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ORIGINAL ARTICLE

Outcomes of liver transplantation in non-alcoholic steatohepatitis (NASH) versus non-NASH associated hepatocellular carcinoma

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Abstract

Background: Non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC) is a rising indication for liver transplantation. This unique population, with multiple comorbidities, has potential for worse post-transplant outcomes. We compared post-transplant survival of NASH and non-NASH HCC patients using a large cohort.

Methods: Adults transplanted for HCC between 2008 and 2018, from United Network for Organ Sharing (UNOS) and University Health Network (UHN) databases were divided into two populations: NASH and non-NASH. Recipient characteristics and post-transplant survival were compared. Subgroup analyses were performed within and beyond Milan criteria.

Results: 2071 of 20,672 (10.0%) patients underwent transplantation for NASH HCC, with annual proportional increase of 1.2%UHN ($p = 0.02$) and 1.3%UNOS ($p < 0.001$). The 1-,3-,5-year post-transplant survival were 90.8%, 83.9%, 76.3% NASH HCC versus 91.9%, 82.1%, 74.9% non-NASH HCC ($p = 0.94$). No survival differences were observed in populations within or beyond Milan. Competing-risk analysis demonstrated no differences in risk for cardiovascular-related death (HR1.24, 95%CI 0.87–1.55, $p = 0.16$), or HCC recurrence-related death (HR1.21, 95%CI 0.89–1.65, $p = 0.23$). NASH HCC patients had lower risk of liver-related deaths (HR0.57, 95%CI 0.34–0.98, $p = 0.04$).

Discussion: NASH HCC is a rising indication for liver transplantation. Despite demographic differences, no post-transplantation survival differences were observed between NASH and non-NASH HCC. This justifies equivalent organ allocation, irrespective of NASH status.

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Abbreviations: AFP, alpha fetoprotein; AIH, autoimmune hepatitis; BMI, body mass index; CIT, cold ischemia time; CI, confidence interval; DBD, donor after brain death; DCD, donor after cardiac death; HR, hazard ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IQR, interquartile range; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, on-alcoholic steatohepatitis; OS, overall survival; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; STAR, standard transplant analysis and research; US, United States; UHN, University Health Network; UNOS, United Network for Organ Sharing.

Introduction

With the obesity epidemic there has been an increase in non-alcoholic fatty liver disease, of which up to 25% progresses to Non-alcoholic steatohepatitis (NASH) and liver cirrhosis.[1,2] Consequently, there has been a significant increase in the incidence of NASH hepatocellular carcinoma (HCC),[3] particularly in women,[4] with a projected increase of 140% by 2030.[5] Other major etiologies of HCC either decreased or remained stable.[4] Additionally, with the advent of direct-acting antivirals for the eradication of hepatitis C virus (HCV), there is expected to be a further decrease in the number of liver transplants for HCV,[4,6,7] while liver transplantation (LT) performed for NASH and HCC rises. NASH has now become the second leading cause of HCC-related LT and waitlist registration in North America.[8,9]

Despite this, few studies have investigated the outcomes of LT in NASH HCC compared with non-NASH HCC. The subset of NASH HCC patients is a unique population, who tend to be older, have higher body mass index (BMI), and often have more comorbidities, including diabetes and cardiovascular disease.[10,11] There is also suggestion that NASH patients have a higher incidence of advanced HCC (beyond Milan criteria) and faster tumour progression, compared to other etiologies of liver disease.[10] Some studies have highlighted the practice of disadvantaging NASH patients from the LT process on the basis of their increased medical comorbidities.[3,12,13]

Recent studies performed at single or dual transplant institutions highlight similarities in post-transplantation survival outcomes between NASH and non-NASH HCC patients.[14,15] Through multivariable model analysis, NASH status has been further demonstrated to be potentially protective in patients with locally advanced HCC beyond the Milan transplant criteria.[15] Additionally, NASH HCC has been associated with fewer high-risk explant features for tumour recurrence, compared to other liver etiologies associated with HCC(16). This challenges the stigma against NASH HCC transplant candidates[3,12,13] and raises area for further studies in a larger cohort. Consequently, our study aimed to retrospectively examine a combined large multinational population database to investigate the differences in post-transplantation survival outcomes between NASH HCC and non-NASH HCC patients within and beyond the Milan criteria.

Methods

Study population

We included consecutive adults (≥18 years) who were primary LT recipients between January 2008 and December 2018 with a pre-transplant diagnosis of HCC, irrespective of the background liver etiology. Patients who did not undergo LT (including waitlist dropouts), underwent multi-visceral transplants (liver plus other organs), or underwent re-transplantation were excluded from the study. This study complies with the STROBE statement for retrospective studies,[17] and a STROBE-compliant diagram of excluded and included patients is available (Fig. 1).

Transplant registries and databases

The data was obtained from the United Network for Organ Sharing (UNOS)/Standard Transplant Analysis and Research (STAR) United States (US) transplant registry, as well as single-institution data from the Toronto General Hospital, part of the University Health Network (UHN) database. The two datasets were appended.

US UNOS/STAR

LT data for HCC was obtained from the US UNOS/STAR database, which captures information on the recipient, graft, waitlist characteristics, explant details, and post-transplantation outcomes for every organ transplant event in the US since 1987. Serial audits are performed for this database to ensure quality assurance in data reporting and to minimize discrepancies or inaccuracies.[17]

UHN

Single-institution HCC-specific LT data was obtained from the Toronto General Hospital UHN database. The UHN database represents one of the largest adult transplant programs in North America, performing approximately 200 liver transplants annually, with 40–50% for HCC(18). This represents over one-third of liver transplants performed annually in Canada.[18,19] This large UHN database was used as a surrogate for Canadian transplant data, given that the Canadian Organ Replacement Registry database compiled from seven transplant centres within Canada did not capture HCC-specific information. Additionally, UHN was included in the retrospective dual centre study by Sadler et al.[15] This allowed our study to test and validate the findings of a previous study comparing post-LT outcomes of NASH HCC and non-NASH HCC patients in a significantly larger North American cohort.

Allocation of organs for HCC patients

The organ allocation policies for deceased donor liver transplants are in constant flux. The US (UNOS) system and the UHN system are both dependent on using the model for end-stage liver disease (MELD) score and timing on the waitlist.[19–22]

US (UNOS) system

Since 2005, stage 2 HCC patients were awarded standard exception points starting at 22 points, and received a 10% increase in exception points every 3 months if they remained within Milan criteria.[20] At this time there was regional sharing of liver grafts for candidates with a MELD score of 15 or higher, which was further expanded to a national organ sharing system in 2013. Then in 2015, a Delay and Cap HCC policy was implemented, which provided a maximum allowable HCC exception score of 34, and required a 6-month delay from waitlist registration to the assignment of an exception score of 28. In 2017, this was further updated to allow the allocation of standard exception points for patients who were downstaged based on the

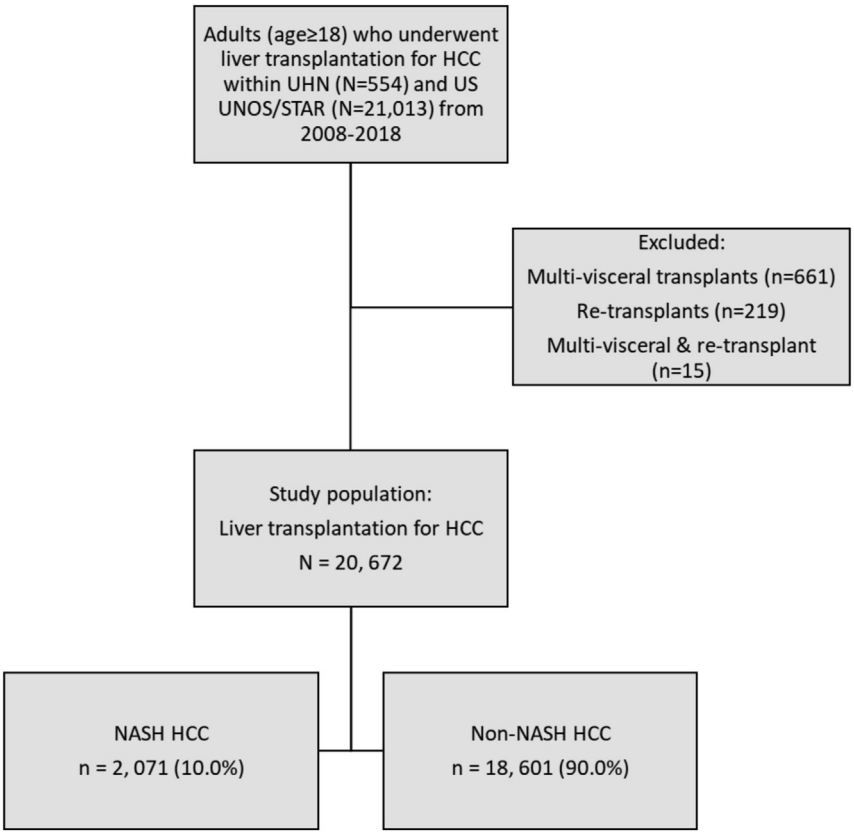

Figure 1 STROBE diagram of included and excluded cohorts. STROBE diagram of included population cohorts (divided into NASH HCC and non-NASH HCC subgroups) and excluded population cohorts from the Canadian University Health Network (UHN) database and the United States (US) United Network Organ Sharing/Standard Transplant Analysis and Research (UNOS/STAR) transplant registry.

University of California San Francisco criteria (up to 5 tumours, largest tumour up to 4.5 cm, and sum of tumours is less than 8 cm) to within Milan criteria.[20] The contraindications to receiving HCC exception points included having stage 1 HCC, ruptured or extrahepatic HCC, invasion of the main portal or hepatic vein, and AFP level >1000 ng/mL.

Canada and UHN system

Canada has province-specific allocation policies, and UHN follows Ontario's listing criteria, with a total tumour volume <145 cm^3 and alpha fetoprotein (AFP) < 1000 ng/mL.[19,21] Standard HCC exception points are provided in cases of a lesion over 2 cm, multiple lesions over 1 cm, or the recurrence of HCC after ablation. Provision of exception points start at 22 points, and increases by 3 points every three months, without a cap for maximum allowable points. Additionally, downstaging of disease to be within this criteria is acceptable. Since 2015, liver allocation also has adopted the use of MELD-Na.

Data collection

Two population groups were defined: 1) patients with a pre-transplantation diagnosis of both NASH and HCC (NASH HCC) and 2) patients with a pre-transplantation diagnosis of HCC in the absence of a diagnosis of NASH (non-NASH HCC).

In the US population database, pre-transplant variables comprised of data from the visit closest to the time of LT. The diagnosis of NASH and HCC was acquired from the UNOS/STAR transplant registry by examining the established pre-transplant liver diagnoses of LT recipients, including their primary, secondary, tertiary, and quaternary listed diagnoses. Given that each patient could have multiple diagnoses for etiology of liver disease, patients that had a mention of HCC in any of the listed pre-transplant liver disease diagnoses were included in the study population. Of the included HCC patients, only those that had coding of NASH within any of their multiple liver disease diagnoses were categorized in the NASH HCC group.

For the UHN cohort, pre-transplant variables comprised of data from any particular time point between the listing process and the transplant event. The diagnosis of NASH was determined based on available explant pathology, histological features on biopsy, or a clinical diagnosis in the presence of metabolic risk factors, with absence of alcohol intake.[23]

Both continuous and categorical variables were collected for pre-transplantation LT recipient characteristics and transplant

procedure-specific variables. The continuous variables included: age [years], BMI [kg/m^2], MELD score, time on the waitlist [months], AFP levels [ng/mL], size of the largest tumor [cm], and cold ischemia time (CIT) [minutes]. The categorical variables included: sex (male or female), etiology of liver disease (Hepatitis C virus (HCV), Hepatitis B virus (HBV), alcoholic cirrhosis, autoimmune liver disease including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), cryptogenic, and other etiologies), bridging therapy while on waitlist (transarterial chemoembolization or ablation), tumour number, year of transplant, graft type (donor after brain death (DBD), donor after cardiac death (DCD), or living donor). Additionally, to account for potential differences in HCC disease stage and response to bridging therapies, explant data was also collected. The explant data included the continuous variable: size of the largest tumour [cm], and the categorical variables: tumour number, tumour grade (well differentiated, moderately differentiated, poorly differentiated), viable tumour cells (presence or absence), and degree of vascular invasion (microvascular, macrovascular, or no invasion). Post-transplantation outcomes, including death, date of death, and recipient cause of death, were also collected.

Recipient causes of death were categorized into six groups: cardiovascular (including cardiac and vascular complications), liver-related (including transplant-related graft failure or liver disease), infection (including sepsis, pulmonary infections, and peritonitis), recurrence of primary malignancy (HCC), and all-cause malignancy (including primary and non-primary malignancy). The causes of death were not mutually exclusive, and some patients had multiple causes reported, all of which were included in the study.

Patients were categorized into "within Milan criteria" as defined by those with solitary lesion $\leq$5 cm or $\leq$3 lesions with diameter $\leq$3 cm, no vascular invasion or extrahepatic involvement,[24,25] or as "beyond Milan criteria" if not in keeping with these criteria. This subgroup categorization was performed based on pre-transplant data, and a separate subgroup categorization was additionally performed based on explant pathology data. Patients who had no existing viable tumour as a result of bridging therapy were considered within the Milan criteria.

Statistical analyses

Descriptive data for continuous variables with non-normal distribution are expressed as medians with interquartile ranges (IQRs). The characteristics of the NASH and non-NASH HCC groups were compared using the Mann–Whitney U test. Categorical variables are expressed as numbers and percentages and compared using the Chi-square test.

The yearly absolute number and proportion of NASH HCC out of all LT for HCC were described for each region, and the trends were assessed using a linear regression least-square model. Kaplan–Meier analyses were used to estimate the overall survival (OS) for the NASH and non-NASH HCC groups. Patients who did not experience an event (death) or were lost to follow-up were censored at their last visit.

Given the multivariable model analysis performed by Sadler et al., which demonstrated NASH status to be protective in patients with tumours beyond Milan,[15] a subgroup analysis was performed for patients within and beyond the Milan criteria (pre-transplant and on explant pathology). To determine whether NASH was independently predictive of post-transplant survival outcomes, after accounting for other confounders, a multivariable Cox proportional hazard regression model was developed to estimate the hazard ratio (HR) and 95% confidence interval (CI) associated with NASH. Of the NASH-related and post-transplant survival-related variables available within our dataset, the following variables were included and adjusted for in the model: recipient sex, transplant year, recipient age, recipient BMI, recipient AFP, CIT, Milan criteria pre-transplant, MELD, donor type, and region of transplant (US vs. UHN). These variables were chosen based on clinical indication, for their potential to be confounding factors in NASH-related post-transplant survival.[3,13,26,27] To determine whether the effect of NASH status on post-transplant outcomes differed between those within and beyond the Milan criteria, we tested an interaction term between these variables in the multivariable model.

In addition, cause-specific hazard ratios (95% CIs) for death were obtained according to various causes of death (cardiovascular, liver-related, HCC recurrence, and all other deaths). In cases where a patient's cause of death was HCC recurrence and cardiovascular (n = 19), the cause of death was listed as HCC recurrence. If patient's cause of death was cardiovascular and liver-related (n = 41), the cause of death was listed as cardiovascular. The causes of death were ranked by prioritization of our outcomes of interest: HCC recurrence, followed by cardiovascular, and then liver related deaths. Additionally, HCC recurrence and cardiovascular-related deaths are the two main causes of death in the long-term setting post-transplantation for HCC.[28] The differences in cause of death according to cardiovascular, liver-related, infection, all-cause malignancy, and HCC recurrence were reported according to NASH status, and compared using a Chi-square test.

Statistical significance was set at $p < 0.05$. All statistical analyses were two-sided and performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Prevalence and trend of NASH

A total of 20,672 adult patients who met the inclusion criteria for first-time liver transplantation for HCC between 2008 and 2018 were identified from the combined dataset. Of these, 2071 (10.0%) were diagnosed with NASH HCC and 18,601 (90.0%) with non-NASH HCC. The proportion of patients with NASH

HCC according to region was similar, with 2025 of 20,118 (10.1%) in the US population and 46 of 554 (8.3%) in the Toronto UHN population (p = 0.17).

The proportion of patients who underwent LT for NASH HCC gradually increased from 2008 to 2018 (Fig. 2). The proportions of liver transplant recipients for NASH HCC in 2008 for the UHN and US populations were 0.0% and 4.9%, respectively, compared to the proportions in 2018 of 13.2% and 18.4%, respectively. The yearly proportional increase in liver transplants for NASH HCC was 1.2% (95% CI 0.2–2.1, p = 0.02) for UHN, and 1.3% (95% CI 0.9–1.6, p < 0.001) in the US population.

Patient characteristics

The median follow-up period was 3.5 years (95% CI 3.3–3.8) for the NASH HCC cohort and 5.0 years (95% CI 4.9–5.1) for the non-NASH HCC cohort. Multiple statistically significant differences were found when comparing the pre-transplantation characteristics of the NASH HCC transplant recipients with those of the non-NASH HCC group (Table 1). The NASH HCC group was significantly older, with a median age of 64.0 years (IQR 59.0–67.0), compared to the non-NASH HCC group, with a median age of 60.0 years (IQR 55.0–64.0), and the NASH HCC group had a higher average BMI (p < 0.001). There were 12% fewer males in the NASH HCC group, and the median year at which patients underwent LT (2015) was later than that in the non-NASH group (2013) (p < 0.001). Additionally, the pre-transplant MELD score was significantly higher in the NASH HCC group than in the non-NASH HCC group (p < 0.001). In contrast, the pre-transplantation AFP levels were higher in the non-NASH group (p < 0.001).

Preoperative liver transplant recipient characteristics comparing NASH HCC and non-NASH HCC patients are showing in Table 1, and further shown individually for the UNOS population (Supplemental Digital Content 1, Table S1a) and the UHN population (Supplemental Digital Content 1, Table S1b). Overall, the time on the waitlist for transplantation was similar between the two groups, but greater proportion of NASH HCC patients received bridging therapy compared to non-NASH HCC (p = 0.04) (**Table 1**). There was no significant difference in the number of patients transplanted beyond the Milan criteria, based on pre-transplantation tumour characteristics, between the NASH HCC and non-NASH HCC groups. Patient characteristics comparing the US and UHN populations for NASH HCC patients (Supplemental Digital Content 2, Table S2a) and non-NASH HCC patients (Supplemental Digital Content 2, Table S2b) are also summarized.

Explant liver pathology data was available for 10,292 patients (49.8%). Explant features were compared between NASH and non-NASH HCC as shown in Table 2, and further compared within the UNOS subgroup (Supplemental Digital Content 3, Table S3a) and UHN subgroup (Supplemental Digital Content 3, Table S3b). On explant evaluation, 77.1% of NASH HCC and 75.4% of non-NASH HCC explants had viable tumor cells (p = 0.22) (Table 2). Based on explant liver pathology, there were greater number of patients transplanted beyond the Milan criteria in the NASH HCC population, compared to the non-NASH HCC population (p = 0.03).

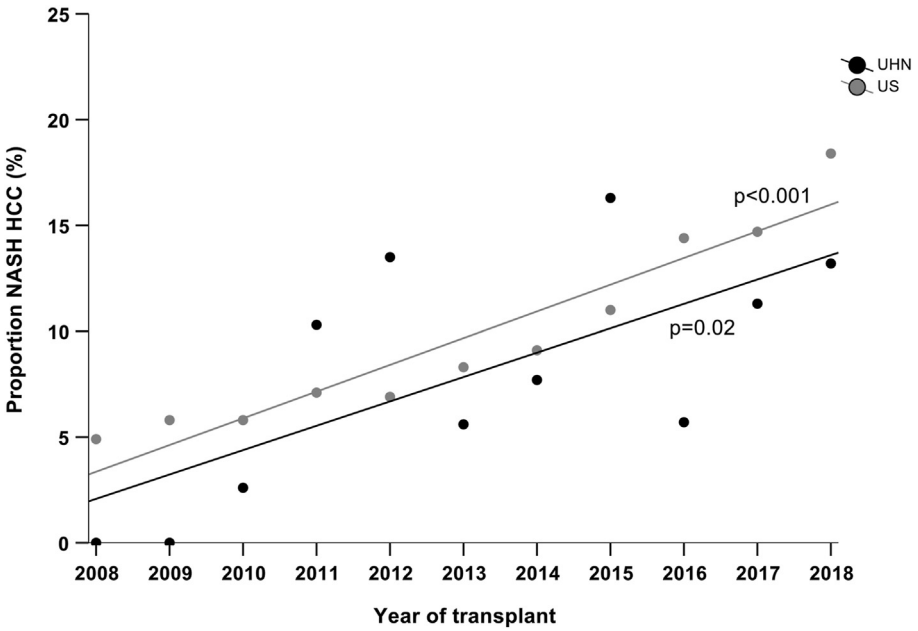

Figure 2 Proportion of liver transplants for NASH HCC over the years. Proportion of patients transplanted for hepatocellular carcinoma (HCC) who underwent liver transplantation for non-alcoholic steatohepatitis (NASH)-associated HCC from 2008 to 2018, as stratified by region: University Health Network (UHN) in Canada and United States (US).

Table 1 Preoperative liver transplant recipient characteristics comparing NASH patients with non-NASH HCC patients

	NASH HCC (N = 2071)	Non-NASH HCC (N = 18,601)	P value
Recipient Characteristics			
Age [years], median (IQR)	64.0 (59.0–67.0)	60.0 (55.0–64.0)	<0.001
Year of transplant, median (IQR)	2015 (2013–2017)	2013 (2011–2016)	<0.001
Sex			<0.001
Male, number (%)	1380 (66.7)	14,612 (78.6)	
Etiology of liver disease			
HCV, number (%)	–	12,062 (64.8)	
HBV, number (%)	–	1236 (6.6)	
Alcoholic cirrhosis, number (%)	–	2105 (11.3)	
AIH/PSC/PBC, number (%)	–	546 (2.9)	
Cryptogenic, number (%)	–	576 (3.1)	
Other, number (%)	–	2072 (11.1)	
Unknown, number (%)	–	4 (0.0)	
BMI, median (IQR)	31.8 (28.0–35.5)	27.8 (24.7–31.5)	<0.001
MELD score, median (IQR)	14.0 (10.0–20.0)	12.0 (9.0–17.0)	<0.001
AFP (ng/ml), median (IQR)	5.0 (3.0–10.0)	9.0 (4.0–27.0)	<0.001
Milan Criteria			0.19
Within Milan, number (%)	1412 (96.6)	13,355 (95.9)	
Beyond Milan, number (%)	49 (3.4)	566 (4.1)	
Tumour Characteristics			
Tumour number, median (IQR)*	1 (0–1)	1 (0–1)	0.001
Size of largest tumour [cm], median (IQR)*	1.7 (0.0–2.5)	1.7 (0.0–2.6)	0.17
Waitlist-related variables			
Waitlist time [months], median (IQR)	6.4 (2.4–11.4)	6.5 (2.3–12.1)	0.33
Bridging therapy, number (%)	688 (42.0)	6251 (39.4)	0.04
Type of bridging therapy, number (%)			<0.001
TACE	441 (64.1)	3821 (61.2)	
Ablation	115 (16.7)	959 (15.4)	
Both	93 (13.5)	1244 (19.9)	
Other	39 (5.7)	220 (3.5)	
Graft-specific variables			
Type of graft			0.16
DBD, number (%)	1864 (90.0)	16,845 (90.6)	
DCD, number (%)	141 (6.8)	1291 (6.9)	
Living donor, number (%)	66 (3.2)	463 (2.5)	
CIT [minutes], median (IQR)	356 (270–449)	360 (278–459)	0.003

Abbreviationsnon-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), interquartile range (IQR), Hepatitis C virus (HCV), Hepatitis B Virus (HBV), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), body mass index (BMI), model of end stage liver disease (MELD), alpha fetoprotein (AFP), transarterial chemoembolization (TACE), donor by brain death (DBD), donor by cardiac death (DCD), cold ischemia time (CIT)*Tumour number and size were based on viable tumour pre-transplant, including after bridging therapy; tumour number range was 0–7 for NASH HCC and 0–20 for non-NASH HCC.

Overall survival

There was no significant difference in overall survival between NASH and non-NASH HCC patients who underwent liver transplantation between 2008 and 2018 (Fig. 3). Additionally, in the subgroup analysis, no difference between the two groups was observed in the UHN (p = 0.10) and US (p = 0.74) population cohorts (Supplemental Digital Content 4, Fig. S1). The one, three, and five-year survival of NASH HCC patients were 90.8% (95% CI 89.4–91.9), 83.9% (95% CI 82.1–85.5), and 76.3% (95% CI 73.8–78.5), respectively, compared to 91.9% (95% CI

Table 2 Explant data in sub-group from UNOS/STAR and UHN data

N = 10,292/20,672 (49.8%)	NASH HCC N = 1066	Non-NASH HCC N = 9226	P value
Number of tumours, median (IQR)	1[1,2]	1[1,2]	0.92
Size of largest tumour [cm], median (IQR)	2.1 (0.7–3.3)	2.0 (0.0–3.2)	0.06
Viable cells, number (%)	822 (77.1)	6958 (75.4)	0.22
Tumour grade[a]			0.42
Well differentiated, number (%)	236 (28.2)	1962 (28.2)	
Moderately differentiated, number (%)	515 (62.9)	4309 (62.0)	
Poorly differentiated, number (%)	68 (8.3)	676 (9.7)	
Microvascular invasion, number (%)	154 (15.4)	1292 (14.7)	0.54
Macrovascular invasion, number (%)	28 (2.8)	175 (2.0)	0.09
Tumour staging			0.03
Within Milan, number (%)	660 (61.9)	6022 (65.3)	
Beyond Milan, number (%)	406 (38.1)	3204 (34.7)	

AbbreviationsUnited Network for Organ Sharing (UNOS), Standard Transplant Analysis and Research (STAR), University Health Network (UHN), non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), interquartile range (IQR).
[a] In those with viable cells.

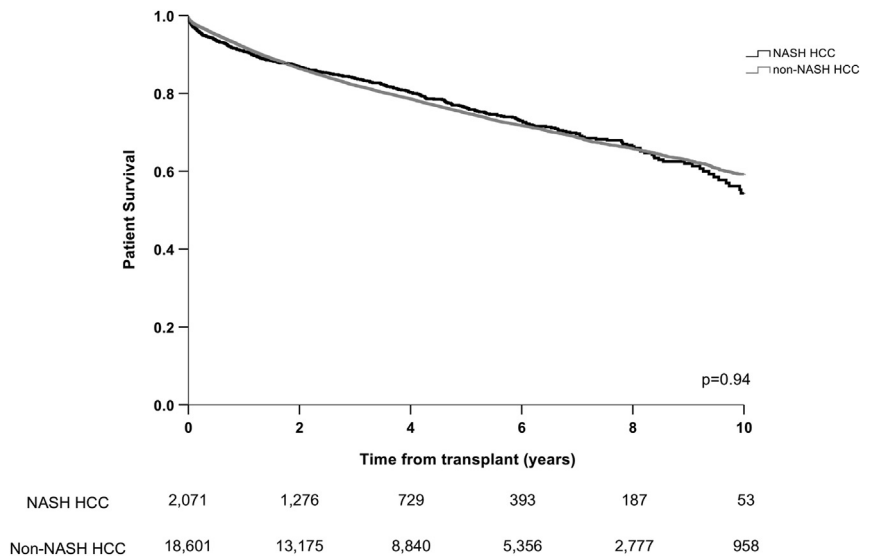

Figure 3 **Overall survival post-transplantation for NASH HCC and non-NASH HCC**. Kaplan–Meier survival curve as a function of time from transplant (in years) comparing overall survival in patients who have undergone liver transplantation for non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC) versus non-NASH HCC.

91.5–92.3), 82.1% (95% CI 81.5–82.7), and 74.9% (95% CI 74.2–75.6) in non-NASH HCC patients (overall p = 0.94) (Fig. 3). Further analysis comparing the NASH HCC and non-NASH HCC groups demonstrated no differences in survival in the subset of patients within and beyond the Milan criteria, based on the pre-transplantation characteristics and explant pathology data (Fig. 4).

On multivariable analysis (Table 3), NASH was not independently associated with post-transplantation survival (HR 1.04, 95% CI: 0.92–1.18, p = 0.54). There was no significant interaction between NASH and Milan. This demonstrates that NASH status does not lead to differences in post-transplantation survival outcomes for patients with HCC according to Milan criteria.

Causes of death

A total of 5091 deaths (432 in NASH HCC and 4659 in non-NASH HCC) were recorded in the transplant recipients (Supplemental Digital Content 5, Fig. 2). Between the NASH HCC and non-NASH HCC population, there was a significantly greater proportion of post-transplantation deaths from cardiovascular complications in the NASH HCC group (21.8% NASH

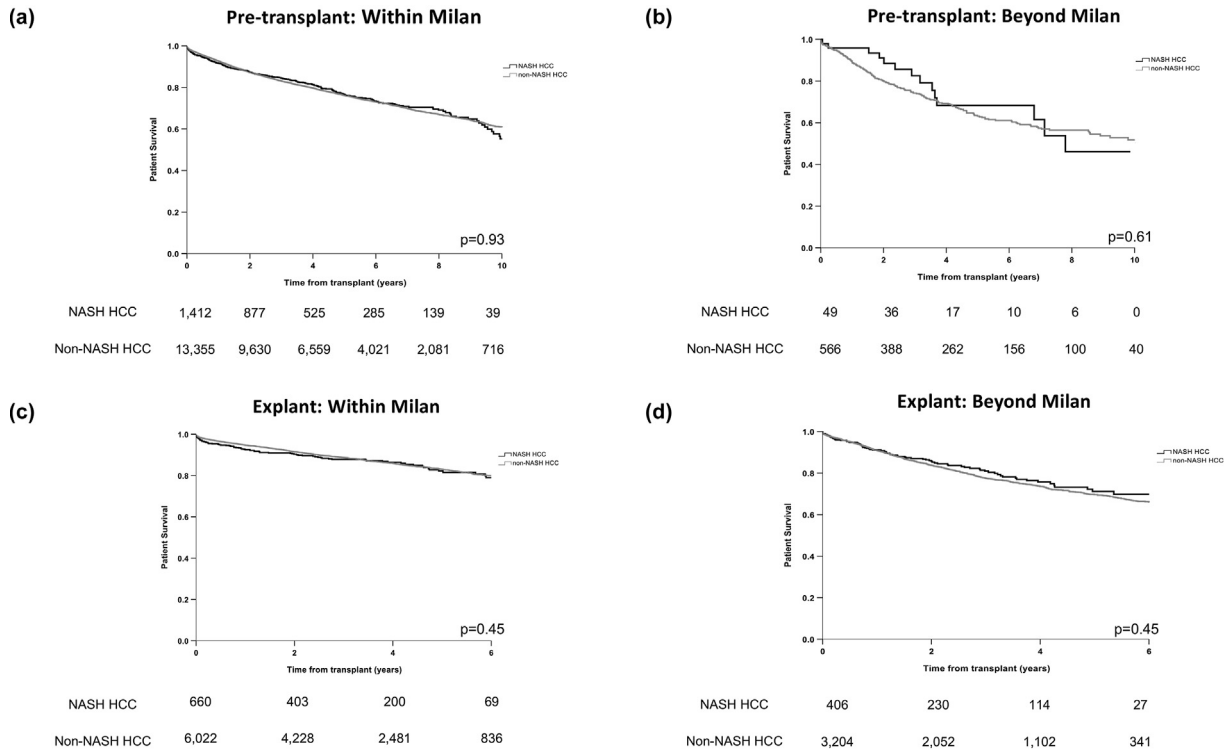

Figure 4 Overall survival post-transplantation for NASH HCC and non-NASH HCC within and beyond Milan criteria. Kaplan–Meier survival curves as a function of time from transplant (in years) comparing overall survival in patients who have undergone liver transplantation for non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC) versus non-NASH HCC in patients with tumours (a) within Milan based on pre-transplantation characteristics (b) beyond Milan based on pre-transplantation characteristics (c) within Milan based on explant data (d) beyond Milan based on explant data.

HCC vs. 13.8% non-NASH HCC, $p < 0.001$). In contrast, the non-NASH HCC group had a significantly greater proportion of deaths attributed to liver-related causes than the NASH HCC group (6.3% vs. 10.3%, $p = 0.007$). No differences were noted between the two groups in the proportions of deaths from infection (14.8% NASH HCC vs. 11.8% non-NASH HCC, $p = 0.06$), all-cause malignancy (29.2% NASH HCC vs. 33.4% non-NASH HCC, $p = 0.07$), or HCC recurrence-related death (14.6% vs. 16.7%, $p = 0.26$). Additionally, there were no differences in the proportion of deaths from all-cause malignancy or specifically from HCC recurrence between NASH and non-NASH HCC, according to the pre-transplantation subgroup analysis within and beyond the Milan criteria. There were differences in the proportions of each of the causes of death between the UNOS and UHN populations, with significantly greater risk for cardiovascular deaths in the US populations, and significantly greater risk HCC-related deaths in the UHN population (Supplemental Digital Content 6, Table 4a, b),

Competing risk cause-specific analysis was also performed. On univariate analysis, NASH patients had a higher risk for cardiovascular death (HR 1.50, 95% CI 1.21–1.87, $p < 0.001$), although this difference was not observed on multivariable analysis (HR 1.24, 95% CI 0.87–1.55, $p = 0.16$) (Table 4). Both univariate and multivariable analyses demonstrated that NASH patients were at a lower risk of liver-related death (multivariable HR 0.57, 95% CI 0.34–0.98, $p = 0.04$). There was no difference in death secondary to HCC recurrence based on NASH status (univariate $p = 0.26$; multivariable $p = 0.23$).

Discussion

Liver transplantation for NASH HCC indications continues to rise. Our retrospective study of 20,672 patients who underwent LT for HCC within the United States and UHN from 2008 to 2018 demonstrated a significant increase in the proportion of NASH HCC associated transplants. This confirms previous findings by others.[8,9,14,26,29] Furthermore, our study demonstrates no differences in post-transplant survival between NASH and non-NASH HCC populations, overall, and within or beyond Milan criteria. Additionally, there were no difference in cardiovascular-related or HCC recurrence-related cause of death, but NASH HCC patients had lower risk for liver-related deaths.

With the growing obesity epidemic, the mounting burden of NASH liver disease and associated HCC has become increasingly recognized in the literature. Studies have demonstrated that with the advent of direct-acting antivirals, improved efforts have been

Table 3 Multivariable Cox regression model analysis of patient survival for all patients who underwent liver transplantation for HCC (n = 15,181)

	HR	95% CI	P value
Male (ref. female)	1.11	1.03–1.20	0.01
Transplant year	0.96	0.95–0.97	<0.001
Recipient age	1.02	1.02–1.03	<0.001
MELD (ln)	1.22	1.13–1.32	<0.001
AFP			<0.001
AFP 0–20 ng/ml	1.00		
AFP 21–400 ng/ml	1.41	1.31–1.51	<0.001
AFP >400 ng/ml	2.11	1.82–2.45	<0.001
Beyond Milan (pre-transplant)	1.49	1.29–1.72	<0.001
CIT (ln)	1.09	1.01–1.18	0.03
BMI (ln)	0.88	0.73–1.06	0.18
Donor type			0.13
DBD	1.00		
DCD	1.14	1.00–1.29	0.04
Living donor liver transplant	1.01	0.75–1.35	0.94
NASH	1.04	0.92–1.18	0.54
Region UHN (ref. US)	0.93	0.77–1.13	0.47

Abbreviationshepatocellular carcinoma (HCC), hazard ratio (HR), confidence interval (CI), model of end stage liver disease (MELD), alpha fetoprotein (AFP), cold ischemia time (CIT), body mass index (BMI), donor by brain death (DBD), donor by cardiac death (DCD), non-alcoholic steatohepatitis (NASH), United States (US), University Health Network (UHN).

Table 4 Univariate and multivariable Cox regression analysis for the risk of overall death and cause-specific death associated with NASH in patients who underwent liver transplantation for HCC (ref non-NASH HCC)

Univariate (N = 20,672)	**HR**	**P value**
Overall (any cause)	0.99 (0.90–1.10)	0.94
Cardiovascular death	1.50 (1.21–1.87)	<0.001
Liver-related death	0.52 (0.34–0.79)	0.002
HCC recurrence death	0.86 (0.67–1.12)	0.26
All other deaths[a]	0.99 (0.88–1.13)	0.94
Multivariable (N = 15,181)[b]	**HR**	**P value**
Overall (any cause)	1.04 (0.92–1.18)	0.54
Cardiovascular death	1.24 (0.87–1.55)	0.16
Liver-related death	0.57 (0.34–0.98)	0.04
HCC recurrence death	1.21 (0.89–1.65)	0.23
All other deaths	1.01 (0.86–1.18)	0.91

Abbreviationsnon-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), hazard ratio (HR).
[a] Deaths secondary to causes other than cardiovascular, liver-related, or HCC recurrence.
[b] Multivariable model adjusted for sex, transplant year, recipient age, model of end stage liver disease, alpha fetoprotein, pre-transplant Milan criteria, cold ischemia time, body mass index, donor type, region.

made to screen and treat HCV(7). This, in conjunction with an increased prevalence of obesity and metabolic syndrome, has led to a decrease in LT and waitlist registrations for underlying HCV liver disease, with an increase for NASH-associated liver disease.[7] One study examining UNOS data demonstrated that in 2016, NASH surpassed HCV as the leading cause for waitlist registrations in the 1945–1965 birth cohort.[29] Additionally, a large study of over 125,000 patients registered for LT demonstrated NASH to be the leading cause for waitlist registration and liver transplantation in females.[8] Despite this, HCV continues to prevail as the leading etiology of HCC-related liver transplants and listings at this time.[7,29] However, the number of liver transplant registrants with NASH-associated HCC has increased over time in conjunction with the rising obesity trend.[30] There is now a greater prevalence of NASH HCC, particularly in younger birth cohorts, which will have a considerably unrecognized future impact on the demand for liver transplantation.[30]

The NASH population is a unique population that tends to be older,[14] with higher BMI, and higher rates of cardiovascular disease and diabetes.[13,31] A national cohort study by Tovikkai et al.[32] highlighted that transplant recipients with cardiovascular disease had significantly higher mortality at all time points in the post-transplantation setting. In relation, several studies have highlighted a potential bias against patients with NASH for LT (3, 12, 13). Patients with NASH HCC undergoing liver transplant evaluation are often more likely to be declined from transplantation (36.1% NASH vs. 15.7% non-NASH, $p < 0.001$)[13] or less likely to receive liver transplantation[3,12] due to their increased medical comorbidities. However, a study by Danford et al., demonstrated no differences in outcomes between the two groups while on the waitlist or post-transplantion.[13]

Though our study is limited in the lack of listing or waitlist outcomes, we similarly demonstrate no differences in NASH HCC vs. non-NASH HCC outcomes in the post-transplantation setting. We showed this to be true in the overall merged UNOS and UHN populations. However, it is also important to note that there are baseline differences in the two populations. This is particularly true in terms of HCC characteristics (higher tumor burden and more patients transplanted beyond Milan criteria in the UHN population) and LDLT access (also expectedly higher in UHN) (Supplementary Content 2, Tables 2a and 2b). Despite these baseline differences, there is also no statistically significant difference in post-transplant survival between NASH HCC and non-NASH HCC in the UHN population ($p = 0.10$) or UNOS population ($p = 0.74$ (Supplementary Content 4, Fig. S1).

Additionally, our subgroup analysis shows that post-transplant survival between NASH HCC and non-NASH HCC is similar for patients transplanted within and beyond the Milan criteria. Other studies have supported similar overall long-term survival outcomes between NASH and non-NASH HCC after patients have undergone transplantation.[15,26] Although our study was limited by the lack of availability of recurrence data, there were no differences in the number of deaths related to HCC

recurrence between the NASH HCC and non-NASH HCC groups both within and beyond the Milan criteria. Additionally, there were no differences in deaths secondary to HCC recurrence on cause-specific multivariable regression analysis. Overall, studies to date comparing NASH HCC versus non-NASH HCC population post-transplant have suggested improved overall survival in NASH patients, but have been limited for recurrence data.[33] However, one recent retrospective study from the UNOS database of 7461 patients with HCC (1405 NASH and 6086 non-NASH), who underwent liver transplantation between 2012 and 2020, demonstrated similar 5-year post-transplant recurrence-free survival, but lower 5-year recurrence rate of HCC in NASH versus non-NASH patients (5.80% vs. 9.41%, p = 0.01).[34] Similarly, other studies have suggested that NASH HCC status may be more protective for post-transplantation disease-free survival.[15,16,31]

One potential explanation for this is that NASH HCC may have less aggressive tumour biology, or less aggressive disease at the time of transplantation, compared to non-NASH HCC.[16,34,35] AFP level is often correlated with tumour aggressiveness in HCC, and studies have demonstrated lower AFP levels in NASH HCC versus non-NASH HCC.[34,35] Furthermore, studies have demonstrated that NASH HCC patients may have a more favourable explant pathology, particularly in tumours exceeding the Milan criteria, with regards to presence of metastasis or vascular invasion, and degree of tumour differentiation.[16] In our study, median AFP level was similarly lower in NASH HCC 5.0 (3.0–10.0), compared to non-NASH HCC 9.0 (4.0–27.0) (p < 0.001), which is in keeping with results of previous studies. Additionally, our study included 10,292 patients for whom explant data was available. A significantly greater proportion of NASH HCC patients were transplanted beyond Milan criteria, compared to non-NASH HCC, suggesting worse disease burden in the NASH HCC population at the time of transplantation.

Due to limitations of the available data, our study was unable to evaluate or account for the pre-transplant diagnosis of cardiovascular disease in association with NASH HCC. However, competing risk analysis with long-term follow up (Supplemental Digital Content 5, Fig. 2) did not demonstrate a difference between NASH HCC and non-NASH HCC in the risk for cardiovascular-related deaths post-transplantation on multivariable Cox regression analysis. On the other hand, NASH HCC patients had a lower risk for liver-related deaths (i.e. deaths secondary to liver disease/failure, recurrent hepatitis, graft failure/rejection, biliary tract complications, vascular thrombosis). This may in part be due to majority (64.8%) of the non-NASH HCC population having hepatitis C virus as the main etiology of liver disease, followed by alcoholic liver disease (11.3%). Patients with NASH HCC have been shown to have less severe liver dysfunction at the time of HCC diagnosis, when compared to HCC in the background of HCV or alcoholic liver disease.[31]

To the best of our knowledge, our study is the largest comparison of post-transplantation outcomes between NASH and non-NASH HCC liver transplant recipients. However, this study has some limitations. First, there were missing pre-transplantation and explant pathology data (Supplemental Digital Content 7, Table S5), and lack of granular data in the UNOS database. There was no data available for variables that can impact survival, including presence of cardiovascular comorbidities, and the use of immunosuppression. Additionally, there was limited information available on HCC recurrence as a post-transplantation outcome. Data was only available for cause of death secondary to HCC recurrence in the UNOS database. Second, given the difficulty of diagnosing NASH in the absence of a biopsy, there are differences in how NASH is defined or diagnosed between various centres[36] and limitations in the availability of the listing diagnoses or reporting of NASH within the various centres and population databases. Third, selection bias exists, as the Canadian dataset stemmed solely from a single institution (UHN), due to the lack of an adequately available multi-centered HCC dataset within Canada.

Additionally, NASH patients may be at higher risk to develop HCC in the absence of cirrhosis, and HCC may be more aggressive in patients in NASH. Consequently, NASH HCC patients may be less likely to be eligible for liver transplantation due to larger tumors at diagnosis, more likely to receive bridging therapy, or more likely to be removed from the waiting list due to tumor progression. An intention-to-treat analysis taking into account waiting list mortality/removal would be more attractive, however, this dataset is limited to post-transplant survival outcomes. It does not provide listing or allocation data for NASH HCC patients. Nonetheless, the equivalent post-transplant overall survival outcomes for NASH HCC vs. non-NASH HCC demonstrated by our large retrospective study, highlights the need for future large multicentre prospective cohort studies comparing OS and disease-free survival outcomes between the two groups.

The global obesity epidemic has significant implications for liver transplantation and organ allocation. The proportion of liver transplantations performed for NASH HCC continues to rise annually and is projected to become a leading indication for liver transplantation for HCC. Although the subset of NASH patients tends to be older, have higher BMI, and have many medical comorbidities, there are no significant differences in the post-transplant overall survival between the NASH HCC and non-NASH HCC groups, irrespective of the Milan criteria. Thus, our study supports equivalent organ allocation towards curative intent for HCC, irrespective of NASH status.

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Author contribution

LR: Conception of the project, literature review, data analysis, interpretation of results, and writing of the manuscript.

CFMP: Conception of the project, interpretation of results, statistical analysis, and writing of the manuscript.

TI: Data acquisition, interpretation of results, and write up of the manuscript.

MPAWC: Data acquisition, interpretation of results, and write up of the manuscript.

BEH: Interpretation of results, statistical analysis, and write up of the manuscript.

DW: Interpretation of results, and write up of the manuscript.

PDY: Conception of the project, interpretation of results, and writing of the manuscript.

GS: Conception of the project, literature review, data analysis, interpretation of results, and writing of the manuscript.

Ethics statement

Institutional review board (IRB) approval was previously obtained for retrospective data collection from the University Health Network population. The use of UNOS data did not require ethical approval as it entails deidentified data from a publicly available database.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.01.019.