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Retrospective Cohort Study

Divergent Trajectories of Lean *vs* Obese Non-alcoholic steatohepatitis patients from Listing to Post-Transplant – A retrospective cohort study

Qazi-Arisar FA *et al*. Lean *vs* Obese NASH outcomes.

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Abstract

BACKGROUND

Non-alcoholic steatohepatitis (NASH) cirrhosis is the second most common indication for liver transplantation (LT). The role of body mass index (BMI) on outcomes of NASH cirrhosis has been conflicting.

AIM

To compare the longitudinal trajectories of patients with lean *vs* obese NASH cirrhosis, from listing up to post-transplant, having adjusted their BMI for ascites.

METHODS

We retrospectively reviewed all adult NASH patients listed for LT in our program from 2012 to 2019. Fine-Gray Competing Risk analyses and Cox Proportional-Hazard Models were performed to examine the cumulative incidence of transplant and survival outcomes respectively.

RESULTS

Out of 265 NASH cirrhosis listed patients, 176 were included. Median age was 61.0 years; 46% were females. 111 patients underwent LT. Obese robust patients had better waitlist survival (HR 0.12 [95%CI: 0.05 – 0.29], p<0.0001) with higher instantaneous rate of transplant (HR 5.71 [95%CI: 1.26 – 25.9], *P* = 0.02). Lean NASH patients had a substantially higher risk of graft loss within 90 days post-LT (1.2% *vs* 13.8% p=0.032) and death post-LT (2.4% *vs* 17.2% *P* = 0.029). 1- 3- and 5- year graft survival was poor for lean NASH (78.6%, 77.3% and 41.7% vs 98.6%, 96% and 85% respectively). Overall patient survival post-LT was significantly worse in lean NASH (HR = 0.17 [95%CI: 0.03 – 0.86], *P* = 0.0142) with 83% lower instantaneous rate of death in obese group.

CONCLUSION

Although lean NASH is considered to be more benign than obese NASH, our study suggests a paradoxical correlation of lean NASH with waitlist outcomes, and graft and patient survival post-LT.

Key Words: Outcomes; Frailty; Waitlist; Liver transplant; Survival.

Qazi Arisar FA, Uchila R, Chen C, Yang C, Chen S, karnam RS, Azhie A, Xu W, Galvin Z, Selzner N, Lilly L, Bhat M. Divergent Trajectories of Lean *vs* Obese Non-alcoholic steatohepatitis patients from Listing to Post-Transplant – A retrospective cohort study. *World J Gastroenterol* 2022; In press

Core Tip: Non-alcoholic steatohepatitis (NASH) continues to rise as an indication for liver transplantation (LT). In this study, we analyzed our single-center data of adult patients listed for LT between 2012 and 2019 and reported their outcomes on the waitlist as well as post-LT based on their BMI.

INTRODUCTION

Non-alcoholic steatohepatitis (NASH) cirrhosis is currently the second most common indication for liver transplantation (LT) and is on track to become the leading indication by 2030 in the U.S. [1, 2]. The ability to cure Hepatitis C with antivirals and the twin epidemics of diabetes and obesity have fueled the rise of NASH as an indication for LT worldwide.

NASH patients are often older at presentation and have some or all the components of metabolic syndrome such as diabetes, hypertension, dyslipidemia, and obesity. Non-alcoholic fatty liver disease (NAFLD) and NASH have also been described in the absence of obesity [3]. About 25% of all NAFLD patients exhibit this lean phenotype [4]. However, the role of body mass index (BMI) on outcomes of NASH cirrhosis has been conflicting. Several studies have disproved the perception of NAFLD being a 'milder' condition in lean individuals. In fact, lean patients with NASH have been shown to

have more severe liver disease, more advanced fibrosis, shorter waitlist survival, and poorer post-transplant graft and patient survival [5-8].

However, these retrospective studies have been limited by their ability to accurately interpret BMI and the paucity of specific details regarding waitlist and post-transplant outcomes such as cardiometabolic disease, recurrent NASH, and graft fibrosis. Previous attempts to correct BMI for ascites have been shown to move at least 20% of patients to a lower BMI group [9]. Therefore, our study's objective is to compare the longitudinal trajectories of patients with lean *vs* obese NASH cirrhosis, from listing up to post-transplant, having adjusted their BMI for ascites.

MATERIALS AND METHODS

The study was approved by the Research Ethics Board of the University Health Network (Toronto, Canada).

Patients:

This was a single-centre retrospective study of all NASH cirrhosis patients listed for LT between November 12th, 2012, and May 31st, 2019, in the Multi-Organ Transplant Program at the University Health Network in Toronto, Canada. The study's start date was decided as November 13th, 2012, as our program transitioned to the MELD-Na system for listing on that day. All patients were followed until May 31st, 2020, yielding a minimum follow-up of 1 year. In our program, NASH cirrhosis was diagnosed either based on findings of significant steatosis on histopathology (pre-transplant liver biopsy or explant pathology), or the presence of risk factors (diabetes, obesity, and metabolic syndrome) in the absence of significant alcohol consumption and evidence of other etiology on serology or histopathology.

We excluded candidates listed for hepatocellular carcinoma with exception points, all other candidates listed with exception points, patients with fulminant liver failure, NASH concomitant with a secondary etiology of chronic liver disease (such as alcohol, viral, autoimmune hepatitis, or cryptogenic cirrhosis), multiorgan transplants and those relisted for transplantation.

Data collected from the database on each recipient at the time of listing included age, gender, height, weight, BMI, Na MELD, Creatinine, eGFR, biochemical parameters (bilirubin, albumin, INR), frailty using clinical frailty scale, complications of cirrhosis including the severity of ascites and associated comorbidities were collected. The severity of ascites (mild, moderate, or severe) is graded according to what was recorded in the patient's clinical notes as determined either by physical or more often by radiological examination. Duration on the waitlist, ICU stay, sepsis, outcomes on the waitlist, reasons for delisting, and cause of death were also collected. Post-transplant data includes the type of transplant, re-hospitalization within 90 days, recurrence of NAFLD and NASH, time to recurrent NAFLD or NASH, metabolic, cardiovascular, and biliary complications, BMI at 1 and 5 years, patient, and graft survival details.

The above data was collected from the Organ Transplant Tracking Registry (OTTR) software, an internal transplant database linked to the electronic medical record of all patients evaluated at the University Health Network.

Our primary outcomes included patient and graft survival at 90 days, 1- 3- and 5 years.

Dry-weight BMI or Adjusted BMI:

The adjusted BMI was calculated by evaluating the patient's dry weight, which is estimated by post-paracentesis body weight or weight recorded before fluid retention if available or by subtracting a percentage of weight-based upon the severity of ascites (mild 5%; moderate 10%; severe 15%) as performed in several studies. The dry-weight BMI or adjusted BMI is then calculated by dividing the patient's estimated dry weight (kg) by the square of the patient's height (m) as performed in several studies [10-12]. We categorized the variable of calculated adjusted BMI at listing into two groups: Group 1 comprising of Overweight (BMI ≥ 25 and <30kg/m^2) or obese group (BMI ≥ 30 kg/m^2) and Group 2 comprising of underweight (< 18.5 kg/m^2) or normal (≥18.5 and < 25 kg/m^2) BMI group.

Adjusted BMI was determined for all the listed patients. The cohort of patients was analyzed according to their weight category.

Statistical analysis:

Descriptive statistics were performed for demographic and clinical variables. Counts and proportions were calculated for categorical variables and the differences between patients with lean *vs* obese NASH were compared using the Chi-squared test or Fisher's exact test. Mean ± standard deviation and median (range) were calculated for continuous variables and the differences between the two groups were compared using two-sample t-tests or Wilcoxon tests, depending on the distribution of the data.

Cumulative incidence of transplant by lean *vs* obese NASH was plotted and group differences were compared using Gray k-sample test and Fine-Gray Competing risk models. Kaplan-Meier plots for waitlist survival and post-transplant survival were also plotted and differences between patients with lean and obese NASH were compared using log-rank tests and Cox proportional hazard (PH) models.

Statistical significance was defined as a p-value of ≤0.05. SAS 9.4 (SAS Institute, Cary NC) was used to perform statistical analyses.

RESULTS

Patient characteristics:

Out of 265 patients listed for NASH cirrhosis, 176 met the eligibility criteria. The median age was 61 (32 – 71.4) years; 46% were females. A total of 111 patients underwent LT, 78 deceased donor LT (DDLT), and 33 living donor LT (LDLT). Table 1 describes the pre-LT clinical and laboratory variables.

Impact of ascites on BMI:

Correcting for ascites volume resulted in patients moving into a lower BMI classification among all groups except the underweight group (BMI < 18kg/m^2). The change was larger among patients in the higher BMI groups with 72.2%, 62.9%, and 78.1% of patients moved to a lower BMI group from Obesity classes 3, 2, and 1, respectively as shown in Table 2.

Waitlist parameters and outcomes:

Patients in lean NASH group were elderly at time of listing (median age 61.6 *vs* 60.3 years, *P* = 0.048), worse renal functions at end of listing (median eGFR 48 *vs* 57 mL/min/1.73m^2, *P* = 0.017), carried more severe ascites (66.6% *vs* 45%, *P* = 0.03) and were more paracentesis dependent (72.2% *vs* 52.9%, p=0.016). Other characteristics such as sex, clinical frailty scale, and frequency of complications were similar between the two groups.

Patients in the overweight/obese group spent a median of 139.5 days on the waitlist which was not dissimilar to the 117 days spent by their counterparts in the lean group. Waitlist events such as episodes of sepsis and ICU stay were similar in the two groups. With regards to waitlist outcomes, a similar number of patients were de-listed or transplanted in both groups. More patients belonging to the lean NASH group compared to the obese group died (31.5% *vs* 20.5% *P* = 0.26); however, the difference was not significant. Time to death or delisting was similar in both obese and lean groups (HR 0.83, [95%CI: 0.46 – 1.50], *P* = 0.53. However, when sub-grouped based on BMI and frailty, patients with obese NASH and none/mild frailty had better survival than lean NASH with moderate to severe frailty (HR 0.12 [95%CI: 0.05 – 0.29], p<0.0001) (Figure 1)

With regards to transplant data, a comparable number of patients underwent DDLT and LDLT in both obese and lean groups (DDLT: 69.5% in overweight/obese group and 72.4% in the lean group; P-value=0.77). The cumulative incidence of transplant was equal in both groups (HR = 1.33 [95%CI: 0.87 – 2.05], *P* = 0.16). However, Obese NASH patients with none/mild frailty had a significantly better instantaneous rate of transplant than lean NASH with moderate to severe frailty (HR: 5.71 [95%CI: 1.26 – 25.9], *P* = 0.02) (Figure 2). The Median cold ischemia time in obese patients undergoing DDLT was significantly longer than that of lean patients (465 *vs* 330.5 minutes *P* = 0.024).

Post-transplant outcomes:

Compared to listing, the obese group had a significant reduction in BMI 1 year post-transplant (β=-2.08, SE=0.87, *P* = 0.006). At 5-year post-transplant, the overweight or

obese group's BMI returned to the same level as listing time (β=1.80, SE=1.54, *P* = 0.52). No change in BMI was observed in the underweight or normal group (overall *P* = 0.3) (Figure 3). There was no difference in post-transplant parameters such as 90-day rehospitalization, biliary complications or recurrence of NASH in lean *vs* obese groups. However, renal function was significantly better in lean NASH patients at 5 years (median creatinine 111 *vs* 153.5 μmol/L, *P* = 0.019). (Table 3)

The graft loss within 90 days post-transplant (1.2% *vs* 13.8% *P* = 0.032) and death following transplant (2.4% *vs* 17.2% p=0.029) were significantly higher in lean patients compared to obese patients. The 1- 3- and 5- year graft survivals were significantly worse for lean patients 98.6%, 96% and 85% *vs* 78.6%, 77.3% and 41.7% respectively, all p <0.05) (Table 3). There was a trend toward worse 1- 3- and 5-year patient survival (98.7%, 96% and 90% *vs* 89.7%, 81.8% and 58.3% *P* = 0.06, 0.07 and 0.07 respectively). The two groups were analysed to compare patient survival using Kaplan Meier Survival Plots and Cox PH models, which noted a statistically significant difference in overall survival between the two groups (HR = 0.17 [95%CI: 0.03 – 0.86], *P* = 0.0142). The instantaneous rate of death in the Overweight/obese group is 83% lower than those in the underweight/normal weight group (Figure 4).

DISCUSSION

Our study highlights the paradoxical impact of pretransplant BMI on the survival of NASH patients post-liver transplant, with lean NASH patients demonstrating inferior 90-day, 1- 3- and 5- year graft survival, and overall patient survival.

Lean NAFLD prevalence varies from 12 to 20% depending on the population. The presence of comorbid conditions such as components of metabolic syndrome along with older age increases the morbidity and mortality of NASH cirrhotic patients. However, it is unclear if the same applies to lean NASH. The prevalence of metabolic syndrome is less common in lean NAFLD patients as compared to obese [4, 13-15]. A long-term follow-up study showed that biopsy-proven lean NAFLD patients are more likely to develop severe liver disease (F3/F4) than overweight patients [5]. Literature is scant about the

outcomes of lean NASH while on the waiting list for liver transplantation. An abstract published in AASLD reported study comprising of 1090 patients revealed shorter cumulative survival in lean NAFLD compared to non-lean NAFLD (log-rank test = 5.6; p<0.02) [6] In a recent study, morbid obesity and diabetes were related to an increased risk of drop out of NASH patients from the waiting list [16].

Frailty, a common complication of cirrhosis, is seen more frequently in NASH cirrhosis patients as compared to other etiologies such as alcoholic liver disease (ALD) [17, 18]. Frailty has previously been shown to determine a patient's overall health, the number of hospitalizations, length of hospital stay, delisting, and waitlist mortality [17, 19-24]. especially in patients older than 65 years of age [25] independent of portosystemic encephalopathy or ascites [26]. However, the impact of frailty in the NASH cohort was not assessed. In a multicentre study, frailty was associated with a 2-fold higher risk of wait-list mortality among nonobese/ class 1 obese patients, while more than 3-fold higher risk of wait-list mortality among class 2 or greater obese liver transplant candidates [27]. However, NASH comprised only 17.5% of their patient population, while BMI was not corrected for ascites which was present in 37.1% of their patients. In a retrospective analysis, a higher frailty score was associated with an increased risk of delisting in NASH patients (HR1.46 [CI 1.06 – 2.03], P = 0.02) [17]. In our study, lean NASH patients with frailty had poor survival (HR 0.12 [95%CI: 0.05 – 0.29], p<0.0001) with lower instantaneous rate of transplant (HR 5.71 [95%CI: 1.26 – 25.9], P = 0.02). Therefore, the convergence of frailty with lean NASH led to significantly worse outcomes on the waitlist as well as in the early period post-transplant.

Though lean NAFLD was considered to be benign, the dysfunctional adipose tissue, in particular, visceral adiposity is related with increase cardiometabolic risk in lean NAFLD. Further, alterations in TM6SF2, a gene conferring susceptibility to NASH and fibrosis, are shown to be increased in lean NAFLD than obese NAFLD patients. However, there is a paucity of data on post-transplant outcomes in lean patients specifically [28]. In the post-transplant setting, a pivotal study looking at the patients on the UNOS database revealed that both short- and long-term survivals were low in

patients who were morbidly obese before transplantation, owing to adverse cardiovascular events [29]. However, none of the patients in this study belonged to the NASH group. On the contrary, obesity was noted to paradoxically favour the NASH patients compared to their non- NASH counterparts. A recent study found that lean patients have both poorer graft and patient survival than their obese counterparts [7]. However, they did not adjust the BMI for ascites, whereas elevated BMI might have reflected fluid overload instead of true obesity. There is still much that is not known or understood, and hence it is challenging to explain the underlying molecular mechanisms linking lean NASH with worse outcomes post liver transplantation. Nonetheless, our study also confirms the enigmatic effect of obesity in the NASH subset. This study also highlighted the importance of correcting BMI for ascites. Despite of correction of BMI for ascites, 69% of NASH patients belong to the overweight/obese group.

NASH has been associated with metabolic syndrome-related complications such as cardiovascular disease and chronic kidney disease (CKD) [30]. Post-transplant the risk of metabolic complications increases further owing to the immunosuppressive medications. Furthermore, calcineurin inhibitors carry direct nephrotoxic effects. In general, obese NAFLD patients appear to have a higher risk of developing CKD than non-obese [31]. In post-LT patients, obesity has been identified as a risk for post-operative severe acute kidney injury [32] as well as renal disease progression needing a kidney transplant after LT [33]. We further augmented this data by showing that median creatinine in our obese patients was significantly higher than in lean patients at 5 years (153.5 *vs* 111 μmol/L, P = 0.019). The incidence of diabetes and hypertension were numerically higher in the obese group at 1 and 5 years, however, this difference was statistically insignificant. Further, the incidence of cardiovascular events was also not significantly different among the two groups. Further expansion of follow-up to 10 years might show a statistically meaningful difference. However, this analysis was not possible in the current study. Given the selection criteria with the start of the study from November 2012, none of the patients has achieved the 10-year benchmark yet.

This study has been limited by its retrospective design, smaller sample size, and lack of a comparison group from a non-NASH subset. We also acknowledge the limitation of missing data given the retrospective design, transfer of care to other local centres post-transplant, and a limited number of patients achieving the 5-year benchmark. The results of this study should be interpreted cautiously as it does not suggest the listing of all morbidly obese NASH cirrhotic patients for liver transplant. Nonetheless, under current practice, outcomes of carefully selected NASH patients with higher BMI are better than their lean counterparts. This conundrum could have been explained by improvement in patient selection protocols, post-transplant critical care support, and immunosuppressive treatment. Moreover, there is need of identifying the factors such as genetic variants, and body fat distribution/visceral adiposity, which can play role in this paradox.

CONCLUSION

Lean NASH is associated with adverse outcomes on the waiting list as well as early post-transplant, in conjunction with often comorbid frailty. Our study emphasizes the need to actively support the nutritional and physical functional status of lean NASH patients on the waiting list. Post-transplant, all NASH patients should have active lifestyle counselling regarding a healthy diet and regular exercise to improve long-term cardiometabolic outcomes.

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ARTICLE HIGHLIGHTS

Research background

Non-alcoholic steatohepatitis (NASH) cirrhosis is the second leading indication for liver transplantation (LT). There is a conflicted role of body mass index (BMI) on outcomes of NASH cirrhosis while on waitlist and post liver transplant.

Research motivation

There are few reports on the waitlist and post liver transplant outcomes of lean *vs* obese NASH patients, and the impact of ascites adjusted BMI have not been fully clarified.

Research objectives

The objective of this study was to compare the longitudinal trajectories of patients with lean *vs* obese NASH cirrhosis, from listing up to post-transplant, having adjusted their BMI for ascites.

Research methods

A retrospective analysis of all adult NASH patients listed for LT at the University Health Network, Toronto between November 2012 and May 2019 was performed. We summarized the clinical characteristics of patients with lean and obese NASH. Competing risk analyses and Cox Proportional Hazard models were used to assess the cumulative incidence of transplant and survival outcomes.

Research results

Out of 265 patients listed for NASH cirrhosis, 176 were included. The median age was 61 (32 – 71.4) years; 46% were females. 111 patients underwent LT. Lean NASH patients were elderly at time of listing (median age 61.6 *vs* 60.3 years, P = 0.048), worse renal functions at end of listing (median eGFR 48 *vs* 57 mL/min/1.73m^2, P = 0.017), carried more severe ascites (66.6% *vs* 45%, P = 0.03) and were more paracentesis dependent (72.2% *vs* 52.9%, P = 0.016). Obese robust patients had better waitlist survival (HR 0.12 [95%CI: 0.05 – 0.29], p<0.0001) with higher instantaneous rate of transplant (HR 5.71 [95%CI: 1.26 – 25.9], P = 0.02). Lean NASH patients had a substantially higher risk of graft loss within 90 days post-LT (1.2% *vs* 13.8% P = 0.032) and death post-LT (2.4% *vs* 17.2% P = 0.029). 1- 3- and 5- year graft survival was poor for lean NASH (78.6%, 77.3% and 41.7% *vs* 98.6%, 96% and 85% respectively). Overall patient survival post-LT was significantly worse in lean NASH (HR = 0.17 [95%CI: 0.03 – 0.86], P = 0.0142) with 83% lower instantaneous rate of death in obese group. Post-transplant

renal function was significantly better in lean NASH patients at 5 years (median creatinine 111 *vs* 153.5 μmol/L, $P = 0.019$).

Research conclusions

Although lean NASH was thought to be more benign than obese NASH, our study suggests a paradoxical correlation of lean NASH with waitlist outcomes, and graft and patient survival post-LT, in conjunction with often comorbid frailty.

Research perspectives

To understand the underlying molecular mechanisms linking lean NASH with worse outcomes, there is need of identifying the factors such as genetic variants, body fat distribution/visceral adiposity, which can play role in this paradox.

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