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REVIEW

Nonalcoholic fatty liver disease and liver transplantation - Where do we stand?

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Abstract

Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) is a challenging and multisystem disease that has a high socioeconomic impact. NAFLD/NASH is a main cause of macrovesicular steatosis and has multiple impacts on liver transplantation (LT), on patients on the waiting list for transplant, on post-transplant setting as well as on organ donors. Current data indicate new trends in the area of chronic liver disease. Due to the increased incidence of metabolic syndrome (MetS) and its components, NASH cirrhosis and hepatocellular carcinoma caused by NASH will soon become a major indication for LT. Furthermore, due to an increasing incidence of MetS and, consequently, NAFLD, there will be more steatotic donor livers and less high quality organs available for LT, in addition to a lack of available liver allografts. Patients who have NASH and are candidates for LT have multiple comorbidities and are unique LT candidates. Finally, we discuss long-term grafts and patient survival after LT, the recurrence of NASH

and NASH appearing *de novo* after transplantation. In addition, we suggest topics and areas that require more research for improving the health care of this increasing patient population.

Key words: Nonalcoholic steatohepatitis; Chronic liver disease; Liver transplantation; Nonalcoholic fatty liver disease; Outcome

Core tip: Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) is a challenging and multisystem disease that has a high socioeconomic impact. NAFLD/NASH is a primary cause of macrovesicular steatosis and has several impacts on liver transplantation (LT), which is transmitted to transplant recipients and organ donors. Current data indicate a new trend in the area of chronic liver disease. Due to the increased incidence of metabolic syndrome (MetS) and its components, NASH cirrhosis and hepatocellular carcinoma caused by NASH will soon become a major indication for LT.

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INTRODUCTION

Parallel to the increasing prevalence of diabetes mellitus type 2 (T2DM) and obesity and a close relationship with insulin resistance (IR) and metabolic risk factors, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease (CLD) in the world over the past 30 years, with an estimated prevalence of 10%-40%[1,2]. NAFLD is characterized by increased fat depositions in the liver with clinical-histological phenotypes that range from a simple steatosis (present in > 5% of hepatocytes, as shown in histological analysis or magnetic resonance spectroscopy) to nonalcoholic steatohepatitis (NASH). NASH is a more aggressive form of the disease and includes a histological presentation of steatosis, ballooning hepatocytes and lobular inflammation that leads to advanced fibrosis and, finally, cirrhosis and hepatocellular carcinoma (HCC)[1,3]. Given the growing prevalence of NAFLD, several studies have attempted to determine the clinical course and progression of the disease, but the exact prognosis remains unclear. A recently published Swedish retrospective study was the largest biopsy-proven NAFLD study to provide insight on the long-term prognosis and outcomes of the disease, with a follow-up period of up to 40 years[4]. In that report, NAFLD patients had an increased risk for mortality and liver-related morbidity (12% of the patients developed severe liver disease, which is defined as liver failure, compensated or decompensated liver cirrhosis and HCC). Interestingly, the presence of NASH did not significantly increase the risk for liver-related morbidity or overall mortality. The fibrosis stage was highly predictive of the risk of developing sever liver disease, with a hazard ratio that ranged from 1.9 in F0 to 104.9 in F4. The primary high fibrosis stages (F3-F4) predicted overall mortality[4], which is similar to previous published research[5,6]. Compared to other etiologies of chronic liver disease, NAFLD has a slower fibrosis progression, with an estimated time for developing severe liver disease at 22-26 years for F0-1, 9.3 years for F2, 2.3 years for F3 and 0.9 years for F4 (for decompensation)[4]. The clinical burden of NAFLD extends beyond the liver, with evidence indicating that NAFLD is a multisystem disease that is closely related to cardiovascular disease (CVD), chronic kidney disease (CKD) and T2DM. It is still not clear whether NAFLD is only a risk factor or is an important component of the pathophysiological mechanisms in the development and progression of those diseases[7]. In addition, a major cause of morbidity and mortality in NAFLD patients is CVD, followed by malignancies and liver-related diseases (cirrhosis and HCC) as the third cause[7]. HCC is the sixth most common cancer in the world that is predisposed with the presence of cirrhosis, but emerging data suggest that HCC can evolve in non-cirrhotic NAFLD and is strongly associated with metabolic syndrome (MetS)[8]. The HCC that is associated with NAFLD/NASH has a distinct phenotype. It is often diagnosed at an older age and in the advanced stages of liver disease, and, compared with the HCC in viral hepatitis, is less aggressive and therefore more commonly missed on routine scans for malignancies[9]. With the continuous increase in the incidence of obesity, T2DM and MetS in United States (US) and Europe, it is predicted that NAFLD/NASH will become the most common cause of HCC in the Western world. NAFLD/NASH has already become the second leading cause of liver transplantation (LT) in the US and, importantly, the number of patients who have NAFLD/NASH and are on the waiting list for transplantation increased by 170% from 2004 to 2013. Thus, end-stage liver disease (ESLD) due to NAFLD/NASH will become the most common indicator for LT in the near future[10].

We expect groundbreaking changes in the area of LT. Therefore, this review discusses the multiple impacts of NAFLD on LT. First, due to the aging of the population and an increasing incidence of MetS and

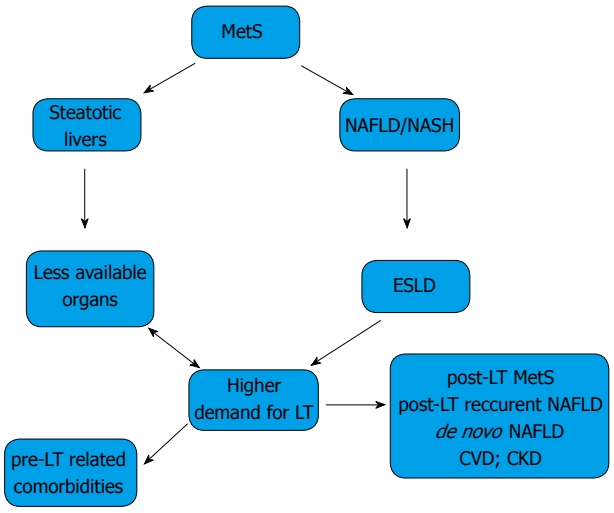

Figure 1 Higher incidence of metabolic syndrome and its complications leads to a higher incidence of nonalcoholic steatohepatitis/nonalcoholic fatty liver disease and, consequently, to more patients who have end-stage liver disease. At the same time, due to MetS and its components, we will have more steatotic livers, *i.e.*, more organs of lower quality that are available for LT. Therefore, in the future, since NAFLD will affect both the demand for LT and the supply of available organs. Patients who have NASH and are candidates for LT have several comorbidities and are unique LT candidates. Post-LT, there are several challenging issues for NAFLD: recurrent NAFLD, de novo NAFLD and the risk for CVD and CKD. MetS: Metabolic syndrome; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; ESLD: End-stage liver disease; LT: Liver transplantation; CVD: Cardiovascular diseases; CKD: Chronic kidney disease.

its liver manifestation (*i.e.*, NAFLD/NASH), ESLD as a consequence of NASH will become a primary driver of LT in the near future. Furthermore, due to the increasing incidence of obesity, and, consequently MetS, the prevalence of NAFLD in the population will also increase[1,2] As such, owing to the growing incidence of NAFLD, we can expect that there will be more steatotic donor livers and fewer high quality organs available for LT. Therefore, NAFLD affects both the demand for LT and the supply of available donors.Moreover, patients who have NASH and are candidates for LT have several comorbidities, such as obesity, T2DM and other MetS components, as well as CVD and CKD. These patients are uniquely challenging LT candidates, and transplantation specialists are continuously exposed to the challenges of transplantation from obese donors, as well as the NASH recipients with their often multiple comorbidities. Finally, we discuss long term grafts and patient survival after LT, the recurrence of NASH and NASH appearing *de novo* after transplantation[11,12] Figure 1. In addition, we suggest topics and areas for further research for improving health care for this increasing patient population.

For this Review, we identified references using PubMed and the terms "NAFLD", "NASH", and "liver transplantation." We only reviewed articles that were published in English. The references were selected based on originality and their relevance to the domain of this Review.

NAFLD RELATED END-STAGE LIVER DISEASE AND HCC AS INDICATIONS FOR LIVER TRANSPLANTATION

NAFLD patients can necessitate the need for LT in two primary ways: developing cirrhosis that manifests with decreased synthetic/excretion function(s) and signs of portal hypertension and HCC development. It is estimated that approximately one-third of the current population in industrialized countries has NAFLD as a consequence of the liver's involvement in the context of MetS. As mentioned above and according to many authors, it is clear that over the next ten or twenty years, the prevalence of NAFLD will increase due to the epidemic rise in obesity, T2DM, arterial hypertension and the prevalence of MetS, as well as people living longer[10-13]. Consequently, NAFLD-related liver disease is currently the most rapidly increasing indication for LT in the US, and it is anticipated that NAFLD-related liver disease will become the leading indication for LT in the near future[14,15]. In the context of the increasing incidence of NAFLD as an indication for LT, it is important to highlight several facts. First, due to the development of direct antiviral agents (DAA) for hepatitis C (HCV), the incidences of cirrhosis and HCC due to HCV as indications for LT will decrease over time. Three years ago, Wong *et al*[10] analyzed the United Network for Organ Sharing and Organ Procurement and Transplantation Network's (UNOS/OPTN) registry data from 2004 to 2013. There were four groups of registrants who were on the liver transplant waitlist: patients who had an HCV infection, NASH, alcoholic liver disease (ALD), or a combination of HCV infection and ALD. Over a period of nine years, the numbers of new patients on the waitlist who had NASH, ALD, and HCV increased by 170%, 45% and 14%, respectively. Moreover, the percentage of registrants who had HCV and ALD decreased by 9% (from 880 to 803)[10].

A recent study by Goldberg *et al*[16] analyzed the prevalence of HCV from 2010 to 2014 from National Health and Nutrition Examination Survey (NHANES) data. They also collected data from patients who had cirrhosis and chronic liver failure (LF) from 2006 to 2014 and were in the Health Core Integrated Research Database. In addition, they analyzed data from liver transplant recipients from UNOS from 2003 to 2015. By combining data from these three databases, the study investigated current changes in liver disease(s); HCV, alcoholic liver disease (ALD) and NAFLD/NASH through the course of liver disease; CLD - compensated cirrhosis, decompensated cirrhosis and HCC; and the waiting list for LT and LT recipients. The study authors found that there were significant changes in CLD etiology that were associated with important alterations

in the occurrence of HCV, ALD and NAFLD/NASH as indications for liver transplantation. They demonstrated that active HCV infection decreased as an indication for LT after DAA use. Subsequently, there was a decrease in the incidence of cirrhosis due to HCV in the larger population with CLD[16]. In contrast, among patients who were on the waiting list and LT recipients, NAFLD became more common. Another interesting finding from this study was that the incidence of ALD as an indication for LT increased more than NASH[16]. A retrospective study by Cholankeril *et al*[17] had similar findings after analyzing the UNOS/OPTN database from 2003 to 2014. The authors discovered that the number of LT that is secondary to NASH increased by 162% from 2003 to 2014, while the number of LT secondary to HCV increased by 33%, and the number of LT secondary to ALD increased by 55%[17].

Recently, there has been a trend of an increased incidence of HCC in developed countries, and according to the literature, this increase is most likely due to an increased incidence of MetS[8,18]. The large Bridge study included 18031 HCC patients from 2005-2012. NAFLD was one of the major risk factors for HCC development, and NAFLD was the cause of chronic liver disease for approximately 10%-12% of patients[19,20]. Similarly, a recently published US study found that HCC as a consequence of NASH is the fastest growing indication for LT. The authors of this study reported that NASH related HCC as an indication for LT had an almost fourfold increase since 2002; on the other hand, HCC that results from HCV, doubled[13,21].

In the context of LT and NAFLD, it is concerning that a recent discovery found that HCC may appear in NAFLD patients who do not have liver cirrhosis or advanced liver fibrosis[8]. Mittal *et al*[22] published data on 13% of patients who had HCC and, at the time of diagnosis, did not have cirrhosis. The primary risk factor for developing HCC was the presence of NAFLD or MetS. In addition, in a study by a group of German authors, 41.7% of the patients with NAFLD/NASH HCC previously had no diagnosis of cirrhosis[23]. Similar findings were also reported by other authors[24,25].

Another concerning issue in the context of NASH and LT is the increase in the incidence of NAFLD in children and young adults (up to age 40). Feldstein *et al*[26] analyzed long-term outcomes and survival for children who had NAFLD. In this study, children who had NAFLD had a 13.8-fold higher risk of requiring LT or dying than the general population of the same age and sex[26]. Recently, Alkhouri *et al*[27] analyzed LT in children and young adults and the frequency of NASH as an indicator for LT. They found an increased incidence of NASH as an indicator for LT in young patients. More than 100 recipients had LT before they were 34 years old, while most patients received their liver transplant closer to the age of 40 years[27].

Current guidelines do not recommend regular screenings for HCC in NAFLD patients who have no signs of liver cirrhosis or advanced fibrosis. According to recent research, NAFLD patients who have not developed cirrhosis have a risk of developing HCC; however, there are no studies that examine the cost-benefit of screening in this population of patients. However, the current data on the increasing incidence of NAFLD combined with the growing incidence of MetS and NAFLD in young people indicate that there will be a need for LT in the context of NAFLD related decompensated cirrhosis and NAFLD related HCC[13,20,21].

Due to the substantial increase in the proportion of transplants due to NAFLD, as well as new waitlist registrants with NAFLD cirrhosis complications, NAFLD/NASH cirrhosis and related HCC are the most rapidly growing indications for LT.

NAFLD PATIENTS ON THE WAITLIST FOR LIVER TRANSPLANTATION

Every CLF patient has unique characteristics and needs an individual approach in the context of LT, and the same individual approach is necessary for patients who have NASH. The risk factors for poor postoperative and long-term outcomes are age the presence of MetS components (especially T2DM and obesity), coronary artery disease (CAD) and chronic kidney disease (CKD). Patients who have NASH on the waitlist often have several or all of these risk factors. For NASH patients on the waiting list there are two problems: patient comorbidities and lower MELD than other etiologies of CLD[28].

First, NAFLD is the liver manifestation of MetS and NAFLD patients on the LT waiting list frequently have one or more components of MetS. They are often obese and have T2DM, hypertension and hyperlipidemia. In addition, NASH recipients are older than recipients who have a different CLD[28]. According to Wong *et al*[10] compared to patients who had an alcoholic, viral or alcoholic/viral etiology of CLD who were on the waitlist for LT, patients with NASH had decreased renal function, were more obese and were more likely to have T2DM. There was higher morbidity and mortality in obese patients who underwent surgical procedures. However, in the context of obesity and LT, the results were not consistent. Several studies reported worse outcomes for obese patients, while other authors found similar risks and outcomes for both obese and non-obese patient groups[28]. For example, Leonard *at al*[29] had similar results for all body mass index (BMI) categories for early and late patients and graft survival. In contrast, La Mattina *et al*[30] found that obese patients had a longer operative time, intensive care unit length of stay, and more infectious and biliary complications that required intervention. There was no significant difference in patient or graft survival for overweight Class Ⅰ and obese Class Ⅲ recipients compared to normal weight recipients. However, patients who had Class Ⅱ obesity experienced decreased patient and

allograft survival[29]. Not long ago, Conzen *et al*[31] found that morbid obesity had negative effects on long-term outcomes regardless of the short-term results. In other words, there were no differences in operative time, intensive care unit or hospital length of stay or perioperative complications. Over 3 years, recipient and graft survival rates were similar across groups. Compared to the non-obese, recipients who had a BMI > 40 kg/m^2 experienced a significantly decreased 5-year graft (49.0% *vs* 75.8%; $P < 0.02$) and recipient (51.3% *vs* 78.8%; $P < 0.01$) survival. Although between group comparisons is difficult given the different endpoints and BMIs between cohorts, in general, obese patients have increased complication rates and more resource utilization compared to non-obese recipients[19]. Given the increase in the incidence of overweight patients and MetS, we can expect an increase in the number of patients with NASH cirrhosis or HCC in NASH with high BMI who are on the transplant list in the future. In addition, the bariatric surgery (BS) methods will become more important in the context of treating obesity for the morbid obesity of NASH patients. There are promising research findings for BS in these patients. There are studies with a small number of patients who were experiencing LT and some form of BS[28]. For example, Heimbach *et al*[32] conducted a small study that combined LT with a sleeve gastrectomy, which resulted in significant weight loss for patients who were not successful with medical treatment. In addition, there were less post-LT metabolic complications[32].

Recently, 11 studies with 56 patients were analyzed in a systematic review[33]. Two studies reported that BS had been previously performed, while two studies performed it during and seven after LT. The most common procedure was the sleeve gastrectomy, while the Roux-en-Y gastric bypass, biliopancreatic diversion and gastric banding were performed in a slightly smaller number of patients. There was no mortality in the early postoperative period, with a 5.3% rate during the first postoperative year. The reoperation rate was 12.2%. Although mortality and morbidity are higher in this population, the authors agreed that BS appears to be possible[33].

In the future, there is a need for randomized studies to determine which patients on the transplant list will benefit from BS, the optimal time for BS (before, during or after LT) and the optimal type of BS. It is important to note that patients who have decompensated cirrhosis have a higher mortality rate after BS than those who have compensated cirrhosis or no chronic liver disease; thus, it is extremely important to optimize the time at which patients should undergo BS[28,34]. Future studies are also needed to demonstrate the long-term impact of BS on liver transplant recipients and graft outcomes[28].

Patients who have NASH and are on the waitlist for LT often have T2DM. Pre-transplant T2DM is a strong predictor of poor short and long-term patient and graft survival. The poor outcomes are primarily attributed to an increased incidence of postoperative infectious complications, CVD complications and kidney failure[35,36]. A recent study by Hoehn *et al*[36] indicated that recipients with pre-LT diabetes in the post-transplant period had a longer hospital length of stay, as well as higher peri-transplant mortality and 30-d readmission rates. In addition, they are less likely to be discharged home and, finally, have lower graft and patient survival than recipients who do not have diabetes[36].

For the above observations, NASH recipients often have one or more and often multiple, comorbidities that significantly affect the CVD risk in these patients so CVD risk assessment in NAFLD recipients is one of the largest problems in context of LT. According to the guidelines from European Association for the Study of the Liver (EASL), aside from obligatory electrocardiogram and transthoracic echocardiography in pre-LT evaluation, further tests need to be done to exclude asymptomatic ischemic heart disease (cardiopulmonary exercise test and if necessary in high risk patients even coronary angiography)[37]. Wray *et al*[38] showed that if coronary artery disease (CAD) is treated effectively before LT, survival after LT is not significantly different between patients with or without obstructive CAD.

Currently, many authors agree that NAFLD is a liver as well as a multisystem disease that is commonly associated with CVD, T2DM and CKD[39]. Research has shown that NAFLD is associated with an increased risk of adverse CVD events[39-42]. It is not clear whether the risk for CVD is increased in NAFLD patients due to coexisting dysmetabolic traits or whether NAFLD is actively involved in the pathogenesis of cardiovascular disease[35,39]. Previous research has shown that patients who have NASH related ESLD, compared to other ESLD recipients, have a higher CVD risk, specifically soon after LT[36]. For example, Patel *et al*[43] analyzed 420 ESLD patients that were assessed for LT: 125 had alcohol-related ESLD, and 295 had non-alcohol-related ESLD. The incidence of severe coronary artery disease (CAD) (defined by a > 70% diameter stenosis) was 13% in the non-alcohol-related ESLD group ($P < 0.005$) and 2% in the alcohol-related ESLD group. Moreover, a retrospective cohort study by Vanwagner *et al*[44] analyzed 242 LT recipients (127 alcohol-related and 115 NASH ESLD) at a post-transplant follow-up that was more than 12 mo. After controlling for recipient sex, age, smoking status, CVD, pre-transplant diabetes and the presence of MetS, the multivariate analyses shown that NASH patients were more likely to have a CVD event than alcohol-related ESLD recipients in the first year after LT. Most of the (70%) CVD events occurred in the perioperative period, and 50% of the mortality was related to the occurrence of a CVD event. However, there were no differences between the two groups in graft and patient survival[44].

According to these observations, it is important to screen all LT candidates for the presence of MeS and/or risk of CVD, especially when they have NASH related ESLD. Prospective studies are needed to answer these important questions and to provide a foundation for a

standardized approach to CVD risk assessment in the population of LT candidates[35].

An additional risk factor in the context of NAFLD is CKD, which is also a well-known CVD risk factor. Previous research has shown that patients who have NAFLD have a higher prevalence of CKD than patients who do not have NAFLD[39,45]. A recent study by Singal *et al*[46] confirmed that the most rapidly increasing indication for simultaneous liver-kidney (SLK) transplantation is NASH, which has poor renal outcomes. The authors of this study found that SLK significantly increased in the group of patients who had NASH and cryptogenic cirrhosis compared to ESLD that was related to other etiologies; the incidence increased from 6.3% from 2002 to 2003 to 19.2% from 2010 to 2011. Five-year LT recipient and graft survival rates did not differ between recipients who had NASH or cryptogenic cirrhosis and those with other etiologies of ESLD. On the other hand, in the group of patients who had NASH and cryptogenic cirrhosis, the risks for a kidney graft loss was more than 1.5-fold higher. Compared to recipients who had ESLD that was related to alcohol, primary biliary cirrhosis or primary sclerosing cholangitis, the estimated glomerular filtration rate remained lower in in the recipients who had NASH/cryptogenic ESLD[46].

When selecting LT candidates who have NASH, the largest challenge is merging these risk factors into one risk stratification tool. As such, a multi-disciplinary approach is needed to evaluate these candidates for LT.

Importantly, in the context of NASH related ESLD candidates for LT, there is an association between NASH and macrovascular venous thrombosis, especially portal vein thrombosis (PVT)[47]. In NASH patients who have cirrhosis, there is a hypercoagulable state that is characterized by increased levels of plasminogen activator inhibitor 1 and factor VIII, while anticoagulant levels of protein C are decreased in patients with cirrhosis due to NASH[47,48]. Stine *et al*[47] recently analyzed 33368 patients who have ESLD and received LT. Of these, 2096 (6.3%) patients had PVT and 12% had NASH. A comparison of NASH related ESLD recipients with all other causes of cirrhosis revealed a higher prevalence of PVT, with 10.1% in the first group versus 6% for those without NASH ($P < 0.001$). NASH cirrhosis was the strongest risk factor that was independently related to PVT in a multivariable analysis. Although the clinical significance of PVT is not entirely clear, especially whether anticoagulant therapy should be used, individual studies have shown that PVT is associated with adverse outcomes in patients who have ESLD. Specifically, several authors have shown that PVT is associated with increased pre- and post-transplant mortality, as well as with technical challenges during the transplant procedure[47,49-51]. However, the connections among NASH and PVT with hypercoagulation state is an ever-expanding field of clinical research. Additional studies on this topic are needed because there will be a significantly higher number of patients who have ESLD due to NASH on the waitlist for LT in the future, and, possibly, a higher number of thromboembolic incidents in these patients, including PVT[47].

The second important issue in the context of NASH patients who are on the waitlist for LT is competition for liver allograft allocations due to a lower MELD than other etiologies of CLD. According to current reports, patients who have ESLD due to NASH and are on the waitlist for LT have better liver functioning and, consequently, lower MELD scores than other etiologies of liver cirrhosis. In addition, these patients have a slower progression of disease[18,28]. A study by O´Leary *et al*[52] compared the data for 218 patients who had NASH or cryptogenic cirrhosis (CC) and underwent LT between 2002 and 2008, with 646 patients transplanted due to ESLD that resulted from HCV infection. Among patients who had NASH and CC, the median progression rate was 1.3 MELD points per year, and in the group of patients who had HCV, it was 3.2 MELD points per year ($P = 0.003$)[52]. Compared to patients who have HCV-related cirrhosis, patients who had NASH/CC and MELD scores $\leqslant$ 15 had fewer chances of receiving LT. They also had a higher risk of dying and a two-times higher risk of rejection or removal from the waiting list due to no suitable operative procedure given the progression of the liver disease or complications with their comorbidities. However, all patients who had MELD scores that were higher than 15 were more likely to undergo LT despite their diagnosis[52]. According to the findings from this study, the aggressive treatment of associated comorbidities is highly important; the components of MetS (hypertension, T2DM, dyslipidemia and obesity) in patients who have low MELD scores can prevent the progression of their comorbid conditions that are likely to cause death or make the patient ineligible for LT[52]. In addition, a recent study by Wong *et al*[10] demonstrated that NASH patients, compared to HCV, ALD or HCV/ALD related ESLD, are less likely to receive LT in the first 90 days on the waitlist. Another interesting finding from this study is that the one-year waiting list survival rate for ESDL patients due to NASH declined over the study period from 42.8% to 25.6%. In contrast, patients who had HCC due to NASH, compared to other etiologies of CLD with HCC, had better liver functioning and lower MELD or Child Pugh scores[18]. Taken together, these data suggest that LT candidates who have NAFLD/NASH related ESLD pose a specific challenge for the transplant community given their longer LT waiting time and associated comorbidities.

NAFLD IN DONOR LIVERS

Another challenge in the context of NASH in LT is liver allograft steatosis. Specifically, the epidemic increase in the incidence of NAFLD/NASH in the general population has a direct influence on the increased prevalence of NAFLD in deceased and living liver donors[11,28]. Based on predictions that the prevalence of MetS and its liver manifestations (*i.e.*, NAFLD) will increase in coming

years, we can expect more donors with NAFLD/NASH. We know that the availability of donor livers depends the success of the LT program. There is a global lack of organs for transplantation, as the gap between patient "demand" and organ "supply" continues to grow[53]. As such, transplant centers must use livers from "extended criteria donors" (ECD). Due to higher risk for ischemia-reperfusion injury (IRI), the severity of liver steatosis is related to a higher risk for graft failure and/or impaired graft function. Upon reperfusion, steatosis can cause microcirculatory and cellular changes in the liver graft that can lead to hepatocyte necrosis. In contrast, there is an impaired potential for regenerating steatotic livers[11,28,54-56]. For donors whose livers are more than 60% steatotic, this is almost a universal scenario; however, for those who are 30%-60% steatotic, there are controversial outcomes for donor livers[11,28,54,55]. For example, Spitzer *et al*[57] have shown that macrovesicular steatosis is an independent risk factor for graft survival. Recently, Chu *et al*[55] published a systematic review that analyzed 34 articles. The authors found that steatotic grafts that were > 60% were associated with an increased risk for poor graft functioning, while grafts that were > 30% of steatosis were related to decreased graft survival rates[55]. The lack of a standardized definition for primary non-functioning or impaired primary functioning and descriptions of the types of steatosis in research are the primary flaw in these studies. With more common utilization of ECD livers, using liver allografts that have less than 30% macrovesicular steatosis should be harmless for recipients[11,28,54,55].

There is no standardized procedure for estimating liver steatosis in potential donors; thus, evaluation procedures of liver grafts for steatosis and the use of steatotic livers for LT differ across transplant centers. Although some centers perform liver biopsies in high risk donors (abnormal liver tests, associated comorbidities, diabetes mellitus, high body mass index, older age, hepatitis B or C infections), others evaluate all potential donors[11,54,58]. Liver biopsies are the "gold standard" for detecting and assessing for steatosis. As an invasive procedure, liver biopsies can damage the organ. Moreover, it can only sample 1/50000 of the liver; thus, there is the potential for significant sampling error and limits in the numbers and sizes of biopsies. In addition, there is significant inter-observer variability for evaluating the degree of steatosis. These disadvantages place the procedure in the "silver standard" position; however, because there is not a better referential method, biopsy is still viewed as the "gold standard". Additionally, waiting for the liver biopsy results before deciding whether to accept the organ extends the cold ischemia time. Therefore, there is a need for simple, rapid and non-invasive methods for detecting steatosis in the donor[11,54,59]. Imaging methods such as ultrasonography, magnetic resonance and computed tomography are not sensitive or exact in detecting steatosis that is below 30%. Moreover, these methods cannot differentiate between micro-vesicular and macro-vesicular steatosis[11,54,58,59]. Recently, elastographic methods have been intensively investigated in the context of the noninvasive assessment of liver steatosis and fibrosis. One of the most investigated is transient elastography (TE), with a controlled attenuation parameter (CAP). In the context of donor livers, Mancia *et al*[60] examined 23 brain-dead potential donors. They analyzed TE with its CAP and reviewed liver stiffness measurements (LSM) to objectively assess liver steatosis and fibrosis. The implementation of TE with both CAP and LSM demonstrated good preoperative assessment for the histological condition and stage of the donors' liver steatosis[60]. Recently, Hong *et al*[61] investigated the usefulness of CAP as a screening tool for detecting liver steatosis in living donor livers. The author found that area under the receiver operator characteristic curve for diagnosing steatosis ($\geqslant$ S2) with CAP was 0.88, with a cutoff value of 276 dB/m. According to the findings from this study, CAP could be an adequate noninvasive method for excluding significant liver steatosis (> 33%) in liver donors[61]. There is a need for more research on using TE with CAP to evaluate steatosis and fibrosis in possible donors. A higher incidence of NAFLD/NASH in the general population will lead to a higher risk of donors who have NAFLD, which will influence on number of suitable organs from both living and deceased donors. Given the increasing incidence of NAFLD, we will face an even greater lack of LT organs or will be forced to accept liver donors that have NAFLD/NASH and are lower quality, with a high risk for poor outcomes after LT[15,54].

LIVER TRANSPLANTATION OUTCOMES FOR NAFLD PATIENTS

Although patients who are transplanted because of ESLD that is related to NASH have several comorbidities and are often older in age, post-LT survival is comparable to other etiologies of ESLD. Multiple, single-center studies of survival in ESLD related to NASH patients who had an LT, as well as several large studies were conducted over the years[28]. The studies that assess post-LT outcomes for NASH are summarized in Table 1.

One of the first studies to report outcomes for NASH patients after LT was conducted by Malik *et al*[62] and was published almost 10 years ago. This was the first study to analyze patients who had a histopathological diagnosis of NASH in the context of LT. The authors analyzed the post-LT outcomes for 98 NASH patients *vs* 686 with other etiologies, including primary biliary cirrhosis/primary sclerosing cholangitis (PBC/PSC), ALD, HCV and cryptogenic cirrhosis (CC). In 71 NASH patients, the diagnosis of NASH was based on pre-LT biopsies, and in 27 patients, the diagnosis of NASH was confirmed upon explant. The five-year survival rates

Table 1 Post liver transplantation outcomes for patients who have nonalcoholic fatty liver disease

Ref.	Study size	NASH group survival (%)	Non-NASH group survival (%)	Study period
Malik *et al*[62]	98 NASH	30-d - 93.9	30-d - 94.4-98.0	1997-2008
	686 Non-NASH group (PBC/PSC, ALD, HCV, CC)	1-yr - 79.6	1-yr - 81.6-87.2	
		5-yr - 72.4	5-yr - 65.3-80.6	
Bhagat *et al*[63]	71 NASH	1-yr - 82	1-yr - 92	1997-2007
	83 ALD	5-yr - 75	5-yr - 86	
		9-yr - 62	9-yr - 76	
Barritt *et al*[64]	21 NAFLD	30-d - 80.9	30-d - 97	2004-2007
	83 Non-NAFLD (ALD, HCV, HBV, PBC/PSC, AIH)	1-yr - 76.2	1-yr - 89.5	
		3-yr - 76.2	3-yr - 83.5	
Agopian *et al*[65]	144 NASH	90-d - 90	90-d - 90-96	1993-2011
	1150 Non-NASH (HBV, HCV, ALD, CC, PBC/PSC)	1-yr - 84	1-yr - 79-87	
		5-yr - 75	5-yr - 54-70	
Kennedy *et al*[66]	129 NASH	1-yr - 90	1-yr - 92	1999-2009
	775 Non-NASH - etiologies not defined	3-yr - 88	3-yr - 86	
		5-yr - 85	5-yr - 80	
Park *et al*[67]	71 NASH	1-yr - 78	1-yr - 87	1998-2008
	472 Non-NASH	2-yr - 78	2-yrs - 85	
Vanwagner *et al*[44]	115 NASH	1-yr - 81.3	1-yr - 88.1	1993-2010
	127 ALD	3-yr - 73.3	3-yr - 85.3	
		5-yr - 60.3	5-yr - 68.8	
Afazali *et al*[68]	1810 NASH	1-yr - 87.6	Variable	1997-2010
	3843 CC	3-yr - 82.2		
	48.085 Non-NASH	5-yr - 76.7		
Charlton *et al*[14]	1959 NASH	1-yr - 84	1-yr - 87	2001-2009
	33822 Non-NASH	3-yr - 78	3-yr - 78	

NAFLD: Nonalcoholic fatty liver disease; ALD: Alcoholic liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; CC: Cryptogenic cirrhosis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis.

after the LT were similar between the patients who were transplanted for NASH and the patients who were transplanted for other etiologies of ESLD. On the other hand, there was a tendency for higher mortality soon after the LT (30-d mortality was 6.1%), and one year after the LT (21.4%). NASH patients who were older (⩾ 60 years), obese (BMI > 30 kg/m^2), and had pre-LT hypertension and pre-LT T2DM had a higher risk for poor post-LT outcomes. Another important finding was that infection was the most common cause of death in the NASH patients compared to the controls[62]. In 2009, Bhagat *et al*[63] published a retrospective study that reported the post-LT outcomes for the NASH and ALD groups of patients who underwent LT. The authors found that overall survival and death rates due to CVD events was higher in the NASH group, but this difference was not significant. Interestingly, acute rejection crises and recurrent steatohepatitis occurred significantly more often in the NASH group but did not lead to higher rates of re-transplantation[63]. Two years later, Barritt *et al*[64] published another retrospective, but small, study. The primary finding of this study was that NASH, as an indication for LT, was the independent factor that influenced early post-LT mortality[28,64]. In 2012, Agopian *et al*[65] published a large, single-center study and found that the frequency of ESLD due to NASH as an indication for LT increased from 3% in 2002 to 19% in 2011. They reported that patients who were transplanted for NASH had a longer operative time, more operative blood loss and a longer post-LT length of stay. On the other hand, recipient and graft survival rates at one, three and five years were comparable to patients who were transplanted for other causes of ESLD. The predictors of poor outcomes for the recipient and its graft were pre-LT obesity and pre-LT hemodialysis[28,65]. Early postoperative mortality due to infections and CVD events in the recipients who were transplanted for ESLD due to NASH was reported in Kennedy *et al*[66]. This study also highlighted that an older age (> 60 years), pre-LT obesity, hypertension and T2DM were associated with lower five-year survival rates after LT. However, the overall survival rates at one, three and five years were comparable to other etiologies of ESLD[28,66]. VanWagner *et al*[44] discovered that NASH recipients had an increased risk for adverse CVD events in the first year after the LT compared to recipients who had ALD. The presence of MetS before LT was the most important risk factor[42]. One of the largest national US studies that addressed the outcomes of LT for ESLD due to NASH was published by Afazali *et al*[67]. The author used the UNOS database and analyzed 1810 LT recipients who had ESLD due to NASH, 3843 recipients who had ESLD due to CC, and 48085 recipients who had ESLD due to other etiologies of ESLD. The author reported an increased proportion of LTs for NASH patients; from 1.2% in 1997-2003 to 7.4% in 2010. NASH and CC recipients had good survival rates that were comparable to other etiologies of CLD. Consistent with other studies, there was a higher rate of early mortality in the NASH patients. In addition, in line with earlier, small studies, an older age, pre-LT T2DM, obesity and pre-LT hypertension were risk factors

for higher mortality rates in the first year after LT[68]. Another large national US study that used the SRTR database and was performed by Charlaton *et al*[14] had similar findings.

Finally, a meta-analysis that was published four years ago by Wang *et al*[69] showed that similar number of patients with and without NASH survived for 1, 3, and 5 years after LT; however, those who had NASH were more likely to die due to adverse CVD events or sepsis[69].

In most studies, patients who were transplanted for ESLD related to NASH had very good survival rates. One-year survival rates were between 85% and 90%, while five-year survival ranged from 70% to 80% in most studies. In addition, patients who underwent LT due to NASH-related ESLD had almost the same outcomes as other etiologies of CLD. It is interesting that NASH recipients, despite multiple comorbidities, have survival comparable to that of other etiologies of CLD. One possible explanations is that the rate of NASH and cirrhosis recurrence is lower than the recurrence of HBV or HCV[35,68]. Another consideration is that these patients undergo a very extensive pre-transplantation screening for risk evaluation and cardiovascular status, thus; those who have significant cardiovascular morbidity are excluded from the transplant list. However, according to the results, overall survival after LT is good in the NASH recipient group, and a higher incidence of post LT CVD events are noted in NASH recipients. However, infections (sepsis) were observed more frequently in this group of recipients. When selecting NASH patients for LT, there is a need for more attention and careful consideration combined with the radical management of sepsis and CVD complications after LT[11,68,69].

NONALCOHOLIC FATTY LIVER DISEASE AFTER LIVER TRANSPLANTATION

Progress in surgical techniques for transplant surgery, as well as the development of immunosuppressive therapy, led to decreased early post-LT mortality and, consequently, to improved survival rates after LT, with a 90% survival rate at the first year and a survival rate of more than 70% five years after LT. The development of metabolic comorbidities, combined with this higher post-LT survival, contributes to morbidity and mortality rates. Subsequently, the focus of research is changing to long-term complications, such as CVD[70-72]. CVD can be initiated with every insulin resistance (IR) associated component of MetS. Furthermore, the clinical features and prevalence of MetS, such as T2DM, hypertension, rapid weight gain and dyslipidemia, often deteriorate in the post-LT period based on transplant specific factors, for example, adverse events in immunosuppression. They are also related to the recipients' morbidity and mortality[70,72]. For metabolic balance, for hyperglycemia, weight gain, hypertension and hyperlipidemia, immunosuppressant drugs, such as corticosteroids, calcineurin inhibitors (CNIs) (cyclosporine (CSA), tacrolimus (TAC)) and mammalian target of rapamycin inhibitors (mTORs) (such as sirolimus (SIR) and everolimus), have a crucial role. Corticosteroids stimulate gluconeogenesis. CNI stimulates the post-LT occurrence of new-onset diabetes (NOD) that is more likely related to TAC use compared to CSA. CNI also initiates the development of post-LT hypertension, and it appears that CSA is highly related to the development of hypertension after LT. For dyslipidemia, CSA has a higher risk of causing dyslipidemia than TAC. Finally, for dyslipidemia, mTORs are the most unfavorable immunosuppressive drugs. These groups of immunosuppressive drugs may, to an extent, affect the development of CVD through metabolic complications[70-72]. Most transplanted patients become obese after LT, with the highest increase in weight occurring after the first six months, as well as one and three years after LT[70,72,73]. Of the liver recipients, 10%-64% develop T2DM, 45%-69% experience hyperlipidemia, and approximately 50%-100% develop hypertension after LT[70-72]. Thus, a significant number of liver recipients met the criteria for MetS, which indicates that these patients have a higher risk for CVD[70-72]. Based on the literature, MetS is present in approximately 50%-60% of transplant patients[71]. Therefore, MetS is an important post transplantation problem. Because NAFLD is a liver manifestation of MetS, it is not surprising that both recurrent and *de novo* NAFLD can be found after LT[70-72]. According to the abovementioned observations, MetS components (*i.e*., NAFLD risk factors) may persist or worsen after LT due to the high incidence of MetS after LT. NAFLD can affect the post-LT course in two ways. First, post-transplant NAFLD can develop as a recurrence of a pre-LT condition, and can progress to cirrhosis and lead to ESLD when re-transplantation is necessary. Second, due to the high incidence of MetS components after LT, NAFLD can also occur *de novo* and complicate the course of the recipients who are transplanted for other etiologies of CLD[28,70-72,74]. More than 25 years ago, Burke *et al*[75] were the first to describe recurrent NAFLD, and authors from San Francisco, CA, United States, reported the first case series of *de novo* NAFLD in 2003[76].

According to the literature, recurrent NAFLD is a relatively common diagnosis after LT. Across reports, the rates of recurring steatosis and NASH range from 30%-100%[28]. For example, Bhagat *et al*[70] found that 33% of patients who were transplanted due to NASH cirrhosis had steatohepatitis in biopsy specimens during the first six months after the LT. On the other hand, none of these patients developed cirrhosis or required re-transplantation during the 10-year follow-up period[70]. A group of Dallas authors[77] conducted a retrospective study and analyzed post-LT outcomes for 257 patients undergoing LT for CC or NASH cirrhosis.

After comparing patients who had NASH/CC with patients who underwent LT due to other etiologies of CLD, they found that more NASH/CC patients developed graft steatosis at one, two, five and 10 years post-LT (8.2%, 13.6%, 24.9% and 32.9%) than those who were transplanted for other etiologies (3.1%, 5.9%, 9.6% and 10%). Of the 257 NASH/CC patients, 13 developed NASH, and 5% and 10% developed bridging fibrosis or cirrhosis after 5 and 10 years. This outcome was more common in patients who had NASH than in those who developed steatosis per se or had no fat (3%). The survival rate during the 10-year follow-up was similar for patients who underwent LT for CC or NASH or LT for other indications. However, the cause of death differed between those two groups, as the NASH group had more adverse CVD events[77]. Moreover, Dureja *et al*[78] evaluated 88 liver transplant recipients that underwent LT due to NAFLD-related cirrhosis from 1993 to 2007. There was recurrent NAFLD in 34 liver transplants, isolated steatosis in 9 and steatohepatitis in 25 recipients, while there was advanced fibrosis in 3 recipients. The survival rate after LT was not affected by NAFLD recurrence, but a higher number of CVD and infectious complications were reported in this group[78]. Recently, Sourianarayanane *et al*[79] published a retrospective study and analyzed data from NASH and ALD transplant recipients between 2001 and 2006. The authors found that NASH recipients had a higher incidence of steatosis and inflammation after LT; however, the progression of fibrosis was slower in NASH than in ALD recipients[79]. Recently, Bhati *et al*[80] analyzed 103 patients who were transplanted for NASH in whom TE and liver biopsies were used to assess steatosis and fibrosis. Of 103 total patients, 56 had TE, while 34 had a liver biopsy. Implementing TE with CAP demonstrated that 87.5% of the patients who had steatosis also had recurrent NAFLD. Most patients had LSM with no fibrosis (42.9%) or F1-F2 fibrosis (30.4%). Overall, 26.8% of the patients had advanced fibrosis, while 5.4% developed cirrhosis. Of the patients who underwent a liver biopsy, 88.2% had recurrent NAFLD, while almost half (41.2%) had NASH. Bridging fibrosis was noted in 20.6% of patients; however, none of the patients had cirrhosis. In most patients, cancer (25%) or infectious complications (25%) were the cause of death in combination with CVD (21.9%). Graft cirrhosis only caused 9% of the deaths. According to this recent study, recurrent NAFLD commonly occurs after LT (88% of all patients), while nearly a quarter of the patients developed advanced fibrosis[80]. An interesting observation was published on the genetic predisposition for NAFLD recurrence. The presence of the rs738409-G allele of the Patatin-like phospholipase in LT recipients is an independent risk factor for post-LT steatosis, as well as obesity and T2DM[72,81].

Most research that investigates the prevalence of recurrent NASH in post-LT patients have shown that the incidence of recurrent NASH is between 20% and 40%, while the incidence largely depends on NASH detection methods, including liver enzymes, imaging techniques or liver biopsies. Most of the studies that investigated the incidence of recurrent NASH were retrospective, without a standard post-LT interval biopsy protocol. In addition, the histological criteria that was used for defining the diagnosis of recurrent NAFLD varied among published studies[74,81,82]. Therefore, there is a need for prospective studies that show the actual incidence and progression for recurrent NAFLD after LT. Also, it is not clear is NAFLD a primitive process, to which follows MetS, or is it just the opposite. Further research on this topic are needed.

A recently published study investigated the incidence of NASH in children and young adults as indications for LT in addition to post-LT patients and graft outcomes. Alkhouri *et al*[27] found that approximately 4% (13) of patients who were transplanted for NASH cirrhosis needed re-transplantation due to NASH recurrence.

Based on the literature, approximately one-third of patients who were transplanted for non-NASH indications developed IR and MetS (risk factors for NAFLD) in the three years post-LT. As such, researchers have attended to understanding the development of *de novo* NAFLD in recipients who underwent LT for indications other than NASH[11]. Ten years ago, Seo *et al*[83] retrospectively analyzed data from 68 recipients who experienced LT due to ESLD that was related to non-NASH indications. They reported that 18% of the recipients developed *de novo* NAFLD, while 9% developed *de novo* NASH. The data analysis showed that the utilization of angiotensin-converting enzyme inhibitors (ACE-I) was related to a decreased risk for developing NAFLD after LT. In contrast, an increased BMI of more than 10% after LT was a risk factor for NAFLD after LT[83]. The observation related to the protective effect of ACE-I in the context of *de novo* NAFLD after LT is interesting given preliminary findings that renin-angiotensin (RAAS) inhibitors have a beneficial effect on the regression of NAFLD in non-transplanted patients[84]. Recently, we have shown that using the RAAS inhibitor is associated with a lower rate of NAFLD as defined by TE with CAP in the population of renal transplant recipients[85]. However, additional research is needed on the benefits of using RAAS inhibitors to prevent the occurrence or progression of NAFLD in post-LT patients[85]. A few years ago, Dumortier *et al*[86] published a retrospective study that analyzed the prevalence of NAFLD in post-LT liver biopsies from 421 recipients who were transplanted for non-NASH indications. Histological evidence of steatosis occurred in 131 (31.1%) patients; and 53% had grade 1, 31% grade 2 and 16% grade 3 steatosis. Interestingly, 51.1% of those with steatosis had normal liver enzymes. There was perisinusoidal fibrosis in 38 patients (29.0%), while 5 patients (3.8%) were diagnosed with NASH. In contrast, there was cirrhosis or extensive fibrosis in 2.25% of recipients at the end of the follow-up. The authors noted that post-LT obesity, tacrolimus-based regimen, hyperlipidemia, hypertension, diabetes mellitus, and alcoholic cirrhosis

were the primary indications for the LT and, combined with pre-transplant liver graft steatosis, were risk factors for steatosis after transplantation[86]. This is the first study that showed an association between the presence of steatosis in the donor liver and the development of new NAFLD after the LT[28,86]. Recently, Kim *et al*[87] showed that preexisting donor graft steatosis is associated with a threefold increased risk for developing post-LT NAFLD (OR = 3.147, P = 0.022). Although the impact of donor steatosis on graft and patient outcomes remains an insufficiently explored area, the growing incidence of NAFLD in general population indicates an urgent need for further investigations on this topic[13].

Another interesting topic in the context of NAFLD after LT is the difference between recurrent and *de novo* NAFLD after LT. Vallin *et al*[88] published the first longitudinal study four years ago with a small number of patients. The authors analyzed the characteristics of 91 patients who experienced LT between 2000 and 2010. They compared biological, clinical, and histological markers for patients who had recurrent NAFLD and patients who had *de novo* NAFLD. During the study, 91 patients were given a diagnosis of post-LT NAFLD: 11 cases were classified as recurrent NAFLD, and 80 cases were classified as *de novo* NAFLD. There were no differences in sex, age and the prevalence of obesity, hypercholesterolemia or hypertension. However, in patients with recurrent NAFLD, there was a higher prevalence of diabetes mellitus (100% *vs* 37.5%). Severe fibrosis (stage 3 or 4) and steatohepatitis at 5 years had a higher incidence in patients who had recurrent NAFLD than in patients with *de novo* NAFLD [71.4% *vs* 12.5% (P < 0.01) and 71.4% *vs* 17.2% (P < 0.01), respectively]. Additionally, after 1 year, NAFLD was diagnosed in 67% of patients who had *de novo* NAFLD, while it was present in all patients who had recurrent NAFLD. For the liver biopsy, steatosis disappeared in 18 patients (22.5%) who had *de novo* NAFLD and in no patients who had recurrent NAFLD[88]. Although this was a small study, it is important to note that recurrent and *de novo* NAFLD after LT are different entities and recurrent NAFLD appears to be a more severe and irreversible condition with an earlier onset[88].

Although many drugs have been examined for treating NAFLD/NASH in the general population, there is still no efficient therapy for NAFLD. Thus, there are no studies that examine treatment options for preventing or treating the development or recurrence of NAFLD/NASH after LT. Because NAFLD is a liver manifestation of MetS, we need to prevent and treat all MetS components in post-LT patients. Given the metabolic effects of immunosuppressive drugs that are used in liver transplant recipients, this can often be challenging. For now, we can attempt to prevent and manage hypertension, dyslipidemia, diabetes and obesity, as well as individualize immunosuppressive therapy in post-LT patients to prevent NAFLD recurrence/development and CVD complications in all recipients[28,70,72].

NAFLD AND CHRONIC KIDNEY DISEASE AFTER LIVER TRANSPLANTATION

CKD is another important area and potential challenge in the context of NAFLD and LT. The survival of the graft and patient as well as the success of LT directly depends on kidney functions. Unfortunately, it is almost impossible to prevent the development of CKD after LT. For the occurrence of CKD after LT, there are three primary risk factors: pre-LT kidney disease, using immunosuppressive drugs and recipient comorbidities. Several authors reported that a risk factor for the development and progression of CVD and CKD is NAFLD[70,72,89-91]. Musso *et al*[89] performed a meta-analysis that included 33 studies 4 years ago. The study showed that NAFLD was related to an increased incidence and prevalence of CKD. There is a close relation between NAFLD and risk factors for CVD and CKD, which makes it difficult to determine whether NAFLD is only a risk marker for CVD and/or CKD or a causal factor[71,90,91]. Park *et al*[67] reported similar results for NASH patients who were on the waitlist. Patients who had ESLD due to NASH on the waiting list had significantly higher levels of serum creatinine than patients who had other etiologies of ESLD, despite similar MELD scores[67]. Moreover, NASH is also important in the context of CKD for the post-LT setting. The first study that highlighted this association was by Houlihan *et al*[91]. They demonstrated that patients who underwent LT for ESLD related to NASH developed worse renal functioning than patients who had ESLD due to other etiologies. Compared to non-NASH patients, three months after LT, NASH patients had a significantly lower estimated glomerular filtration rate (eGFR). During the next two years 31.2% of the NASH patients (15/48) developed stage IIIb CKD, which only occurred in 8.3% of the non-NASH patients (4/48)[91]. Three years later, Fussner *et al*[92] reported that female gender and NASH were independent predictors of $\geqslant$ stage 3 CKD development at 5 years post-LT.

Given the increase in the incidence of ESLD due to NASH, and based on the MELD allocation system, which favors LT for patients with higher creatinine (kidney injury), the incidence of CKD after LT is also likely to increase. In order to prevent pre- and post-LT CKD, more effective methods of treatment are needed, such as, delayed usage of CNIs or immunosuppressive protocols without CNIs which may be effective way for saving kidney function after LT. Therefore, immunosuppressive protocols should be considered in the context of LT and NASH, and more pro-perspective studies are needed on this topic[28,91,93].

CONCLUSION

NAFLD/NASH is a challenging and multisystem disease

that has a high socioeconomic impact. NAFLD/NASH, as a primary cause of macrovesicular steatosis, has several impacts on LT; on patients on the waiting list for transplant, on post-transplant setting as well as on organ donors. Current data indicate a new trend in the area of CLD. Because of the increased incidence of T2DM and obesity, *i.e.*, the growing incidence of MetS, there is a parallel rise in the HCC incidence[13,19,25,54,94]. Consequently, NASH cirrhosis and HCC due to NASH will soon become the major indications for LT. Importantly, recent investigations and observations indicate that HCC can occur in patients who have NAFLD without liver cirrhosis. Because screening for HCC is not a part of standard approach for a patient with NAFLD without cirrhosis, HCC is often diagnosed in advanced stages. One of the primary goals of health care practitioners should be to increase awareness of NAFLD/NASH and to develop and conduct useful screening programs for this increasing patient population[13,19,25,54].

An increased incidence of MetS and, consequently, NAFLD/NASH effects the demand for LT and the supply of available donors. Thus, we can expect that there will be a higher number of steatotic livers for LT in the future. The lack of organs is a global problem and could result in one of two possible scenarios. We will either choose low quality organs that have a greater risk for post-transplantation complications and, consequently, a higher risk for worse outcome of LT. The second option is that we will decrease steatotic livers but the time on the waiting list will become longer and, consequently, there will be an increase in wait-list mortality. To develop appropriate method for optimizing the allocation of steatotic grafts prior to LT, research needs to examine procedures to protect it from IRI or primary graft non-functioning and to expand the pool of available donors. Moreover, future research should identify new non-invasive diagnostic methods for the exact detection and quantification of steatosis in donor organs. In addition, more data on other potential risk factors that are associated with the development of steatotic livers is necessary[28,54].

There are two problems with keeping NASH patients on the waiting list: their comorbidities and lower MELD scores compared to other etiologies of CLD. These patients often have different metabolic risk factors and coexisting CVD and/or CKD, which makes managing these patients complicated and demanding. As such, there is a need for more detailed and personalized screening and evaluations of NAFLD/NASH patients, particularly for assessing CVD. According to available research, there are no universal guidelines or clear recommendations for the optimal screening method for CVD in patients who have NASH related ESLD and are candidates for LT. We need new prospective studies that will answer this important question and provide a basis for a standardized approach to assessing CVD risk in this population of LT candidates[13,28,35] In addition, randomized studies are needed to determine which NASH patients on the transplant list will benefit from treatment with BS, the optimal time for BS (before LT, during LT, after LT) and the type of BS to apply[28,34]. Future research is also needed to demonstrate the long-term impact of BS on LT recipients[28].

Patients who have ESLD due to NASH and underwent LT have similar post-transplant outcomes as other etiologies of CLD[35,68]. However, according to research, the total survival rates after LT are good, but NASH recipients have a higher incidence of CVD events after LT. Interestingly, infections (sepsis) were also more frequently observed in this group of recipients. The NASH LT recipients should be viewed as population at high risk for CVD, thus, there is a need for more studies on how to follow and treat these patients[11,68,69].

The prevalence of MetS clinical features, such as T2DM, hypertension, rapid weight gain and dyslipidemia, are often higher in the period after LT, are frequently caused by transplant specific factors, including immunosuppression, and can be valuable predictors of recipients' morbidity and mortality. Immunosuppressant drugs, such as corticosteroids, CNIs and mTORs, have a specific role in metabolic balance and favor hyperglycemia, weight gain, hypertension and hyperlipidemia. These groups of immunosuppressive drugs may, to an extent, contribute to the formation of CVD by affecting metabolic complications[70,72]. Most studies that examine the prevalence of recurrent NASH in the post-LT setting have shown that the incidence of recurrent NASH is between 20% and 40%, but the incidence largely depends on NASH detection methods, such as liver enzymes, imaging techniques or liver biopsies. Most of the studies that investigated the incidence of recurrent NASH have been retrospective, without the standard Post-LT interval biopsy protocol. In addition, the histological criteria that are used for the diagnosis of recurrent NAFLD varied in the published studies[74,81]. Therefore, prospective studies with well-defined biopsy protocols are needed to show the actual incidence and progression of recurrent NAFLD after LT. According to the literature, in one-third of patients who were transplanted for non-NASH indications, IR and MetS developed within three years post-LT. As such, more research has focused on understanding the development of *de novo* NAFLD in recipients who underwent LT for indications other than NASH[11]. Another interesting topic in the context of NAFLD after LT is the difference between recurrent and *de novo* NAFLD after LT. Although the results from previous studies were conducted with a small number of patients, it is important to note that recurrent NAFLD and *de novo* NAFLD after LT are different entities and that recurrent NAFLD appears to be much more severe and irreversible and has an earlier onset[88].

Preliminary data indicated that preexisting donor graft steatosis is associated with a threefold increase in the risk for developing post-LT NAFLD. However, the influence of donor steatosis on the graft and patient outcomes has been minimally explored, and given the growing incidence of NAFLD in the general population,

there is an urgent need for further investigations on this topic[13,87].

NASH is important in the context of CKD and in the post-LT setting. Preliminary data outline that NASH is an independent predictor of ⩾ stage 3 CKD development after LT[91,92]. Given the increase in the incidence of ESLD due to NASH, there is also likely to be an increase in the incidence of CKD after LT. The transplant society will have to identify a more useful approach to these patients to prevent pre- and post-LT CKD. The delayed use of CNIs or immunosuppressive protocols without CNIs may be an effective way for saving kidney function after LT. Therefore, immunosuppressive protocols should be considered in the context of LT and NASH, and more pro-perspective studies are needed on this topic[28,91,93].

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