ORIGINAL ARTICLE

Liver transplantation for nonalcoholic steatohepatitis in young patients

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Conflicts of interest
None to declare.

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SUMMARY

Nonalcoholic steatohepatitis (NASH) is the hepatic manifestation of obesity and insulin resistance. The aim of this study was to determine the frequency of NASH as an indication for liver transplantation (LT) in children and young adults and to characterize patient and graft survival. The study included all children and young adult patients (up to the age of 40 years) who underwent LT in the United States for NASH cirrhosis from the 1987 to 2012 United Network for Organ Sharing (UNOS) database. Kaplan–Meier analysis was used to assess patient and graft survival. A total of 330 patients were included, 68% were Caucasian, and the mean BMI was 33.6 ± 6.3. Age at time of LT ranged between 4 and 40 years (mean 33.9 ± 6.6 years). Fourteen subjects were <18 years of age at time of LT and 20 were between the ages of 18 and 25 years. Median follow-up after 1st LT was 45.8 months [10.7, 97.3]. During this time, 30% of subjects (n = 100) died and 11.5% (n = 38) were retransplanted including 13 for NASH recurrence. In conclusion, NASH can progress to end-stage liver disease requiring LT in childhood and early adulthood. A significant number of young patients transplanted for NASH cirrhosis required retransplantation.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the obesity and metabolic syndrome epidemics and now affects up to 45% of adults and 10% of children in the United States [1,2]. Nonalcoholic steatohepatitis (NASH) is the aggressive form of NAFLD that can progress to cirrhosis and end-stage liver disease requiring liver transplantation (LT) [3,4]. Recent adult data have shown that NASH is the third most common indication for LT in the United States and is expected to become the leading indication over the next 1–2 decades [5]. Recipients of LT for NASH cirrhosis are generally older with one study showing a mean age of 58.5 ± 8 years for patients transplanted for NASH compared to 53 ± 8.9 years for those transplanted for other indications [6]. Therefore, LT for pediatric patients is exceedingly rare and the natural history of NASH in children is still being elucidated. Feldstein *et al.* [7] reported on the long-term survival

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of children with NAFLD who were followed for up to 20 years and demonstrated the progressive potential of NAFLD in children with two patients developing NASH cirrhosis and portal hypertension that required LT at the ages of 20 and 25 years. An alarming finding from this study was that NASH recurred in the transplanted liver in both patients with one of them requiring retransplantation within 2.3 years from the first transplantation and eventually dying from multi-organ failure at the age of 27 years.

Given the high prevalence of NAFLD in children and adolescents and its potential to progress to end-stage liver disease early in life, understanding the burden of NASH cirrhosis on the need for LT in young adults and its natural history after transplantation in this group is especially important. The aim of this study was to perform a comprehensive analysis of a large national liver transplantation registry in the United States to determine the frequency of NASH as an indication for LT in children and young adults and to characterize patient and graft survival in this cohort.

Materials and methods

Study population

The study included all children and young adult patients [up to the age of 40 years (based on previous literature) [8,9]] who underwent LT in the United States from the 1987 to 2012 United Network for Organ Sharing and Organ Procurement and Trans- plantation Network (UNOS/OPTN) database. The cutoff value of 40 years for age to define young adults was based on previously published literature.

A significant proportion of cryptogenic cirrhosis (CC) patients are believed to have undiagnosed NASH. Previous studies have included CC patients into the NASH category if they had obesity (body mass index [BMI] $\geq$30 kg/m^2) [6,10]. Our study employed similar methods to more accurately ascertain the prevalence of NASH diagnoses among our cohort. We created a modified NASH category that included LT recipients who were given a primary diagnosis of NASH plus obese patients with primary diagnosis of CC. Because NASH can coexist with other liver disease etiologies, we did not include patients with secondary diagnosis of NASH or CC.

All demographic data, laboratory values, pediatric end-stage liver disease (PELD) and model for end-stage liver disease (MELD) scores, and graft and patient survival were obtained from the database.

Statistical analysis

Data are presented as mean $\pm$ standard deviation or median [25th, 75th percentiles] for continuous variables and N (%) for categorical factors.

Patient survival

Kaplan–Meier analysis was used to assess patient survival. Time of follow-up was defined as time from 1st LT to death or censoring. Subjects were censored at time of 2nd LT or last follow-up.

Retransplantation

As death precludes retransplantation, it was treated as a competing event and competing risk analysis was performed. Time of follow-up was defined as months from transplantation to event; subjects were censored at time of last follow-up. Retransplantation cumulative incidence rates were estimated.

Graft survival

No subject died before experiencing graft failure so Kaplan–Meier estimates were used to assess graft survival. Follow-up time was defined as time from 1st LT to either last follow-up or time of graft failure.

A P-value < 0.05 was considered statistically significant. SAS version 9.4 (The SAS Institute, Cary, NC, USA) was used to perform all analyses.

Results

Patient demographics and frequency of NASH as the primary indication for LT in young subjects

A total of 330 patients were included in the analysis, 111 with a primary diagnosis of NASH as the indication for LT and 219 with CC and BMI of 30 kg/m^2 or greater. The frequency of NASH as an indication for LT in young patients in the UNOS/OPTN database was 1.67% (330/19 904). Table 1 presents a summary of patient characteristics. About 52% were male, 68% were Caucasian, 12% were African American, and 16% were Hispanic. The median BMI was 32.9 [30.8, 36.7], and diabetes was present in 18% of patients. Age at time of LT ranged between 4 and 40 years with a median of 36 [31,39] years. Four subjects (4%) were children <18 years of age at time of LT (Fig. 1). Twenty patients were between the ages of 18 and 25 years, 77 were

Table 1. Characteristics of young liver transplant recipients.

Factor	Total (N = 330) Summary
Gender	
Female	157 (47.6%)
Male	173 (52.4%)
Age (years)	36.0 [31.0, 39.0]
Age <18 years	14 (4.2%)
18–29 years	54 (16.4)
30–40 years	262 (79.4)
BMI	32.9 [30.8, 36.7]
Liver diagnosis at transplant	
NASH	111 (33.6%)
Cryptogenic cirrhosis & BMI ≥30	219 (66.4%)
Race	
Caucasian	68.4%
African American	11.6%
Hispanic	16.4%
Other	3.6%
Diabetes	18.2%
Hypertension	6.5%
Serum Creatinine at LT	1.00 [0.75–1.6]
Total Bilirubin at LT (mg/dL)	6.7 [2.6–17.6]
Albumin at LT (g/dL)	2.8 [2.4–3.4]
MELD/PELD Score at LT	28.0 [21.0–34.0]
Days on waiting list	46.0 [9.0–166.0]
Total cold ischemic time (hours)	8.0 [5.7–11.0]
Cadaveric donor	330 (100.0)
Partial/Split transplant	2 (0.61)

MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease.

Values presented as Mean ± SD, Median [P25, P75] or N (%).

between 26 and 33 years, and 219 were between 34 and 40 years.

Figure 2 presents the number of NASH/CC patients transplanted per year since 2001 when NASH was added as a diagnostic category in transplant center databases. A progressive increase in NASH as the primary indication for LT in young subjects is seen from 2001 to 2012.

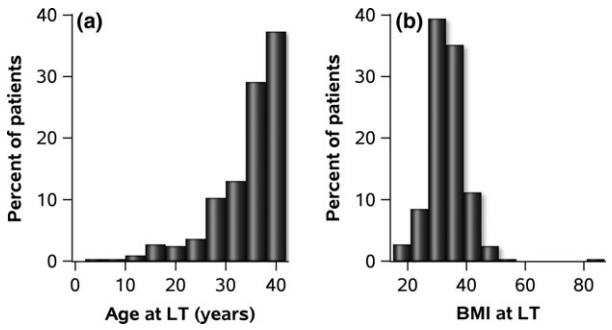

Figure 1 Age and BMI distribution in children and young adults who received LT for NASH.

Outcomes after first LT for NASH in young subjects

Median follow-up after 1st LT was 45.8 months [P25-P75: 10.7–97.3 months]. During this time, 100 subjects died (30%) and 38 were retransplanted (11.5%) (Fig. 3). The most common cause of death was infection (25%) followed by graft failure (17%). Overall, graft failure occurred in 55 subjects (38 were retransplanted and 17 died) (Table 2). One-, 3-, and 5-year survival rates were 88.7%, 83.5% and 77.5% for patient survival and 82%, 76.5%, and 68.8% for graft survival as shown in the Kaplan–Meier plots in Figs 4 and 5.

Retransplantation outcomes

Of the 38 subjects who were retransplanted, 28 (73.7%) had a diagnosis of CC at their 1st LT and 4 (10.5%) were pediatric patients. Fourteen (37%) of retransplanted subjects died and two (5%) required a 3rd transplant (Fig. 3). Both subjects who received a 3rd LT died; the cause of death was graft failure for 1 and generalized sepsis for the other. Overall, 116 patients (35.1%) died during the study duration (100 patients died after the 1st LT, 14 after the 2nd LT, and 2 after the 3rd LT).

Importantly, 13 of 38 subjects were retransplanted for NASH/CC recurrence, 2 were pediatric patients, and 10 had a diagnosis of CC at their 1st LT. Six patients died (2 for cardiac reason, 1 for infection, and 3 for other reasons), and one required a 3rd transplant. Figure 6 presents the time-to-event plot for retransplantation after undergoing initial LT for NASH cirrhosis.

Discussion

The principal findings of this study are as follows: (i) since 2001, the frequency of NASH as an indication for LT in young subject has been increasing, (ii) although 1-, 3-, and 5-year survival rates were good, long-term outcomes after LT for NASH cirrhosis in this population are suboptimal with only 58% (192/330) of patients being alive at last follow-up after their first LT, (iii) approximately 12% of young patients transplanted for NASH cirrhosis required retransplantation with one-third being performed for NASH recurrence.

In parallel with the obesity epidemic that is sweeping our nation, the prevalence of pediatric NAFLD in the United States has more than doubled over the past

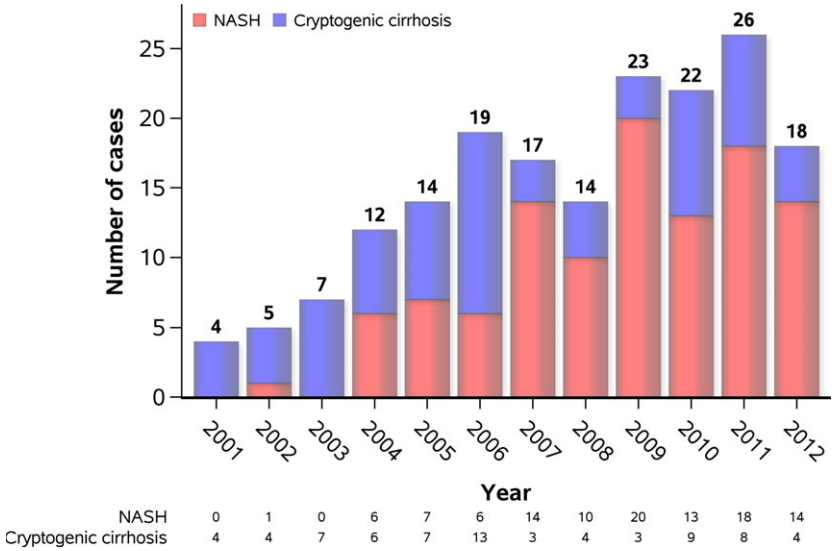

Figure 2 The frequency of NASH as an indication for LT in young patients in the UNOS/OPTN database (2001–2012).

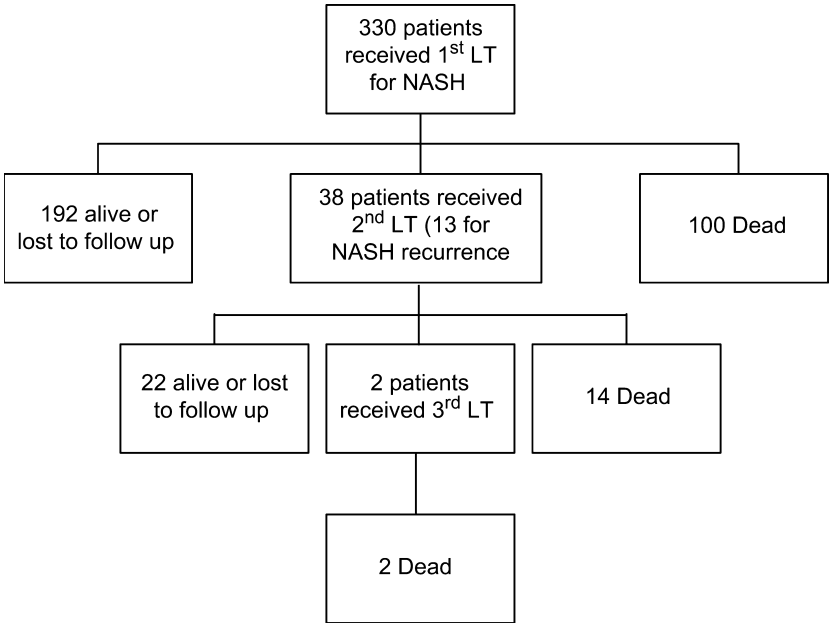

Figure 3 Long-term outcomes after LT for NASH in young patients.

20 years and currently affects approximately 11% of adolescents and 50% of obese males [11]. Although the progression of NASH to cirrhosis and portal hypertension is well documented during childhood [7,12], the disease progression is generally slow which may delay the need for LT until early adulthood. The overall increasing prevalence of NAFLD and NASH will undoubtedly lead to an increase in the prevalence of NASH as an indication for LT in young adults and even in children. Although the majority of patients in our study were transplanted closer to the age of 40 years, over 100 subjects received LT before they reached the age of 34 years. NASH is a slowly progressive disease which indicates that most of these patients developed fatty liver during childhood and adolescence. In terms of survival after LT in our cohort of young patients with NAFLD, the short-term outcomes at 1, 3, and 5 years for both patient and graft survival were similar to previous studies that evaluated outcomes of LT for NASH in older adults including the study by Agopian *et al.* [13] with a mean age of 57 years and the study by Charlton *et al.* [6] with a mean age of

Table 2. Outcomes of liver transplant in children and young adults with NASH.

Factor	Initial LT for NASH (N = 330)	
	n	Summary
Outcome	330	
Alive/Lost to follow-up		192 (58.2)
Retransplanted		38 (11.5)
Deceased		100 (30.3)
Reason for re-LT	38	
NASH		3 (7.9)
Cryptogenic cirrhosis		10 (26.3)
Alcoholic cirrhosis		2 (5.3)
HCV cirrhosis		5 (13.2)
Autoimmune cirrhosis		3 (7.9)
Cirrhosis, other (histiocytosis, sarcoidosis, granulomatous)		1 (2.6)
AHN		3 (7.9)
Other		11 (28.9)
Cause of death	100	
Operative		1 (1.0)
Graft Failure		17 (17.0)
Cardiac		9 (9.0)
Pulmonary		3 (3.0)
Hemorrhage		4 (4.0)
Infection		25 (25.0)
Malignancy		3 (3.0)
Cerebrovascular		1 (1.0)
Renal failure		3 (3.0)
MSOF		9 (9.0)
Other		9 (9.0)
Unknown		16 (16.0)
Median follow-up time (months)	330	45.8 [10.7, 97.3]

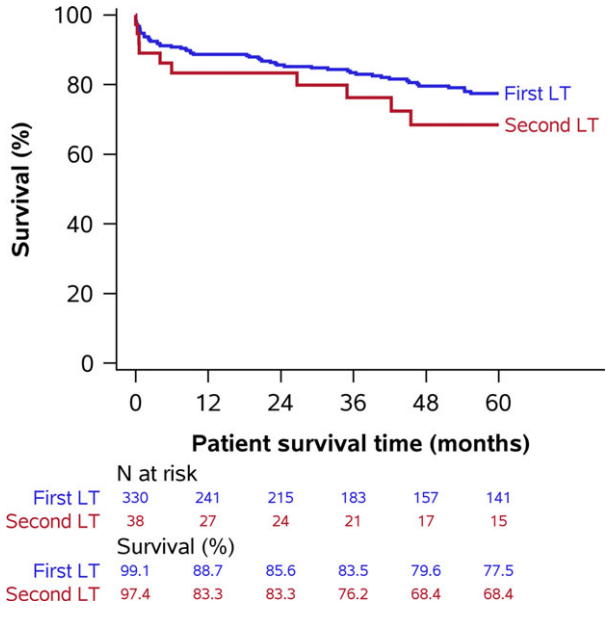

Figure 4 Kaplan–Meier plot showing 5-year patient survival rate.

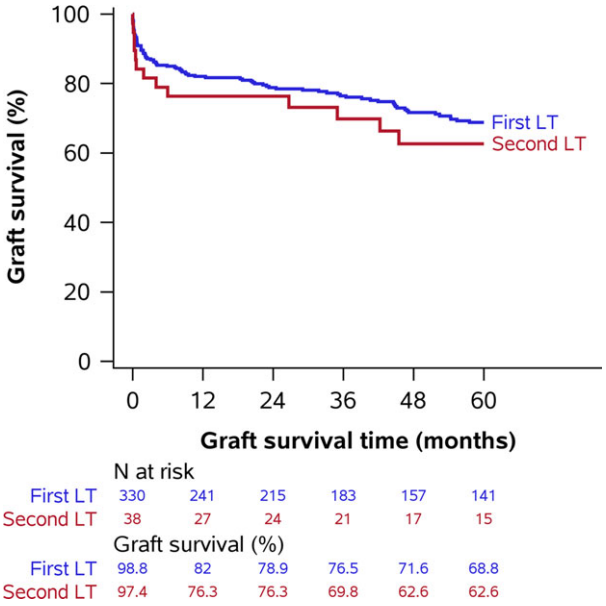

Figure 5 Kaplan–Meier plot showing 5-year graft survival rate.

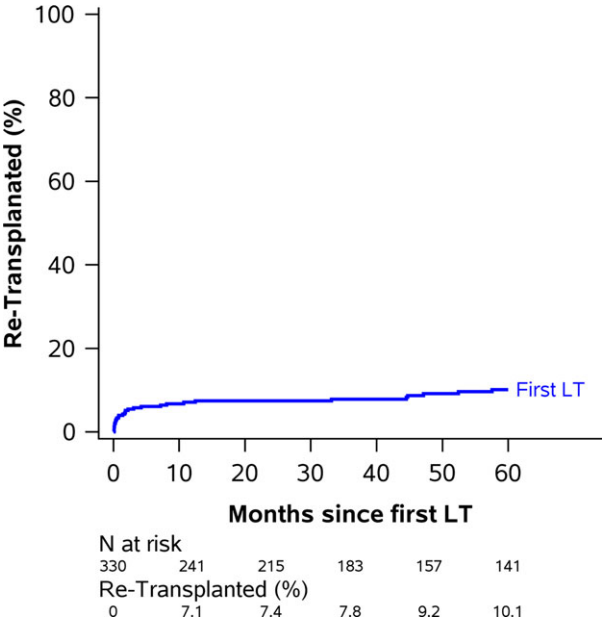

Figure 6 Time-to-event plot for retransplantation after undergoing initial LT for NASH cirrhosis.

58.5 years. However, at last follow-up, only 58% of patients in our study were alive after the first LT indicating that long-term outcomes are suboptimal.

We hope that our findings will raise awareness of the true consequences of pediatric NAFLD and help improve strategies for screening and prognostication. With the development of reliable noninvasive diagnostic tests to predict the presence of significant fibrosis in

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children and adults [14–16] and the development of NASH-specific therapies [17–19], we anticipate that early identification of patients at risk for progression to cirrhosis may modify the course of their disease and eliminate the need for LT.

Another important finding of our study was the fact that around 4% of young patients (n = 13) transplanted for NASH cirrhosis required retransplantation for NASH recurrence.

Risk factors that are associated with the severity of NASH such as obesity and metabolic syndrome tend to get worse following LT [20–22], which can contribute to aggressive disease recurrence culminating in the development of cirrhosis and the need for retransplantation. This is a bigger concern in young adults who are projected to live longer and are less likely to die from cardiovascular disease. Therefore, the management of obesity before and after LT in this population is of paramount importance and should include aggressive lifestyle modifications, pharmacotherapy, and even bariatric surgery when feasible [5,23]. Both corticosteroids and calcineurin inhibitors may contribute to post-transplant metabolic syndrome and NASH recurrence [5]. The roles of corticosteroids minimization and calcineurin inhibitor dose reduction in preventing NASH recurrence are not known and deserve further investigations.

The main strength of this study is the use of a large nationally representative LT database which allowed for the ability to evaluate the frequency and long-term outcomes of NASH as an indication for LT in young subjects. The study has several limitations that are mainly inherent to the use of large registry type databases. The assignment of NASH or CC as the primary indication for LT cannot be confirmed by an independent mechanism and errors in coding can occur. The use of subject with CC and BMI ≥30 kg/m^2 may have led to the inclusion of patients without true NASH such as those with true CC and significant ascites; however, it is more likely that this definition underestimates the real prevalence of NASH cirrhosis because NASH can affect overweight and normal weight patients especially those with type 2 diabetes and insulin resistance. The fact that some patients required retransplantation for reasons other than NASH recurrence, such as hepatitis C, alcohol, and autoimmune liver disease, could imply that the initial diagnosis of NASH was incorrect or it could be related to the *de novo* development of these diseases in the transplanted graft. The data on retransplantation rate and outcomes should be interpreted with caution.

In summary, NASH is a rising indication for LT in children and young adults and may recur after transplantation leading to the need for retransplantation. These findings support the need for more aggressive approaches for screening and management of NAFLD in children and adolescents to prevent disease progression and avoid the need for LT at a relatively young age [24].

Authorship

NA, IAH, NNZ, BE, DK and JJF: involved in developing study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript. RL: performed statistical analysis and provided critical revision of the manuscript for important intellectual content.

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