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Implications of non-alcoholic steatohepatitis as the etiology of end stage liver disease prior to and after liver transplantation

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Nonalcoholic steatohepatitis (NASH) is the clinically aggressive variant of NAFLD has a propensity for fibrosis progression and cirrhosis. While the prevalence of NAFLD and NASH is high, it is projected to increase rapidly in the near future and is expected to dramatically add to the already substantial healthcare burden. Cirrhosis and end-stage liver disease resulting from NASH is now the fastest growing indication for liver transplantation (LT) in the United States. Patients with NASH cirrhosis have higher prevalence of cardiometabolic diseases, which poses unique challenges as patients decompensate and undergo LT. Following LT, recurrence of NAFLD and NASH is common, however, the mortality resulting from NASH cirrhosis is rare as other competing causes of mortality such as cardiovascular, malignancy and infections are more common. The aim of the current manuscript is to review the current landscape of burden of NASH particularly as patients progress to cirrhosis and post-LT outcomes.

Keywords

Liver fibrosis; NAFLD; NASH; liver transplantation; cirrhosis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of elevated liver enzymes and has rapidly risen as the leading etiology of chronically liver disease[1,2]. NAFLD is commonly seeing in the presence of metabolic syndrome and is considered the hepatic manifestation of metabolic syndrome[3]. NAFLD comprises a histological spectrum from non-alcoholic fatty liver (NAFL) characterized by presence of hepatic steatosis with none to minimal inflammation to non-alcoholic steatohepatitis (NASH) characterized by lobular

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inflammation, ballooning and varying degree of hepatic fibrosis[1]. From a liver perspective, while NAFL has a relatively low risk of liver related complications, NASH is associated with increased risk of fibrosis progression, cirrhosis, hepatocellular carcinoma (HCC) and need for liver transplantation[1,2,4,5]. NAFLD is asymptomatic and serum aminotransferases are often normal to mildly elevated[6]. This coupled with lack of FDA or EMA approved therapy for treatment of NASH, the incidence of NASH related cirrhosis is rapidly increasing[7] and the current review will evaluate the impact of NASH on cirrhosis and liver transplantation (LT).

NAFLD patients are at increased risk of cardiovascular disease (CVD) including coronary artery disease and stroke[8]. Studies have shown a significant association of NAFLD with subclinical CVD outcomes, particularly coronary artery calcium (CAC) and carotid intima-media thickness (CIMT), independent of many metabolic diseases with a trend towards association of NAFLD and clinical CVD outcomes[9,10]. There is a bidirectional relationship between NAFLD and CVD risk factors[11]. Cardiovascular disease is the most common cause of death in NAFLD[12].

Hepatitis C is currently the most common indication for liver transplantation (LT) in the United States but the proportion of patients who require LT for hepatitis C is projected to decrease due to better screening measures and the advent of highly effective anti-viral therapies for hepatitis C. In contrast, given the rise in obesity and metabolic syndrome in the United States, the incidence of NASH and its impact on end stage liver disease is expected to increase[13,14]. Expectedly, NASH is poised to become the leading indication for LT in the United States and globally in countries with rising prevalence of obesity[15,16]. Similarly, while hepatitis B and hepatitis C have been the most common etiologies of end stage liver disease and hepatocellular carcinoma (HCC), NASH is now the fastest growing cause of HCC among patients listed for LT[17]. In this review, we have discussed the management of NASH pre and post-transplant and the implications of NASH on cirrhosis.

Prevalence of NASH related end stage liver disease (ESLD)

Prevalence and trends of NASH in the United States and globally

The reported prevalence of NAFLD has continued to increase but is dependent on the diagnostic modality used to diagnose NAFLD (i.e. ultrasonography, liver enzymes and liver histology) and the study population (i.e. primary care vs. tertiary care[18]. Within these limitations, recently, the global prevalence of NAFLD was estimated to be approximately one billion and is projected to increase even further[19]. In a meta-analysis comprising of 729 studies (sample size of 8,515,431) from 22 countries, the estimated global prevalence of NAFLD was 25.24% globally[20]. In the United States, the NAFLD is estimated to affect nearly 80 to 100 million individuals[19], while the estimated prevalence of NASH is 1.5–6.45%[20]. The economic and public health burden from NAFLD and co-existing metabolic diseases place a growing strain on healthcare utilization and systems[20]. Using dynamic modeling, the estimated US prevalence of NASH cirrhosis is estimated to be 20–25% in patients with NAFLD and rates of decompensation in those with cirrhosis is about 3–4% annually[14]. The 15-year projection of the disease burden, showcases a significant 150% increase in the disease burden of advanced fibrosis[14]. The greatest increase in incidence of

advanced fibrosis is expected to occur in countries with older populations[18]. Estimates from the NHANES and Organ Procurement and Transplantation Network (OPTN) projected a decrease in active HCV prevalence to 1 million and an increase in NASH prevalence to 17 – 42 million depending on a linear or exponential trend[21]. Thus, the societal, medical, and economical impact of NAFLD, particularly cirrhosis resulting from NASH cirrhosis, cannot be understated.

Effect on the waitlist and transplant lists—Registry data from United Network for Organ Sharing (UNOS) and OPTN indicates that the number of adult patients with NASH related cirrhosis being registered on LT waitlist has nearly tripled from 2004 to 2013[22] and is the fastest growing indication for LT among new LT waitlist registrants. Hepatocellular carcinoma (HCC) is an expected complication of cirrhosis[22] and LT is the only curative therapy[23]. As a result, HCC is the most common indication for awarding model of end stage liver disease (MELD) score exception points to facilitate LT for patients with HCC[24]. Recent data from UNOS underscores the rapid increase in the number of patients with NASH cirrhosis and HCC in need of LT[22]. Furthermore, analysis of NHANES, HealthCore and UNOS database reinforce these trends by demonstrating that LT waitlist registrants or patients receiving LT for chronic hepatitis C virus infection is decreasing while patients with NASH cirrhosis is increasing[15]. An analysis of the OPTN database from 2000 to 2014 revealed that the number of NASH cirrhosis related waitlist additions increased nearly 4-fold and the projected annual NASH-related waitlist additions to increase by 55.4% between by 2030[13]. Thus, NASH cirrhosis is the fasted growing indication for LT in the United States[25]. There is currently paucity of data with regards to clinical outcomes in patients with decompensated NASH cirrhosis and most is extrapolated from cirrhosis data from non-NASH and mixed etiologies[26]. However, patients with NASH are less likely to undergo liver transplant and less likely to survive for 90 days on the waitlist than patients with other etiologies of chronic liver disease[22]. Single center data suggests that patients listed with a MELD of less than 15 were less likely to progress and receive a LT compared to those with HCV[27]. The median progression rate among patients with NASH was 1.3 MELD points per year compared to 3.2 MELD points per year for those with HCV and patients with NASH cirrhosis were more likely to die or be taken off the wait list due to clinical deterioration. However, no differences between NASH and non-NASH groups were noted in patients who were listed with a MELD scores > 15.

Pre-Transplant Management

The optimal management of patients with compensated cirrhosis remains poorly defined. Using data from mixed etiology of cirrhosis, the annual risk of hepatic decompensation is 5% per year[26]. Much like NASH, there is currently no approved therapy to reduce the risk of hepatic decompensation in patients with NASH cirrhosis. However, in a single center, retrospective study, the use of vitamin E improved transplant free survival (78% vs. 49%; $P<0.01$) and lower rates of hepatic decompensation (37% vs. 62%; $P=0.05$) in patients with compensated NASH cirrhosis[28]. However, once a patient cirrhosis decompensates, LT is the only therapeutic modality with survival benefit[26]. Since patients with NASH cirrhosis have

higher risk of cardiometabolic disease, they present with unique peri- and post-LT challenges that will be discussed in detail below[29].

NASH and Obesity (particularly as it affects survival among patients with cirrhosis and LT)

Although bariatric surgery is an effective treatment for morbid obesity, it is associated with reduced survival in patients with cirrhosis and 5 year survival of patients with cirrhosis were lower when compared to patients without cirrhosis (58% 63% $p<0.04$)[30]. Furthermore, a stepwise reduction in survival ($p<0.01$) was noted when patients were stratified by compensated vs. decompensated cirrhosis (54% vs. 61%)[30]. History of bariatric surgery in obese patients can improve the likelihood of LT waitlist registration, however, patients undergoing bariatric surgery (vs. age, gender and MELD matched) patients were more likely to be delisted or die on the waitlist. Additionally, the transplant rate was considerably lower (49% vs. 65%, P=0.03) in patients with history of bariatric surgery[31]. This is likely due to increase prevalence of sarcopenic obesity in patients with bariatric surgery, which is likely exacerbated by bariatric surgery[32]. Thus, the decline in muscle mass, a strong negative prognosticator in patients with cirrhosis[33], is likely responsible to the increased mortality observed in patients with cirrhosis and history of bariatric surgery.

NASH and Diabetes (particularly as it affects survival among patients with cirrhosis and LT)

The liver plays an important role in glucose metabolism by modulating glycolysis and gluconeogenesis[34]. A close association between insulin resistance and NASH has been described extensively[35,36,37]. Hepatogenous diabetes results from portosystemic shunting of insulin and is characterized by elevated postprandial hyperglycemia and insulin resistance[38]. Hyperinsulinemia in the cirrhotic patient is caused by decreased hepatic extraction and portosystemic shunts. Furthermore, since diabetes is a key risk factor for fibrosis progression, the relative prevalence of diabetes and associated complications is considerably higher among patients with NASH cirrhosis compared to other etiologies of cirrhosis[39]. Hypoglycemia in patients with cirrhosis is caused by impaired gluconeogenesis and is associated with increased mortality in patients with acute decompensated liver cirrhosis[40]. Several studies have documented the negative impact of diabetes on survival and clinical outcomes in patients with cirrhosis[41–47]. Theoretically, since patients with NASH cirrhosis have higher prevalence of diabetes, they may be at higher risk for decompensation, however, this requires further validation.

NASH and CVD—NAFLD is closely associated with cardiovascular disease (CVD) and is an independent risk factor for CVD above and beyond the traditional risk factors such as diabetes, obesity and hypertension[48]. As such, CVD is the leading the cause of long-term mortality in patients with NAFLD. This is in part due to the central role liver plays in glucose and lipid homeostasis[49]. In NAFLD and NASH lipid homeostasis is perturbed and is characterized by significantly increased lipid synthesis and atherogenic dyslipidemia[50,51]. Thus, NASH patients who have progressed to cirrhosis have higher risk of coronary artery disease (CAD) compared to non-NASH etiologies[39]. Furthermore, the prevalence of obstructive and multi-vessel disease was considerably higher among patients with NASH (vs. non-NASH) cirrhosis[39].

Traditionally available clinical tools such as the lipid profile and non-invasive cardiac stress testing may not be as reliable tools for CVD risk stratification in patients with cirrhosis. Since the liver is responsible for lipid synthesis, progression of hepatic fibrosis and synthetic failure results in artificial improvement in the lipid profile that fails to capture the true CVD risk in these patients[50,52]. In fact, in patients with cirrhosis serum lipid profile is unable to predict the presence or severity of CAD[39]. Furthermore, the systemic hypotension resulting from dysregulated splanchnic vasodilation and 'splanchnic steal' phenomenon due to cirrhosis and portal hypertension may lead to amelioration of hypertension, another key risk factor for CVD[53].

Accurate assessment of CAD in patients undergoing LT is of utmost importance as operative morbidity and mortality has been reported to be as high as 81% and 50%, respectively, in patients with significant CAD undergoing LT[54]. This is especially germane to patients with NASH cirrhosis given the close relationship between CAD and NASH[39]. Dobutamine Stress Echocrdiogarphy (DSE) has been used as a screening test in potential LT candidates with low-risk of CVD, however, its diagnostic accuracy is marginal as over 50% of patients had a non-diagnostic evaluation largely due to negative chronotropic effects of concomitant β–blocker use and failed to predict major CVD events in nearly 15% of patients who had a LT[55]. Myocardial Perfusion Imaging (MPI) also was unable to predict major CVD events after LT in a significant portion of patients[56]. Thus, coronary angiography remains the most accurate tool for assessing and managing obstructive CAD in patients with cirrhosis. However, coronary angiography is often deferred in patients with decompensated cirrhosis due to perceived high risk of complications, however, these risks are minimal as recently demonstrated[39].

After diagnosis of CAD, its management centers around optimizing medical therapy and achieving revascularization of obstructive lesions prior to LT[57]. Optimal medical therapy in patients with CAD is initiation of statin and aspirin therapy. However, both statin and aspirin are often deferred in patients with decompensated cirrhosis due to perceived and hypothetical risk of hepatic, renal and bleeding complications[57]. Despite these perceived risks, both statin and aspirin were demonstrated to be safe in patients with decompensated cirrhosis as they did not increase the risk of hepatic decompensation or other complications[58]. In patients with obstructive disease revascularization can be achieved via percutaneous coronary angiography with minimal risk of complications[39]. However, in patients with severe multi-vessel disease, revascularization options may be limited to coronary artery bypass surgery (CABG)[57]. CABG in patients with decompensated cirrhosis should be recommended with extreme caution as the risk of morbidity and mortality is exceedingly high and presence of severe multi-vessel disease should be a contraindication to LT.

NASH and Sarcopenia—Sarcopenia is defined by generalized and progressive loss of skeletal muscle mass and strength and is generally associated with a poor prognosis in patients with end stage liver disease[59,60]. While it is common in patients with cirrhosis, it is historically less common in patients without cirrhosis. While sarcopenia is present in patients with NASH cirrhosis, sarcopenia has also been described in patients with NAFLD in the absence of cirrhosis. In patients with NAFLD, the severity of sarcopenia is directly

associated with severity of hepatic fibrosis and independent of obesity and insulin resistance[60,61]. Furthermore, patients with NASH are more likely to have sarcopenia when compared to non-NASH patients (35% vs. 18%, P<0.001)[62]. NASH cirrhosis is also an independent predictor of sarcopenic obesity after controlling for age, gender, and hepatocellular carcinoma[63]. In a meta-analysis of six studies showing that sarcopenia served not only as a risk factor for the onset of NAFLD but is also related to the progression hepatic fibrosis[64]. Sarcopenia and sarcopenic obesity is common in patients with cirrhosis undergoing LT and among LT waitlist registrants, NASH was associated with a 6-fold increased risk of having sarcopenic obesity[63]. Clinically, presence of sarcopenia is important in patients awaiting LT as sarcopenic patients are much more likely be delisted and die while waiting for LT[65]. Finally, while the theoretical impact of persistence of pre-LT sarcopenia on post-LT is profound in patients with NASH cirrhosis, additional studies are necessary to clearly delineate this relationship.

Impact of NAFLD donor liver

Effect of steatosis on graft function

In the addition to the impact of NAFLD on cirrhosis, increasing prevalence of NAFLD is being felt on liver donation as there is an increase in donor livers with hepatic steatosis leading to fewer high quality donors for LT[66]. The potential effect on graft steatosis on the postoperative liver function remains controversial[67,69,70]. The initial study to evaluate the impact of donor steatosis on outcomes, reported worse outcomes in patient receiving a graft that had greater than 30% liver fat content[69]. Liver fat in grafts maybe more susceptible to ischemia-reperfusion injury than are normal grafts, which may lead to decreased survival, delayed graft function and higher rates of primary dysfunction[67]. A systematic review which included 34 articles that met the inclusion criteria showed that severely steatosis in liver grafts were associated with increased risk of poor graft function, while moderate-severely steatosis in liver grafts were also associated with sub-optimal graft function[68]. The impact of normothermic machine perfusion as means of improving the function and utilization of marginal liver grafts with significant steatosis is promising but requires further validation[71,72].

Post Liver Transplant Outcomes for patients with NASH

Outcomes after LT in patients with NASH cirrhosis remain poorly defined and are usually reported at the level of SRTR database. A retrospective cohort study comparing post-transplant outcomes in patients with NASH, hepatitis C (HCV) and alcoholic liver disease (ALD) showed that patients with NASH had a higher post-transplant survival compared to patients with HCV (HR = 0.75, 95% CI 0.71 – 0.79, p<0.001) and ALD (HR = 0.80, 95% CI 0.76 0.84, p<0.001)[75], however, these studies were conducted in the era prior to advent of highly effective direct acting anti-viral therapy. A systematic review and meta-analysis of nine studies showed that survival after LT was similar in patients transplanted for NASH vs. non-NASH cirrhosis[76]. The reported 1-year, 3-year, and 5-year survival was 90%, 88%, and 85%, respectively[71]. Cardiovascular disease, malignancy, renal failure and infectious complications are the leading causes of mortality after LT in patients transplanted for NASH

cirrhosis[78], likely representing exacerbation of underlying cardiometabolic disease by chronic exposure to immunosuppression.

While LT may instantly addresses decompensated liver disease, it does not address the lifetime of risk factors that lead to not only development of NAFLD but also fibrosis progression and cirrhosis. Thus, it is no surprise that recurrence of NAFLD after LT is nearly universal[78,79] Additionally, the prevalence of advanced fibrosis was reported to be 21% after a median follow up of 47 months and suggestive of an accelerated course post-LT[78]. While patients transplanted for NASH cirrhosis are at higher risk of disease recurrence and fibrosis progression, mortality related to decompensated graft cirrhosis is uncommon as this is overshadowed by other causes of mortality[78]. In addition to a higher prevalence of metabolic syndrome and associated medical conditions among patients with NASH cirrhosis, the environment also likely plays a key role. The prevalence of NAFLD and advanced fibrosis was considerably higher among related and unrelated caregivers of patients with decompensated NASH cirrhosis[80]. This was related to significant lifestyle choices which were shared between caregivers and patients. Furthermore, donor and recipient PNPLA3 status may also promote the development of hepatic steatosis following LT[81].

Diagnosing post-LT NAFLD

Recurrent NAFLD after LT is common and the development of de novo NAFLD after LT in patients who did not carry the diagnosis of NAFLD has also been reported[85]. The use of liver enzymes alone is not very sensitive as a large proportion of patients with recurrence in NAFLD have normal liver enzymes[86]. Liver biopsies and imaging techniques have also been used to characterize post-LT NAFLD, however, their diagnostic performance remains sub-optimal[87]. Vibration controlled transient elastography (VCTE) is being increasingly utilized in clinical practice as a point of care test to risk stratify patients with chronic liver disease[88,89]. While the PPV of VCTE in chronic liver disease is lower, its NPV is high making it an excellent “rule out” test. Recently, the diagnostic performance of VCTE was evaluated in patients after LT and found to have excellent NPV albeit higher cutoff values than the general population[89]. Noninvasive fibrosis models, such has FIB4, AST:platelet ratio index (APRI) and NAFLD fibrosis scores have been evaluated to risk stratify patients with NAFLD in the general population[89], however, their diagnostic performance in patients transplanted for NASH cirrhosis remains unknown.

Managing obesity post-LT

Weight gain following LT is complex and multifactorial, occurring in most patients even among those who were underweight and normal weight prior to LT[90]. Several factors including chronic exposure to immunosuppressive medications, improved nutrient absorption and increased caloric intake have all been implicated post-LT weight gain[90]. Post-LT obesity negatively impacts clinical course as weight gain is associated with adipose tissue inflammation and proinflammatory adipokine profile characterized by reduction in serum adiponectin (a protective adipokine) and increase in inflammatory adipokine (resistin and IL-6). Pre-LT adiponectin level was associated with a 16% increase risk of cardiovascular event for every 1μg/mL decrement in adiponectin[91]. Furthermore, post-LT hypoadiponectemia is associated with increased risk of post-LT CVD, an association that is

independent of other traditional co-morbid conditions[92]. Weight gain post-LT is difficult to manage and there is limited data with regards to it. Office-based approach to weight loss via lifestyle modification advice delivered in hepatology clinic was recently demonstrated to be woefully ineffective[93], thus, underscoring the importance of additional research and novel approaches to combating post-LT weight gain and obesity.

Diabetes post-LT

Diabetes mellitus develops in about 30% of patients after liver transplantation and has been associated with an increased risk of mortality[94]. This is due to a combination of the use of immunosuppressive medications especially the calcineurin inhibitors causing insulin secretory dysfunction and steroids[94]. Other factors that increase the risk of developing post-LT DM include post-LT weight gain, sarcopenia, diet and metabolic perturbations that are commonly seen in patients with NASH[94]. Currently, metformin, dipeptidyl peptidase-4 inhibitor and insulin are the preferred agents for long term management, however, the newer classes of medications particularly sodium-glucose co-transport-2 inhibitors offer more robust options given their positive impact on weight, muscle mass, renal function and cardioprotective benefits[94].

Dyslipidemia post-LT

Dyslipidemia is common after LT occurring in up to 70% of patients and is likely due to a combination of factors including exposure to chronic immunosuppression, weight gain, NASH, diet, and insulin resistance[95]. Historically, a lipid profile consisting of LDL-C, HDL-C, total cholesterol and triglycerides are used in clinical practice to diagnose and titrate therapy for dyslipidemia[95]. However, the risk of CVD in patients after LT may not be fully captured via a traditional lipid profile[96]. This is due to the fact that development of NAFLD is associated with production of more pro-atherogenic lipoprotein which are smaller and denser allowing for easier translocation into the sub-epithelial layers where they can promote development of atherosclerotic events[97]. The importance of small dense LDL (sdLDL) in predicting CVD events were highlighted in a recent study that demonstrated that sdLDL was associated with higher likelihood of CVD events, while the parameters of a traditional lipid profile were not[96]. The change in serum lipid profile, particularly the more atherogenic lipoprotein sub-particles is more profound after LT when compared to matched non-LT cohort[98]. Furthermore, use of cyclosporine and presence of hepatic steatosis in the graft exacerbates the atherogenic dyslipidemia[99]. Recently, statin therapy was demonstrated to have a mortality benefit in LT patients with dyslipidemia [HR:0.20, 95%CI:0.11, 0.38], however, significant number of patients who qualified for statin therapy did not receive it[97]. This likely represents perceived risk of statin therapy and system-based failures and additional studies are required to better address this issue.

Renal function post-LT

Chronic kidney disease (CKD) is common following LT especially after the introduction of the MELD allocation system which favors patients with higher creatinine as serum creatinine is an integral component of the MELD score[100]. Pre-LT kidney disease, use of immunosuppressive protocols (especially calcineurin inhibitors) and recipient comorbidities are key risk factors for post-LT CKD[101]. An independent association between NASH as the

etiology of cirrhosis requiring LT and post-LT decline in renal function has been reported[102]. In a retrospective study, 31% of patients transplanted for NASH had developed stage IIIb chronic kidney injury compared to only 8% in patients transplanted for non-NASH cirrhosis[101]. These findings supporting the independent association between NASH and CKD have been reported in multiple studies[100]. While mTOR inhibitors are thought to be less nephrotoxic than calcineurin inhibitors[103], the use of immunosuppressive protocols utilizing early introduction of everolimus produced modest improvement in renal function[104]. Since mTOR inhibitors are associated with several metabolic perturbations, their use in patients transplanted for NASH cirrhosis remains undefined[103]. Additional mechanistic studies are necessary to better understand the relationship between post-LT CKD in patients transplanted for NASH cirrhosis.

Summary

Cirrhosis related to NASH is increasing rapidly and will be the major indication for LT in the near future. Due to presence of metabolic co-morbidities, patients with NASH cirrhosis present unique challenges that center not only optimizing complications of decompensated cirrhosis but also cardiometabolic diseases. While the overall survival after LT is similar in patients transplanted for NASH vs. non-NASH cirrhosis, the risk of cardiometabolic disease is considerably higher and requires an integrated approach to manage.

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Key Points:

- Cirrhosis related to NASH is increasing rapidly and will be the major indication for LT in the near future.
- Due to presence of metabolic co-morbidities, patients with NASH cirrhosis present unique challenges that center not only optimizing complications of decompensated cirrhosis but also cardiometabolic diseases.
- While the overall survival after LT is similar in patients transplanted for NASH vs. non-NASH cirrhosis, the risk of cardiometabolic disease is considerably higher and requires an integrated approach to manage.