NAFLD in 18%, and 9% developed *de novo* NASH after transplantation[176]. Development of *de novo* NAFLD/NASH could not be attributed to steatosis in the donor liver. Interestingly, a 10% increase in recipient BMI after LT correlated with a 35% increase in *de novo* NAFLD on biopsy. This study also found no significant effect of immunosuppressive regimens on the development of NAFLD. Conversely, a single-center retrospective review of 170 patients found that higher steroid dosage after LT contributed to the development of *de novo* metabolic syndrome in 33% of the study population, 50% of whom had *de novo* NAFLD within 1 year[177].

The most common risk factors for post-LT *de novo* NASH are metabolic syndrome, PNPLA3 genotype, alcoholic cirrhosis, and the use of immunosuppressive agents, including tacrolimus and steroids[153,162,178-180]. *De novo* NASH is most commonly recognized around 6 mo post-LT[178,179]. Furthermore, the incidence of *de novo* NASH has been shown to increase from 30% at 1 year to 47% at 10 years[180]. Importantly, no survival differences were found in patients with *de novo* NASH after LT who had more advanced fibrosis (F3 or F4 on transient elastography) compared to those with minimal or no fibrosis[153,178,180].

There are little data on re-transplantation for recurrent or *de novo* NASH after LT. One single-center study reported 30% (n = 6) of recipients with NASH recurrence underwent re-transplantation—three patients had graft failure from recurrence, two had hepatic artery thrombosis and one had concomitant autoimmune hepatitis[120].

Management recommendations

Management guidelines for post-LT patients with NASH are the same as those for non-transplant NASH patients, with emphasis on diet and exercise. Considering the propensity for NASH patients to develop metabolic syndrome after LT, careful attention should be placed on weight loss, strict glucose control and exercise[181]. Management of obesity and hyperglycemia is crucial in the pre-transplant phase, as postoperative weight gain and metabolic complications are exacerbated by debility and immunosuppression[152]. Considering the prevalence and mortality risk from cardiovascular complications post-LT for NASH, patients with cardiac comorbidities and risk factors should be diligently screened and managed in the pre-transplant phase[157].

CONCLUSION

NAFLD/NASH cirrhosis is an increasingly frequent indication for liver

transplantation. The association of NAFLD/NASH with metabolic syndrome, cardiovascular disease and chronic kidney disease complicate the pre-and post-LT course and management. Physicians should appreciate the need for early optimization of transplant candidates to improve both pre- and post-transplantation survival. Multi-disciplinary teams which include dieticians, bariatric surgeons, endocrinologist, and other specialists could be important in the management of the unique problems facing this patient population.

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