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International Liver Transplantation Consensus Statement on end-stage liver disease due to nonalcoholic steatohepatitis and liver transplantation

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Abbreviations

American Association of the Study of Liver Disease; AASLD

American Heart Association; AHA

European Association for the Study of the Liver; EASL

Organ Procurement and Transplantation; OPTN

Scientific Registry of Transplant Recipients; SRTR

United Network for Organ Sharing; UNOS

Alcoholic liver disease; ALD

Angiotensin-converting-enzyme inhibitors; ACEI

Angiotensin-receptor blockers; ARB

Bariatric surgery; BS

Body mass index; BMI

Cardiac magnetic resonance; MRA

Cardiovascular; CV

Coronary artery disease; CAD

Coronary angiography; CAG

Coronary artery bypass grafting; CABG

Coronary artery calcium score; CACS

Coronary computed tomography angiography; CCTA

Diabetes Mellitus; DM

Dobutamine stress echocardiography; DSE

Electrocardiography; EKG

Estimated glomerular filtration rate; eGFR

Hepatitis B virus; HBV

Hepatitis C virus; HCV

Hepatic venous portal gradient; HVPG

Hepatocellular carcinoma; HCC

Liver transplantation; LT

Model for end-stage liver disease; MELD

Negative predictive value; NPV

Nonalcoholic fatty liver disease; NAFLD

Nonalcoholic steatohepatitis; NASH

Percutaneous coronary intervention; PCI

Positive predictive value; PPV

Randomized controlled trials; RCTs

Roux-en-Y gastric bypass; RYGB

Simultaneous liver- kidney transplantation: SLK

Single-photon emission computed tomography; SPECT

Sleeve gastrectomy; SG

Abstract: Nonalcoholic steatohepatitis (NASH)-related cirrhosis has become one of the most common indications for liver transplantation (LT), particularly in candidates over the age of 65 years. Typically, NASH candidates have concurrent obesity, metabolic and cardiovascular risks, which directly impact patient evaluation and selection, waitlist morbidity and mortality and eventually posttransplant outcomes. The purpose of these guidelines is to highlight specific features commonly observed in NASH candidates and strategies to optimize pretransplant evaluation and waitlist survival. More specifically, the working group addressed the following clinically-relevant questions providing recommendations based on the GRADE system supported by rigorous systematic reviews and consensus: (1) Is the outcome after LT similar to that of other etiologies of liver disease? (2) Is the natural history of NASH-related cirrhosis different from other etiologies of end-stage liver disease? (3) How should cardiovascular risk be assessed in the candidate for LT? Should the assessment differ from that done in other etiologies? (4) How should comorbidities (hypertension, diabetes, dyslipidemia, obesity, renal dysfunction, etc.) be treated in the candidate for LT? Should treatment and monitoring of these comorbidities differ from that applied in other etiologies? (5) What are the therapeutic strategies recommended to improve the cardiovascular and nutritional status of a NASH patient in the waiting list for LT? (6) Is there any circumstance where obesity should contraindicate LT? (7) What is the optimal time for bariatric surgery: before, during, or after LT? and (8) Donor steatosis: how much relevant is it for LT in NASH patients

In the United States (US), nonalcoholic steatohepatitis (NASH) cirrhosis has become the second most common indication for liver transplantation (LT) waitlisting, and the third indication for LT, particularly in candidates over the age of 65 years [1-10]. In addition, NASH is the most rapidly growing indication for simultaneous liver- kidney transplantation (SLK) also in the US[7]. Similar trends, but still not reaching the numbers of US registries, have been reported elsewhere. Because of frequent comorbidities that increase the risk of cardiovascular (CV) disease, the outcome and management of NASH candidates may differ from that of other indications [1-11].

The ILTS convened a consensus conference in Venice on February 15, 2018, comprised of a global panel of expert hepatologists and transplant surgeons, to develop guidelines on key aspects of NASH in relation to liver transplantation. This is 1 of the 6 manuscripts that have been put together by the various working groups and focuses on end stage liver disease and liver transplantation related to NASH. There were 8 predefined questions that were addressed by the consensus panel. These questions were addressed through critical literature review, followed by working group proposals and subsequent consensus, which was reviewed by the whole group. The guidelines are presented using the Grading of Recommendations Assessment Development and Evaluation approach [1]. This method includes consideration of the quality of evidence, benefits and harms, values and preferences, resource use, and cost effectiveness. Quality of the evidence was rated as very low, low, moderate, or high. The strength of the recommendation was rated as strong or conditional (weak) and reflects confidence that adherence to guidance will result in more good than harm

1-Is the outcome after LT similar to that of other etiologies of liver disease?

Recommendations

The outcome of LT in patients with NASH-related cirrhosis with or without hepatocellular carcinoma (HCC) does not differ from that of other liver transplant etiologies as posttransplant survival is similar (Quality of evidence High level; Strength of recommendation: strong)

Background

A systematic review published in 2014 which included 9 publications with a total of 717 transplants in NASH patients and 3520 transplants in non-NASH indications found that survival at 1 (OR: 0.77; 95% CI: 0.59-1; p=.05;), 3 (OR: 0.97; 95% CI: 0.67-1.40; p=.86); and 5 (OR: 1.09; 95% CI: 0.77-1.65; p=.63) years postliver transplantation was similar between these 2 groups [2]. The same study demonstrated a higher mortality due to CV causes (OR: 1.65; 95% CI: 1.01-2.70; p=.05) and sepsis (OR: 1.71; 95% CI: 1.17-2.50; p=.006) in NASH-indications. However, patients with NASH were at lower risk of graft failure compared with patients without NASH (OR, 0.21; 95% CI, 0.05-0.89; P = .03).

Interestingly, NASH-cirrhotic patients had distinctive features at time of transplantation compared to the non-NASH candidates including older age, higher body mass index (BMI) and greater frequency of diabetes (DM), arterial hypertension, dyslipidemia, obesity and history of CV events; in addition, the prevalence of women was higher and that of concurrent HCC lower. Importantly, model-for-end-stage liver disease (MELD) score at transplantation was similar between the 2 groups.

Two large studies using large North American Registries also found similar survival rates following LT. In the first study by Charlton et al[3] based on the Scientific Registry

of Transplant Recipients (SRTR), both graft and patient survival at 3 years posttransplantation did not differ between the 1959 NASH-patients and 33 822 non-NASH patients (p=0.67) undergoing transplantation from 2001 to 2009. Patient survival estimates at 1 and 3 years after LT for NASH were 84% and 78%, respectively, compared with 86% and 79% for cryptogenic cirrhosis and 87% and 78% for other indications (p= .67). Patient and graft survival after LT for recipients with NASH was similar to that of other indications in multivariate analysis after adjusting for creatinine level, gender, age, and BMI.

In the study by Afzali et al[4], the authors used data provided by the United Network for Organ Sharing (UNOS) for first-time adult deceased donor LT performed in the US between 1997 and 2010. Posttransplant survival of patients with NASH (n = 1810) at 1 (87.6%), 3 (82.2%), and 5 years (76.7%) was superior to the survival of patients with HCC, hepatitis C virus (HCV), alcoholic liver disease (ALD), acute hepatic necrosis, hemochromatosis, or cryptogenic liver disease and was inferior to the survival of only 4 groups of patients (those with primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, or hepatitis B virus-HBV), with results not differing after adjusting for both donor and recipient characteristics.

More recent analyses of US registries [5,6] confirm previous findings. In the recent cohort study utilizing the UNOS and Organ Procurement and Transplantation (UNOS/OPTN) 2003-2014 database, the outcome of 63,061 adult patients undergoing LT from 2003 to 2014 was evaluated [5]. The study included 20 782 HCV (32.96%), 9470 ALD (15.02%), and 8262 NASH (13.11%) patients. Posttransplant survival in NASH was significantly higher compared to HCV (5-year survival: NASH -77.81%, 95% CI 76.37-79.25 vs. HCV -72.15%, 95% CI 71.37-72.93, P < .001). In the multivariate Cox proportional hazards model, NASH demonstrated significantly higher posttransplant survival

compared to HCV (HR 0.75; 95% CI 0.71-0.79, P < .001). As in previous studies, patients with NASH were more likely to be women, had higher body mass index and a higher prevalence of diabetes and history of cardiac disease.

Similar findings have been reported in NASH patients with additional comorbidities such as severe renal disease requiring SLK transplantation[7], or coexistence of HCC[8]. In one registry study based on UNOS database (2002-2011)[7], of the 38 533 liver transplants performed during that study period, about 5.6% (N = 2162) received SLK transplantation with 584 (6.2%), 320 (8.7%), and 1258 (5%) belonging to immune- or alcohol-related indications (primary biliary cholangitis, primary sclerosing cholangitis or alcoholic cirrhosis (group I), NASH, and cryptogenic cirrhosis with BMI greater than 30 (group II), and HCV with and without alcohol, HBV, and HCC (group III), respectively. Five-year outcomes were similar comparing the NASH group (group II) versus group I for liver graft (78 vs 74%, P = 0.14) and patient survival (81 vs 76%, P = 0.07). In contrast, kidney graft outcome was worse for group II (70 vs 79%, P = 0.002). Risk of kidney graft loss was over 1.5-fold higher among group II SLK recipients compared to group I after controlling for recipient characteristics.

Using a 2-center retrospective design, Sadler et al analyzed the outcome of all patients from 2004-2014 that received LT for HCC and compared the outcome of those transplanted for HCC on top of NASH (60/929, 6.5%) vs the remainder non-NASH patients[8]. There were no significant differences between groups for pretransplant or explant tumor characteristics. The actuarial 1-, 3- and 5-year overall survival was 98%, 96% and 80% in NASH vs. 95%, 84% and 78% in non-NASH (p=0.1).

In summary, in most studies NASH patients have been shown to have similar survival rates compared to patients without NASH even though their profile is consistent with a high-risk candidate (older, greater rate of obesity, more likely to be diabetic, more likely

to have prior history of CV events)[1-17]. It is likely that these results may be explained in part, by the lower risk of graft failure compared to other indications, particularly HCV. These results may change with the introduction of the extremely effective oral antiviral drugs against HCV. Alternatively, extensive screening for CV disease in patients with NASH-related cirrhosis may have led to an exclusion of the "poor NASH candidates (with significant CV disease)" allowing the inclusion in the LT waiting list of those considered "the best NASH candidates". Interestingly though, both single center studies, studies from large registries and systematic reviews have demonstrated that CV deaths constitute a higher proportion of deaths among NASH patients compared to non-NASH transplant recipients [1-17]. In addition, mean follow up in many of these studies is less than 5 years. It is still unknown if results will change with longer follow up, as more CV disease develops in NASH-patients.

2-Is the natural history of NASH-related cirrhosis different from other etiologies of end-stage liver disease?

Statements: Limited data are available. Patients with NASH-related cirrhosis have increased cardiovascular morbidity and mortality compared to patients with cirrhosis of other etiologies. Patients with NASH cirrhosis have lower mortality rates in the compensated state (Child Pugh A) but similar mortality in the decompensated state (Child Pugh B and C) compared to HCV-related cirrhosis.

Background:

In a prospective follow-up of 256 adult patients with compensated NASH-related cirrhosis, 49 subjects (19%) experienced liver-related clinical events after a follow-up of 26.7 months[18]. At 24 months, event free survival was 92% in patients with a hepatic

venous portal gradient (HVPG)<10 mmHg compared to 75% in those with HVPG ≥10 mmHg. In the multivariate analysis, independent predictors of clinical events were higher baseline HVPG, greater change in HVPG over time and lower baseline albumin.

In a case control study from Australia that included 23 patients with NASH cirrhosis and 46 patients with HCV cirrhosis, the prognosis of patients with NASH cirrhosis was similar to or better than that of HCV-related cirrhosis[19]. In a case control study from Japan that included 68 patients with NASH-related cirrhosis and 69 patients with HCV-related cirrhosis, the 5-year HCC rate was higher in HCV cirrhosis (30.5% in HCV versus 11.3% in NASH) but the 5-year survival rates were similar (73.8% in HCV versus 75.2% in NASH)[20]. The authors of these 2 studies did not perform comparisons according to Child Pugh class. In a US case-control study of 152 patients with NASH-related cirrhosis and 150 patients with HCV-related cirrhosis, patients with Child class A NASH cirrhosis had lower mortality compared to Child class A HCV cirrhosis (3/74 vs. 15/75, P<0.004) whereas there was no difference in mortality in Child Pugh B/C cirrhosis[21]. Patients with Child class A cirrhosis due to NASH also had a significantly lower risk of decompensation (P<0.07). Patients with NASH had higher cardiac mortality (8/152 vs. 1/150, P<0.03)[21].

In a follow-up of 218 patients with NASH cirrhosis listed for LT, NASH-patients were older and had more comorbidities despite a similar MELD score compared to patients with HCV cirrhosis[22]. Patients with NASH cirrhosis and MELD ≤15 were less likely to receive LT and more likely to die or delisted from the wait list because of comorbidities compared with patients with HCV-related cirrhosis. The median progression rate among patients with NASH was 1.3 MELD points per year versus 3.2 MELD points per year for the HCV group (P=0.003). Among patients with MELD scores >15, there were no differences between groups in percentage that received transplants or rate of MELD score progression[22].

In a study from the UNOS database, among US adults with HCC listed for LT, patients with NASH-HCC were significantly less likely to have active MELD exceptions compared with HCV-HCC, and those without active exception had a lower likelihood of receiving LT [23]. The authors postulated that this could be due to a higher rate of comorbid conditions in patients with NASH and/or better hepatic function and slower progression of cirrhosis in the NASH-HCC group.

3-How should CV risk be assessed in the NASH-candidate for LT? Should the assessment differ from that done in other etiologies?

Recommendations

1- Liver transplant candidates with NASH should be considered at high risk of developing cardiovascular events before and after transplantation (Quality of evidence: high; Strength of recommendation: strong).

2- The accumulation of cardiovascular risk factors should be carefully assessed by a multidisciplinary team, which should include a cardiologist and anesthesiologist with special interest in transplantation (Quality of evidence: low; Strength of recommendation: strong).

3- While NASH is considered an independent risk factor for cardiovascular events similar to other traditional risk factors, there is not enough evidence to support a different approach to the pre-LT cardiovascular assessment. (Quality of evidence: moderate; Strength of recommendation: strong).

4- There is insufficient evidence to recommend a specific cardiovascular risk algorithm for NASH patients undergoing liver transplantation evaluation. The algorithm, and particularly the place of stress tests will be determined in part by local expertise (Quality of evidence: moderate; Strength of recommendation: moderate IIa)

Background:

NAFLD and cardiovascular disease

Typically, NASH patients have a metabolic profile compatible with high CV risk, which makes them more likely to present with silent CV disease [2,10-14,24]. Indeed, a growing body of evidence supports the existence of a bidirectional relationship between nonalcoholic fatty liver disease (NAFLD) and the metabolic syndrome, particularly hypertension and type II DM [24]. Importantly, the metabolic syndrome, at the heart of NASH, encompasses well-known CV risk factors, including central obesity, atherogenic dyslipidemia, together with hypertension and type II DM. It should not be a surprise then that NASH is strongly linked to an increased risk of developing fatal and nonfatal CV events. Whether NAFLD by itself (though multiple pathophysiological derangements, including chronic inflammation, hypercoagulation, chronic kidney disease, etc..) independently contributes to the development of CV disease is still a topic of debate but increasingly data points towards that independent effect.

The spectrum of CV complications associated with NAFLD is very wide ranging from premature atherosclerosis to aortic valve sclerosis and left ventricular dysfunction/hypertrophy leading to congestive heart failure and cardiac arrhythmias (mainly atrial fibrillation and QTc interval prolongation)[24]. In a recent metaanalysis including almost 34 000 individuals from 16 observational studies, the authors

concluded that the presence of NAFLD (diagnosed through imaging or histology) was associated with a 65% increased risk of developing fatal and nonfatal CV events over a medium follow up of almost 7 years [25]. Importantly, the authors also showed how this risk increased with increased severity of the liver disease [25]. Based on this strong link between the presence and severity of NAFLD and the increased risk of CV disease, most Societies have suggested that NAFLD by itself, regardless of other known risk factors, identifies a subset of patients with a higher risk of CV disease mortality and morbidity over time, and thus recommend a thorough CV risk assessment [26]. It is important to highlight that cirrhosis is the end-spectrum of NAFLD, representing those with the most severe form of liver disease, and as such, in theory at least, at highest risk of CV disease. Cohort studies as well as systematic reviews and metaanalysis have shown that waitlist patients with NASH are typically older compared to those with other etiologies, more likely to be female, more likely to be diabetics and obese and with worse renal function[2,6]. Compared to other cirrhotic patients, NASH-cirrhosis is associated with a higher risk of CV events after LT, particularly in the early postoperative period[14]. In addition, several studies have also documented that patients with end-stage liver disease due to NASH have higher rates of coronary artery disease (CAD) than those of other etiologies [27-31].

CV risk assessment of the LT candidate

The stress inherent to transplantation, including surgery itself, and complications that may occur in the postoperative period, can transform silent CV disease into serious CV events, eventually increasing mortality. Therefore, it is essential that the pretransplant evaluation includes a thorough CV evaluation both structural and functional in conditions of rest and stress to reveal (and correct if possible) any significant CV

disease. Unfortunately, defining what should be the best approach to adequately assess the CV risk in LT candidates is a focus of intense and moving debate. Recognizing the hemodynamic challenges encountered by LT patients in the perioperative period and how these responses can be exacerbated by underlying cardiac pathology is critical in developing recommendations for the preoperative risk assessment and management of these patients[32]. Overall, CV assessment should reveal subclinical CAD, porto-pulmonary hypertension and myocardial disease and should be used to either treat abnormal findings and/or deny transplantation to those where the risk is too high and who are nontreatable. Patients with overt heart failure due to cardiac disease will most likely not benefit from LT and have significant postoperative morbidity and mortality related to worsening heart failure[32]. In addition, patients with moderate to severe porto-pulmonary hypertension who do not respond to vasodilator therapy should not be considered for LT[33]. Finally, high-risk patients with CAD not amenable to revascularization or those with concurrent left ventricular dysfunction will also not likely benefit from LT [31].

Unfortunately, despite a clear understanding that CV events represent a source of morbidity and mortality, risk stratification approaches and performance characteristics of different cardiac testing modalities remain unclear. In a recent systematic review aimed at characterizing the incidence and risk factors for CV events post-LT, which included 29 studies representing 57 493 patients, definitions of CV outcomes were highly inconsistent. Incidence rates were widely variable: 1% to 41% for outcomes at 6 months or shorter and 0% to 31% for outcomes longer than 6 months. Multivariate analyses demonstrated that older age and history of cardiac disease were the most consistent predictors of CV events posttransplant. Unfortunately, the predictive capacity of various cardiac imaging modalities was also discrepant. Based on these data, the

authors concluded that the true incidence of CV outcomes post-LT remains unknown in large part due to lack of consensus regarding outcome definition[34].

Of note, patients with established CAD who undergo LT have worse outcomes than patients without CAD. In one study, 1-year mortality rate of about 40% was reported[31], although improvements in screening and perioperative care have reduced early posttransplant deaths substantially. More recent reports indicate mortality hazard ratios in patients with clinical CAD of 2.0 – 3.9 against 1-year all-cause mortality rates of 4-5%, suggesting a risk of 8 – 18%[34-38]. Since severe multivessel disease or inducible ischemia may justify intervention in these patients, a strategy of stress-testing and coronary angiography (CAG) is generally accepted.

Addressing the impact and management of patients with clinically silent disease is less clear[39]. The prevalence of angiographically demonstrated CAD in transplant candidates is known to be similar to that reported in the general population and higher in NASH [40, 41], but functional impairment caused by encephalopathy, sarcopenia, fluid retention and/or acute decompensation often prevents clinical assessment of cardiac reserve.

Tools to evaluate CV risk in liver transplant candidates

- ***Classical noninvasive tools***

CV evaluations are challenging in LT candidates. The majority of these patients cannot undergo cardiopulmonary exercise testing due to deconditioning, malnutrition-associated muscle weakness, ascites or anemia. Cardiac evaluation with electrocardiography (EKG) and echocardiography is done on a routine basis in most centers. A prolonged QTc is not a contraindication to LT, but should prompt a search for reversible causes, such as electrolyte disturbance (eg, hypokalemia or hypomagnesemia) or the use of QT interval-prolonging drugs[34,35]. Transthoracic

echocardiography with Doppler is recommended for all LT candidates to assess left and right ventricular size and function, valvular function, and pulmonary artery pressure. Generally, when an abnormal finding is detected using these methods, further investigations are recommended, particularly through noninvasive techniques (cardiopulmonary exercise testing, dobutamine stress echocardiography-DSE-, myocardial perfusion imaging by single-photon emission computed tomography – SPECT- and/or cardiac computed tomography), positive findings typically leading to the use of invasive CAG [42]. This has been assumed to enhance risk prediction and outcomes by identifying both candidates with disease so severe as to preclude transplant and those suitable for risk-reducing intervention. However, neither of these potential benefits has been demonstrated beyond reasonable doubt.

First, noninvasive functional testing for ischemia has limited predictive value for obstructive CAD in this population. Most patients cannot undergo exercise testing. In addition, while previous metaanalysis has suggested that DSE detects CAD with a high degree of sensitivity and specificity in the general population[42], its performance is clearly reduced in the LT setting where poor sensitivity has been reported, possibly secondary to an inability to achieve target heart rate and peak double product (heart rate multiplied by blood pressure)[43]. The use of β-blocking agents for the prevention of esophageal variceal bleeding has been found to be a common cause of failure to achieve the target heart rate in DSE. In a retrospective study of 105 cirrhotic patients who underwent both DSE and CAG, DSE was found to have a sensitivity of 13% and negative predictive value (NPV) of 75% for obstructive CAD[44]. In another analysis of LT candidates, DSE compared with CAG had 75% sensitivity and 57% specificity in detecting CAD[45]. Another series reported 9% sensitivity, 33% positive predictive value (PPV), and 89% NPV for predicting early cardiac events after LT[46]. In a large

retrospective study of 400 LT patients, preoperative DSE had a PPV of only 27% for the identification of posttransplant cardiac events (death/nonfatal myocardial infarction) within 1 month after LT but the NPV reached 89%[37]. The majority of patients in this study though had relatively low MELD scores. In a quantitative systematic review assessing DSE's use in detecting CAD and predicting perioperative and long term cardiac events in patients undergoing LT, based on 7 studies, including a total of 580 patients, the authors confirmed the limited accuracy of DSE for the detection of CAD in candidates for LT. However, among patients selected for LT, the NPV of DSE for both perioperative and long term cardiac events was found to be high[47,48]. Similarly, nuclear SPECT stress imaging cannot be effective because of the relatively low sensitivity to detect CAD in LT candidates due to the chronic vasodilatory state exhibited by patients with end-stage liver disease[49,50]. Overall, in 2 recent systematic reviews[34,51], the authors concluded that DSE and SPECT do not satisfactorily predict increased risk of perioperative major CV events or all-cause mortality among cirrhotic patients listed for LT, among small and heterogenous studies. In summary, noninvasive stress imaging has been shown to predict major adverse cardiac events no more effectively than conventional clinical risk scoring.

- ***Invasive tools***

In response to the low sensitivity of noninvasive stress imaging in the LT setting, many US centers have adopted CAG as a primary investigation in up to 80% of prospective recipients, with or without noninvasive testing[50,52]. Comparable 1-year posttransplant outcomes have been reported in retrospective studies of patients undergoing CAG compared to recipients with no CV disease, but these make no distinction between those investigated on the basis of CAD history or symptoms and those with risk factors

alone[52-54]. Therefore, although the authors interpreted their outcomes as evidence of the effectiveness of aggressive investigation and revascularization, it is also possible that a low mortality risk in a high proportion of recipients with untreated silent disease masked a lack of benefit in those undergoing intervention. Furthermore, one recent study questions routine angiography and intervention, reporting 50% posttransplant mortality in revascularized recipients[55]. In this study, among 13 patients with severe CAD, 3 underwent percutaneous coronary intervention (PCI), and 6 underwent coronary artery bypass grafting (CABG). Overall, 50% of patients who underwent either intervention died of cardiac-related causes, whereas no patient died of a cardiac-related cause after undergoing neither intervention. Some clinicians, especially outside the US, argue that an emphasis on angiographic findings of obstructive disease may underestimate the role of nonobstructive plaque and microvascular dysfunction as causes of major cardiac events in this setting. Both are common in NAFLD, and impaired microvascular perfusion is often present in the absence of obstructive epicardial disease[56]. The view that CAG and revascularization may not be beneficial in silent disease is supported by randomized studies showing that, outside the context of acute coronary syndromes, PCI offers no survival advantage in the community, nor in major vascular surgery[42]. The latter is especially significant because vascular surgery is associated with higher perioperative cardiac mortality than LT. Given the risks and delays incurred by intervention, and the absence of diagnostic randomized controlled trials (RCTs), current AHA/ACC guidelines do not recommend routine preoperative stress-testing, PCI or CABG in asymptomatic patients in other noncardiac surgical settings[42]. Moreover, the current AHA/ACC scientific statement on cardiac evaluation of LT candidates states only that noninvasive testing in LT candidates 'may be considered' in the presence of multiple (3 or more) risk factors (particularly diabetics

aged > 50 years), rating the evidence as Class IIb, Level C[42]. Despite its low sensitivity and PPV, DSE is the tool recommended by these associations because of its high NPV[39].

- ***Newer noninvasive tools***

Newer alternative modalities and strategies have recently been proposed in pretransplant cardiac evaluation, including coronary artery calcium score (CACS) and coronary computed tomography angiography (CCTA), cardiac magnetic resonance (MRA) and contrast-enhanced DSE [38, 41,56-60]. There is again debate about whether these new tools should be considered routinely for all LT candidates due to the low a priori probability of detecting severe stenosis. For instance, in a large study of 1045 asymptomatic cirrhotic patients (no history of chest pain or CAD), CCTA revealed a similar frequency of obstructive CAD in the cirrhotic (7.9%) and healthy (7.2%) cohorts[41]. In addition, although observational studies of some of these confirm threshold values of test-generated variables associated with increased risk of cardiac events and mortality [56, 60], none has been reported to be associated with hazard ratios that are prohibitive as a single factor (that is, a hazard ratio >7, which when multiplied by average risk yields an early mortality risk >30%). Again, none has been assessed in a diagnostic RCT in LT.

Finally, it is arguable that the scale of the problem of early CV mortality in LT has been overstated. 30-day CV mortality in LT was reported as 1.16% in a recent analysis of 54 697 liver recipients in the UNOS database, a low figure despite the inclusion of fatal stroke, thromboembolism and intraoperative cardiac arrests, which are often multifactorial and not conclusively cardiac[61]. Dating from 2002 – 2012, this cohort must have included a high proportion of candidates with subclinical CAD who did not

undergo CAG, but mortality was equal or lower than that seen in other high-risk surgical groups[42].

On the basis of this limited evidence, and of unpublished reports of fatal complications of CAG in this setting[62], some units are reluctant to pursue angiography and intervention on the basis of risk factors alone. Given the perceived deficiencies of noninvasive tests, some will choose to follow current AHA/ACC guidelines for noncardiac surgery and request these only in candidates with poor functional status and multiple CAD risk factors, particularly diabetics over the age of 50 years[31,63,64]. In addition, in the absence of a recognized indication for revascularization, a finding of inducible ischemia is treated as an additional risk factor, which may tip the balance against transplant without recourse to angiography[56]. The same reasoning can be applied to CCTA, CACS, and MRA, which may be useful in determining significant added risk in support of a decision not to list.

In essence, no gold standard has yet been developed for cardiac evaluation in LT candidates. LT candidates are at risk of developing a variety of cardiac-related complications, particularly those related to cardiomyopathy or CAD. However, in the US population, reported early CV mortality in LT is similar to that seen in other major procedures, for which aggressive investigation and intervention in subclinical disease is not recommended in AHA/ACC guidelines.

Routine noninvasive stress imaging may not be sufficient alone for preoperative testing as these tests do not accurately predict early cardiac risk, do not quantify plaque burden and are confounded by microvascular dysfunction in end-stage liver disease. Newer noninvasive modalities have not yet been adequately assessed in this population. To date, none has revealed new parameters reliably indicating prohibitive risk, nor has any

been shown to be of value in a diagnostic RCT in other surgical settings. However, findings on these may contribute to an overall clinical judgment of risk. These new tools seem to be reliable screening options for preoperative noninvasive evaluation of CAD in selected patients, such as those with DM or ≥ 2 traditional risk factors for CAD (age > 45 years for male or > 55 years for female, hypercholesterolemia, hypertension, tobacco use, and family history of early CAD) but further work is needed. Whether NASH patients alone without the consideration of these additional risk factors should undergo these noninvasive techniques for pre-LT evaluation is still unclear, although increasing data support the concept that it should be considered a traditional risk factor.

An abnormal noninvasive test (such as coronary artery stenosis ≥ 50% on CCTA or CACS > 400) or a high pretest probability of CAD should prompt consideration for CAG and coronary revascularization should be considered in LT candidates with obstructive CAD if the extent of CAD contraindicates transplantation. However, to date, there are no diagnostic RCTs in LT demonstrating superior outcomes with any preoperative screening strategy in patients with clinical but particularly subclinical CAD, and furthermore in other types of high-risk surgery, RCTs of noninvasive testing followed by PCI or CABG show no benefit and a potential for added risk associated with delayed surgery. Whether revascularization results in enhanced LT outcomes requires also further investigation. In units not advocating routine stress testing and CAG in candidates with silent disease, local guidelines may advocate a case-by case multidisciplinary approach, ideally involving a cardiologist with a special interest in this field.

4-How should comorbidities (hypertension, diabetes, dyslipidemia, obesity, renal dysfunction, etc.) be managed in the candidate for LT? Should treatment and monitoring of these comorbidities differ from that applied in other etiologies?

Recommendations:

- A multidisciplinary approach is recommended to establish a risk minimization plan (endocrinology and nutrition, psychology, cardiology, hepatology, surgery, anesthetist) (Quality of evidence: Moderate; Strength of recommendation: Strong).

- Appropriate screening for hypertension, diabetes, and dyslipidemia is recommended in NASH-patients with indication for LT and medical optimization is strongly recommended (Quality of evidence: moderate; Strength of recommendation: Strong).

- NASH is an independent risk factor for pre and post-LT renal dysfunction; appropriate screening and management of kidney disease is highly recommended in this patient population (Quality of evidence: high; Strength of recommendation: Strong).

- There is no data to support a different approach for the treatment and monitoring of comorbidities in NASH patients compared to other etiologies.

Background:

Age, severity of liver disease, CAD, DM, obesity, hypertension and renal failure are individual risk predictors of poor postoperative and late outcomes after LT. Among LT

candidates, patients with NASH represent a particularly challenging group because they are most likely to have these risk factors, which may contribute in both an independent and additive manner to patient selection and outcomes after LT [2,10-15,20, 25,31, 43]. There are currently no specific guidelines for preoperative assessment in this population or regarding specific treatment and monitoring strategies.

Arterial hypertension, dyslipidemia and diabetes mellitus

Each traditional risk factor such as DM, hypertension, or dyslipidemia, should be treated and medical strategies maximized. In addition to diet and physical activity that could have a beneficial impact on each condition, adequate pharmacotherapy is strongly encouraged.

For DM in compensated cirrhosis, pioglitazone could be considered, as it has both demonstrated efficacy in DM treatment as well as improvement of NASH-histological features, but concerns remain regarding potential adverse effects such as weight gain, bladder cancer or cardiac events. Glucagon-like peptide 1 agonists represent a promising therapeutic Class but data remain insufficient to recommend these agents as first line treatment[65]. The potential efficacy of pioglitazone and glucagon-like peptide 1 agonists has been demonstrated in noncirrhotic NASH and data in cirrhosis is lacking. For decompensated cirrhosis, insulin is the first line treatment.

For dyslipidemia, statin therapy should be considered as first line treatment. The potential rare occurrence of drug-induced liver injury needs to be balanced with the beneficial impact on preventing CAD but also its effects on the natural history of cirrhosis, portal hypertension, and HCC prevention[66]. Furthermore, a cross-sectional study evaluated the effect of statins in 1201 high-risk NAFLD patients (age 50, severe obesity, 50% DM) without cirrhosis who underwent liver biopsy. Prior statin therapy

for at least 6 months was associated with less steatosis (OR: 0.09), less inflammation according to NAS and less risk of advanced fibrosis stage F2-F4[67]. Fibrates have also been studied as they may promote hepatic fatty acid oxidation and reduce hepatic triglyceride synthesis and VLDL production and export through their action as PPAR-α agonists. However, mixed effects have been observed on liver histology, with one study showing improvement only in ballooning while another study showed no effect with fibrates[68].

For hypertension, noncardio selective beta-blockers is probably the best option to treat both hypertension and portal hypertension when recommended, although evidence supporting this recommendation is lacking. When beta-blockers are indicated to prevent or treat CAD, cardioselective beta-blockers can be used (see question 5). The second line option is angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB). There is some evidence suggesting that blocking the renin-angiotensin system may impact on NAFLD histology including fibrosis [69].

Renal dysfunction

NASH is an important risk factor for renal dysfunction both pre and post-LT [70]. Renal dysfunction in this setting is multifactorial due to other comorbidities (hypertension, DM) but also related to the severity of liver disease. Importantly, renal dysfunction is a risk factor for posttransplant CV disease and mortality [71,72]. Even mild renal disease at the time of LT has been shown in one study to be a risk factor for posttransplant all-cause and CV mortality [72]. In one study, more rapid declines in estimated glomerular filtration rates (eGFR) soon after LT correlated with risk of adverse CV outcomes, highlighting the need to study whether early renal preservation interventions also reduce CV complications [72]. Consequently, the main therapeutic goal is to prevent kidney

function deterioration by treating risk factors and consider SLK transplantation when needed.

Differences with other etiologies

To date, there is no data to support a different approach for the management of comorbidities in NASH patients compared to other etiologies. The peculiarity of patients with NASH lies in the fact that the number of comorbidities [2,10-15,70] seems greater and their age more advanced than for other LT indications. It is difficult to establish groups of patients based on their risk from literature data. A multidisciplinary approach is necessary to optimize the management of these patients whose complex and often contradictory pathologies are intricate.

5-. What are the therapeutic strategies recommended to improve the CV and nutritional status of a NASH patient in the waiting list for LT?

Recommendations:

- Patients with Child A/B NASH cirrhosis and cardiovascular comorbidities can be considered for a cardioselective beta-blocker and statin (Quality of evidence: low, Strength of recommendation: Moderate IIb)
- A protocol of moderate exercise is recommended with the dual objective of losing weight and improving muscle mass (Quality of evidence: Low-moderate, Strength of recommendation: Moderate)

Background:

CV disease remains a leading cause of death in LT recipients, with the highest rates occurring immediately after transplantation. Pretransplant hypertension, diabetes and

atrial fibrillation are all risk factors that contribute to post-LT CV morbidity[73]. Patients with NASH cirrhosis are at increased risk of posttransplant CV events independent of traditional cardiac risk factors[14,25]. Therefore, CV comorbidities such as obesity, hypertension, DM and hyperlipidemia need to be assessed and adequately controlled in the pre and posttransplant setting [74,75] (see questions 3 and 4).

Beta-blockers and statins improve CV outcomes in patients with CV risk factors undergoing noncardiac surgery, but data on the transplant setting are missing. In a randomized controlled trial involving 1066 intermediate cardiac risk patients, patients randomized to bisoprolol at least 7 days before surgery had a lower incidence of perioperative cardiac death and nonfatal myocardial infarction than those randomized to bisoprolol-control (Hazard ratios 0.34, 95%CI 0.17-0.67)[76]. In a randomized controlled study of 8351 patients at risk of atherosclerotic disease undergoing noncardiac surgery, extended release metoprolol started in the perioperative period was associated with less CV deaths, nonfatal myocardial infarction and nonfatal cardiac arrest at the expense of an increased incidence of stroke[77]. Therefore, beta-blockers, if used, should be started and titrated well before the perioperative period.

In a metaanalysis of 15 trials, statin use perioperatively reduced mortality by 44% in noncardiac surgery[78]. Several studies have established the safety of statins in patients with liver disease, including those with compensated cirrhosis [79]. Thus, if needed for hyperlipidemia, statins may be used in patients with NASH-cirrhosis in the waiting list for LT, but data in the decompensated patient is missing, and some guidelines contraindicate their use in NASH patients with decompensated cirrhosis[65]. In one study, statins were started in 19 (23%) of LT candidates with CAD, while aspirin was used in 30 (36%). Use of statin therapy was not linked to hepatic decompensation,

hospitalization or rise in MELD [80]. If needed after LT, pravastatin is the statin of choice as it does not interact with calcineurin inhibitors.

Patients with NASH are frequently obese and/or have diabetes, and both conditions are associated with an increased risk of mortality before and after LT due to CV events or sepsis[81,82]. Screening and treating diabetes on the waiting list is mandatory, preferentially using insulin sensitizers which could have beneficial effect in both insulin resistance and NASH. There is no evidence for a histological efficacy of metformin in NASH based on 3 randomized studies, therefore metformin is not currently recommended for the treatment of NASH in the EASL–EASD–EASO and AASLD Clinical Practice Guidelines[83-85]. Pioglitazone, a PPARg agonist, showed improvement in all histological features except for fibrosis and achieved resolution of NASH more often than placebo in 3 randomized controlled trials[86]. This option is currently the one with the strongest evidence to treat both NASH and diabetes but might increase weight gain and also increases the risk of bladder cancer. Other medications are emerging such as liraglutide, an incretin mimetic that acts as an agonist of glucagon-like peptide-1 receptor[87].

Nutrition is an integral part of patient care before LT. Nutrition status has been associated with various factors which are related to the success of LT such as morbidity, mortality, and length of hospital stay[88]. A high-calorie diet is associated with NAFLD. High fructose consumption may increase the risk of NASH and advanced fibrosis but data are controversial. While lifestyle correction measures are mandatory in all NASH patients, there does not seem to be any specific weight loss requirements for patients with end-stage liver disease or on the waiting list. In overweight/obese patients, a 7 to 10% weight loss is the target of most lifestyle interventions and may result in improvement of liver enzymes and histology[89]. Pragmatic approaches combine dietary

restriction together with a progressive increase in aerobic exercise/resistance training. In a recent prospective, multicenter, uncontrolled pilot study, 16 weeks of diet and moderate exercise (personalized hypocaloric normoproteic diet and 60 min/wk of supervised physical activity) were found to be safe with reduction of portal pressure documented in 50 obese patients with cirrhosis and portal hypertension (from 13.9 ± 5.6 to 12.3 ± 5.2 mmHg; $P < 0.0001$) [90].

The main challenge in the pretransplant area is to diagnose malnutrition in NASH patients, even if obese. Several studies have demonstrated that around 25% of obese patients suffer from malnutrition[89,91]. It should be underlined that exercising under inadequate nutrients and proteins intake could be dangerous in patients with decompensated cirrhosis, given that it could promote further protein catabolism and loss of muscle mass. Therefore, a proper nutritional assessment and supplementation are indicated before initiating low-calorie diet and physical activity in this population[89]. A personalized, adapted physical activity program based on cycloergometry plus muscle strengthening according to ventilatory threshold for 12 weeks demonstrated to be safe and feasible in patients awaiting LT, improving peak VO_2, maximum power, ventilator threshold power, 6 minutes walking distance, and strength of knee extensor muscles [92]. A previous controlled pilot study demonstrated similar results in 9 cirrhotic patients who did 8-weeks of supervised exercise on a cycle ergometer 3 days/week [93].

Finally, increasing evidence is now available supporting the presence of low bone mineral density and low vitamin D in patients with NAFLD as well as in cirrhotic patients[94]. Screening and surveillance of skeletal system regarding osteoporosis/osteomalacia in patients with NASH cirrhosis should be considered an important goal.

6-. Is there any circumstance where obesity should contraindicate liver transplantation?

Recommendations:

Class I-III obesity alone does not constitute a contraindication for liver transplantation. However, in the presence of medical comorbidities, particularly concurrent diabetes, rigorous patient selection is strongly recommended. (Quality of evidence: Moderate; Strength of recommendation: Strong)

Background:

One of the largest studies conducted by Nair et al[81] showed that "morbid obesity should be considered a relative contraindication to LT". In this SRTR-based review including over 23 000 recipients, morbid obesity was an independent predictor of mortality. However, this pre-MELD era study was criticized due to overestimation of obesity in the setting of ascites. In a prospective multicenter study including 1300 patients, corrected BMI after ascites volume removal was not found to be independently predictive of both patient and graft survival[95]. In each weight class, no difference was observed regarding postoperative complications and hospital stay. In a registry study based on the UNOS database (2003-2012)[96], of 57 255 LT performed during the study period, patients in all obesity classes had similar survival. Interestingly, overweight and class 1 obese patient had better survival compared to those with normal BMI values even after adjusting the data for both ascites and albumin levels. Presence of diabetes at the time of LT but not obesity was found to be an independent predictive factor for worse posttransplant survival (HR 1.29; CI 1.21-1.36). In addition, posttransplant survival among class I and II obese patients with concurrent diabetes was lower compared to patients with the same class obesity but without DM (for BMI $\geq$30 kg/m^2,

69 % vs. 75%, p<0.001). CV cause of death and recurrent HCV and malignancy were more common in DM patients compared to non-DM patients. In another UNOS database[97] study that included 73 583 adult LT performed from 1987 to 2007, Dick et al reported that underweight status and class III obesity were associated with significantly lower posttransplant survival. One study also reported highest rate of waitlist dropout in these patients[98]. Finally, in a systematic literature search from 1990 until July 2013 where the main outcome was to evaluate the impact of obesity on survival in adult LT recipients, and where 13 studies with a total 2275 obese and 72,212 nonobese patients were included, BMI did not specifically impact patient survival[99]. Moreover, no differences in mortality were noted in subgroup analysis comparing different BMI thresholds. There were also no differences in survival when BMI was adjusted for ascites or in studies where the liver disease severity was similar.

In more recent reviews[100] investigating the impact of obesity on posttransplant outcome, there were conflicting data considering BMI cut-off values and outcome parameters. While 5 studies reported significant posttransplant mortality, particularly in patients with BMI ≥40 kg/m^2 [81,97,101,102], the remaining studies reported similar posttransplant outcome regardless of BMI cut-off (BMI>35 kg/m^2 or BMI≥40 kg/m) [95, 96,103,1048]. Given the conflicting results about cut-off of BMI to determine the posttransplantation risk in obese patients, Barone et al suggested that BMI is not a satisfactory tool to stratify the risk of obesity, and that visceral adipose tissue and muscle mass should be the parameters that should be added to complete an adequate pretransplantation evaluation [100].

Interestingly, in the recent observational, retrospective population-based study using the UNOS/OPTN database that included 84 254 liver transplant candidates (2002-2013)[98], in addition to Class II (BMI:35-39.9 kg/m2) and III (BMI ≥40 kg/m^2) obesity, DM was

also identified as a predictor of poor waitlist outcome. However, NASH etiology was not associated with a greater dropout risk (HR 0.96, CI 0.84-1.09). The authors attributed these results to a selection bias considering that NASH patients were more frequently "ideal" candidates who presumably had undergone careful waitlist selection excluding those with CV disease.

In the study by Younossi ZM et al[105], the authors used data from the SRTR database between 1994 and 2013 that included over 80 000 adult LT recipients. There was no association between BMI values and posttransplant mortality but the DM status of both patient [pretransplant (HR:1.21 CI 1.12-1.30) or posttransplant (HR:1.06 CI 1.02-1.11)] and donor (HR: 1.10 CI 1.02-1.19)] impacted posttransplant outcomes. Pretransplant DM was found to be associated with CV mortality. This study has limitations due to its retrospective design and incomplete clinical data. Another single center retrospective design study by Dare et al[106] investigated the adequacy of using BMI to assess obesity in patients with end-stage liver disease. In addition, the authors also evaluated the potential impact of comorbidities, including obesity and DM, on outcome. Body fat percentage and BMI were compared and BMI was found to be an adequate tool to determine obesity-associated risks in LT. On the other hand, obesity with concomitant DM was the strongest predictor of posttransplant event rates (CR: 1.75, $p<0.001$).

In essence, most studies investigating the effect of obesity on posttransplant survival have found that outcome is similar in all classes of obesity. All but 1 out of 5 studies that showed significant increase of posttransplant mortality underscored that the negative effects were only observed with BMI $\geq$40 kg/m^2. Most studies though, considering variable cut-off values of BMI, have reported similar posttransplant patient survival across all BMI categories in the absence of concurrent comorbidities. However,

most studies are limited by lack of DM-specific data, or ascites status of the patients to provide corrected BMI and therefore, it is not plausible to draw definite conclusions regarding these associations. In addition, most studies are retrospective and/or include an unmatched patient population. It is still unclear whether different posttransplant outcomes will be achieved by performing immediate transplantation or, alternatively, undergoing optimal control of comorbidities such as obesity and diabetes before transplantation.

7. Optimal time for bariatric surgery: before, during, or after liver transplantation?

Recommendations: Bariatric surgery seems to be feasible and effective in morbid obese patients in the setting of liver transplantation, though associated to high postoperative complication rate; however, comparative data on long-term outcomes regarding optimal timing and type of bariatric procedure are lacking. Sleeve gastrectomy is currently the preferred approach. We suggest a tailored approach based on stringent selection criteria (Quality of Evidence: low, Strength of recommendation: weak)

Background:

Patients with morbid obesity have more infectious and surgical complications after LT [107,108] (see question 6). However, bariatric surgery (BS), which is performed to solve this problem, may also complicate posttransplantation period. It is still unknown "when is the optimal time to perform" BS and which BS procedure is best for this specific patient population, as all of them have some pros and cons to be considered.

Timing of the BS includes 3 options: *Bariatric first approach* for appropriate patients with low-MELD score will fulfill, in theory at least, the primary aim of this intervention and potentially improve the outcome of LT. Takata and Lin [109,110] reported promising results concerning metabolic comorbidities but significantly higher postoperative complication rates compared to the general population. Likewise, complication rates up to 35% were reported in patients incidentally diagnosed with cirrhosis after BS [111]. Secondly, *concomitant LT-BS* procedure should only be performed in very selected patients, particularly with high MELD scores that are not appropriate for pretransplantation BS. In addition to increased operative time and complexity of the procedure (requiring both bariatric and transplant surgeon), early immunosuppressive therapy and poor nutritional status of the patients may complicate and limit the use of this approach [112]. The third option is *posttransplantation BS* [113,114]. It will however not solve the problem of morbid obesity during waitlisting or in the immediate posttransplant period. Its only advantage is the proper selection of the patient requiring BS. However, disadvantages include difficult access to the abdomen and high postoperative morbidity and reoperation rates reported in the literature.

Technical feasibility and plausible posttransplant complications should be considered when choosing the type of bariatric procedure. In many studies, the most common procedure has been sleeve gastrectomy (SG)[115-119]- up to 100% in some series (excluding case reports). There are several advantages compared to Roux-en-Y gastric bypass (RYGB): it can be performed with minimal additional operative time and does not require intestinal anastomosis, it does maintain adequate immunosuppression levels without altering the absorption of medications and allows endoscopic access to the biliary system for management of posttransplant biliary complications. Although, long-term outcome regarding durability of SG is not available, reported series have

demonstrated steady and gradual EWL%. In the study by Takata et al including both RYGB and SG, SG reported acceptable EWL% (25-75%) but lower compared to RYGB [109]. Efficacy of gastric banding is limited to case reports. Disadvantages include placement of a foreign body in an immunosuppressed patient with a risk of gastric wall erosion and relative difficulty to access the gastrointestinal system [115-119].

NASH patients constitute a very specific group of increasing LT candidacy. Since these patients have already metabolic syndrome and other comorbidities, such as CV problems, bariatric first or LT-SG combined approach might be reasonable for these patients to manage these modifiable risk factors and improve both pre and posttransplant outcome (see questions 3-6). Strong recommendations cannot be made since most of the studies are case reports, small-sized, with a retrospective design and short mean follow-up, generally less than 5 years [115]. Importantly, one small recent prospective study comparing LT alone to LT-SG demonstrated that patients who underwent LT + SG maintained a significantly higher percentage of total body weight loss after 3 years of follow-up. They also had a lower prevalence of hypertension, insulin resistance, and hepatic steatosis and required fewer antihypertensive medications and lipid agents at last follow-up [120]. In the light of the limited available data, pretransplantation BS might be a reasonable approach for obese patients with low-MELD score, whereas concomitant/posttransplantation BS might be considered for highly selected patients. Bariatric first or concomitant approach might be reasonable for NASH patients who have pre-LT comorbidities including metabolic and CV problems that may complicate the post-transplant period. The optimal type of BS remains unclear, but sleeve gastrectomy seems to be the preferred approach by most surgeons [115-117,120].

8- Donor steatosis: how relevant is it for LT in NASH patients.

Recommendation: While steatosis, particularly moderate to severe macrosteatosis, is considered an independent risk factor for post-transplant worse outcome, there is not enough evidence to support a different approach to donor steatosis in NASH as opposed to non-NASH candidates. (Quality of evidence: low; Strength of recommendation: weak IIb).

Background:

Increased fatty liver disease in the donor population is an indirect effect of the increasing rates of NAFLD in the world-wide population with prevalence rates estimated to be around 25% with significant geographic variability. Hepatic steatosis was seen on biopsy in 76% of potential living liver donors with a BMI greater than 28 [121]. In a recent study evaluating 612 living-related liver donor candidates between 2001 and 2017, 196 liver biopsies (32%) had pathological findings, of which fatty changes was the commonest found in 86 livers (44%) [122]. There is insufficient data on the impact of donor steatosis in patients with NASH-related cirrhosis who receive a LT. As with other aetiologies, it is expected that donor steatosis will disappear soon after LT and the main impact is perceived to be in the immediate posttransplant period[123]. Steatotic donor livers, particularly those with >60% of steatosis, are associated with poor graft function due to ischemia-reperfusion injury [124]. The outcomes of transplants with donor liver steatosis 30-60% varies and depends on recipient factors as well, with acceptable outcomes only when the cumulative risk at transplant is low [125]. Existing evidence does not support a different selection process or approach to recipients with NASH cirrhosis.

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