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Liver Transplant Outcomes in Young Adults with Cirrhosis Related to Nonalcoholic Fatty Liver Disease

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Abstract

Background.—The prevalence of nonalcoholic fatty liver disease (NASH) and cryptogenic cirrhosis (CC) is constantly increasing in adolescents and young adults (AYAs).

Methods.—In a retrospective UNOS database evaluation, we analyzed postoperative outcomes of AYAs with nonalcoholic NASH/CC undergoing LT between January 1st, 2003 and March 5th, 2021. After exclusions, 85,970 LT recipients, 393 (47.1%) AYAs with NASH/CC and 441 (52.9%) AYAs with other metabolic conditions, were analyzed.

Results.—During the study period, the number of LTs performed for AYAs with NASH/CC increased from 4%-7% but decreased from 6.6%-5.3% compared to LTs performed for NASH/CC in all ages. In comparison to AYAs with other metabolic conditions, AYA LT recipients with NASH/CC had a higher prevalence of metabolic syndrome (MetS) components, including diabetes and increased body mass index ($P < .0001$ for both). Patient and graft survival in AYAs with NASH/CC were significantly lower in comparison to AYAs transplanted for other metabolic conditions ($P < .0001$) (Hazard Ratio = 1.93, $P < .001$). Patient survival in AYAs with NASH/CC was significantly better in comparison to older (40-65-year-old) patients with the same diagnosis ($P = .01$).

Conclusions.—Our study found that the overall number of LTs in AYAs with NASH increased significantly, but to a lesser degree compared to the older population with the same diagnosis. Outcomes after LT in AYAs with NASH/CC were worse compared to LT for other metabolic

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conditions, but significantly better in comparison to older patients. The prevalence of LT for NASH/CC in AYAs is growing. MetS may contribute to worse outcomes in AYAs.

NONALCOHOLIC fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide with a global prevalence of 25%-30% [1]. Nonalcoholic fatty liver disease includes 2 histologic types: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Nonalcoholic fatty liver disease is typically associated with a relatively low degree of inflammation and is potentially reversible. Nonalcoholic fatty liver disease is characterized by lobular inflammation and hepatocyte ballooning. It can lead to the development of hepatic fibrosis and progress to cirrhosis ultimately leading to hepatic decompensation and hepatocellular carcinoma necessitating lifesaving liver transplantation (LT) [2–4]. In fact, NASH cirrhosis is the fastest growing indication for LT in adults and is only expected to further increase as a result of physical inactivity and weight gain seen during the COVID-19 pandemic [5]. The cluster of metabolic factors that include abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels is known as Metabolic Syndrome (MetS). If present, it greatly increases the risk of a person developing diabetes, heart disease, and stroke. As more and more patients present for LT related to NASH, greater attention will need to be focused on the management of MetS given that patients with NASH have a higher incidence of MetS [1]. Additionally, current post-transplant immunosuppression regimens all promote the development or progression of MetS through metabolic mediators such as dyslipidemia, hypertension, and/or diabetes mellitus (DM). MetS can lead to greater rates of major adverse cardiovascular events (MACE) in LT recipients [6]. It has been demonstrated that LT recipients with NASH have higher prevalence of MACE compared to other populations [7,8].

Rates of NAFLD and NASH are also increasing in adolescents and young adults (AYAs) 15-39 years old. Historically, LT for NASH cirrhosis in this population was felt to be relatively rare. However, a recent report by Doycheva et al suggested that this may not be the case with nearly 5% of LT in AYAs performed in candidates with NASH [9]. While 5-year patient survival rates were similar when comparing NASH to other metabolic liver diseases (e.g. Wilson’s Disease, alpha-1 antitrypsin deficiency, and hereditary hemochromatosis), rates of graft survival were inferior and re-transplantation was much more common in AYAs with NASH. Whether the presence of MetS in AYAs leads to either the need for LT at a younger age or promotes recurrent NAFLD leading to graft loss and re-transplantation remains unknown.

The objectives of this study were to 1) estimate the trends of LT in AYAs with NASH and cryptogenic cirrhosis (CC) by age group, body mass index, and year of transplantation; 2) investigate survival of AYAs with NASH/CC in comparison to recipients with other metabolic liver diseases (hereditary hemochromatosis, Wilson’s Disease, and alpha-1 antitrypsin deficiency).

MATERIALS AND METHODS

The study was approved by the Institutional Review Board at the Penn State Milton S. Hershey Medical Center. No organs from executed prisoners were used. Data on all LT performed in the United States from January 1st, 2003-March 31st, 2021 were obtained with permission from the Organ Procurement Transplantation Network. Patients who were status 1a or received either multi-visceral or living donor graft(s) were excluded from evaluation. Adolescents and young adults was defined as 15-39 years old. MetS was defined as BMI ≥30kg/m^2 and DM. The UNOS database does not contain information about hypertension or hyperlipidemia; however, taking into consideration that DM is involved in the development of the other elements of MetS, we decided to modify the definition of MetS for this study and use only 2 of 4 classic components. Patients transplanted with CC were included in the evaluation along with patients with NASH. This approach was chosen because of solid evidence that LT recipients diagnosed with CC are often patients with NASH who were misclassified and because both conditions have similar prevalence of MetS [10–12]. Additionally, several previous database evaluations analyzed NASH and CC as single group because of the same reasons [13–15]. Target groups for evaluation were AYAs (15-39 years old) with NASH/CC and AYAs with other metabolic diseases (e.g., alpha-1 antitrypsin deficiency, Wilson's Disease, and hereditary hemochromatosis). We did not include any other metabolic conditions in this investigation because most of these patients underwent LT at an age younger than 15 years old.

The first step of our analysis examined overall trends in 3 6-year periods with the number of LTs performed in AYAs with NASH/CC in comparison to the number of all LTs performed each year. Trends regarding LT performed in AYAs with NASH/CC in comparison to all AYAs, as well as in comparison to older patients with NASH/CC, were evaluated. Additionally, we evaluated the number of LTs performed in AYAs with NASH/CC for each year. Jonckheere-Terpstra (JT) Test for Ordered Differences were reported. A student *t* test is a non-parametric, rank-based trend test, which is used to determine the significance of a trend in a data set.

A comparison of baseline characteristics was then performed between AYAs with NASH/CC and AYAs with other metabolic conditions. Variables evaluated included demographics (age, sex, and BMI), race/ethnicity (African American, Asian, Caucasian, Hispanic), Model for End Stage Liver Disease (MELD) score (both at time of listing and at the time of LT), as well as progression of MELD while on the waitlist. Perioperative times included were length of time on the waiting list, total graft cold ischemic time, postoperative patient and graft survival time, as well as days since first transplant (for re-transplants). Other variables used for univariate comparison were prevalence of other clinical conditions including portal vein thromboses (PVT), DM, spontaneous bacterial peritonitis (SBP), need for preoperative dialysis, re-transplantation, prevalence of ascites and hepatic encephalopathy (HE), and donor risk index (DRI) [16]. We also compared several laboratory values (including serum albumin, bilirubin, and creatinine), both at time of listing and at time of LT, as well as serum sodium level at time of listing.

Kaplan-Meier product limit estimates were used to assess patient and graft survival in several comparisons. Survival of AYAs with NASH/CC were compared with all other AYAs without NASH/CC. Also, a comparison between AYAs and older (40-65 years old) patients with NASH/CC was performed. Because NASH is considered a metabolic disease, AYAs and graft survival between AYAs with NASH/CC and other metabolic diseases was performed.

In the multivariable regression analyses, we looked for an association between mortality and the following variables: AYAs with NASH/CC, age and BMI (both as continuous variables), hepatitis C (HCV), cholestatic and malignant causes of ESLD, Black, Asian, and Hispanic race (with Caucasian as the reference group), PVT, ascites, HE, history of preoperative dialysis, and DRI (as a continuous variable).

Statistical Analysis

Models included AYA LT recipients with NASH/CC vs AYAs with other metabolic diseases (e.g., alpha-1 antitrypsin deficiency, Wilson's Disease, and hereditary hemochromatosis). Statistics were performed on multiple variables including demographics, waitlist characteristics, medical comorbidities, transplantation characteristics, donor characteristics, and key outcomes. Bivariate comparisons were performed for log-transformed Kaplan-Meier Survival curves. In addition, student *t* test, Wilcoxon sign rank test, χ^2 test, or Fisher's exact test were used as appropriate. Multivariable logistic regression modeling was used to explore the relationship between AYA LT recipients with NASH/CC vs AYAs with other metabolic diseases after adjusting for potential confounders as determined in prior literature and results of the bivariate analysis (i.e., sex [female reference group] and MELD at time of LT). Final logistic regression results were presented as adjusted Hazard Ratios (HR) accompanied by 95% confidence intervals (95% CI), outputted and weighted using a propensity score (i.e., inverse probability weighting). Five-year (i.e., 2,000 days) patient and graft survival were estimated using Kaplan-Meier curves and Log-rank tests. Cox Proportional Hazard models were adjusted for: race/ethnicity (Caucasian reference group), PVT at time of LT, manifestations of portal hypertension (including ascites and HE grade 2 and above), DRI, dialysis at time of LT, BMI at time of LT, and DM at listing. All statistical tests for significance were two-sided with a significance level of $P < .05$. No significance level adjustments for multiple analyses were imposed. All data set manipulation and statistical analyses were performed with SAS (version 9.4; Cary, NC).

RESULTS

Between January 1st, 2003-March 5th, 2021, 119,880 candidates underwent LT in the US. Patients excluded from this evaluation were: 1,500 (1.18%) patients with 1a status; 6,635 (5.2%) patients with multi-visceral transplantations; 5,812 (4.6%) patients who underwent living donor LT; and 6,839 (5.4%) patients younger than 15 years and 13,124 (10.9%) older than 65 years. In the final analysis, we included 85,970 LT recipients. Our targets groups included 393 (47.1%) AYA (15-39-year-old) patients with NASH and CC and 441 (52.9%) AYA patients with other metabolic causes of ESLD, for a total of 834 (100%) patients.

The overall number of LT performed on AYAs for NASH/CC in the period between 2003 and 2020 significantly increased. Six-year trends demonstrated that the percent of LTs performed for NASH/CC almost doubled (from 4.1%-7.3%) (Table 1, Fig 1).

In the years 2003-2020, the percent of LTs performed for NASH/CC in AYAs in comparison to other indications in AYAs remained rather stable over the observation period at about 7% (Table 1). Importantly, the proportion of LTs performed in AYAs with NASH/CC decreased from 6.6%-5.3% in comparison to LTs performed for NASH/CC in patients of all ages. Most AYA LT recipients were 25-39 years old (Fig 2). The prevalence of LT in the subset of patients between 15 and 24 years old did not exceed 2% and only at 33 years of age did it start to increase, exceeding 7% at 35 years of age. When evaluating BMI, we found that, most frequently, AYAs transplanted for NASH/CC had a BMI above 30 kg/m^2 (Fig. 3).

Kaplan-Meier survival analysis of postoperative survival between AYAs with NASH/CC and AYAs with metabolic disease demonstrated that both patient and graft survival in AYAs with metabolic disease was associated with a significant survival benefit ($P < .0001$ for both) (Figs 4A and 4B). No statistically significant difference in patient and graft survival between AYAs with NASH and AYAs with diagnoses other than NASH/CC was found. Comparison of postoperative survival between AYAs with NASH/CC and older patients (40-65 years old) with the same diagnosis demonstrated that younger patients had significantly better survival ($P = .01$) (Fig 5A), but no difference in graft survival ($P = .87$) (Fig 5B).

A univariate comparison of basic characteristics between AYAs with NASH/CC and those with other metabolic conditions demonstrated that despite no difference in MELD score, waiting time, or cold ischemic time, AYA patients with metabolic disease had significantly better patient and graft survival ($P < .001$ for both). There was no difference in the rate of re-transplantation (the overall prevalence in patients with NASH/CC was higher but did not reach statistical significance) or DRI. Adolescents and young adults with NASH/CC had a higher prevalence of DM ($P < .001$), PVT ($P = .02$), and need for dialysis ($P < .001$). Laboratory values demonstrated that at both time points (registration and transplantation), AYAs with NASH/CC had lower INR and bilirubin levels as well as higher albumin and creatinine levels in comparison to AYAs with metabolic disease (all differences were statistically significant) (Table 2).

Regression analysis confirmed that AYAs with NASH/CC had increased post-transplant mortality both in comparison to AYAs with metabolic disease (HR = 1.93, $P < .001$) and in comparison to all other LTs performed in this age group (HR = 1.14, $P < .001$).

DISCUSSION

The purpose of this study was to examine the trends by BMI, age, and year of LT for AYAs with NASH/CC and to determine comparisons in LT between AYAs with NASH/CC and AYAs with other metabolic liver diseases (hereditary hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency). Findings for this analysis indicated statistically significant trends between AYAs with NASH/CC and BMI, age, and year of LT. When accounting for the survival of AYAs with NASH/CC and other metabolic liver diseases, there

was lower survival for AYAs with NASH/CC as compared to AYAs with metabolic liver diseases.

Our study found that, similar to adults, the overall number of LT AYAs with NASH/CC has significantly increased during the last 2 decades. During the 6-year period from 2015-2020, more than 7% of all LTs were performed in AYAs with NASH/CC vs only 4% over the period from 2003-2008. These findings are concordant with the trend shown in the landmark study previously published by Doycheva et al [9]. The overall prevalence of LTs due to NASH/CC in AYAs at all time points, however, was higher in our investigation. This is likely related to a difference in inclusion and exclusion criteria as well as duration of the evaluation period. Overall, our investigation included slightly younger patients over a longer period of time. Our target group (AYAs with NASH/CC) was over 2 times larger than that of the other study and our results reflect the generally increasing trend of both NASH prevalence in the world [1] as well as LT related to NASH/CC, which now makes this condition the second most common cause for LT. [17]. Despite this tendency, the proportion of LTs due to NASH/CC performed in AYAs was rather stable and even decreased in comparison to the entire population of patients transplanted for NASH/CC over the evaluation period. We also found that the proportion of LT in AYAs related to NASH/CC in the US reached 6% in 2016 and 8% in 2018, but did not increase after that. In contrast to adult patients, the number of NASH-related LTs compared to LTs for all causes has constantly increased both in Europe and US and by 2019, it reached 28% [17,18]. Additionally, the results of our study demonstrate that the alarm regarding a rapid increase in the need for LT in the pediatric population is valid but is less concerning than initially expected. Although the prevalence of both pediatric obesity [19] and NAFLD in children and adolescents has greatly increased over last 20 years [20], and although some publications describe the current situation (NAFLD in the pediatric population) as a ‘pandemic’ [21,22], it has not led to a disproportionate increase in the need for LT in AYAs for NASH cirrhosis. This is likely related to the specifics of pediatric NASH, disease progression, and disease management in the pediatric population. The progression of NAFLD to NASH and NASH cirrhosis in children is usually relatively slow and is more frequently seen after a patient has reached early adulthood [23]. In our study, LT in patients younger than 25 years old with NASH/CC was rather uncommon and the prevalence of NASH/CC started to rise only after patients reached 33-35 years of age. The overall prevalence of NASH in children and adolescents is 5%-10% [24]. In the adult population, the overall prevalence of NASH requiring LT is higher and continues to increase [25,26]. Younossi et al found that the worldwide pooled prevalence of NASH in patients with NAFLD who were biopsied was almost 60% [1]. It has been demonstrated that 20%-50% of children with NAFLD have NASH at the time of diagnosis and about 10%-20% have advanced fibrosis [24]. The progression of NAFLD to advanced fibrosis in adults varies in different studies but is around 30% [27]. Successful treatment of NAFLD and NASH in children, including dietary change and increased physical activity, would be expected to slow the progression of NAFLD to fibrosis and cirrhosis and the need for LT.

Another important finding of our investigation was inferior patient and graft survival in AYAs with NASH/CC in comparison to AYAs with other metabolic diseases such as alpha-1 antitrypsin deficiency, Wilson’s Disease, and hereditary hemochromatosis. A previous

investigation found similar trends even though differences in post-transplant patient survival in their study did not reach statistical significance [9]. This might be related to lower statistical power in comparison to our study and possibly to slightly different inclusion and exclusion criteria [9].

Patients in both groups (AYAs with NASH/CC and those with metabolic disease) were very comparable, with no differences in MELD score, demographics, waiting list or cold ischemic time, DRI, or the type of liver graft used. It is important to note that AYAs with NASH/CC were older, more frequently had components of MetS, such as obesity and DM, and more often required dialysis before LT. These results are not surprising considering the excellent LT outcomes performed for metabolic conditions (with pulmonary function being the major limiting factor for patients with alpha-1 antitrypsin deficiency), as well as the fact that these diseases are usually not associated with MetS [28–30]. The overall prevalence of MetS in patients with NASH is estimated to be about 70% [1]. Nonalcoholic steatohepatitis is considered to be a hepatic manifestation of MetS [31,32]. It has been previously demonstrated that NASH is an independent predictive factor for CV mortality after LT in adults [8,33].

In children with NAFLD, the exact prevalence of the components of MetS is unknown. It has been shown, however, that in children, NAFLD is associated with a higher prevalence of atherosclerosis [34,35], dyslipidemia [34,36], increased arterial stiffness [37], DM [38] (the prevalence in our study was 20% in AYAs but can reach 50% at the time of adulthood) [39], impaired ventricular function (defined as elevated left ventricular mass and systolic and diastolic dysfunction which correlates with the degree of steatosis) [40], and hypertension [41]. Although these associations demonstrate a higher probability of CV events in children with NAFLD [42], information regarding CV events after LT in children is very limited. Simon et al retrospectively evaluated long-term mortality in pediatric and AYA patients with NAFLD using nationwide data from Sweden. They included 718 young patients with NAFLD and over 3,000 controls. The results demonstrated that the HR for death due to cardiometabolic disease in patients younger than 25 years old was 4.32, 95% CI 1.73-10.79 [43]. Cancer was found to be another cause of long-term mortality in this study. It has been previously demonstrated that MetS and obesity frequently persist and even worsen after LT and can lead to disease recurrence and the need for re-transplantation [44,45]. Alkhouri et al in a retrospective evaluation regarding long-term outcomes after LT in AYAs with NASH found that over 46 months of evaluation, 30% of patients died and 12% needed re-transplantation because of the recurrence of NASH. The most frequent causes of death were infection (25%), graft failure (17%), and cardiac death (9%) [23]. Infection was previously shown to be one of the main factors related to mortality in LT recipients because of NASH and is also likely associated with MetS [7,18].

Our study has demonstrated that our target population (AYAs 15-39 years old with NASH/CC) had significantly better survival compared to patients 40-65 years old with NASH/CC. The most likely reasons for this are that, in these patients, MetS has not fully developed and they have fewer other comorbidities. For example, the prevalence of DM in our target population was 20% vs 53% in adult patients with NASH/CC.

Any differences in postoperative patient or graft survival between AYAs with NASH/CC and AYAs transplanted for other indications was not found. The regression analysis after adjustment to several variables found to be significant in the univariate analysis demonstrated that LT in AYAs with NASH/CC is associated with worse outcomes in comparison to other causes of ESLD in the same age group. Several previous comparative evaluations and meta-analyses performed in AYAs [9] and adults [8,13,46] did not find any differences in patient or graft survival between patients with and without NASH. There are likely several factors contributing to these results that balance the final outcome, including removal of high-risk NASH/CC patients from the waitlist because of being too ill and longer waitlist times for LT candidates with NASH. Patients with NASH have better graft survival in comparison to some subpopulations [47] and a lower risk of disease recurrence in comparison to patients with hepatis B and C. These should be prospectively evaluated in the future. These results, however, (no difference in survival between patients with and without NASH) are still difficult to explain considering the high prevalence of MetS in this population as well as the known association of NASH with cardiovascular disease and infection [8,18]. In the metanalysis performed by Wang et al, the higher likelihood of MACE in LT recipients with NASH has been demonstrated (odds ratio =1.65, $P = .05$) [8]. In a retrospective evaluation, Malik et al found that in a ‘high-risk’ NASH group (defined as patients older than 60 years old with a BMI above 30 and a history of pre-transplant DM and hypertension), postoperative 1-year mortality was 50%, which was significantly higher than in other younger patients transplanted because of NASH [7]. Most deaths in this subpopulation were attributed to CV events and sepsis. It would be, however, speculation to say that only MetS is responsible for these outcomes. Most likely, there are number of other factors, including disease recurrence, de-novo NASH, and HCC, responsible for these results.

Enrolling LT candidates in a weight reduction program before and after surgery is a potential strategy for improving postoperative outcomes. After receiving LT, being obese increases the likelihood of NASH recurring, as well as the risk of developing CAD, MACE, and cancer [48]. In many LT programs, weight loss is a requirement that can be accomplished through lifestyle changes, a low-calorie diet, exercise, or even surgical options, like bariatric surgery [48]. There is currently no clear evidence indicating that weight reduction before or after surgery leads to improved long-term postoperative outcomes.

This study had several limitations. The most significant limitation is related to the structure of the UNOS database. All information must be entered manually. This can be associated with error, which can affect the quality of the data. There is also a potential for misclassification of the diagnoses of NASH and CC, which can lead to a deviation in the overall patient number included in the study. Even though NASH and CC have similar diagnostical features and share several risk factors for MetS, there is no absolute agreement that these 2 conditions can be lumped together in the same category for evaluation. Several potentially important data points, such as individual MetS components (hypertension and hyperlipidemia), and type of perioperative therapy, are not included in the database. Despite the significant number of patients involved in this study, this analysis was performed based on retrospective data and therefore does not have the same effect as prospective investigations [49]. In addition, a statistical significance might not have clinical relevance

because when using a large sample size, very high statistical power might not be relevant in detecting small effects [50].

In conclusion, our study demonstrated that outcomes after LT in AYAs with NASH or CC were worse when compared to LT for other metabolic conditions but significantly better in comparison to outcomes for older patients with NASH/CC. We also found that, although there was an overall increase in the number of LT in AYAs with NASH/CC, the proportion of LT because of NASH/CC remained stable and even decreased compared to all LT performed for NASH/CC. Nevertheless, this increase in need for transplantation in AYAs should be alarming. All measures to prevent and treat NAFLD in children, and to avoid and/or slow down the development of NASH cirrhosis, should be implemented. All measures to prevent and treat NAFLD in children, and to avoid and/or slow down the development of NASH cirrhosis, should be implemented.

Special attention should also be paid on preventing pediatric obesity and the development of MetS. Prospective studies are necessary to better understand both the progression of NASH in AYAs and the role of MetS in postoperative survival.

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DECLARATION OF COMPETING INTEREST

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DATA AVAILABILITY

This a public data available by request at https://optn.transplant.hrsa.gov

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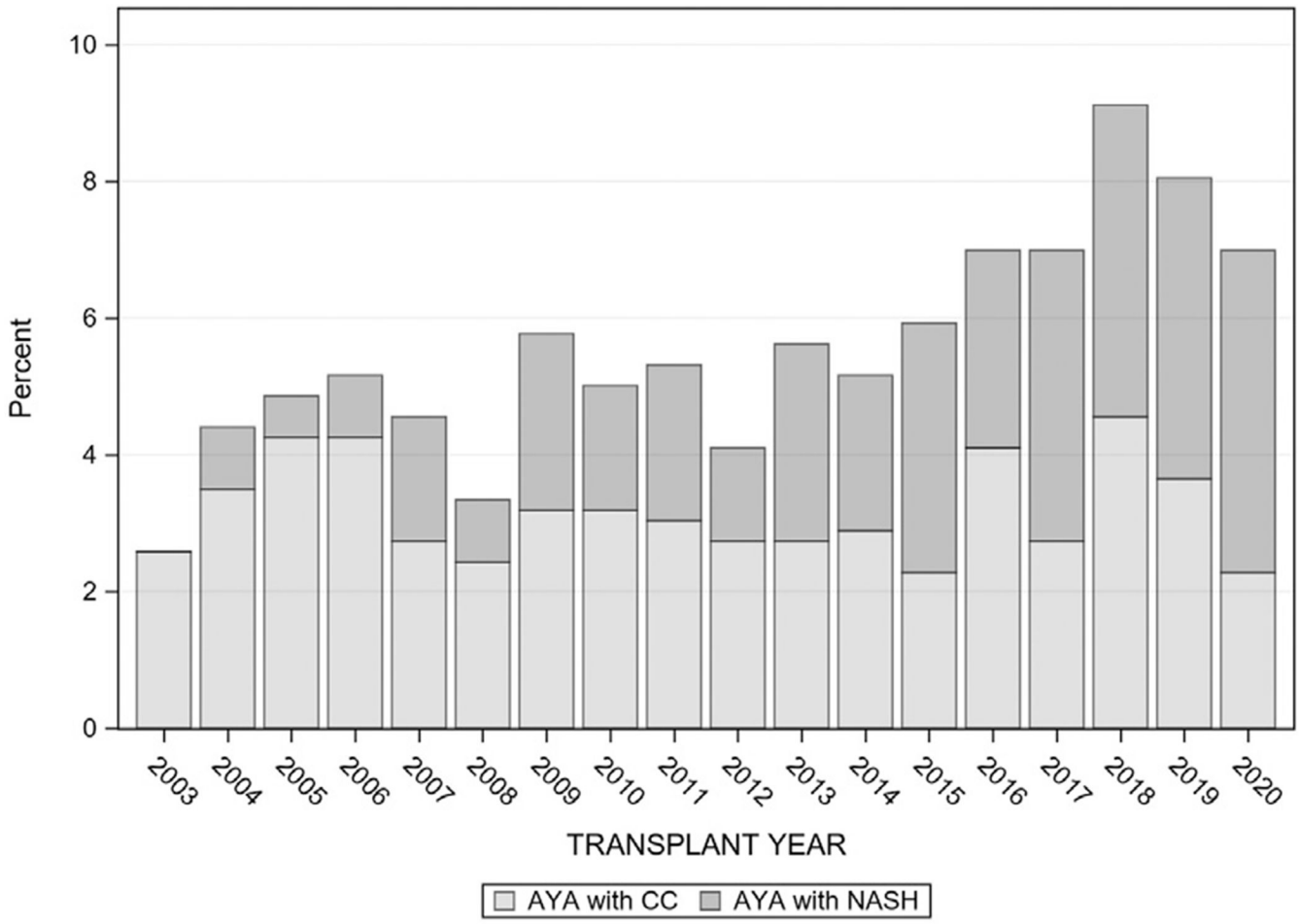

Fig 1.

Distribution of nonalcoholic steatohepatitis/cryptogenic cirrhosis (NASH/CC) in adolescents and young adults (AYAs) by liver transplantation (LT) year, 2003-2020 (n=658; Jonckheere-Terpstra Test for Ordered Differences [JT] *P* value <.0001).

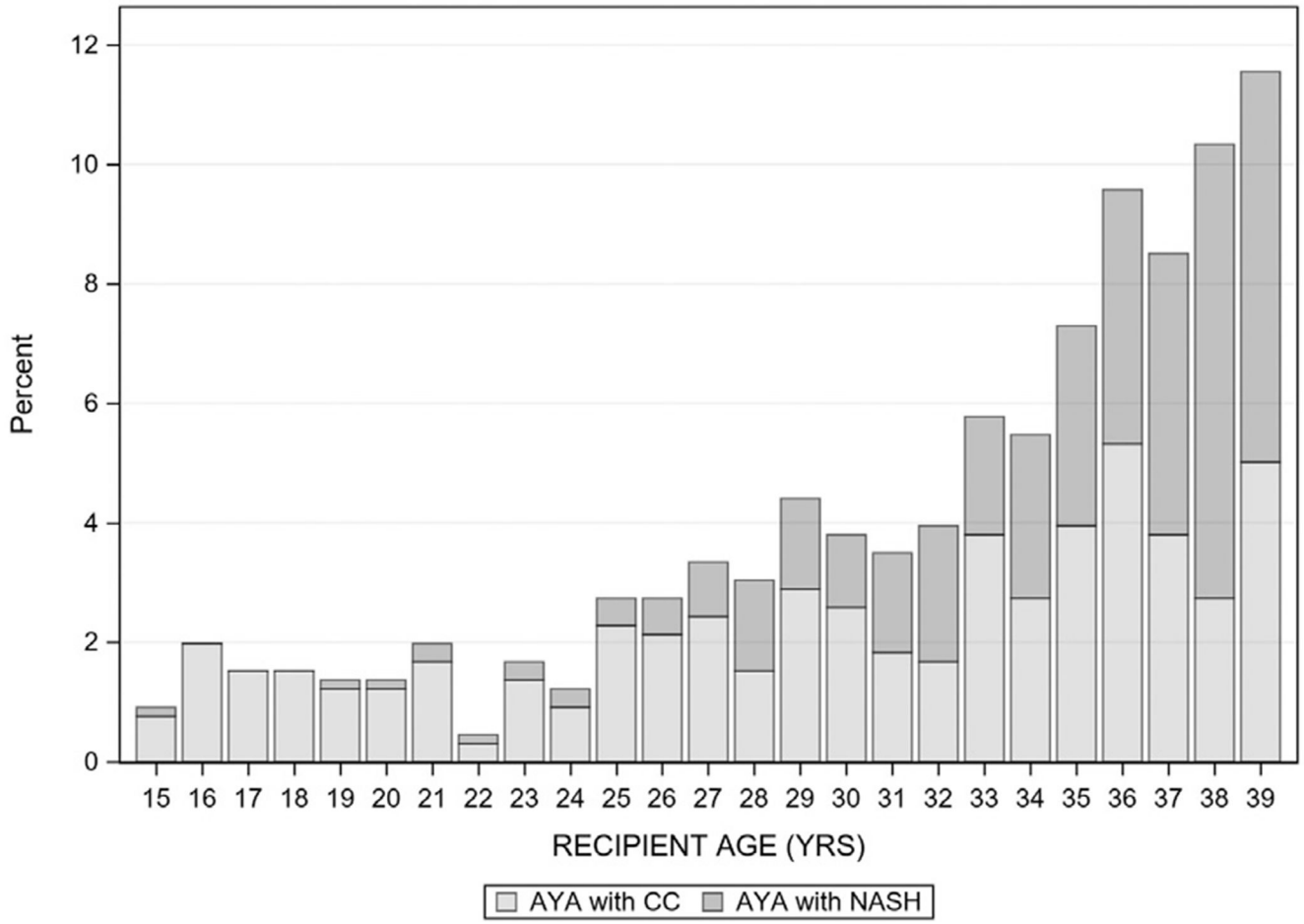

Fig 2.

Distribution of nonalcoholic steatohepatitis/cryptogenic cirrhosis (NASH/CC) in adolescents and young adults (AYAs) by age at the time of liver transplantation (LT), 2003-2020 (n=658; Jonckheere-Terpstra Test for Ordered Differences [JT] *P* value <.0001).

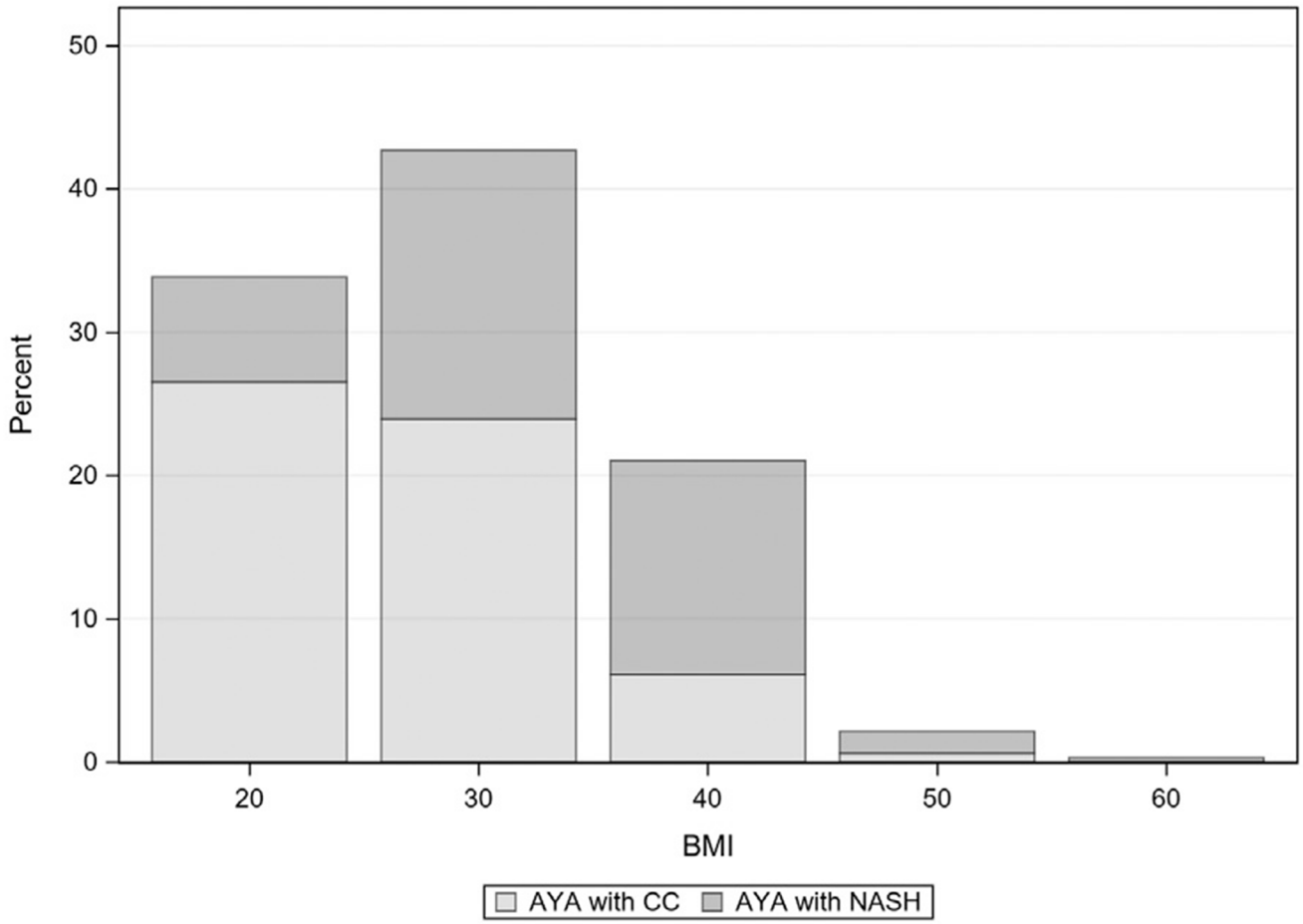

Fig 3.

Distribution of nonalcoholic steatohepatitis/cryptogenic cirrhosis (NASH/CC) in adolescents and young adults (AYAs) by body mass index (BMI) at the time of liver transplantation (LT), 2003-2020 (n=656; Jonckheere-Terpstra Test for Ordered Differences [JT] *P* value <.0001).

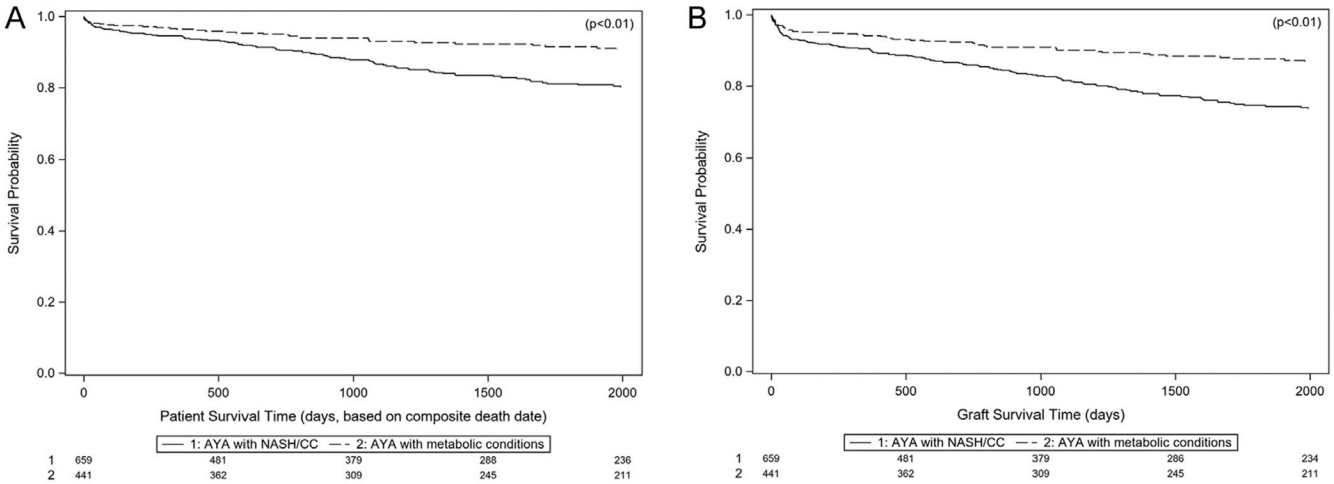

Fig 4.

(A) Patient survival: adolescents and young adults (AYAs) with nonalcoholic steatohepatitis/cryptogenic cirrhosis (NASH/CC) vs AYAs with other metabolic conditions, 2003-2021.

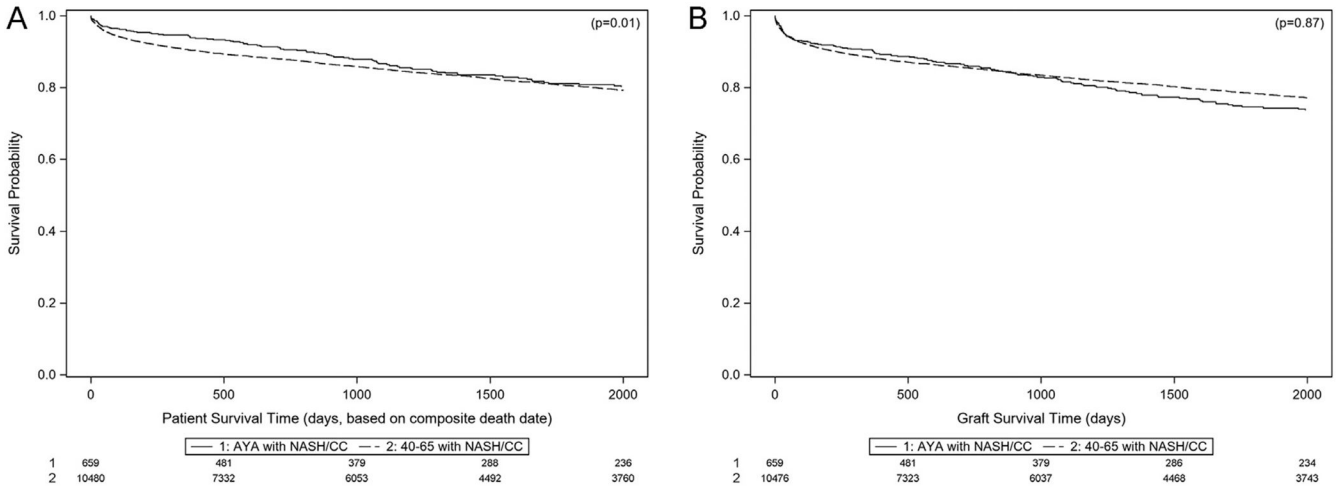

Fig 5.

(A) Patient survival: adolescents and young adults (AYAs) with nonalcoholic steatohepatitis/cryptogenic cirrhosis (NASH/CC). (B) Graft survival: adolescents and young adults (AYAs) with nonalcoholic steatohepatitis/cryptogenic cirrhosis (NASH/CC) vs 40-65 year-olds with NASH/CC, 2003-2021.

Table 1.

Trends in Liver Transplantation for AYA by Year, 2003-2020 (n = 658).

	Years																	
	2003	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
LT for AYA due to NASH/CC (%),	2.6	4.4	4.9	5.2	4.6	3.3	5.8	5.0	5.3	4.1	5.6	5.2	5.9	7.0	7.0	9.1	8.0	7.0
Years			**2003-2008**						**2009-2014**						**2015-2020**			
6-years trend: LT for AYA due to NASH/CC (%)			4.1						5.1						7.3			
LT for AYA due to NASH/CC in relation to all LT performed for AYA (%)	4.8	7.9	7.5	6.5	6.0	5.3	8.3	7.2	7.9	6.6	8.4	7.0	6.9	7.4	7.0	8.3	6.4	5.1
Years			**2003-2008**						**2009-2014**						**2015-2020**			
6-years trend: LT for AYA due to NASH/CC in relation to all LT for AYA (%)			6.3						7.6						6.9			
LT for AYA due to NASH/CC in relation to all LT for NASH/CC (%)	6.2	7.6	7.4	7.4	6.3	4.6	7.8	6.3	6.6	5.4	7.0	6.9	6.1	5.0	5.1	6.3	4.9	4.6
Years			**2003-2008**						**2009-2014**						**2015-2020**			
6-years trend: LT for AYA due to NASH/CC in relation to all LT for NASH/CC (%)			6.6						6.7						5.3			

AYA, adolescents and young adults; CC, cryptogenic cirrhosis; LT, liver transplantation; NASH, nonalcoholic steatohepatitis.

Table 2.

Comparison of Basic characteristics between AYA Populations with NASH/CC and other Metabolic Conditions, 2003-2021.

	AYA with NASH/CC (n = 393)	AYA with other metabolic conditions (n = 441)	*P* value
Demographics			
Age mean (SD)			
Age at transplant	33.92 (4.97)	27.40 (7.81)	<0.0001 *
Sex and Ethnicity, n (%)			
Male sex	185 (52.93)	239 (54.20)	0.7138
Ethnicity			
African American	28 (7.12)	18 (4.08)	0.0547
Asian	13 (3.31)	22 (4.99)	0.2269
Caucasian	265 (67.43)	324 (73.47)	0.0560
Hispanic	78 (19.85)	68 (15.42)	0.0930
BMI, mean (SD)			
At transplant	33.24 (6.93)	27.78 (6.74)	<0.0001 *
MELD, mean (SD)			
At listing	27.21 (10.05)	27.53 (10.62)	0.6521
At transplant	29.45 (9.84)	29.77 (11.04)	0.6660
Change between listing and transplant	2.34 (7.16)	2.34 (7.51)	0.9934
Perioperative Times, mean (SD)			
Waiting list time	115.8 (278.4)	132.9 (441.1)	0.4980
Total cold ischemic time	6.47 (2.37)	6.52 (2.52)	0.7708
Patient survival time	1.542.9 (1.458.1)	2.196.7 (1.652.8)	<0.0001 *
Graft survival time	1.541.9 (1.457.7)	2.196.5 (1.652.4)	<0.0001 *
Days since First Liver Transplant (Retransplants)	904.3 (1.091.5)	1.199.5 (1.582.1)	0.4202
Clinical Conditions, n (%)			
DM	80 (20.36)	16 (3.63)	<0.0001 *
PVT	22 (5.60)	11 (2.49)	0.0217 *
SBP	42 (10.69)	39 (8.84)	0.3695
Dialysats (preoperative)	99 (25.19)	63 (14.29)	<0.0001 *

	AYA with NASH/CC (n = 393)	AYA with other metabolic conditions (n = 441)	*P* value
Type of Transplant, n (%)			
Re-Transplant	32 (8.14)	22 (4.99)	0.0647
Portal Hypertension, n (%)			
Ascites > grade 2 at transplant	137 (34.86)	160 (36.28)	0.6688
HE > grade 2 at transplant	57 (14.50)	82 (18.59)	0.1136
DRI, mean (SD)			
DRI	1.67 (0.33)	1.67 (0.32)	0.9827
Laboratory Value, Median (IQR)			
INR, at listing	1.96 (1.00)	2.30 (1.64)	<0.0001*
INR, at transplant	2.10 (0.99)	2.30 (1.41)	<0.0001*
Serum albumin, at listing	2.90 (1.20)	2.60 (0.90)	<0.0001*
Serum albumin, at transplant	3.00 (1.10)	2.80 (1.00)	0.0005*
Serum bilirubin, at listing	8.75 (18.35)	11.00 (22.65)	0.0137*
Serum bilirubin, at transplant	11.10 (19.70)	15.30 (26.20)	0.0018*
Serum creatinine, at listing	1.07 (1.31)	0.90 (0.70)	0.0007*
Serum creatinine, at transplant	1.27 (1.33)	1.00 (0.93)	0.0001*
Serum Sodium, at listing	136.00 (8.00)	136.00 (6.00)	0.5763

AYA, adolescents and young adults; BMI, body mass index; CC, cryptogenic cirrhosis; DM, diabetes mellitus; DRI, donor risk index; HE, hepatic encephalopathy; MELD, Model for End Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PVT, portal vein thromboses; SD, standard deviation; SPB, spontaneous bacterial peritonitis.

*Statistically significant.