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Nonalcoholic Fatty Liver Disease: Key Considerations Before and After Liver Transplantation

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common etiology of chronic liver disease in developed countries and is on trajectory to become the leading indication for liver transplantation in the USA and much of the world. Patients with NAFLD cirrhosis awaiting liver transplant face unique challenges and increased risk for waiting list stagnation and dropout due to burdensome comorbidities including obesity, diabetes, cardiovascular disease, and kidney disease. Thus far, patients transplanted for NAFLD cirrhosis have excellent mid- and long-term patient and graft survival, but concerns regarding short-term morbidity and mortality continue to exist. Post-liver transplantation, NAFLD occurs as both a recurrent and de novo manifestation, each with unique outcomes. NAFLD in the donor population is of concern given the growing demand for liver transplantation and mounting pressure to expand the donor pool. This review addresses key issues surrounding NAFLD as an indication for transplantation, including its increasing prevalence, unique patient demographics, outcomes related to liver transplantation, development of post-liver transplantation NAFLD, and NAFLD in the liver donor population. It also highlights exciting areas where further research is needed, such as the role of bariatric surgery and preconditioning of marginal donor grafts.

Keywords

Obesity; Outcomes; NAFLD; Cirrhosis; Liver transplantation; NASH; Steatosis; Review

Introduction

The next several decades will experience an unprecedented alteration in the liver transplantation (LT) landscape. Highly effective antiviral treatments promise to reduce the burden of end-stage liver disease (ESLD) and need for LT from chronic hepatitis C virus (HCV) infection. Meanwhile, the population continues to age, become increasingly obese

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Compliance with ethical standards

Conflict of interest None.

and insulin resistant, and suffer the liver-related consequences of the metabolic syndrome. Hence, it is predicted that cirrhosis and ESLD from nonalcoholic fatty liver disease (NAFLD) will become a primary driver for LT in the USA and much of the world. Given the complexity surrounding NAFLD cirrhosis, providers caring for these patients both pre- and post-LT will continue to face unique yet increasingly common challenges. The goal of this review is to address the key issues surrounding NAFLD as an indication for LT, including its increasing prevalence, unique patient characteristics, outcomes post-LT, development of NAFLD post-LT, and NAFLD in the liver donor population. It also highlights areas where further research is needed to improve the care of this growing patient population.

Increasing Prevalence of Liver Transplantation for NAFLD Cirrhosis

Currently, HCV represents the leading etiology for LT for both hepatocellular carcinoma (HCC) and non-HCC in the USA [1–4]. NAFLD is projected to replace HCV as the leading indication for LT in the USA within the near future coinciding with the steady rise of NAFLD and nonalcoholic steatohepatitis (NASH) prevalence, as well as stabilization and eventual decline of HCV-related cirrhosis due to highly effective antiviral treatments [2] (Fig. 1). Data suggest NASH cirrhosis to already be gaining steam as it was recently found to be the second leading etiology among adult waitlist registrants in the USA, with a 170 % increase between 2004 and 2013 [5]. Another study using data from the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) registry found that although HCV remained the leading etiology for HCC patients undergoing LT in the USA in 2012, NASH was the most rapidly rising etiology, increasing fourfold from 2002 to 2012 [4]. A study of Scientific Registry of Transplant Recipients (SRTR) data between 2001 and 2009 reported NASH the third leading indication for LT, behind HCV and alcoholic cirrhosis, and the only indication increasing in frequency [2]. NAFLD/NASH-related cirrhosis has also become the most common non-HCC indication for LT in patients age 65 or older [6]. Prevalence estimates for NASH-related cirrhosis as an indication for LT, while already quite high, are likely underestimated given that the majority of cryptogenic cirrhosis is considered to be unrecognized NASH [7, 8]. Collectively, these studies demonstrate the growing demand for LT for NAFLD/NASH cirrhosis in several cohorts, including older patients and those with and without HCC. They also hint of the progressively changing LT landscape and the need to closely assess the impact of NASH on post-LT morbidity and patient and graft survival.

NAFLD Cirrhosis: A Uniquely Challenging LT Patient

Just as every etiology of ESLD presents unique considerations and needs surrounding LT, so do those with NAFLD. Because NAFLD characteristically exists as part of the larger metabolic syndrome, NAFLD/NASH patients on the LT waiting list usually have obesity, diabetes mellitus (DM), hypertension, and hyperlipidemia and contend with the medical complications surrounding these comorbidities. On average, they are older than those patients listed with chronic viral hepatitis or autoimmune etiologies [6]. Patients who eventually are transplanted for NASH cirrhosis are also more likely to be female as compared to other etiologies [9–11].

In a recent study of etiology-specific annual trends of new LT waitlist registrants, Wong et al. highlighted some important differences with NAFLD. They found waitlist patients with NASH were significantly older compared to those with alcoholic liver disease (ALD) or HCV cirrhosis [5]. NASH patients were also significantly more likely to be white (78.5 %), and have DM (43.6 %), a higher median body mass index (BMI) (31.6 kg/m^2), and a lower glomerular filtration rate (GFR) (55.2 mL/min) [5]. Model for End-Stage Liver Disease (MELD) scores at listing were not significantly higher than those in patients with HCV or ALD, however.

While all of these factors impact the course of LT from the waitlist period through post-LT outcomes, obesity appears to be the most influential comorbidity, if not the most widely studied. To date, a number of studies have evaluated the impact of obesity on waiting list mortality, surgical outcomes, and post-LT survival. Existing data are somewhat conflicting, however, with several authors reporting worse outcomes in the obese, while others suggest similar risks and outcomes for obese and non-obese populations. For example, in an analysis of perioperative morbidity of 813 LT patients, LaMattina et al. [12] found that obesity was significantly associated with prolonged mean operative time, intensive care unit stay (4.1 vs. 2.6 days; $p = 0.04$), increased transfusion requirements, infections (HR 7.21, CI 1.6–32.4, $p = 0.01$), biliary complications (HR 2.04, CI 1.27–3.3, $p = 0.003$), and decreased patient survival (HR 1.82, CI 1.02–2.65, $p = 0.04$) depending on the class of obesity. Two other groups, using both UNOS and United Kingdom (UK) data, reported similarly worse outcomes in obese patients with higher rates of graft dysfunction, cardiovascular adverse events, and perioperative morbidity due to infectious complications and longer hospital stays as compared to normal-weight patients [13, 14]. However, another smaller study of 230 LT patients found no significant differences in perioperative morbidity and mortality between patients when stratified by BMI into a lean group (BMI 20–26 kg/m^2) and an obese group (BMI > 38 kg/m^2) [15].

Obese cirrhotic patients are also significantly more likely to be turned down for organ offers (10 % higher likelihood for severely obese, 16 % for morbidly obese) than non-obese cirrhotics [16]. In this study by Segev et al. [16], obese patients received significantly less MELD exception points even after adjusting for factors potentially meriting MELD exception (10.3 % for severely and 8.0 % for morbidly obese compared to 15.2 % of non-obese). The authors suggest that reluctance to transplant obese patients may stem from concerns for increased postoperative complications and inferior outcomes, especially in the era of diminishing financial reimbursement for transplantation and publicly available transplant data. It will be interesting to see how obesity impacts transplant rates and post-LT morbidity and mortality as the number of transplants for NASH increases in coming years.

Dieting, medications, physical activity, and behavioral therapy to address obesity prior to LT are acceptable but often poorly effective or tolerated given the severity of patients' liver disease [17]. Another option that has been used to address the possible negative impact of obesity on LT is bariatric surgery (BS). BS effectively treats morbid obesity through weight loss and improves obesity-related conditions such as Type 2 DM, hypertension, and NAFLD [18]. Obese NAFLD patients awaiting LT should benefit from BS given the improvements seen in these metabolic syndrome conditions as well as with possible resultant reduction in

complications associated with obesity following LT. Given these tangible benefits, BS has been described before, in conjunction with, and after LT for NASH cirrhosis as well as other etiologies of ESLD. Relatively few studies on BS and LT exist, however, with most reporting case series of 1–20 patients [19, 20]. Randomized trials addressing the type and/or timing of BS (i.e., before, during, or after) in relation to LT have not been conducted. Different types of BS procedures have been performed, including sleeve gastrectomy, gastric banding, and Roux-en-Y gastric bypass, with the most common being sleeve gastrectomy [19]. Sleeve gastrectomy does not include an intestinal bypass and thus theoretically should not affect absorption of immunosuppression medications. This choice has also been justified by the fact that it does not alter endoscopic access to the biliary tract, which is important as biliary complications after LT are not uncommon [19]. Given the paucity of data regarding the benefits of BS, further study is needed to evaluate the feasibility, safety, and optimal type and timing of BS in obese patients with NASH cirrhosis.

The other well-known risk for patients with NASH cirrhosis is cardiovascular disease (CVD) [21]. Several studies report higher rates of coronary artery disease (CAD) in patients with ESLD due to NAFLD than with other etiologies. In one such study, Patel et al. [22] compared the frequency of CAD in alcohol versus non-alcohol-related ESLD. The incidence of severe CAD (>70 % diameter stenosis) was significantly higher in the non-alcohol-related group (2 vs. 13 %, p <0.005). Importantly, dobutamine stress echocardiography had poor predictive value for CAD in the non-alcohol-related group. Whether patients with ESLD due to NAFLD should be more intensively screened remains somewhat controversial, but it has been suggested that NAFLD patients over a certain age be screened with angiography rather than stress testing [23]. This is an important issue as several studies have documented an increased risk of perioperative cardiovascular mortality. VanWagner et al. [11] found that patients who underwent LT for NASH cirrhosis were significantly more likely than patients with alcoholic cirrhosis to experience an adverse cardiac event<1 year after transplant, even after controlling for age, sex, BMI, smoking, previous history of CAD, and previous history of metabolic syndrome (OR 4.12, 95 % CI 1.91–8.90). The majority (70 %) of these NAFLD patients had perioperative cardiovascular events. 90 % of these patients underwent noninvasive stress imaging (and 37 % of these achieved suboptimal heart rate with the subsequent majority of these leading to further testing) and 40 % of these patients underwent cardiac catheterization with minimal or no CAD noted [11]. A prolonged QT interval was common and found in 77 % of patients with NAFLD who experienced a cardiovascular event [11].

We recommend that attention be given to optimizing glucose control, weight, frailty, and CVD risk in NAFLD patients awaiting transplant. Optimal glucose control is of marked importance, especially in light of increased postsurgical complications with poor glucose control and the substantial risk of new onset or progressive DM related to post-LT immunosuppression [24, 25]. A multi-disciplinary approach with the involvement of a dietician and physical therapist is essential and is a common feature of academic transplant programs to reinforce and improve nutritional and physical habits. Frailty is an established risk factor for LT waitlist mortality and may be particularly important to evaluate and address in this generally older waitlist population as well [26]. NAFLD patients with concurrent CVD should optimize CV risk and consider statin therapy for possible benefit in

reducing risk of CVD mortality [27]. Consideration should also be made for a more rigorous pre-transplant cardiac evaluation including cardiac catheterization in NAFLD patients with metabolic syndrome given the increased CVD burden in this population.

Liver Transplantation Outcomes for NAFLD Cirrhosis

When considering outcomes of LT, it again is difficult to separate the effects of comorbidities of NAFLD such as obesity, DM, and CVD from those of NAFLD itself. In the previous section, we discussed how the comorbidities of NAFLD make it a challenging patient population to manage and bring safely to transplant surgery. In this section, we will discuss the impact of NAFLD and its associated comorbidities on waiting list survival and post-LT outcomes. Whether NAFLD confers an independent risk for poor outcomes of LT will also be addressed.

The Waiting List

Prior to successful receipt of a liver allograft, patients with ESLD due to NAFLD must navigate the waiting list and the risk of dropout due to death or progression of comorbidities that may make transplant unsuccessful. The time on the waiting list can often represent a particularly challenging period for patients with NAFLD given their comorbidities of higher BMI and difficult organ size matching, older age, and CVD. Studies have documented increased waitlist dropout, waitlist mortality, and waitlist stagnation for patients with NAFLD. Whether this is due to NAFLD itself, or its associated comorbidities, remains unclear. For example, in a study of outcomes for cirrhotic patients listed with MELD < 22, DM was associated with an increased risk of waitlist dropout [28]. Irrespective of associated comorbidities, the recent study by Wong et al. [5] reports significantly lower rates of receiving LT within 90 days of waitlisting and lower 1-year waitlist survival for NASH patients compared to those listed for ALD or HCV, with findings persisting on multivariate analysis. The 1-year waiting list survival for NASH patients actually declined significantly over the study period from 42.8 to 25.6 % [5]. Etiology-specific differences in disease progression may explain some of these discrepancies. The steady rise in MELD score needed to achieve LT in parts of the USA with the highest prevalence of obesity that occurred during their study period likely also contributes. Because HCV typically has a more aggressive course than NASH, MELD scores increase more rapidly, resulting in sooner LT, lower waitlist mortality, and higher LT frequency [5]. An earlier study by O'Leary et al. [29] reported similar findings with NASH cirrhosis and cryptogenic cirrhosis. They found slower progression of disease by MELD for NASH as compared to HCV among patients with MELD ≤ 15. NASH patients were also more often removed from the waitlist due to being too sick and were more likely to die without LT as compared to HCV-cirrhosis patients [29]. Among those with MELD ≥ 15, however, there was no difference in frequency of LT or MELD progression across groups [29].

Post-LT Survival

Despite the comorbidities and older age of NASH patients undergoing LT, post-LT survival is comparable to, or even surpasses, that of other etiologies of ESLD. Several large database studies conducted over the last 5 years all report excellent survival rates in NASH patients

(approximately 88 % at 1 year, 82 % at 3 years and 77 % at 5 years) [2, 9, 30]. These studies have employed both UNOS and SRTR data to compare survival rates between NASH and other indications for LT for patients transplanted between the late 1990s and early 2010s. These studies all find comparable post-LT survival for NASH even with higher BMI, and higher prevalence of DM and CVD pre-LT [30].

Multiple single-center studies of survival and other post-LT outcomes in NASH have also been conducted. These corroborate the larger database findings and add granularity to the information by identify specific factors associated with poorer outcomes (Table 1). Malik et al. [31] retrospectively compared all adult patients undergoing LT for NASH cirrhosis with a control group of patients transplanted for other etiologies including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), ALD, and HCV cirrhosis. NASH patients were older, more likely to be female, and suffer from hypertension and DM at the time of LT compared to controls. 5-year survival was similar between patients transplanted for NASH and controls matched for age, sex, and MELD, but there was a tendency for higher 30-day and 1-year mortality in NASH patients. Malik defined a high-risk phenotype at increased risk of mortality as those with increased age (≥60 years), obesity (BMI ≥ 30 kg/m^2), and pre-transplant DM and hypertension. Infection/sepsis was the most common cause of death in NASH patients, significantly higher than controls [31]. A smaller, retrospective study by Barritt et al. also found short-term, 30-day transplant mortality was higher for transplant recipients with NAFLD cirrhosis even after controlling for recipient and donor covariates (81 vs. 97 %, $p = 0.001$). Four NAFLD patients died within 30 days: 2 died from hepatic artery thrombosis, 1 from multi-organ failure, and 1 from cardiac complications [32]. DM was also an independent risk factor for mortality at 3 years (63 vs. 89 %, $p = 0.006$) [32]. Poorer outcomes for diabetic patients have been reported before. The increased risks here, however, may be influenced by selection of their NAFLD cohort as they used metabolic syndrome criteria.

In one of the largest single-center studies, Agopian assessed graft and patient survival after LT for NASH versus non-NASH controls as well as predictors of poor outcome [33]. Similar to other groups, they found NASH patients were older, more likely to be female, and have more features of the metabolic syndrome. Patient and graft survival rates at 5 years were comparable to patients transplanted for hepatitis B virus (HBV), ALD, cryptogenic cirrhosis, PBC, and PSC, but significantly better than for those transplanted for HCV [33]. Predictors of worse graft and patient survival in patients with cirrhosis attributed to NASH included severe obesity (BMI ≥ 35 kg/m^2) and pre-transplant hemodialysis [33]. Significantly, NASH patients in this study had a high acuity of illness at the time of LT with many hospitalized (62 %), on hemodialysis (45 %) or intubated (16 %). Despite the high acuity, survival rates were comparable across etiologies and comparable to national data. Comparing NASH to ALD, Bhagat et al. [34] found that overall and cardiovascular mortality post-LT were not significantly different at 1, 3, 5, and 9 years. A higher number of patients died from CVD causes in the NASH group (26 vs. 7 %), but the difference was not statistically significant. Interestingly, acute rejection was more common in the NASH group (41 vs. 23 %, $p = 0.023$), though there were no differences in graft failure or need for re-transplantation [34]. It is not clear whether this difference was due to immunosuppressant therapy, but the observation emphasizes the important struggle to balance sufficient immunosuppression and

control of metabolic syndrome risks in this population. Increased early postoperative mortality, but comparable 1-, 3-, and 5-year survival rates, were also reported by Kennedy et al. for patients with NASH compared to non-NASH patients. Similar to the findings reported by Malik, they defined a high-risk NASH phenotype (age >60 years, BMI >30 kg/m^2, hypertension and DM) that was associated with lower 5-year survival [35]. Finally, a recent meta-analysis and systematic review including 9 studies and 717 patients with NASH cirrhosis found similar 1-, 3-, and 5-year survival between NASH and other etiologies [36]. Graft failure was lower in NASH as compared to other etiologies [36].

Role of Renal Dysfunction

Kidney disease impacts successful transplantation as well as post-LT outcomes for many patients. This is particularly true in NAFLD, as evidence suggests NASH is an emerging risk factor for renal dysfunction both pre- and post-LT [37]. In a study of LT referrals, Park et al. [10] observed that NASH patients had significantly higher creatinine and lower pro-thrombin time than other etiologies for LT despite similar MELD scores. Renal dysfunction in NASH is felt secondary to effects of DM, hypertension, and atherosclerotic disease, rather than intrinsic to liver dysfunction, but the true pathogenic links remain unclear [10]. NASH is also a risk factor for renal impairment after LT. For example, Houlihan et al. reported significantly lower GFRs in NASH cirrhosis patients at 3 months after LT, even in their adjusted analysis. Survival at 1 and 5 years was the same, however [38]. Within 2 years, 31.2 % (15/48) of NASH patients developed stage IIIb chronic kidney disease versus only 8.3 % of non-NASH (4/48) patients ($p = 0.0009$) independent of BMI, DM, hypertension, HCC, and tacrolimus levels [38]. In another analysis of the UNOS database between 2002 and 2011, investigators found the frequency of combined liver–kidney transplantations for NASH cirrhosis increased disproportionally compared to other etiologies [39]. As NASH cirrhosis becomes the most common indication for LT, the incidence of subsequent chronic kidney disease may increase. The transplant community will therefore need more effective methods to prevent renal dysfunction both pre- and post-LT. Methods for preventing chronic kidney disease progression through vigilant immunosuppression management and pharmacologic treatments associated with benefits in renal function will also need to be developed.

HCC and NAFLD/NASH Cirrhosis

The impact of HCC on survival post-LT for NASH has been evaluated in only a few studies. Reddy et al. [40] compared survival post-LT in NASH with HCC versus HCV/ALD with HCC and found no difference in overall survival at 3 years. Of note, albumin<3.5 mg/dL and HCV infection were independently associated with decreased overall survival on multivariate analysis [40]. A recent study used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database between 2004 and 2009 to evaluate mortality in NAFLD with HCC [41]. They found that patients with NAFLD and HCC were older at time of diagnosis and more likely to be white and male. Fewer patients with NAFLD-related HCC received a liver transplant as compared to other HCC patients. It was speculated that this is related to higher overall 1-year mortality in patients with NAFLD-related HCC as well as metabolic comorbidities associated with poorer prognosis.

Role of Cardiovascular Disease

CVD increases long-term morbidity and mortality in the post-LT population of all etiologies, but is of particular importance in NASH cirrhosis [11, 42]. Several studies document increased risk of cardiac events including sudden cardiac death and acute heart failure within 1 year of LT for this population [11, 43]. Renal dysfunction was again an important predictor of CVD mortality in NASH patients [43].

Overall, existing data suggest LT for NASH results in excellent mid- and long-term patient and graft survival. The exception seems to be a negative impact on early post-LT survival with early postoperative deaths due to CVD and infectious complications. Moving forward, it will be important for transplant centers caring for patients with NASH and comorbidities such as obesity, DM, renal dysfunction, and CVD to develop focused clinical practice guidelines that address immunosuppression, mobility issues, perioperative pulmonary hygiene, and more invasive cardiac testing pre-LT. Adequately addressing donor quality for the group of older, high-risk NASH patients will also play an important role in improving short-term outcomes.

NAFLD Development After Liver Transplantation

NAFLD complicates the post-LT period for many recipients. This can occur in two different scenarios. First, it can represent recurrence of the initial disease that led to cirrhosis and ESLD requiring LT [44]. Second, it can complicate other etiologies of ESLD [45]. De novo NAFLD likely results from an accumulation of metabolic risks, including increased risk of hyperlipidemia, hypertension, and DM with exposure to immunosuppressive drugs (i.e., calcineurin inhibitors and steroids) [45–47] as well as other factors such as a more sedentary lifestyle post-LT and promotion of NAFLD by the allograft itself [48].

Recurrent NAFLD is common post-LT. Studies report a wide range of steatosis and NASH reappearance rates over time following LT, from about 30–100 %. Fortunately, for most, the risk of advanced fibrosis and cirrhosis or need of re-transplantation is low. For example, Yalamanchili et al. evaluated 257 patients transplanted for cryptogenic cirrhosis or NASH cirrhosis from 1986 to 2004 and found that steatosis developed in 32.9 % of patients at 10 years. This was significantly higher than for other indications, but recurrent NASH only developed in 4 % of patients on serial biopsies [49]. Short- and long-term survival was similar in both cohorts as well [49]. Dureja et al. [50] evaluated NAFLD recurrence via liver biopsies in a cohort of 88 patients transplanted for NAFLD cirrhosis between 1993 and 2007. NAFLD recurred in 39 %, with steato-hepatitis occurring in 25 of those. Severe recurrence, defined as a NAFLD Activity Score (NASH) ≥5, was seen in 3 patients, and advanced fibrosis developed in 3 patients [50]. NAFLD recurrence significantly correlated with higher pre-transplant ($p = 0.001$) and post-transplant ($p < 0.0001$) BMI, as well as increased post-LT triglyceride levels [50]. Average steroid dose at 6 months post-LT was significantly higher in those with NAFLD recurrence [50]. Again, post-LT survival did not differ, but NAFLD recurrence was significantly associated with CVD and infection-related morbidity and mortality [50]. In a retrospective study of 30 post-LT NASH cirrhosis and age and weight matched controls, Contos et al. [51] noted a time-dependent increase in risk of allograft steatosis that approached 100 % by 5 years compared to only 25 % in the non-

NASH controls. All patients underwent the same standard immunosuppression protocol [51]. On multivariable analysis, cumulative steroid dose was the only finding correlated with time to development of steatosis [51]. Three of 30 patients in the NASH group developed recurrent steatohepatitis; one of these developed progressive fibrosis [51]. Another older study by Charlton et al. [1] published in 2001 reported similarly high rates of recurrent steatosis (60 %) and steatohepatitis (33 %) at 1 year.

Additional studies have compared features of recurrent allograft NAFLD with de novo allograft NAFLD in order to highlight similarities and differences in the two processes as well as to identify associated risk factors and outcomes. Bhagat et al. [34] observed a recurrence of moderate to severe steatohepatitis in 33 % of patients on liver biopsy specimens obtained after six months versus no recurrence (0/77) of de novo steatohepatitis in an alcoholic cirrhosis cohort. Of note, none of the patients in the NASH group developed cirrhosis or required re-transplantation at 10-year follow-up [34]. Another retrospective analysis of 68 LT patients assessed risk factors for the development of de novo NAFLD and NASH using donor pre-LT and recipient follow-up liver biopsies at 28 ± 18 months. 18 % of patients developed de novo NAFLD, and 9 % developed de novo NASH [52]. In multivariable logistic regression analysis, increase in BMI greater than 10 % after LT was associated with a higher risk of developing de novo NAFLD [odds ratio (OR) 19.38; 95 % CI 3.5–107; $p = 0.001$] and the use of angiotensin-converting enzyme inhibitors (ACE-I) was associated with reduced risk (OR 0.09, 95 % CI 0.01–0.92, $p = 0.04$) [52]. In another study, Dumortier et al. [48] retrospectively reviewed liver biopsies from 421 patients who subsequently underwent LT for non-NAFLD indications without recurrent liver disease and found that steatosis developed in 31.1 % and NASH developed in 5.3 %. On multivariate analysis, patient obesity at the time of liver biopsy, tacrolimus-based immunosuppression regimen, DM, hyperlipidemia, hypertension, ALD as primary indication for initial transplantation, and pre-transplant liver graft steatosis were all significant independent risk factors for the development of de novo NAFLD [48]. This was the first study to show that pre-transplant graft steatosis, defined as involving >5 % of hepatocytes, was a risk factor for de novo NAFLD, supporting a possible genetic predisposition to the disease [48]. A recent study by Vallin et al. [53] in France characterized recurrent ($n = 11$) and de novo ($n = 80$) NAFLD through biopsies at 1-, 3-, and 5-year intervals post-LT. De novo NAFLD was present in 67, 69, and 78 versus 100 % of NAFLD patients with recurrent NAFLD at 1, 3, and 5 years, respectively. Severe fibrosis and steatohepatitis were more frequent in patients with recurrent NAFLD at all three time periods as well (e.g., 5 years: 71.4 vs. 12.5 %, $p < 0.01$; and 71.4 vs. 17.2 %, $p < 0.01$, respectively). While these higher rates of severe disease must be interpreted with caution given the small number of patients, the study is the first to assess these developments longitudinally rather than cross-sectionally. These results suggest that recurrent NAFLD is a more concerning disease than de novo NAFLD and that providers should be performing liver biopsies for these patients at more regular intervals and vigilantly addressing risks for recurrent NAFLD such as obesity, DM, hyperlipidemia, and hypertension when caring for these patients.

The impact of patatin-like phospholipase domain-containing protein 3 (PNPLA3) genotype on post-transplant NAFLD has also been evaluated. Finkenstedt et al. [54] examined 237 transplant patients and 255 liver organ donors to evaluate whether the G-allele in position

rs738409 conferred an increased risk of post-transplant graft steatosis, as this is a well-established risk of steatosis and liver injury in NAFLD. The study found that this risk allele was significantly more frequent in transplant recipients than in donors and that the prevalence of graft steatosis of >30 % significantly increased from 11.6 % at year 1 to 32.6 % at year 5 after LT [54]. Steatosis was noted in 63.2 % of patients homozygous for the risk allele, in 31.4 % of heterozygotes, and in 12.0 % of patients with wild-type [54] alleles. Donor genotypes were not associated with development of post-LT graft steatosis [54].

Collectively, these studies document the occurrence of NAFLD in many patients after LT. Survival does not seem to be impacted thus far. De novo and recurrent NAFLD may be different entities, and further research is needed to understand the key patient, medication, and genetic factors influencing the risk of more severe disease, as well as methods that could be successfully implemented to mitigate factors associated with development of allograft NAFLD such as exercise and weight loss [55].

NAFLD in the Donor Liver

The increasing prevalence of NAFLD in the general population corresponds directly with the increasing prevalence of NAFLD in the both the deceased and living liver donor populations. With the severely limited organ resources for LT and resultant long waiting lists and waiting list mortality, there has been a push for utilization of marginal donors or “extended criteria donors” (ECD) liver allografts [56]. ECD is defined as any donor over the age of 60 or a donor over 50 years with two of the following: a history of hypertension, a creatinine ≥1.5 mg/dL, or death resulting from stroke. A frequent reason for a suboptimal allograft from ECD or even standard criteria donors (SCD) is hepatic steatosis [57]. Use of steatotic donor organs has been associated with an increased risk of graft failure and/or impaired graft function as many of these organs suffer from ischemia reperfusion injury (IRI) after transplantation [58]. There is ongoing debate regarding what constitutes significant and acceptable risk in terms of the amount and type of fat in a steatotic graft [56]. Typically steatotic grafts with >60 % fat are not transplanted, while those with 30–60 % fat when transplanted have been associated with poor results, such as decreased graft function, graft survival, and patient survival [59]. The pattern of fat distribution appears to also play a role; livers with macrovesicular steatosis are more intolerant of ischemic injury than those with microvesicular steatosis [60]. A study by Spitzer et al. [61] using SRTR LT data between 2003 and 2008 showed that >30 % of macrovesicular steatosis on donor liver biopsies was an independent risk factor for graft failure at 1 year in transplanted patients. Steatosis in the donor graft constitutes a significant risk factor that requires careful consideration during assessment for use in LT.

Living donor transplantation outcomes are also impaired by steatosis. Most transplant programs exclude donors with macrovesicular steatosis >10–15 % [62]. The practice of transplant programs varies as some perform liver biopsies on all potential donors, whereas others perform them only when significant steatosis cannot be ruled out [62]. Interestingly, a study by Ahn et al. [63] assessed 492 living liver donors who had normal serum aminotransferase levels and liver ultrasound without features concerning for fatty liver. They found histologically severe steatosis (≥60 %) in only 4 (0.8 %), but moderate steatosis (30–

59 %) in 53 (10.8 %) of donors, suggesting that noninvasive preoperative assessment for liver steatosis was not sufficient to exclude moderate steatosis in living donors [63].

Multiple studies have been performed in attempts to optimize the steatotic liver graft prior to LT. A short-term intensive treatment with protein-rich diet (1000 kcal/day), exercise (600 kcal/day), and bezafibrate (400 mg/day) for 2–8 weeks in a small trial of 11 living donors significantly improved macrovesicular steatosis and reduced body weight and BMI [64]. For deceased donor organs, a number of techniques have been developed such as ischemic preconditioning (IP) to improve the detrimental affects of IRI on marginal donor grafts, in particular steatotic ones [65]. Since the first description of IRI in steatotic livers in 2000, serious efforts have been made to ameliorate its effects experimentally and to translate the benefits of IP into clinical practice [66]. While gains have been made in improved injury from warm ischemia during hepatic resection, results have been less impressive in transplantation. In fact, a Cochrane review found no evidence to support or refute the use of IP in LT [67]. Clinical studies have shown benefit, however, in hepatocyte swelling and enzyme release after LT as well as less autophagy and possibly less rejection in steatotic livers exposed to IP [68, 69]. Pharmacological preconditioning such as with anesthetics, antioxidants, and/or steroids has been suggested as potential hepatoprotective strategies for steatotic livers, but few have been reported in humans. A randomized control trial of sevoflurane anesthesia by Beck-Schimmer et al. [70] hypothesized that this would reduce postoperative liver injury and promote beneficial effects from an inducible nitric oxide pathway. In the sevoflurane group, aminotransferase elevations were significantly decreased and this was particularly beneficial to steatotic livers [70].

Given the mixed clinical results and lack of data to support improved graft and patient survival, researchers continue to investigate various experimental systems for their effectiveness at reducing IRI in steatosis. A recent systematic review of experimental IP in steatotic rat livers was published in 2014 [65]. The authors identified 18 articles meeting inclusion criteria, but with heterogeneity in model, duration, and type of IRI. Despite this, they concluded that animals with preconditioned livers had improved outcomes including increased survival, less histologic injury and improved liver function. Translating these findings into the clinical setting remains a major obstacle, however, given the lack of accurate animal models of human liver steatosis. It has been recommended though that organs with >30 % steatosis only be used if other factors are controlled (i.e., donor age<40 years, short cold ischemia time of<5 h, and non-circulatory cause of death) [61].

Given the growing demand for LT and need to use increasingly marginal donor organs, information is needed on how best to protect steatotic livers from IRI in order to expand the pool of available donors. Whether this will be through optimizing preconditioning or via another method requires much needed further research.

Summary and Future Directions

NAFLD will likely become the leading indication for LT in the USA in the very near future. The increased prevalence parallels the worsening obesity epidemic as well as a decline in HCV resulting from new antiviral therapies. Patients who undergo transplantation for

NAFLD have comparable post-transplant outcomes to other etiologies of liver disease, though NAFLD has its own distinct challenges, such as an older listed population and frequent comorbid conditions such as kidney disease and obesity. The critical assessment of pre-transplant pre-habilitation strategies for waitlisted NAFLD cirrhotics is hoped to favorably impact waitlist mortality for this group and may well be able to positively impact some of the short-term negative outcomes seen following transplantation. Identification of optimal timing, and type, of BS to manage the morbidly obese transplant candidate or recipient needs further refinement, but once clarified, has the potential to markedly impact transplant candidacy and recovery in patients with NASH cirrhosis. Development of NAFLD in the donor graft is a significant finding, and further study is needed into limiting its development and to clarify management. Lastly, NAFLD in the donor population is a rising concern, and further evaluation should be performed with regard to optimizing preconditioning for steatotic livers with an attempt to expand the donor pool to fit the growing demand for LT. The use of metabolic preconditioning of the allograft either in situ in the donor or during post-procurement perfusion is an exciting area of active research and if accomplished could greatly expand the limited donor allograft pool. Results from trials that are just entering human study are eagerly awaited in this regard.

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Key Messages

- NAFLD is expected to become the leading indication for liver transplantation in the near future corresponding to the increasing prevalence of diabetes mellitus and obesity.
- NAFLD patients with end-stage liver disease on the transplant waiting list face unique challenges as they are older and have significant comorbidities including obesity, diabetes, cardiovascular disease, and kidney disease that require astute clinical assessment and management to counter waiting list mortality and dropout.
- Liver transplantation for NAFLD results in excellent mid- and long-term patient and graft survival, though concerns for short-term outcomes remain and NAFLD-specific liver transplantation practice guidelines are lacking at this time.

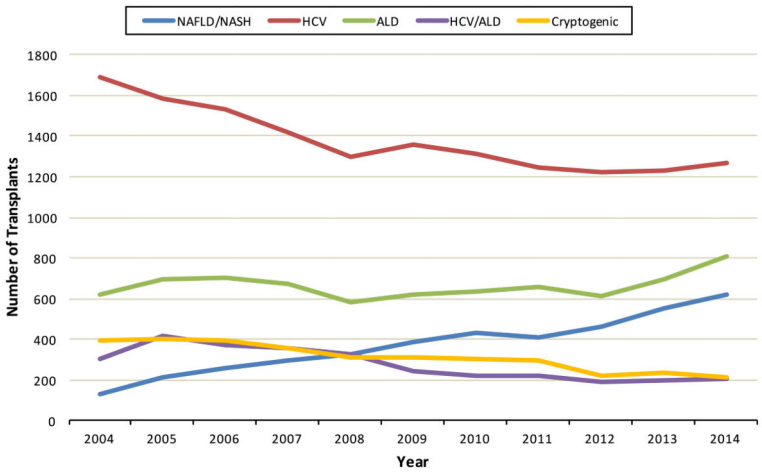

Fig. 1.

Annual trends in the number of adult liver transplants performed in the USA between 2004 and 2014 by etiology. Based on Organ Procurement and Transplantation Network (OPTN) data as of October 5, 2015. Data for hepatocellular carcinoma are not included

Table 1

Studies examining survival after liver transplantation for NAFLD/NASH versus other etiologies

Reference and survival outcome	Number of patients	NASH/ NAFLD group survival (%)	Non-NASH/non-NAFLD group survival (%)	Remarks
Malik et al. [31]	98 NASH			Non-NASH: PBC, PSC, ALD, HCV, CC
24-h	686 Non- NASH	95.9	96.9–99.5	Study years: 1997–2008
30-Day		93.9	94.4–98.0	Study site: University of Pittsburgh
1-Year		79.6	81.6–87.2	
3-Year		74.5	70.4–84.2	
5-Year		72.4	65.3–80.6	
Bhagat et al. [34]	71 NASH			Non-NASH: ALD
1-Year	83 ALD	82	92	Study years: 1997–2007
3-Year		79	86	Study site: University of Miami
5-Year		75	86	
9-Year		62	76	
Barritt et al. [32]	21 NAFLD			Non-NAFLD: HCV, ALD, HBV, PBC, PSC, AIH
30-Day	97 Non- NAFLD	80.9	97.0	Study years: 2004–2007
1-Year		76.2	89.5	Study site: University of North Carolina at Chapel Hill
3-Year		76.2	83.5	
Agopian et al. [33]	144 NASH			Non-NASH: HCV, HBV, ALD, CC, PBC, PSC
90-Day	1150 Non- NASH	90	90–96	Study years: 1993–2011
1-Year		84	79–87	Study site: University of California—Los Angeles
3-Year		75	62–76	
5-Year		70	54–70	
Kennedy et al. [35]	129 NASH			Non-NASH etiologies not defined
1-Year	775 Non- NASH	90	92	Study years: 1999–2009
3-Year		88	86	Study site: University of Alabama
5-Year		85	80	
Park et al. [10]	71 NASH			Non-NASH etiologies not defined
1-Year	472 Non- NASH	78	87	Study years: 1998–2008
2-Year		78	85	Study site: University of Hawaii
Houlihan et al. [38]	48 NASH			Non-NASH: PSC, PBC, HBV, ALD, HCV, A1AD, HC, AIH
1-Year	48 Non- NASH	88	86	Study years: 2000–2008
5-Year		82	82	Study site: University of Birmingham, UK
VanWagner et al. [11]	115 NASH			Non-NASH: ALD
1-Year	127 ALD	81.3	88.1	Study years: 1993–2010
3-Year		73.3	85.3	Study sites: Northwestern and University of Chicago
5-Year		60.3	68.8	

A1AD alpha-1 antitrypsin deficiency, *AIH* autoimmune hepatitis, *ALD* alcoholic liver disease, *CC* cryptogenic cirrhosis, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HC* hemochromatosis, *NASH* nonalcoholic steatohepatitis, *NAFLD* nonalcoholic fatty liver disease, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis