Review Article

Evaluation of liver transplant candidates with non-alcoholic steatohepatitis

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Abstract: Non-alcoholic steatohepatitis (NASH) is anticipated to become the leading indication for liver transplantation (LT) in the United States in the near future. LT is indicated in patients with NASH-related cirrhosis who have medically refractory hepatic decompensation, synthetic dysfunction, and hepatocellular carcinoma (HCC) meeting certain criteria. The objective of LT evaluation is to determine which patient will derive the most benefit from LT with the least risk, thus maximizing the societal benefits of a limited resource. LT evaluation is a multidisciplinary undertaking involving several specialists, assessment tools, and diagnostic testing. Although the steps involved in LT evaluation are relatively similar across different liver diseases, patients with NASH-related cirrhosis have unique demographic and clinical features that affect transplant outcomes and influence their LT evaluation. LT candidates with NASH should be assessed for metabolic syndrome and obesity, malnutrition and sarcopenia, frailty, and cardiovascular disease. Interventions that treat cardiometabolic co-morbidities and improve patients' nutrition and functionality should be considered in order to improve patient outcomes in the waitlist and after LT.

Keywords: Non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); end-stage liver disease; cirrhosis; liver transplantation (LT); transplant evaluation; cardiac risk assessment

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Non-alcoholic fatty liver disease (NAFLD) and liver transplantation (LT)

NAFLD affects 75 to 100 million Americans and up to 25% of the global population (1,2). The prevalence of NAFLD is expected to increase by 60% in the next decade, in parallel with the obesity epidemic, making NAFLD the most common chronic liver disease (3,4). Non-alcoholic steatohepatitis (NASH), affecting 10–30% of patients with NAFLD, is the progressive form of NAFLD that leads to cirrhosis and is associated with cardiovascular (CV) and liver-related morbidity and mortality (5). Hepatic fibrosis is the most important predictor of mortality in NASH (6). One in four NASH patients will progress to cirrhosis over 8 years on average (7). Patients with NASH-related cirrhosis are at increased risk of hepatocellular carcinoma (HCC), occurring at an annual incidence of 0.3–4.3% (8).

NASH is currently the 2nd most common indication for LT in the U.S., but is the fastest growing indication for LT and simultaneous liver-kidney (SLK) transplants and the fastest growing cause of HCC in LT recipients (9-13). NASH is expected to overtake chronic hepatitis C as the most common indication for LT. In the last two decades, waitlist registrations, liver transplants, and SLK transplants for NASH increased 3-fold each (9-11), while the number of LT registrants and recipients with HCC attributable to

NASH increased 4- and 8-fold, respectively (12,13).

Due to the rapidly growing incidence of NASH-related cirrhosis and HCC that may require LT, a review on the LT evaluation of patients with NASH is timely. In this paper, we will provide a brief overview of LT evaluation, review unique features of NASH patients that impact their transplant outcomes, and discuss how the LT evaluation may be modified for patients with NASH-related cirrhosis using available evidence.

General overview of the liver transplant evaluation

Demand for LT outstrips supply of available organs. In 2016, there were 11,340 patients in the waitlist for LT, but only 7,841 transplant surgeries were performed (14). The objective of LT evaluation is to determine which patient derives the most benefit from LT with the least risk, thus maximizing the societal benefits of a limited resource (15). Indications for LT in NASH patients are no different from patients with other liver diseases. LT is indicated in patients with cirrhosis complicated by medically refractory hepatic decompensation (e.g., ascites, hepatic encephalopathy, variceal hemorrhage), synthetic dysfunction [i.e., model for end-stage liver disease (MELD) score ≥15], or HCC meeting certain criteria (16,17). With few center-specific differences, the steps involved in LT evaluation are common to all liver diseases. LT evaluation is a multidisciplinary undertaking that involves hepatologists, transplant surgeons, anesthesiologists, cardiologists, infectious disease specialists, social workers, psychiatrists, nutritionists, and financial counselors. Hepatologists optimize medical management of the underlying liver disease and typically determine if LT is indicated. Some contraindications to LT include severe cardiopulmonary disease, uncontrolled sepsis, and extrahepatic malignancy (16). Social workers and psychiatrists evaluate the LT candidate's social support and for substance use and co-morbid psychopathology, which may negatively affect the candidate's ability to cope with major surgery and adhere to lifelong immunosuppression and medical care. Dietitians assess the LT candidate's nutritional status and provide dietary education. The transplant surgeon and anesthesiologist discuss technical issues and risks related to the operation and anesthetic plan. LT candidates are tested for underlying infections that include human immunodeficiency virus, tuberculosis and, in appropriate settings, parasites and fungi. Doppler ultrasound (US) or contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans assess portal vein patency, screen for HCC, and stage HCC, if present, to ensure appropriateness of LT.

Features of NASH that increase transplant risk

LT candidates with NASH have unique clinical features that distinguish them from patients with other liver diseases and potentially increase their risk of having poor LT-related outcomes.

Advanced age

In registry studies, the average age of LT recipients with NASH is 58 years, compared to 52 years in non-NASH LT recipients (10,18). Older LT candidates aged ≥65 years are twice as likely to die in the waitlist or be delisted for being "too sick" [subhazard ratio (SHR) 1.7–2.0] (19). However, a retrospective study shows that LT recipients aged ≥70 years do not have increased risk of mortality [relative risk (RR) 1.00, 95% CI, 0.43–2.31, P=1.00] and graft loss (RR 1.17, 95% CI, 0.54–2.52, P=0.70) after LT (20).

Frailty

Frailty refers to the condition of decreased physiologic reserve, as a result of decline in multiple bodily systems, that predisposes a person to adverse outcomes (21). Although the concept of frailty originated in the geriatric population, it has been validated to predict adverse outcomes in chronic diseases like cirrhosis. In the field of liver disease and transplantation, frailty mostly pertains to physical frailty, which includes functional performance, functional capacity, and disability (22). The prevalence of frailty in patients with cirrhosis is 20–25% (23,24) and approaches 50% in patients undergoing LT evaluation (25,26). In cirrhosis, frailty is associated with more frequent hospitalizations, longer hospital stays, higher healthcare costs, and greater mortality (23,24,27,28). Frailty is a predictor of waitlist morbidity and mortality in LT candidates, independent of patient age and liver disease severity (25,29,30). Frailty is more prevalent in LT candidates with NASH (49–60%) than in those with alcohol-related liver disease (0–34%) or viral hepatitis (20%) (24,31). Obesity further increases waitlist mortality in frail patients (32). In a prospective study of LT candidates with NASH, frailty increases the likelihood of being removed from the waitlist (per 0.1 unit change in frailty index: HR 1.46, 95% CI, 1.06–2.03, P=0.02) (31). Frail patients have

poor post-LT outcomes, with significantly higher incidence of mortality, infection, and re-operation (66% *vs.* 26%, P=0.008) (33).

Sarcopenia

NASH patients are not only typically obese, but also suffer from sarcopenia. Sarcopenia, a state of reduced muscle mass and function, is an objective measure of malnutrition and a major driver of frailty in patients with cirrhosis (22,34). The prevalence of sarcopenia in cirrhosis is 50% and 20–70% in LT candidates with NASH (31,35,36). LT candidates with NASH are likely to be obese and sarcopenic simultaneously (37). Sarcopenic patients with cirrhosis have worse survival (1-year 53% *vs.* 85%, P<0.005) and higher infection-related mortality (22% *vs.* 8% of all deaths, P=0.02) than non-sarcopenic patients (38). Sarcopenia is associated with increased waitlist mortality [waitlist mortality 29%; hazard ratio (HR) 2.36, 95% CI, 1.23–4.53, P=0.009], but does not appear to affect post-LT survival (1-year survival 90%) (36,39). In a recent study on LT candidates with NASH, sarcopenia affects neither waitlist mortality (1-year 15%; HR 2.1, 95% CI, 0.7–6.3, P=0.21) nor post-LT survival (1-year survival 85%) (31,40). However, the combination of sarcopenia and obesity has been associated with lower post-LT survival (1-year 66%) (37).

Obesity, diabetes and metabolic syndrome

NASH is widely considered the hepatic manifestation of the metabolic syndrome (MetS), composed of abdominal obesity, insulin resistance, atherogenic dyslipidemia, and hypertension (41). There is high prevalence of MetS (70.7%), obesity (81.8%), diabetes mellitus (DM) (43.6%), hypertension (HTN) (68.0%), and hyperlipidemia (HLD) (72.1%) in NASH patients (1). Among LT recipients with NASH, the prevalence of obesity, DM and HTN are equally high at 53–68%, 49–73%, 38–75%, respectively (42). Patients with NASH-related cirrhosis are significantly more likely to have MetS than patients with cirrhosis from other liver diseases (43). MetS is associated with poor outcomes in patients and LT recipients with NASH (44-51). Among NHANES-III participants with presumed NAFLD, liver-related mortality is significantly increased by MetS (HR 12.1, 95% CI, 1.1–132.2), insulin resistance (HR 53.6, 95% CI, 9.2–344.3), and obesity (HR 11.2, 95% CI, 2.4–51.5) (44). LT recipients with DM have higher all-cause (HR 1.21, 95% CI, 1.12–1.30) and cardiovascular disease (CVD)-related mortality (HR 1.93, 95% CI, 1.55–2.41) after LT (45). At time of transplant, morbidly obese LT recipients (i.e., Body mass index (BMI) ≥40 kg/m^2) tend to be sicker and are more likely to be in intensive care (*vs.* non-obese: 11.5% *vs.* 7.6%, P<0.05), on life support (7.7% *vs.* 4.1%, P<0.05), and mechanically ventilated (6.7% *vs.* 3.7%, P<0.05) (46). Morbidly obese and diabetic waitlist registrants are 15-20% more likely to be delisted or die in the waitlist (47). Morbidly obese patients spend more time in the waitlist, are less likely to receive MELD exception, and more likely to be turned down for an organ, which combined may account for their increased waitlist mortality (48). Morbidly obese organ recipients have longer LT operative times (8.2 *vs.* 7.2 hours, P=0.003) and higher incidence of primary non-function (10% *vs.* 6%, P<0.05), lower short-term (30-day 88% *vs.* 94%, P<0.05) and long-term (5-year 49% *vs.* 56%, P<0.05) survival, and higher mortality from CVD, infection and malignancy after transplant (49-51). Correcting for ascites downgrades 20% of LT recipients to lower obesity grades and abolishes the negative effect of BMI on post-LT survival, suggesting that previously described poor outcomes in high BMI patients may be mediated by more severe liver disease and portal hypertension (52). Indeed, recent studies, including a meta-analysis, find no association between obesity and post-LT patient and graft survival unless there is co-morbid DM (53-55). In fact, morbidly obese patients have been shown to derive greater survival benefit from LT than non-obese patients (56).

Chronic kidney disease

LT candidates with NASH have lower glomerular filtration rate (GFR) than patients with chronic hepatitis C infection (55.2±20.0 *vs.* 61.6±19.9 mL/min/m^2) (9), presumably due to higher prevalence of DM and HTN. The prevalence of chronic kidney disease (CKD) in NASH patients is 20-30% (57,58). NAFLD patients are more likely to have co-morbid CKD [odds ratio (OR) 2.12, 95% CI, 1.69–2.99] and develop incident CKD (HR 1.79, 95% CI, 1.65–1.95) than patients without NAFLD (59). The magnitude of association between NAFLD and CKD is unaffected by DM and HTN, suggesting that NAFLD *per se* may increase CKD risk. Patients with steatohepatitis and advanced fibrosis have greater risk for CKD than patients with simple steatosis (59). CKD predicts CVD-related mortality after LT in patients with NASH (60). SLK transplantation should be offered to patients with NASH-related cirrhosis

who have GFR <60 mL/min for ≥90 consecutive days or sustained acute kidney injury, defined as need for renal replacement therapy or GFR <25 mg/min for 6 weeks (61). In patients with end-stage liver disease (ESLD) and CKD, SLK transplantation is associated with better patient and graft survival than LT alone (62).

Cardiovascular disease

Due to their unfavorable metabolic profile, NASH patients are at risk for clinical CVD, including atherosclerosis, valvular heart disease and arrhythmias, and subclinical CVD markers such as greater carotid-intima media thickness, more severe coronary calcification, endothelial dysfunction, and increased arterial stiffness (63,64). A meta-analysis shows increased risk of fatal and non-fatal CV events in patients with NAFLD (OR 1.64, 95% CI, 1.26–2.13, P<0.001) and even greater risk in those with NASH and fibrosis (OR 2.58, 95% CI, 1.78–3.75, P<0.001) (65). LT candidates with NASH conceivably have the most severe disease in the NAFLD spectrum and, thus, the highest CVD risk. The prevalence of angina, peripheral vascular disease, and stroke in LT candidates with NASH are 7%, 2%, and 1%, respectively, all higher than other chronic liver diseases (60). Coronary artery disease (CAD) is present in 10–30% of patients being evaluated for LT, and patients with NASH-related cirrhosis are significantly more likely to have CAD than patients with other liver diseases (43,57,66,67). In a prospective cohort of patients undergoing coronary angiography (CAG), 84.6% of patients with hepatic steatosis have >50% stenosis in at least one coronary artery and 68.3% required a coronary intervention (68). Perioperative morbidity and mortality rates in LT candidates with severe CAD are 80% and 50%, respectively, even if they receive medical therapy or surgical revascularization before LT (69). Although LT outcomes, in general, have improved in the last 2 decades, LT recipients with significant CAD continue to have worse mortality and CV-related morbidity after LT (70). Cardiac-related deaths are more common in cirrhosis due to NASH than chronic hepatitis C (28% *vs.* 2% of deaths) and a higher percentage of deaths in NASH patients is due to CVD rather than liver disease (25–37% *vs.* 2–13% of all deaths) (71,72).

Portal vein thrombosis (PVT)

PVT affects 2–26% of cirrhotic patients and appears to occur more frequently in LT candidates with NASH than those with other liver diseases (10% *vs.* 6%, P<0.001) (73,74). NASH is hypothesized to be a hypercoagulable state due to elevated levels of procoagulant factors (e.g., factor VIII, PAI-1) and reduced levels of endogenous anticoagulants (e.g., protein C) (75). PVT at time of LT is associated with worse perioperative outcomes including greater transfusion requirements (mean 10 *vs.* 5 units, P<0.001) and higher rates of primary non-function (6.6% *vs.* 1.4%, P=0.02), post-LT renal dysfunction (20.0% *vs.* 9.4%, P=0.01) and post-LT mortality (30.0% *vs.* 12.4%, P<0.001) (76). A recent publication on LT recipients with NASH shows that PVT increases risk of post-LT mortality and graft failure by 30–40% (77).

Hepatocellular carcinoma

HCC has an incidence of 1–4%/year in patients with NASH-related cirrhosis (8,78). Older age, male gender, DM, and HTN are risk factors for HCC development in NASH-related cirrhosis (79). Although the majority of HCC arises in cirrhotic livers, 15% of NASH-related HCC occur without cirrhosis and, interestingly, are also likely to be larger and unresectable (80). About 20% of LT waitlist registrants have co-morbid HCC (9). LT should be considered in HCC meeting Milan criteria as such tumors are associated with low rates of mortality, graft failure, and recurrent HCC (81).

Tailoring liver transplant evaluation for patients with NASH

Although LT candidates with NASH undergo the same steps in LT evaluation as patients with other liver diseases, their LT evaluation may be modified to address some unique characteristics of patients with NASH (*Figure 1*).

Screening for metabolic syndrome

LT candidates with NASH should be routinely screened for DM, HTN, and HLD due to high prevalence of these co-morbidities. These conditions should be medically optimized before LT according to standards of care, but considering the physiologic changes of ESLD (82). The PPAR-γ agonist pioglitazone and the GLP-1 agonist liraglutide may be considered in non-cirrhotic diabetic (or non-diabetic) patients with NASH as these have been shown to improve steatohepatitis and fibrosis (83,84). Data is lacking on the efficacy and safety of these drugs in cirrhosis.

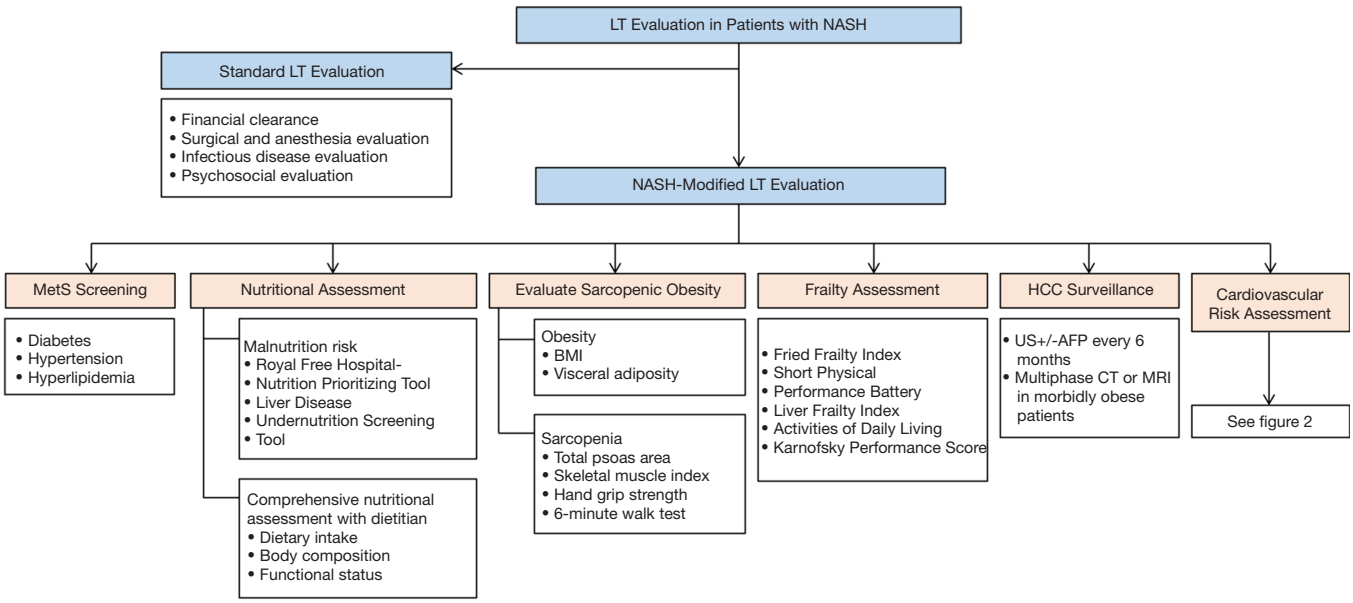

Figure 1 Components of liver transplantation evaluation in patients with NASH. AFP, alpha fetoprotein; BMI, body mass index; CT, computed tomography; LT, liver transplant; MetS, metabolic syndrome; MRI, magnetic resonance imaging; US, ultrasound; NASH, non-alcoholic steatohepatitis.

Treating diabetics in cirrhosis is challenging since almost all anti-diabetic agents are metabolized in the liver, which creates a potential for hypoglycemia and hepatotoxicity (85). Insulin is first-line treatment in diabetics with decompensated cirrhosis since its pharmacokinetic profile is not affected by hepatic impairment (82,86). Endocrinology consultation may be required in patients with inadequate glycemic control.

Systemic HTN affects less than 5% of patients with decompensated cirrhosis due to the state of systemic vasodilation found in these patients (87). Diuretics and non-selective beta-blockers are ideal first-line antihypertensive therapies in cirrhotic patients with ascites or varices. NASH patients with co-morbid heart failure and CAD may preferentially be treated with carvedilol, which is also effective in variceal hemorrhage prophylaxis (88). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are potential second-line antihypertensive agents. Some data suggest that inhibiting the renin-angiotensin system attenuates steatohepatitis and fibrosis (89).

NASH may be accompanied by a pro-atherogenic lipid profile, characterized by elevated serum triglycerides (TG) and low-density lipoprotein (LDL) and low high-density lipoprotein (HDL), which has an important role in CVD development (90). Statins may be considered in non-cirrhotic or compensated cirrhotic patients. Randomized trials in patients with compensated NAFLD/NASH show that statins lower serum TG and LDL and reduce risk of CV-related morbidity and mortality without significant hepatotoxicity (in fact, statin-treated patients actually had lower transaminases) (91,92). However, the vast majority of LT candidates with NASH will have decompensated cirrhosis. Statins are not recommended in decompensated cirrhosis due to lack of safety data, potential for hepatic and non-hepatic drug-related toxicity, and their overall poor prognosis that negates statins' CV benefits (93).

Obesity assessment

Around 50–70% of LT candidates with NASH are obese (42). BMI is currently the most widely used method to assess obesity. Patients with BMI of 25.0–29.9 kg/m^2 are categorized as overweight, while those with BMI of 30.0–34.9 kg/m^2, 35.0–39.9 kg/m^2, and ≥40.0 kg/m^2 are have class I, II, and III obesity, respectively (94). Morbid obesity (BMI ≥40 kg/m^2) is associated with higher waitlist mortality, but data is conflicting on whether it impacts post-LT mortality and graft loss (47,53-55). A recent retrospective study suggests a trend towards increased patient mortality (HR 2.36, 95% CI, 0.91–6.09, P=0.07) and graft loss (HR 2.60, 95% CI, 0.99–6.60, P=0.05) in LT recipients with BMI ≥

50 kg/m^2 (95). Morbid obesity should not necessarily preclude LT and, indeed, upper limits of BMI that contrandicate LT vary widely across transplant centers. However, more stringent patient selection should be observed in obese LT candidates with co-morbid CVD and DM or those with BMI ≥50 kg/m^2.

Due to conflicting data on its prognostic value and the confounding effect of ascites, BMI may not be the optimal tool to define obesity and assess obesity-related risk in LT candidates. Body composition and body fat distribution are potentially more important determinants of LT outcomes (96). Visceral adiposity, estimated as abdominal visceral fat area on CT, independently predicts post-LT mortality (HR 1.06 per 10 cm^2, 95% CI, 1.04–1.10, P<0.001) (97). The combination of visceral adiposity and sarcopenia portends the worst outcomes, with 1- and 5-year post-LT survival rates of 72% and 37%, respectively (97). Waist circumference and waist:hip ratio are simple, inexpensive ways of measuring central obesity that correlate with radiographic measurements and predict CVD in the general population (98). Although central obesity predicts mortality in kidney transplant recipients (99), the current metrics are inappropriate in LT candidates with ascites. Further research is needed to identify and validate standardized measures of visceral adiposity that are can be used in routine clinical practice and predict LT outcomes (96).

Weight reduction through lifestyle interventions is the cornerstone of management in NASH. Caloric restriction and physical activity resulting in 7–10% weight loss improves liver histology, potentially reverses hepatic fibrosis, and lowers portal pressure (100,101). A prospective study shows that 85% of LT candidates with BMI > 35 kg/m^2 can achieve their target pre-LT weight through a multidisciplinary approach to lifestyle interventions (102). While there is no consensus on the best weight loss strategy for LT candidates, recommended lifestyle interventions should probably differ if patients have compensated or decompensated NASH-related cirrhosis (96). Patients with compensated cirrhosis may observe traditional lifestyle interventions that include reducing caloric intake by 500–1,000 kcal/day, moderate-intensity aerobic exercise and/or resistance training for 150–200 minutes/week, and avoiding fructose-containing food and beverages (103). Patients with decompensated cirrhosis are at risk for sarcopenia and malnutrition and should focus less on weight loss and more on optimizing nutrition to maintain muscle mass. Recommendations on nutrition and physical activity are reviewed in the section on sarcopenia.

Morbidly obese LT candidates with NASH who are unable to lose weight through lifestyle interventions may be considered for bariatric surgery (BS) in order to reach their center's prerequisite pre-LT weight. BS may be considered before LT in select patients with compensated cirrhosis. In a case series of 20 morbidly obese patients with ESLD (mean MELD 11), laparoscopic sleeve gastrectomy before LT reduced patients' weight by 50% on average, resulting in 7 (35%) successful transplants, but with a 25% complication rate (e.g., infections, leak, bleeding) (104). Patients with decompensated cirrhosis should not undergo BS alone due to unacceptably high post-operative mortality (16% *vs.* 0.9% in compensated cirrhosis and 0.3% in no cirrhosis, P<0.001) (105). BS at time of LT should be considered for patients with decompensated cirrhosis. The largest case series involves 29 patients who underwent combined sleeve gastrectomy and LT (102,105). No deaths or graft losses have been reported after the combined procedure, although a leak from the gastric staple line occurred in 1 patient (102). Compared to non-surgical weight loss, combined sleeve gastrectomy-LT maintains weight loss after LT (weight loss of 34.8% *vs.* 3.9% of body weight, P<0.001) and resolves MetS, insulin resistance, and hepatic steatosis (106). BS before or at time of LT should only be performed in carefully selected patients by centers with adequate LT and BS volume and expertise due to potential for complications. While BS after LT is feasible, it will not address obesity-related problems in the waitlist and immediate post-LT period and is associated with early post-operative complications due to adhesions (107). The ideal bariatric procedure for obese LT candidates is unknown since there have been no direct comparisons of different bariatric procedures in this population. Sleeve gastrectomy is employed in the majority of studies due to several presumed advantages over Roux-en-Y gastric bypass (108). Sleeve gastrectomy is a less complex procedure, will not affect intestinal absorption of immunosuppressives, and permits endoscopic access to the biliary tree in cases of post-LT biliary complications.

Nutrition and sarcopenia assessment

Malnutrition and sarcopenia are highly prevalent in NASH-related cirrhosis (37). The etiology of malnutrition in cirrhosis is multifactorial and involves impaired dietary intake, decreased nutrient absorption, and altered macronutrient metabolism (109). About 40–90% of LT candidates are undernourished and only 25% meet daily

protein requirements (34). Malnutrition in cirrhosis is associated with hepatic decompensation, infections, HCC, and mortality (110,111). Validated nutrition screening tools that are specific to patients with cirrhosis are available. The Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) is a provider-administered tool that estimates malnutrition risk based on the presence of fluid overload, BMI, unintentional weight loss, reduction in dietary intake, and presence of alcoholic hepatitis (112). RFH-NPT correlates with liver disease severity and predicts hepatic decompensation and transplant-free survival (113). Another cirrhosis-specific nutritional screening tool, the Liver Disease Undernutrition Screening Tool asks patients 6 questions pertaining to nutrient intake, weight loss, subcutaneous fat loss, muscle mass loss, fluid accumulation, and decline in functional status (114). The tool has good positive predictive value (PPV) (>90%) in diagnosing undernutrition, but has poor negative predictive value (NPV) (40%) and has not been validated against clinical outcomes in cirrhosis. LT candidates at high risk for malnutrition and those with decompensated disease should undergo a comprehensive nutritional assessment, preferably by a registered dietitian, that includes assessments of dietary intake, body composition, and functional status (115). Nutritional assessment is recommended at the initial evaluation and at regular intervals until LT.

Sarcopenia is a core component of malnutrition and is a better measure of malnutrition in patients with NASH-related cirrhosis than BMI or weight loss. Sarcopenia is assessed and managed through standardized measurements of muscle mass and function performed at the initial LT evaluation and longitudinally until LT. Cross-sectional imaging is currently the gold standard in quantifying skeletal muscle mass. Sarcopenia can be assessed using the total psoas area at L3 or L4 vertebrae or the skeletal muscle index (SMI) which refers to the cross-sectional area of all muscles at L3 normalized for height (cm^2/m^2) (30). SMI cutoffs of 50 cm^2/m^2 in men and 39 cm^2/m^2 in women have been identified to optimally predict waitlist mortality in ESLD patients awaiting LT (116). Total psoas area and SMI correlate with poor outcomes in the LT population (36,117-120). LT candidates at the lowest percentiles of total psoas area are 2 to 3.5 times and 4.5 times more likely to die and acquire severe infections after LT, respectively (117-119). SMI is predictive of post-LT hospital length of stay (36). In a meta-analysis, sarcopenia increases risk of waitlist (HR 1.72, 95% CI, 0.99–3.00, P=0.05) and post-LT (HR 1.84, 95% CI, 1.11–3.05, P=0.02) mortality, independent of the MELD score (120). Muscle function may be assessed by hand-grip strength test and a 6-minute walk test (34). Cirrhotic patients whose hand-grip strength is more than 2 standard deviations from the mean have lower transplant-free survival (1 year: 69.0% *vs.* 100.0%) and more frequent hepatic decompensation events (1 year: 65.5% *vs.* 11.8%) (121). Patients who perform better in 6-minute walk tests have lower waitlist mortality (HR 0.58 per 100 meters, 95% CI, 0.37–0.93, P=0.02) (122). Modifying the MELD score to include sarcopenia enhances the prediction of waitlist mortality in patients with cirrhosis, potentially opening room for improvement in donor and organ allocation (123).

Sarcopenic LT candidates should consume adequate amounts of calories and protein and exercise regularly. Calorie intake in NASH-related cirrhosis, where obesity is prevalent, should be stratified by BMI using ideal body weight: 20–25 kcal/kg/day for BMI ≥40 kg/m^2, 25–35 kcal/kg/day for BMI 30–40 kg/m^2, and 35–40 kcal/kg/day for BMI 20-30 kg/m^2 (124). The recommended protein intake is 1.2–1.5 g/kg/day (124). Small frequent meals during waking hours and a carbohydrate-rich nighttime snack should be encouraged to avoid starvation which increases muscle and lipid breakdown (124,125). Supervised moderate-intensity aerobic exercise improves exercise endurance, muscle mass and strength, and quality of life without associated adverse events (126,127). LT candidates may be advised to engage in 30- to 60-minute sessions of light to moderate aerobic exercise and low-weight resistance training daily, under a physiotherapist's supervision if possible, to achieve ≥150 minutes of physical activity weekly for at least 3 months (128). Balance training and stretching are recommended, especially in severely sarcopenic patients, to strengthen core muscles and improve range of motion (128). Exercise should match patients' baseline function and effort level since fatigue is a major barrier (129). It is worth noting that trials of exercise in cirrhosis exclude patients with decompensated cirrhosis who make up the majority of LT candidates. There is concern that exercise increases risk of variceal bleeding since a previous showed that exercise increases portal pressure by up to 30% (130). However, recent randomized trials prove that light-moderate physical exercise actually reduces portal pressure (1.5–2.5 mmHg on average) and are not associated with variceal bleeding (101,131). However, it is probably prudent to screen and eradicate high-risk varices before embarking on an exercise program. Pre-exercise evaluation is rarely required since LT candidates already require cardiopulmonary work-up and clearance as part of LT evaluation.

Frailty assessment

The increasing number of successful LT in elderly patients suggests that perhaps frailty, instead of chronologic age, may be a better criterion of transplant candidacy. Several validated frailty assessment tools are available. The Fried Frailty Instrument (FFI) assesses patients' gait speed and hand grip strength, physical activity, and self-reported exhaustion and unintentional weight loss (23). The Short Physical Performance Battery (SPPB) measures patients' performance on repeated chair stands, balance testing and 13-foot walk (25). Both tools predict waitlist mortality and unplanned hospitalizations in outpatients being evaluated for LT (23,25). Recently, a Liver Frailty Index (LFI), composed of hand grip strength, chair stands and balance time, was developed specifically for LT candidates and has been shown to improve waitlist mortality prediction when combined with the MELD score (132). Activities of daily living (ADL) and the Karnofsky Performance Score (KPS) are easy-to-use tools that are also validated to predict mortality in LT candidates (133,134). Transplant centers are recommended to include frailty screening using standardized tools in LT evaluation (22). A one-time assessment of frailty should not contraindicate LT; instead, frailty should be integrated with the rest of the evaluation to guide transplant decision-making (22). Frailty assessments over time are recommended to assess for a decline in physical frailty, which predicts waitlist mortality (135). No single frailty assessment tool is recommended for routine use. Tools should be selected based on the clinical setting (outpatient *vs.* inpatient, transplant *vs.* non-transplant), available time and resources, and the impact of the test result on clinical decision-making (22).

Frailty is potentially reversible. While all LT candidates should receive guidance on nutrition and physical activity, the degree of frailty guides the intensity of recommended interventions. A short course of inpatient rehabilitation, with possible inactivation from the waitlist and close follow-up every 2–4 weeks, may be considered for severely frail LT candidates, while supervised home-based exercise programs and follow-up every 1-3 months may be prescribed for the less frail (22).

Screening for alcohol use

Although NAFLD by definition excludes significant alcohol use (≥21 and ≥14 standard drinks per week in men and women, respectively), 60% of patients with NAFLD will consume alcohol in their lifetime (136). Some data suggest that light alcohol drinkers are less likely than lifetime abstainers to have histologic NASH or advanced fibrosis (137,138). However, the typical LT candidate with decompensated cirrhosis is not represented in these studies. Any alcohol use increases risk of HCC in patients with NASH-related cirrhosis (HR 3.8, 95% CI, 1.6–8.9, P<0.01) and the risk is not modified by volume of alcohol consumed (139). Despite lack of direct data, light alcohol use can be inferred to increase risk of hepatic decompensation in NASH-related cirrhosis since light alcohol use increases portal pressures and accelerates fibrosis progression (140,141). Hence, LT candidates with NASH should be screened for alcohol use and advised to abstain completely.

HCC surveillance

LT candidates with NASH should be enrolled in an HCC surveillance program. NASH patients are less likely to undergo HCC screening and receive treatment for HCC than patients with alcohol- or hepatitis C-related liver disease (142). Patients found to have large or multifocal HCC exceeding Milan or UCSF criteria, macrovascular tumor invasion, or extrahepatic disease should not undergo LT due to high rates of post-LT mortality and HCC recurrence (83,143). HCC surveillance also permits identification of patients eligible for MELD exception points and those who may benefit from tumor downstaging to facilitate LT (61,144). Abdominal US, with or without alpha fetoprotein (AFP), every 6 months is the recommended modality for HCC surveillance (145). US has pooled sensitivity of 84% in detecting HCC of all stages, but only 47% for early HCC (146). AFP, at a diagnostic cut-off of 20 ng/mL, has sensitivity and specificity of 90% and 85%, respectively, in detecting NASH-related HCC (147). Combining AFP with US increases sensitivity (from 45% to 63%), but lowers specificity (from 92% to 84%) for detection of early HCC (146). HCC surveillance is associated with a 30–40% reduction in mortality risk and higher likelihood of early stage HCC and receipt of curative treatment (148,149).

Obesity complicates HCC surveillance in LT candidates with NASH as it increases the likelihood of false negative US exams. In patients with BMI >35 kg/m^2, up to 35–40% of US are inadequate to exclude HCC, compared with <10% in patients with normal BMI (150). Guidelines recommend considering multiphase contrast-enhanced CT or MRI for HCC surveillance in patients likely to have an inadequate US such as the morbidly obese (145).

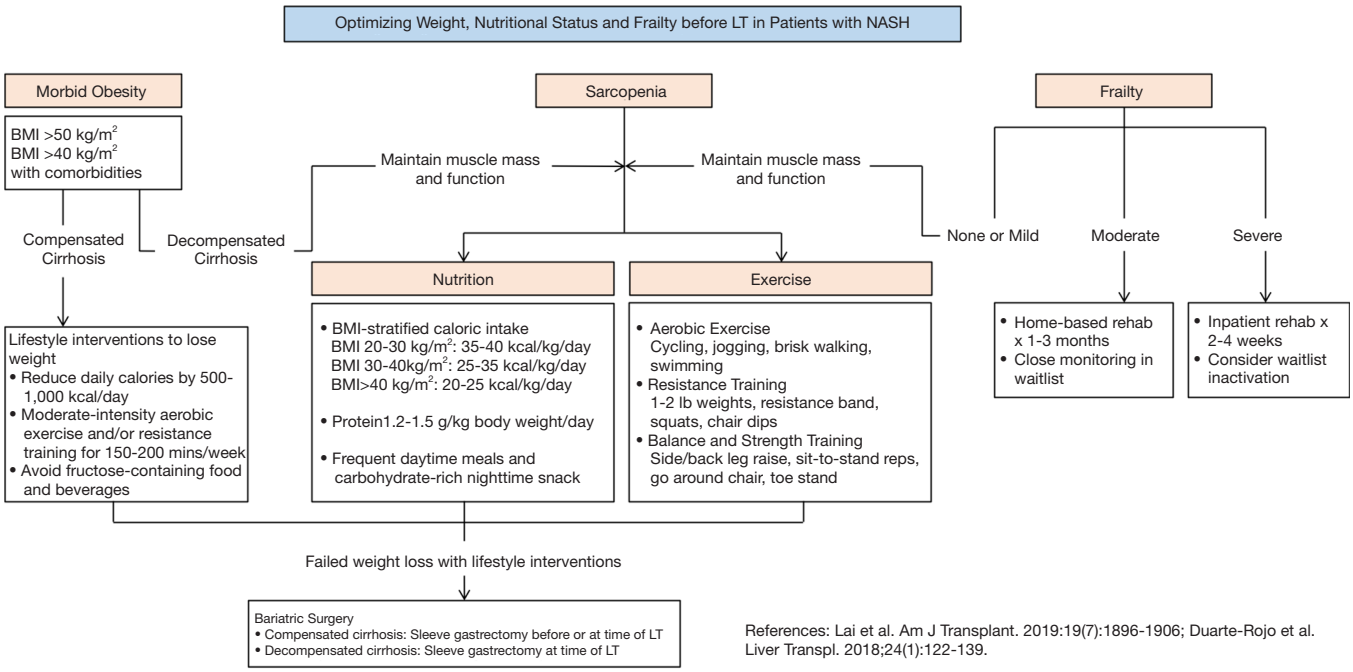

Figure 2 Optimizing pre-transplant weight, nutritional status and frailty in patients with NASH. LT, liver transplantation; NASH, non-alcoholic steatohepatitis. Abbreviations: BMI=body mass index, kcal kilocalories, kg=kilogram, lb=pounds.

Triple phase CT and gadoxetic acid-enhanced MRI have sensitivities of 85-90% and 88% and specificities of 85–90% and 94%, respectively, in detecting HCC (151,152). Head-to-head comparisons of US-, CT- and MRI-based HCC surveillance show that CT has slightly lower sensitivity (66.7% *vs.* 71.4%) and specificity (94.4% *vs.* 97.5%), while MRI has higher HCC detection rate (86.0% *vs.* 27.9%, P<0.001) and lower false positive rate (3.0% *vs.* 5.6%, P=0.004) than US (153,154). Routine use of CT and MRI is generally limited by cost, although a new study suggests that MRI may be more cost-effective than US for patients at highest risk for HCC (155). To address long MRI scan times and high costs, an abbreviated MRI protocol has been developed that has >80% sensitivity and >90% specificity for HCC detection (156). However, only a small percentage of patients included in these studies have NAFLD/NASH. Hence, there is insufficient data at present to recommend routine CT- or MRI-based HCC surveillance for patients with NASH-related cirrhosis.

Cardiovascular risk assessment

Serious perioperative CV complications are a threat to LT candidates with NASH-related cirrhosis due to the presence of co-morbid CVD, CV risk factors, and CV physiologic derangements in decompensated cirrhosis that include high cardiac output, systemic vasodilation, blunted inotropic and chronotropic responses to stress, and diastolic dysfunction (43,60,157,158). CV risk assessment includes an appraisal of clinical CV risk factors and a battery of diagnostic cardiac testing. The objective of CV risk assessment is to identify patients with very severe CVD who should not undergo LT and patients who may benefit from CV risk-reducing interventions that will facilitate safe LT (*Figures 2,3*).

Clinical risk factors

Traditional coronary risk factors include age >45 years for males and >55 years for females, hypercholesterolemia, HTN, DM, tobacco use, and family history of early CAD. CAD risk increases in parallel with number of risk factors (159,160).

12-lead electrocardiogram (12-L EKG)

12-L EKG identifies cardiac arrhythmias and may detect asymptomatic CAD. The presence of Q waves pre-LT predicts acute coronary syndrome and cardiac arrhythmias after LT (161). Half of patients with cirrhosis will have QTc

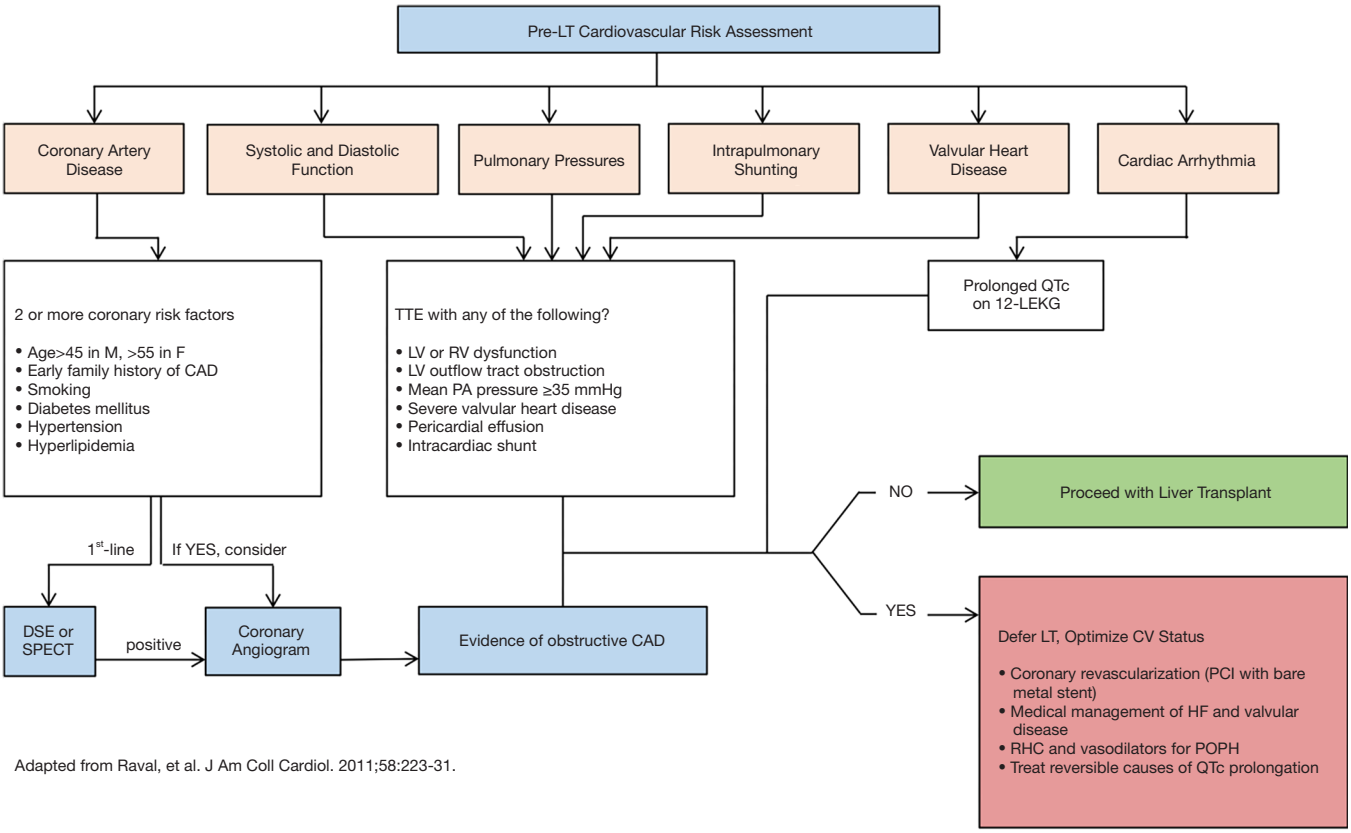

Figure 3 Algorithm for pre-transplant cardiovascular risk assessment in patients with NASH. TTE, transthoracic echocardiography; NASH, non-alcoholic steatohepatitis. Abbreviations: 12-LEKG=12-lead electrocardiogram, CAD=coronary artery disease, CV=cardiovascular, DSE=dobutamine stress echocardiography, HF=heart failure, LT =liver transplantation, LV=left ventricle, PA=pulmonary artery, PCl=percutaneous coronary intervention, POPH=portopulmonary hypertension, RHC=right heart catheterization, RV=right ventricle, SPECT=single-photon emission computed tomography.

prolongation ≥440 milliseconds, which is associated with decreased survival (162). Diagnosis of QTc prolongation should prompt a search for and treatment of reversible causes such as electrolyte disturbances and QTc-prolonging medications, although QTc prolongation is potentially part of the overall CV disturbance in cirrhosis (163).

Contrast-enhanced echocardiography (CE-TTE)

CE-TTE assesses left and right ventricular size and function, valvular function, intracardiac or intrapulmonary shunting, and pulmonary artery (PA) pressure. Even mildly depressed left ventricular (LV) ejection fraction should prompt an evaluation for underlying cardiomyopathy or CAD since patients with decompensated cirrhosis typically have a hyperdynamic circulation (164). LV systolic dysfunction is not an absolute contraindication for LT, but requires aggressive medical management to reduce risk of perioperative CV complications (159,165). Diastolic dysfunction and impaired systolic response to stress are frequently found in cirrhosis and are potentially reversible with LT (166). LT is contraindicated in patients with moderate to severe tricuspid regurgitation due to increased risk of post-LT mortality (167,168), although successful simultaneous LT and tricuspid valve repair has been previously reported (169). A retrospective study does not find increased mortality in LT candidates with aortic stenosis (170). None of the patients in this study has severe aortic stenosis and LT is typically not offered to patients with severe aortic stenosis. However, successful LT followed by aortic valve replacement has previously been reported (171). CE-TTE should evaluate for clinically significant LV outflow tract obstruction due to LV

hypertrophy and hyperdynamic circulation as this may cause intraoperative hypotension (172).

CE-TTE is useful in diagnosing hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). HPS is characterized by hypoxemia due to intrapulmonary shunting in patients, while POPH refers to pulmonary arterial hypertension in the setting of portal hypertension after excluding alternative etiologies (173). Intrapulmonary shunting is indicated by the appearance of agitated saline bubbles in the left atrium after 3–5 cardiac cycles (174). Increased PA pressure on TTE is 97% sensitive, but only 77% specific, in diagnosing POPH (175). Although 20% of LT candidates have elevated PA pressures, <5% are due to POPH and the rest are due to volume overload or cirrhotic cardiomyopathy (176). Patients with PA systolic pressure ≥45 mmHg should undergo right heart catheterization to confirm POPH (16). Vasodilators should be considered in moderate (mean PA pressure 35–50 mmHg) or severe (mean PA pressure ≥50 mmHg) POPH. Persistent moderate and severe POPH despite vasodilator therapy are contraindications to LT, with post-LT mortality approaching 100% (177).

Non-invasive stress testing

Abnormal findings on 12-L EKG and CE-TTE, cardiac symptoms, or the presence of multiple coronary risk factors warrant testing for obstructive CAD (159,178). First-line non-invasive testing for CAD includes dobutamine stress echocardiography (DSE) and single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). Coronary artery calcium (CAC) score and coronary CT angiography (CCTA) are newer modalities that have been proposed for pre-LT CV risk assessment due to modest accuracy in predicting post-LT CV events (179,180). Non-invasive stress testing has important limitations in the ESLD population. First, most LT candidates are unable to exercise due to a combination of sarcopenia, anemia, and ascites. Second, patients with decompensated cirrhosis may not reach target heart rate due to chronotropic incompetence or beta-blockade, hence limiting the accuracy of DSE. Third, systemic vasodilation increases false negatives, while coronary microvascular dysfunction increases false positives in SPECT MPI (181). With coronary angiography (CAG) as gold standard, DSE and SPECT have poor sensitivity (<35%) and PPV (20%), but modest specificity (60–90%) and NPV (75–90%) (182-184). Two systematic reviews conclude that pre-LT non-invasive stress testing does not satisfactorily predict post-LT CV events and all-cause mortality (185,186). Current data indicate that non-invasive stress testing is potentially no better than conventional clinical risk scoring in predicting major adverse cardiac events and need for invasive cardiac testing in LT candidates. The role of stress testing in pre-LT CV risk assessment should be decided by individual transplant centers, based on local experience and expertise (84).

Coronary angiography

CAG is recommended in patients with abnormal non-invasive stress testing and may be considered as first-line cardiac testing in patients with high pre-test probability of CAD who are unable to undergo non-invasive testing. In one center, up to 70% of LT candidates undergo CAG as first-line screening for CAD on the basis of coronary risk factors alone, and this approach predictably increased percutaneous coronary intervention (PCI) rates (8% *vs.* 1%) and interestingly reduced 1-year mortality (6% *vs.* 10–16%, P<0.001) and myocardial infarction rates (0.6% *vs.* 1.7%, P<0.001) (187). PCI should be considered in symptomatic patients or in asymptomatic patients with significant CAD (e.g., ≥70% occlusion) where the extent of disease precludes LT. Drug-eluting stents should be avoided because of the need for prolonged dual antiplatelet therapy, which delays LT and increases bleeding risk in already coagulopathic patients. Major bleeding occurs more frequently after CAG in LT candidates compared to matched controls without ESLD (14.8% *vs.* 3.8%, P=0.014) (188). ESLD patients are theoretically at risk for contrast-induced nephropathy due to their usually tenuous renal function, although the incidence of acute kidney injury after CAG is <5% (189). Simultaneous coronary artery bypass grafting (CABG) and LT can be considered and has been reported without major post-operative complications (190). No study to date has evaluated if routine pre-LT CAG and revascularization in asymptomatic LT candidates with NASH improves outcomes. However, pre-operative coronary revascularization before major vascular surgery, which ostensibly carries higher perioperative cardiac mortality than LT, does not improve survival (191). Moreover, the incidence of early post-LT CV mortality in registry studies (1.2%) is comparable to that in other major surgeries where CAG and revascularization are not recommended in asymptomatic patients because of lack of survival benefit, associated risks, and potential for

procedural delays (178,192).

Should CV risk assessment be different in NASH?

Although CVD is highly prevalent in LT candidates with NASH, there is insufficient evidence to support utilizing a different approach to pre-LT CV risk assessment in LT candidates with NASH. Assessment for CV risk factors, 12-L EKG and CE-TTE should be routinely performed. Non-invasive stress testing should likely be performed due to high likelihood of multiple CV risk factors, including NASH itself, and silent CAD. There is currently no evidence to support routine CAG in asymptomatic patients with NASH despite their increased CV risk. CAG is probably best reserved for symptomatic patients, patients with abnormal non-invasive stress test, or patients with multiple coronary risk factors who are unable to undergo non-invasive stress testing.

In conclusion, LT evaluation in patients with NASH is a multidisciplinary undertaking that takes into consideration the unique demographic and clinical features of patients with NASH-related cirrhosis that impact LT outcomes. Nutritional status, sarcopenia, frailty, and CV and metabolic co-morbidities and risk factors should be assessed during LT evaluation and optimized in preparation for LT.

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Footnote

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