ORIGINAL ARTICLE

Cardiovascular mortality among liver transplant recipients with nonalcoholic steatohepatitis in the United States—a retrospective study

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SUMMARY

Nonalcoholic steatohepatitis (NASH) has become an increasingly important indication for liver transplantation (LT), and there has been a particular concern of excessive cardiovascular-related mortality in this group. Using the United Network for Organ Sharing-Standard Transplant Analysis and Research (UNOS STAR) dataset, we reviewed data on 56,995 adult transplants (January 2002 through June 2013). A total of 3,170 NASH liver-only recipients were identified and were matched with 3,012 non-NASH HCV+ and 3,159 non-NASH HCV− controls [matched 1:1 based on gender, age at LT (±3 years), and MELD score (±3)]. Cox regression analysis revealed significantly lower hazard of all-cause (HR 0.669; $P < 0.0001$) and cardiovascular-related mortality (HR 0.648; $P < 0.0001$) in the NASH compared to the non-NASH group after adjusting for diabetes, BMI, and race. Relative to the non-NASH HCV-positive group, NASH group has lower hazard of all-cause (HR 0.539; $P < 0.0001$) and cardiovascular-related mortality (HR 0.491; $P < 0001$). A lower hazard of all-cause mortality (HR 0.844; $P = 0.0094$) was also observed in NASH patients compared to non-NASH HCV-negative group, but cardiovascular mortality was similar (HR 0.892; $P = 0.3276$). LT recipients with NASH have either lower or similar risk of all-cause and cardiovascular-related mortality compared to its non-NASH counterparts after adjusting for diabetes, BMI, and race.

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Key words
cardiovascular mortality, liver transplant, nonalcoholic steatohepatitis, survival, United Network for Organ Sharing-Standard Transplant Analysis and Research dataset

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Background

Nonalcoholic steatohepatitis (NASH) is a common cause of liver disease in the United States [1]. Although NASH as an indication for liver transplantation (LT) was rare prior to 2002, it has been steadily increasing in LT frequency over the past 15 years [2] and is likely to surpass hepatitis C virus (HCV) as the leading indication for transplantation in the next decade [3,4]. Several studies suggest that the overall survival for patients transplanted for NASH is equivalent [4–7], or even superior [2], to those transplanted for other reasons. However, cardiovascular events are the leading cause of nongraft-related mortality in patients after LT [8]. NASH is frequently associated with components of metabolic syndrome, such as obesity, diabetes, and hypertension. Several studies confirm that NASH and components of metabolic syndrome may serve as independent predictors of cardiovascular disease [9–12], but research with respect to whether the presence of NASH is a risk factor for cardiovascular events after LT is limited and has not been studied systematically. A few studies have shown conflicting results. For example, a recent study noted NASH to be an independent predictor of cardiovascular complications after LT, although it did not affect overall mortality [13]. Cardiovascular events occurred with similar frequency in transplant recipients for nonalcoholic steatohepatitis or alcoholic cirrhosis in another recently published study [14]. Another meta-analysis, however, concluded that recipients with NASH are more likely to die from cardiovascular complications or sepsis after LT [15].

Endothelial dysfunction has been reported as another contributing factor for increased risk of cardiovascular events in NASH [16]. Given the concurrent obesity epidemic and its negative implications on the general population's cardiovascular health, the ability to identify the relative contribution of NASH as an indicator of cardiovascular mortality could have important implications for the national healthcare burden as alternative treatments are considered for this group of patients. Using a large national level clinical dataset, the UNOS STAR with adequate follow-up, the aim of this study is to determine whether LT recipients with NASH are at increased risk of cardiovascular-related mortality compared to non-NASH counterparts after adjusting for diabetes, BMI, and race.

Methods

Research procedure

Data were abstracted from the UNOS STAR dataset and were limited to primary liver transplant patients over 18 years old who were transplanted between January 1, 2002, and June 30, 2013. The study was approved by the University of Tennessee Institutional Review Board. To ensure a homogenous study population, patients with a diagnosis of hepatocellular carcinoma (HCC), living donors, split liver donors, nonheart beating donors, and multi-organ transplants were excluded. We particularly excluded HCC patients to nullify the effect of mortality related to recurrent HCC. Additional exclusions were made based on missing data and implausible values which are considered more extreme than can be accounted by abnormal values. In addition, patients with missing data for cold ischemic time (CIT), donor body mass index (BMI), recipient BMI, serum albumin level, total bilirubin, serum creatinine, diabetes status, and cause of death were excluded. Patients with donors less than 18 years old or greater than 75 years old, CIT <1 or >24 h, BMI <15 or >55 km/m^2, serum albumin <0.5 or >6 g/dl, total bilirubin <0.1 or >50 mg/dl, or a creatinine level of <0.1 or >15 mg/dl were also excluded. Patient diagnoses were identified using the primary diagnosis numeric code for NASH in the dataset. Cryptogenic cirrhosis with BMI ≥30 was included in the NASH group. In an effort to ensure inclusion of all eligible patients, free-text descriptions in the "Other" primary diagnosis code were also carefully reviewed for NASH and cryptogenic cirrhosis diagnoses. Cardiac deaths were identified by the cause of death variable and included cardiac arrest, myocardial infarction, arrhythmia, congestive failure, arterial embolism, and other cardiac causes of death.

Study population

There were 56 995 adult patients who had first liver transplant from January 2002 through June 2013. After

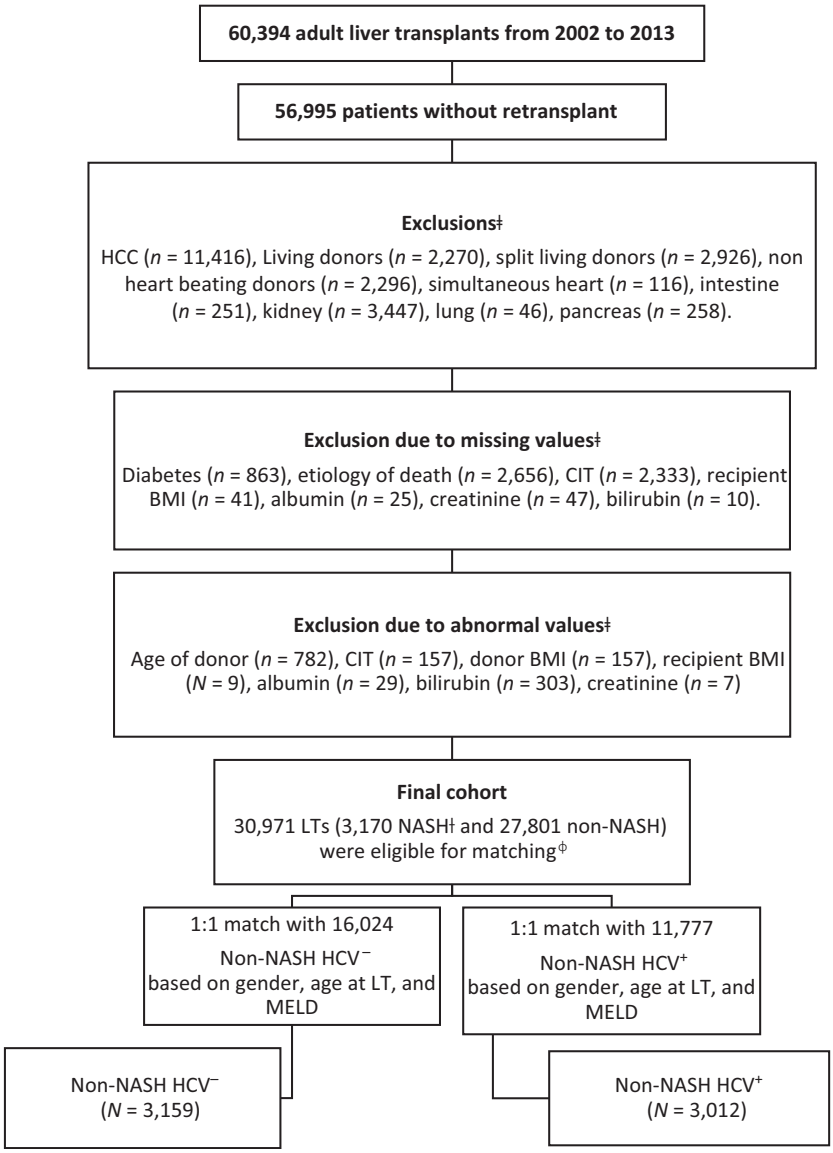

Figure 1 Algorithm showing the inclusion and exclusion criteria. *Note:* ‡Some patients had more than one reason for exclusion. †Patients with NASH and a primary diagnosis of HCV (hepatitis C virus) were excluded from the NASH group, $^{\phi}$Sampled without replacement.

exclusions, there were 30,971 patients eligible for matching, 3,170 with NASH or cryptogenic cirrhosis with BMI ≥30 and 27,801 of non-NASH etiologies (Fig. 1).

Statistical analysis

To ensure a representative control group, transplant recipients in the NASH group were matched 1:1 to non-NASH patients HCV+ (11,777), non-NASH patients HCV− (16,024) on the basis of gender, age at transplant (±3 years), and MELD score (±3). Matching was carried out using a local SAS macro "gmatch" written by Erik Bergstralh and Jon Kosanke (mayoclinic.com, 10/2003). Controls were selected randomly without replacement. Cox proportional hazard model was used to estimate hazard ratios and 95% confidence intervals (CI). Statistical models included diabetes, BMI, and race as covariates. Laboratory variables were not included because differences at transplantation were not clinically meaningful. Patient survival stratified by NASH status was evaluated using the Kaplan–Meier (KM) method. The effects of NASH status on patients survival was conducted using Cox regression model stratified by matched sets. An alpha of <0.05 was considered significant for all methods used in this study. Data were statistically analyzed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Clinical and demographic profile

Clinical and demographic profiles of recipients of NASH and non-NASH recipients (HCV+ and HCV−

Table 1. Characteristics of nonalcoholic steatohepatitis (NASH), non-NASH HCV+ and on-NASH HCV− groups at transplant from 2002 to 2013.

Variables	NASH (n = 3170)	Non-NASH HCV+ (n = 3012)	Non-NASH HCV− (n = 3159)	P-value
		n (%)		
Gender (Male)	1776 (56.03)	1728 (57.37)	1771 (56.06)	0.4813
Race				
White	2700 (85.17)	2085 (69.22)	2429 (76.89)	<0.0001
Black	63 (1.99)	365 (12.12)	215 (6.81)	
Hispanic	339 (10.69)	434 (14.41)	368 (11.65)	
Other	68 (2.15)	128 (4.25)	147 (4.65)	
Diabetes	1576 (49.72)	630 (20.92)	682 (21.59)	<0.0001
Ascites present	2817 (89.03)	2662 (88.38)	2712 (85.85)	0.0003
BMI (≥30)	2284 (72.05)	1057 (35.09)	894 (28.30)	<0.0001
Albumin (<3.5 g/dl)	2504 (78.99)	2467 (81.91)	2502 (79.20)	0.0064
	Mean (SD)			
Age	57.61 (8.30)	57.32 (7.86)	57.62 (8.28)	0.2630
Albumin (g/dl)	2.95 (0.65)	2.85 (0.69)	2.92 (0.68)	<0.0001
Creatinine (g/dl)	1.62 (1.12)	1.53 (1.05)	1.46 (1.01)	<0.0001
MELD score	23.16 (8.73)	22.98 (8.68)	23.11 (8.71)	0.6993
BMI	32.92 (5.60)	28.55 (5.44)	27.73 (5.51)	<0.0001
Bilirubin	7.76 (9.16)	7.91 (9.46)	9.60 (10.25)	<0.0001
INR	1.94 (0.8)	1.95 (0.73)	1.94 (0.90)	0.8137

group) matched (1:1) by gender, age at LT (±3 years), and MELD score (±3) are presented in Table 1. Matching resulted in 3,170 NASH and 6,171 non-NASH controls (3,012 non-NASH with HCV+ and 3,159 with HCV− controls). Some disparities in the racial distribution were noted with higher proportions of Blacks in the non-NASH group compared to the NASH group. As expected, compared to the non-NASH group, the NASH patients have a higher proportion with diabetes mellitus (DM) (49.72% vs. 20.92% and 21.59%, $P < 0.0001$), and with BMI ≥30 (72.05% vs. 35.09% and 28.30%, $P \leq 0.0001$). Statistically significant differences were noted among the three groups on the serum levels of albumin (2.95 ± 0.65, 2.85 ± 0.69, 2.92 ± 0.68, $P < 0.0001$), creatinine (1.62 ± 1.12, 1.53 ± 1.05, 1.46 ± 1.01, $P < 0.0001$), and total bilirubin (7.76 ± 9.16, 7.91 ± 9.46, 9.60 ± 10.25, $P < 0.0001$).

Survival analysis

Nonalcoholic steatohepatitis patients had a lower adjusted hazard ratio of all-cause death when compared to their non-NASH counterparts (controls) [HR 0.669, 95% CI (0.597, 0.749); $P < 0.0001$], after controlling for diabetes, BMI, and race (Table 2). Survival analysis using Kaplan–Meir curves also further revealed significantly better overall survival for the NASH group compared to the non-NASH group ($P < 0.0001$, Fig. 2). Further subgroup analysis showed similar results comparing NASH versus non-NASH HCV+ patients [HR 0.539, 95% CI (0.476, 0.610); $P < 0.0001$], and NASH versus non-NASH HCV− patients [HR 0.844, 95% CI (0.743, 0.959); $P = 0.0094$] (Table 2). We also noted non-NASH HCV− patients have a lower hazard of all-cause death compared to non-NASH HCV+ LT recipients [HR 0.638, 95% CI (0.575, 0.709); $P < 0.0001$] (Table 2). Additionally, Kaplan–Meier curves demonstrated NASH recipients survived longer than non-NASH HCV+ and non-HCV− patients ($P < 0.001$, Fig. 3). In addition, we performed a separate survival analysis comparing non-NASH HCV+ and non-NASH HCV− patients (Figure S1). It also revealed lower all-cause death in the non-NASH HCV− counterparts as compared to non-NASH HCV+ patients ($P < 0.0001$).

In general, there was a significant difference in NASH vs non-NASH group for cardiovascular-related death [HR 0.648; 95% CI (0.531, 0.791); $P < 0.0001$; Table 2]. When only cardiovascular death was considered, no difference was detected between NASH versus non-NASH HCV− with regard to the overall hazard of death [HR 0.892; 95% CI (0.711, 1.121; $P = 0.3276$, Table 2]. However, NASH have a significantly lower hazard ratio for cardiovascular death compared to non-NASH HCV+ group [HR 0.491, 95% CI (0.396, 0.609), $P < 0.0001$, Table 2]. Additionally, a significant

difference in the risk of cardiovascular mortality was noted in the non-NASH HCV− with better outcomes compared to non-NASH HCV+ groups [HR 0.550, 95% CI (0.458, 0.660); $P < 0.0001$, Table 2]. This was further confirmed by Kaplan–Meier survival analysis ($P < 0.0001$, Figure S2). The NASH and non-NASH HCV− groups were similar with respect to survival time when only cardiovascular deaths were considered, and both of them have longer survival than non-NASH HCV+ ($P < 0.0001$, Fig. 4). Figure 5 depicts that the difference between the NASH and non-NASH groups with respect to mortality attributable to causes of death other than cardiovascular etiology ($P < 0.0001$).

Table 2. Cox regression analysis for cardiovascular deaths of NASH and non-NASH patients transplanted between 2002 and 2013.

	Unadjusted hazard ratios			
	Overall death		Cardiovascular death	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
NASH versus non-NASH	0.712 (0.647,0.784)	<0.0001	0.691 (0.584, 0.818)	<0.0001
NASH versus non-NASH HCV+	0.573 (0.515,0.638)	<0.0001	0.520 (0.432, 0.626)	<0.0001
NASH versus non-NASH HCV−	0.896 (0.801,1.002)	0.0538	0.960 (0.785, 1.173)	0.6891
Non-NASH HCV− versus non-NASH HCV+	0.640 (0.577, 0.710)	<0.0001	0.541 (0.451, 0.649)	<0.0001
Diabetes	1.021 (0.912, 1.144)	0.7139	0.987 (0.813, 1.199)	0.8950
BMI (high versus low)	0.887 (0.801,0.982)	0.0210	0.935 (0.787, 1.110)	0.4403
Race*	0.887 (0.781,1.007)	0.0636	0.740 (0.596, 0.919)	0.0064
	Adjusted hazard ratios			
NASH versus non-NASH	0.669 (0.597,0.749)	<0.0001	0.648 (0.531, 0.791)	<0.0001
NASH versus non-NASH HCV+	0.539 (0.476, 0.610)	<0.0001	0.491 (0.396, 0.609)	<0.0001
NASH versus non-NASH HCV−	0.844 (0.743,0.959)	0.0094	0.892 (0.711,1.121)	0.3276
Non-NASH HCV− versus non-NASH HCV+	0.638 (0.575, 0.709)	<0.0001	0.550 (0.458, 0.660)	<0.0001
Diabetes	1.175 (1.040, 1.327)	0.0093	1.104 (0.897, 1.359)	0.3523
BMI (high versus low)	1.033 (0.918, 1.163)	0.5916	1.144 (0.933, 1.402)	0.1952
Race*	1.045 (0.915, 1.194)	0.5122	0.860 (0.686, 1.078)	0.1914

*Race was compared as "White" versus "all others" for comparable sample sizes in each race category.

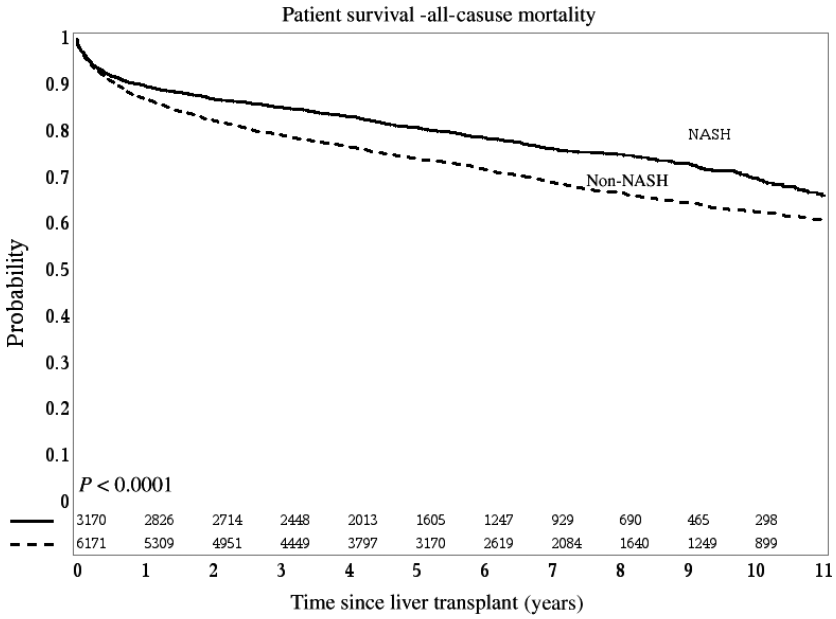

Figure 2 Kaplan–Meier survival curves showing comparison of all-cause mortality in nonalcoholic steatohepatitis (NASH) and non-NASH patients transplanted between 2002 and 2013.

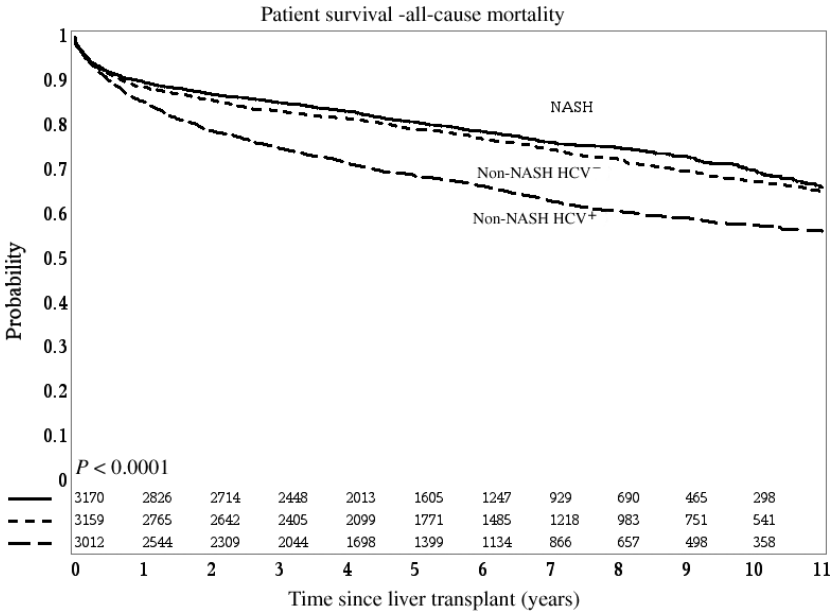

Figure 3 Kaplan–Meier survival curves showing comparison of all-cause mortality in nonalcoholic steatohepatitis (NASH) and non-NASH HCV-positive and HCV-negative patients transplanted between 2002 and 2013.

A positive association between diabetes and all-cause mortality [HR 1.175, 95% CI (1.04, 1.327) $P = .0093$] was detected after controlling for NASH, HCV status, BMI, and race. In addition, we did not find any impact of BMI in this matched population when BMI <30 and ≥30 were compared [HR 1.033, 95% CI (0.918, 1.163), $P = 0.5916$] for both overall mortality and cardiovascular-related death [HR 1.144, 95% CI (0.933, 1.402), $P = 0.1952$]. Race was compared as "White" versus "all others" for comparable sample sizes in each race category.

We also analyzed the impact of diabetes on long-term survival in the NASH and non-NASH patients. Analysis of long-term all-cause mortality based on diabetes status in the NASH and non-NASH group revealed no impact of diabetes in the NASH group ($P = 0.22$, Figure S3a), but survival was significantly impacted in the non-NASH diabetic group ($P = 0.001$, Figure S3b). No difference in cardiovascular-related mortality was noted in the patients with diabetes and without diabetes in NASH ($P = 0.68$, Figure S4a) but once again, there was a significant difference in the non-NASH group ($P = 0.001$, Figure S4b). Further, we analyzed the impact of BMI on both all-cause mortality (Figures S5a and S5b) and cardiovascular mortality in the NASH and non-NASH group (Figures S6a and S6b). There was trend for increased all-cause (P=0.097) and cardiovascular mortality (P=0.069) in the NASH group with higher BMI (BMI ≥30). Cardiovascular mortality was however significantly increased in the non-NASH group with high BMI (BMI ≥30, P=0.019).

Discussion

Several important observations were made from these findings resulting from a large cohort sampled from a national dataset. First, we note that LT recipients with NASH have superior long-term survival compared to their non-NASH counterparts. The results of this study are in alignment with those of earlier published studies [2,4–7,17]. This finding may appear counterintuitive given that NASH patients as a group have an increased prevalence of the aggregate conditions that constitute metabolic syndrome, which in turn have been shown to predict cardiovascular disease [18]. A previous analysis of the UNOS STAR dataset found that NASH patients have better overall survival than patients with hepatocellular carcinoma (HCC), hepatitis C virus (HCV), alcoholic liver disease (ALD), acute hepatic necrosis, hemochromatosis, or cryptogenic liver disease despite being older, more obese, and more often diabetic [2]. The lower rate of graft failure-related deaths (8.6% in NASH versus 16.6% in non-NASH) was suggested as the explanation for their better survival. Such difference in the graft failure-related deaths could be due to the lower rates of NASH and cirrhosis recurrence in transplanted livers versus the recurrence of other diseases such as HCV and HBV [2]. In the current study, comparison of NASH recipients with a matched control group of HCV+ and HCV− patients revealed worst overall survival of the HCV+ group. We suspect the higher recurrence of HCV with its increased graft failure-related deaths could have been a factor in the overall lower survival of the non-NASH HCV+ groups.

Transplant International 2017; 30: 1051–1060

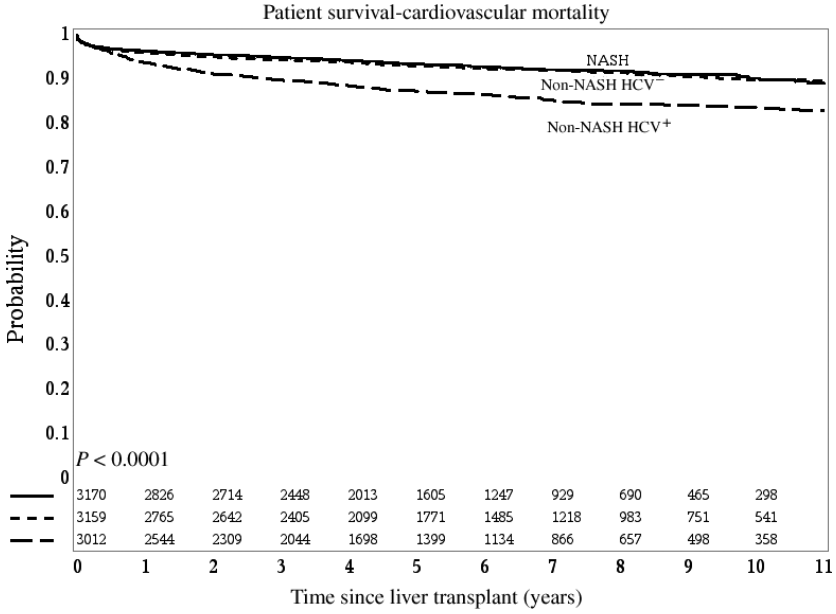

Figure 4 Kaplan–Meier survival curves showing comparison of cardiovascular mortality in nonalcoholic steatohepatitis (NASH) and non-NASH HCV-positive and HCV-negative patients transplanted between 2002 and 2013.

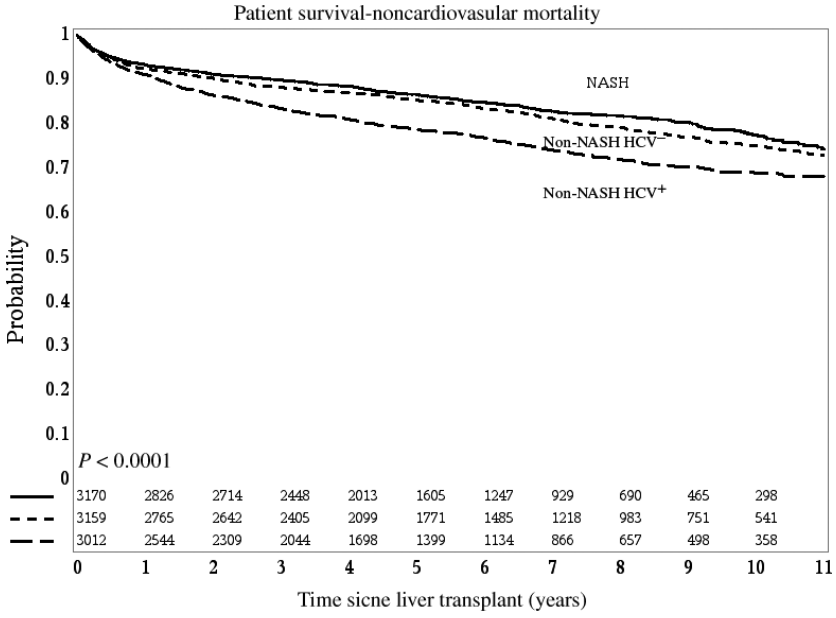

Figure 5 Kaplan–Meier survival curves showing comparison of noncardiovascular mortality in nonalcoholic steatohepatitis (NASH) and non-NASH HCV-positive and HCV-negative patients transplanted between 2002 and 2013.

Secondly, NASH recipients are not at higher risk of cardiovascular-related deaths than their non-NASH counterparts, when matched on gender, age at transplantation, and MELD score and adjusted for diabetes, BMI, and race. Cardiovascular complications are the leading causes of nongraft-related deaths after liver transplant [8], and a previous study has shown that patients with post-transplant hypertension and post-transplant diabetes were more likely to experience cardiovascular events [19]. NASH patients often have an increased incidence of the metabolic syndrome issues, which include obesity, hyperlipidemia, hypertension, and diabetes [18]. Because of this, it is often inferred that NASH patients may be at increased risk of cardiovascular deaths after transplant [18]. Afzali *et al.* [2] noted that the lack of association between NASH and cardiovascular death may be explained by the extensive screening for cardiovascular disease prior to liver transplantation, which results in exclusion of patients with substantial cardiovascular disease prior to the procedure. Additionally, it is possible that the increasing prevalence of metabolic syndrome among non-NASH recipients due to exposure to immunosuppression therapy may have increased the risk of cardiovascular events and death for these patients, thereby equilibrating the risk of both groups. VanWagner *et al.* [18] found that

NASH patients were more likely than patients with alcoholic cirrhosis to experience a cardiovascular event (not death) within the first year after transplant. However, they reported no difference in cardiovascular mortality in their study. Kennedy *et al.* [20] reported that NASH patients experienced higher early postoperative deaths (within 4 months). However, 1-, 3-, and 5-year survival rates, as well as overall survival, were equivalent in NASH and non-NASH groups, and early deaths were not exclusively caused by cardiovascular events. In contrast, Wang *et al.* [21] in their meta-analysis did report a higher rate of cardiovascular deaths for NASH recipients. However, their meta-analysis only included six studies each with small sample sizes.

Thirdly, we evaluated the impact of diabetes mellitus (DM) on long-term survival in LT recipients with NASH and its relationship to cardiovascular mortality. It has been suggested that nonalcoholic fatty liver disease (NAFLD), particularly among type 2 diabetes, may be more important for predicting the risk of cardiovascular death [9,10,12] in nontransplant setting. The impact of DM on long-term survival of the transplant recipients has been reported [22,23]. Diabetes has been associated with a higher risk of liver graft rejection and cardiovascular events [24]. Despite evidence for such association with diabetes, a recent study has also reported no impact of diabetes on the post-transplant outcome [25]. Subgroup analysis of the NASH patients in the current study revealed no significant impact on overall and cardiovascular-related mortality based on diabetes status although survival was significantly impacted in the non-NASH patients. In addition, we noted no impact of BMI on both all-cause mortality and cardiovascular-related mortality when BMI <30 and BMI ≥ 30 were compared. The presence of type 2 diabetes has been associated with an increased risk of adverse post-transplant outcomes in an earlier study using the SRTR (The Scientific Registry of Transplant Recipients) data [24]. Another study using UNOS data noted obesity alone was not associated with lower post-transplant survival. However, DM, either alone or comorbid with obesity, is associated with significantly greater post-transplant mortality [21]. These studies have clearly demonstrated an influence of diabetes with potential additive effects of the components of metabolic syndrome on overall survival and cardiovascular events independent of the underlying liver disease in LT recipients. However, we have shown the impact of diabetes on overall and cardiovascular-related mortality in NASH patients after liver transplant appears similar to those without diabetes. These findings may reflect the influence of the various NASH-associated conditions (such as hyperlipidemia, hypertension, and obesity), independently or in concert, having an impact on survival in the diabetes and nondiabetes groups in NASH.

The current study has several strengths, which include its larger sample size, prospective recording of demographic and clinical characteristics, and the representativeness of the patients in both groups. Although retrospective analyses of large national level datasets make important contributions to health outcomes research, these analyses suffer from certain limitations. For example, it is difficult to determine the reliability of the data, which is generated by multiple clinical sites. Further, the quality of protocols of individual transplant centers can be expected to differ and can change over time, which increases the variability of the resulting data. There is also no requirement for centers to complete all data fields, and the accuracy of the resulting data is impossible to verify. Moreover, the cause of death was listed as unknown for a large number of recorded deaths in the dataset (about 25%). "Cause of death" is captured from the Transplant Recipient Registration (TRR) form; however, entering the specific causes is not required. This deficiency poses a substantial challenge and can introduce a potential source of bias when determining associations with specific causes of mortality.

Another difficulty is posed by the dynamic nature of NASH as a disease, because it has a spectrum of clinical, environmental, and socioeconomic causes prior to the occurrence of cirrhosis, making the consideration of all relevant variables is essentially impossible. Furthermore, a few important clinical variables included in the dataset had large numbers of missing data. For example, hypertension, a key element of the metabolic syndrome and important consideration when discussing NASH, was missing in 90% of patients. An attempt to handle these missing data by excluding patients without drug-treated hypertension reported was unsuccessful as doing so resulted in an insufficient number of matched pairs. Given the importance of such national datasets, it is necessary to identify variables that are helpful to study outcomes such as cardiovascular death and continue to seek methods in which key data can be recorded with a high degree of reliability.

Our study included recipients transplanted since 2002 to provide homogeneity of the MELD scores. We looked for changes in patient characteristics during the observation period (2002–2013) and noted no significant trend for changes in age and diabetes, and patients with BMI ≥ 30. However, until 2004, NASH as a primary diagnosis was only entered as free text under the "other" variable. In general, free-text variables are less

likely to be entered in the clinical records, as it is more time-consuming than numeric choice variables. Thus, the prevalence of NASH during the first 2 years may be underestimated. Additionally, this study combined NASH diagnoses with cryptogenic cirrhosis. Previous studies suggest that a significant portion of cryptogenic cirrhosis is due to NASH, given the similar distribution of the metabolic syndrome and similar outcomes among these patients. However, this inclusion criterion does present a possible inconsistency in the study population compared to previous investigations. We have included recipients with a diagnosis of cryptogenic cirrhosis with BMI ≥30, thus minimizing any false inclusion of etiology other than possible underlying "burnt out" NASH.

Despite these limitations, our current study provides important insights and provides contrary findings regarding the prevailing notion that patients with NASH may experience increased risk of overall and cardiovascular deaths compared to those without NASH. Excellent post-transplantation outcomes for NASH are certainly encouraging and will result in future wider acceptance for liver transplantation in NASH patients as their burden increases.

Author Contributions

SKS: was responsible for the conceptualization of study design, data interpretation, drafting the manuscript and final revisions. YJ: was responsible for data analysis, data interpretation, drawing the figures, responding to reviewers' comments and final revisions. JDE: was responsible for data analysis, data interpretation and revision of the manuscript. SKK: was responsible for data interpretation, responding to reviewers' comments and revision of the manuscript. EW: was responsible for the data collection, initial data analysis, data interpretation and drafting the manuscript. AKS: was responsible for intellectual input and revision of the manuscript. EAT: was responsible for supervision of statistical analysis, data analysis and data interpretation. DH: was responsible for the conceptualization of the study design and revision of the manuscript. SN: was responsible for clinical interpretations of the findings and revision of the manuscript. JMV: was responsible for data interpretation and revision of the manuscript.

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Conflict of interests

The authors have no conflict of interests to disclose related to this research or data presented in this article.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Kaplan–Meier survival curves showing comparison of all-cause mortality of non-NASH HCV− and non-NASH HCV+ patients transplanted between 2002 and 2013.

Figure S2. Kaplan–Meier survival curves showing comparison of cardiovascular mortality in non-NASH HCV− and non-NASH HCV+ patients transplanted between 2002 and 2013.

Figure S3a. Kaplan–Meier survival curves showing comparison all-cause mortality of patients with Diabetes and without Diabetes in NASH groups transplanted between 2002 and 2013.

Figure S3b. Kaplan–Meier survival curves showing comparison all-cause mortality of patients with Diabetes and without Diabetes in non-NASH groups transplanted between 2002 and 2013.

Figure S4a. Kaplan–Meier survival curves showing comparison cardiovascular mortality of patients with Diabetes and without Diabetes in NASH groups transplanted between 2002 and 2013.

Figure S4b. Kaplan–Meier survival curves showing comparison cardiovascular mortality of patients with Diabetes and without Diabetes in non-NASH groups transplanted between 2002 and 2013.

Figure S5a. Kaplan-Meier survival curves showing comparison all-cause mortality of patients with High BMI (≥30) and Low BMI (<30) in NASH groups transplanted between 2002 and 2013.

Figure S5b. Kaplan-Meier survival curves showing comparison all-cause mortality of patients with High BMI (≥30) and Low BMI (<30) in non-NASH groups transplanted between 2002 and 2013.

Figure S6a. Kaplan-Meier survival curves showing comparison cardiovascular mortality of patients with High BMI (≥30) and Low BMI (<30) in NASH groups transplanted between 2002 and 2013.

Figure S6b. Kaplan-Meier survival curves showing comparison cardiovascular mortality of patients with High BMI (≥30) and Low BMI (<30) in non-NASH groups transplanted between 2002 and 2013.

REFERENCES

1. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. *Clin Liver Dis* 2007; **11**: 1.
2. Afzali A, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. *Liver Transpl* 2012; **18**: 29.
3. Koehler E, Watt K, Charlton M. Fatty liver and liver transplantation. *Clin Liver Dis* 2009; **13**: 621.
4. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249.
5. Malik SM, deVera ME, Fontes P, Shaikh O, Ahmad J. Outcome after liver transplantation for NASH cirrhosis. *Am J Transplant* 2009; **9**: 782.
6. Bhagat V, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steato hepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl* 2009; **15**: 1814.
7. Hashizume H, Sato K, Yamazaki Y, Horiguchi N, Kakizaki S, Mori M. A prospective study of long-term outcomes in female patients with nonalcoholic steatohepatitis using age- and body mass index-matched cohorts. *Acta Med Okayama* 2013; **67**: 45.
8. Therapondos G, Flapan AD, Plevris JN, Hayes PC. Cardiac morbidity and mortality related to orthotopic liver transplantation. *Liver Transpl* 2004; **10**: 1441.
9. Targher G, Bertolini L, Poli F, *et al.* Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes* 2005; **54**: 3541.
10. Picardi A, Vespasiani-Gentilucci U. Association between non-alcoholic fatty liver disease and cardiovascular disease: a first message should pass. *Am J Gastroenterol* 2008; **103**: 3036.
11. Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. *Diabet Med* 2007; **24**: 1.
12. Bhatia LS, Curzen NP, Byrne CD. Nonalcoholic fatty liver disease and vascular risk. *Curr Opin Cardiol* 2012; **27**: 420.
13. Vanwagner LB, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. *Hepatology* 2012; **56**: 1741.
14. Piazza NA, Singal AK. Frequency of cardiovascular events and effect on survival in liver transplant recipients for cirrhosis due to alcoholic or nonalcoholic steatohepatitis. *Exp Clin Transplant* 2016; **14**: 79.
15. Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroen terol Hepatol* 2014; **12**: 394.
16. Villanova N, Moscatiello S, Ramilli S, *et al.* Endothelial dysfunction and cardio vascular risk profile in nonalcoholic fatty liver disease. *Hepatology* 2005; **42**: 473.
17. Singal AK, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755.
18. Vanwagner LB, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. *Hepatology* 2012; **56**: 1741.
19. Albeldawi M, Aggarwal A, Madhwal S, *et al.* Cumulative risk of cardiovascular events after orthotopic liver transplantation. *Liver Transpl* 2012; **18**: 370.
20. Kennedy C, Redden D, Gray S, *et al.* Equivalent survival following liver transplantation in patients with non-alcoholic steatohepatitis compared with patients with other liver diseases. *HPB* (Oxford) 2012; **14**: 625.
21. Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 394.
22. Tsai MS, Wang YC, Wang HH, Lee PH, Jeng LB, Kao CH. Pre-existing diabetes and risks of morbidity and mortality after liver transplantation: a nationwide database study in an Asian population. *Eur J Intern Med* 2015; **26**: 433.
23. Wong RJ, Cheung R, Perumpail RB, Holt EW, Ahmed A. Diabetes mellitus, and not obesity, is associated with lower survival following liver transplantation. *Dig Dis Sci* 2015; **60**: 1036.
24. Ramos-Prol A, Hervás-Marín D, García-Castell A, Merino-Torres JF. Outcomes in patients with diabetes 10 years after liver transplantation. *J Diabetes* 2016. https://doi.org/10.1111/1753-0407.12520. [Epub ahead of print].
25. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open* 2015; **5**: e006971.