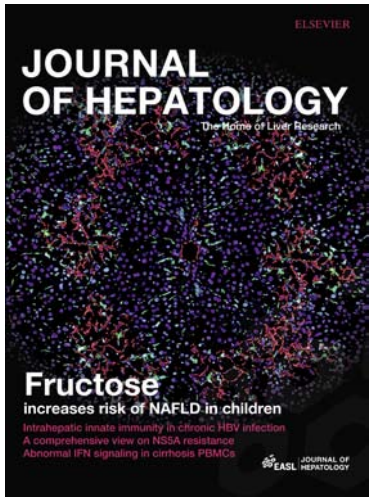

Outcomes of Liver Transplantation for Non-alcoholic Steatohepatitis: a European Liver Transplant Registry Study

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Title: Outcomes of Liver Transplantation for Non-alcoholic Steatohepatitis: a European Liver Transplant Registry Study

Short Title: Liver Transplantation for NASH in Europe

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Y Tokat	Nothing to declare
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Author Contributions:

D Haldar	Study concept and design, analysis and interpretation of data, statistical analysis, and writing of manuscript
B Kern	Study concept and design, acquisition of data, drafting of manuscript, revision of manuscript
J Hodson	Statistical analysis and critical revision
M J Armstrong	Critical revision of the manuscript for intellectual content. Significant contribution to final revisions.
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S Schneeberger	Study concept and design, critical revision of the manuscript for intellectual content, study supervision

Abbreviations

AiLD	autoimmune liver disease
ARLD	alcohol-related liver disease
BMI	body mass index
CC	cryptogenic cirrhosis
CI	confidence interval
DBD	donation after brainstem death
DCD	donation after circulatory death
ELTR	European Liver Transplant Registry
HBV	hepatitis B virus
HCC	hepatocellular cancer
HCV	hepatitis C virus
HR	hazard ratio
INR	international normalized ratio
IQR	interquartile range
LT	liver transplantation
MELD	Model for End-Stage Liver Disease
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NHSBT	National Health Service Blood and Transplant
OR	odds ratio
UK	United Kingdom
UNOS	United Network of Organ Sharing

USA United States of America

Abstract:

Background & Aims: Little is known about outcomes of liver transplantation for patients with non-alcoholic steatohepatitis (NASH). We aimed to determine the frequency and outcomes of liver transplantation for patients with NASH in Europe and identify prognostic factors.

Methods: We analyzed data from patients transplanted for end-stage liver disease between January 2002 and December 2016 using the European Liver Transplant Registry database. We compared data between patients with NASH versus other etiologies. The principle endpoints were patient and overall allograft survival.

Results: Among 68,950 adults undergoing first liver transplantation, 4.0% were transplanted for NASH – an increase from 1.2% in 2002 to 8.4% in 2016. A greater proportion of patients transplanted for NASH (39.1%) had hepatocellular carcinoma (HCC) than non-NASH patients (28.9%, *P*<.001). NASH was not significantly associated with survival of patients (HR 1.02, *P*=.713) or grafts (HR 0.99; *P*=.815) after accounting for available recipient and donor variables. Infection (24.0%) and cardio/cerebrovascular complications (5.3%) were the commonest causes of death in NASH patients without HCC. Increasing recipient age (61-65 years: HR 2.07, *P*<.001; >65: HR 1.72, *P*=.017), elevated MELD (>23: HR 1.48, *P*=.048) and low (<18.5kg.m^{-2}: HR 4.29, *P*=.048) or high (>40kg.m^{-2}: HR 1.96, *P*=.012) recipient BMI independently predicted death in patients transplanted for NASH without HCC. Data must be interpreted in the context of absent recognised confounders, such as pre-morbid metabolic risk factors.

Conclusions: The number and proportion of liver transplants performed for NASH in Europe has increased from 2002 through 2016. HCC was more common in patients transplanted with NASH. Survival of patients and grafts in patients with NASH is comparable to that of other disease indications.

Key words: ELTR database; etiology; long-term follow up; prognosis

Lay Summary: NASH is a growing indication for liver transplantation in Europe, with good overall outcomes, although careful assessment for risk factors is required to maintain favorable post-transplant outcomes.

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased dramatically, in parallel with the worldwide increase in obesity and diabetes[1,2]. Approximately a quarter of the European adult population have NAFLD, representing an increase of 10% since 2005[3].

Non-alcoholic steatohepatitis (NASH) and any associated fibrosis, confer a greater risk of liver-related morbidity and mortality amongst patients with NAFLD[4]. NASH is an increasingly common indication for liver transplantation (LT), and is now second only to alcohol-related liver disease (ARLD) in the United States of America (USA)[5]. Similarly, NASH accounts for an increasing proportion of patients undergoing LT in the UK (4% in 1995; 12% in 2013)[6]. However, pan-European data to describe the burden of NASH on transplantation services are lacking.

Given the frequent co-existence of obesity, diabetes and related co-morbidities, patients with NASH requiring LT are considered to be at a higher risk[7]. In contrast to the USA[8–10], European reports of post-transplant outcomes of NASH have been limited to single center datasets[11]. in the absence of well-validated contraindications it remains a challenge to effectively risk-stratify patients with NASH being considered for LT[7].

We have undertaken a comprehensive analysis of liver transplantation using a prospectively updated pan-European database (N=68,950) to determine the frequency

and outcomes of patients transplanted for NASH. Building on this assessment, we have identified variables that predict a risk of poorer clinical outcome following LT for NASH.

Patients and Methods

Study Population

We performed a retrospective cohort analysis of all adult patients (> 18 years old) who underwent primary LT for chronic liver disease between 1 January 2002 and 31 December 2016 using the European Liver Transplant Registry (ELTR) database. A study request was reviewed and approved by the ELTR data committee. The ELTR prospectively collects LT data from 174 centers in 33 countries and ensures data quality and validity by annual audit and cross checking with key European Organ Sharing Organizations as previously described[12–14].

Data were analyzed for patients transplanted for ARLD, hepatitis C virus infection (HCV), hepatitis B virus infection (HBV), autoimmune liver disease (AiLD) (including primary sclerosing cholangitis, primary biliary cholangitis and autoimmune hepatitis), cryptogenic cirrhosis (CC), NASH and "other" including non-B, non-C chronic viral hepatitis, polycystic liver disease, Wilson's disease, hereditary haemochromatosis and alpha-1-antitrypsin deficiency. The cohort included patients who had hepatocellular cancer (HCC) on the background of these chronic liver diseases (ELTR database code E1: "Cancers – Hepatocellular carcinoma, cirrhosis"). The primary liver diagnosis stated in the ELTR database was used to assign diagnoses in these analyses; secondary diagnoses were disregarded unless the primary diagnosis was HCC or cryptogenic, for which the secondary diagnosis was considered as the primary. Furthermore, patients with a primary diagnosis of NASH and a secondary diagnosis of ARLD in the ELTR database were assigned a diagnosis of ARLD for the study.

For the purposes of this study, patients coded as having cryptogenic disease (ELTR database codes D10 “Cirrhosis – other cirrhosis specify”, D11 “Cirrhosis – cryptogenic unknown cirrhosis” and E1 [as above] without a second diagnosis in the ELTR) were designated as “presumed” NASH if their body mass index (BMI) was ≥30 $kg.m^{-2}$, or CC if their BMI was <30 $kg.m^{-2}$. As such, the NASH cohort comprised patients with “pure” NASH, defined as those coded as NASH in the ELTR database (F91: “Metabolic disease – NASH”), and those with “presumed” NASH as described above[8–10,15,16].

Recipient factors analysed included age at transplant, sex, height, weight, BMI, blood group, primary liver diagnosis, presence of HCC, serum creatinine, serum bilirubin, international normalized ratio (INR) and the Model for End-stage Liver Disease (MELD) score. Creatinine, bilirubin and INR had high frequencies of missing data (>50%), and thus were not used as independent variables in analyses, but contributed to MELD when possible. Of note, other metabolic risk factors including smoking, type 2 diabetes, hypertension, hyperlipidemia and a prior history of ischaemic heart disease were not included in the dataset. Donor factors included age at death/donation, sex, BMI, blood group, and type of donor (donation after circulatory death (DCD), donation after brainstem death (DBD), living related donor, domino donor).

Outcome domains comprised of patient and graft survival status, re-transplant rates, duration of follow up and causes of death, as coded in the ELTR database. Primary

causes of death were used for analyses. Secondary, tertiary and un-coded free-text causes of death were considered if the primary cause was coded as other or unknown.

Only data from a patient's first LT were analysed.

Patient and overall allograft survival were the principle endpoints. Overall allograft survival was calculated from the date of primary LT to the date of re-transplantation or date of death (event) or the date of last follow up during the period when the transplant was still functioning (censored). Death-censored graft survival was not reported due to the high proportion of deaths from unknown causes (28.7% overall; 42.2% NASH, 28.2% non-NASH) which may have made this outcome subject to informative censoring.

For the purpose of survival outcomes analyses and cause of death analyses, patients were subdivided into cohorts defined by the presence or absence of concomitant HCC.

The primary comparison of interest was between patients transplanted for NASH and those transplanted for other indications (non-NASH).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, N.Y., USA), with *P*-values of <0.05 deemed significant throughout.

Parametric continuous variables were summarized with means and standard deviations, and groups compared by independent Student *t*-test, whereas non-parametric continuous variables were summarized by median and inter-quartile range (IQR), and groups compared by Mann-Whitney U test. Categorical variables were summarized with frequencies and percentages, and groups compared by chi-squared test.

Survival outcomes were compared between groups using Kaplan-Meier curves and log-rank tests. Hazard ratios were calculated using univariable Cox regression models. Multivariable Cox regression models were produced to determine whether NASH was independently predictive of patient outcome, after accounting for other confounding factors. A backwards stepwise approach was used to select factors for inclusion in the final model, whereby variables with a significance of $P>0.10$ were iteratively excluded from the input model. All available and clinically relevant factors were included in the input models. Where NASH was excluded due to non-significance, it was added into the final model alongside the factors identified as significant by the stepwise procedure. The analysis was then repeated for the subgroup of patients transplanted for NASH, to identify independent predictors of patient survival in this cohort.

For the purposes of Cox regression analyses continuous variables were converted to categorical fractions based on conventional thresholds (e.g. WHO classification of BMI), or to yield relatively equal numbers of patients in each bracket (in the absence of a widely accepted convention). Hazard ratios (HR) from regression analyses were expressed relative to a reference category defined either by the group that was closest to

physiological normal, the group estimated to have the lowest associated mortality or the largest group (HR=1). Specifically, for the model that was produced to identify independent predictors of patient survival in NASH patients, risk was assigned against a recipient BMI of 25-30 $kg.m^{-2}$ (N=233), rather than 18.5-25 $kg.m^{-2}$ (N=71) due to there being significantly fewer patients in that bracket, and the recognised curvilinear association between BMI and mortality, whereby the perceived lowest risk has shifted to a value between 25 and 30 $kg.m^{-2}$ in more recent years[17].

Cases with missing data were excluded on a per-analysis basis. However, three key variables had a significant number of missing values – MELD (31.4%), recipient BMI (33.7%), and donor BMI (30.2%). We ensured maximal case inclusion in the multivariable analyses by including the cases with the missing values by assigning them to a separate "missing" category.

The frequencies of deaths due to specific causes were apportioned relative to the total number of deaths in patients transplanted for a specific indication. Cause-specific survival analyses were then performed using univariable Cox regression models, with comparisons between NASH and non-NASH recipients.

Results

Prevalence of NASH as an indication for liver transplantation over time

After exclusions, 68,950 patients underwent a primary LT for chronic liver disease in the study period (Figure 1). NASH was the primary indication in 2,741 patients (4.0%), and ARLD was the most common indication (22,226; 32.2%). The proportion of transplants performed for patients with NASH increased significantly over time from 1.2% in 2002 to 8.4% in 2016 (*P*<0.001) (Figure 2, Supplementary Table 1).

Characteristics of transplant recipients and donors

In comparison to patients transplanted for other indications (Table 1), recipients with NASH were older (median: 60 vs. 55 years, *P*<0.001) and had a greater BMI (mean: 32.6 $kg.m^{-2}$ vs. 25.8 $kg.m^{-2}$, *P*<0.001). HCC was more common in recipients transplanted for NASH (39.1% vs. 28.9%, *P*<0.001). Moreover, the proportion of patients with underlying NASH amongst those transplanted with HCC increased from 1.3% in 2002-04, to 8.3% in 2014-16 (*P*<0.001) (Supplementary Figure 1). Patients with NASH received organs from donors who were marginally older (median: 53 vs. 52 years, *P*=0.030), more likely to be male (62.3% vs. 57.6%, *P*<0.001) and of a greater BMI (26.9 $kg.m^{-2}$ vs. 25.5 $kg.m^{-2}$, *P*<0.001) and received more DCD organs (6.6% vs. 2.6%, *P*<0.001). However, after adjusting for the increase in use of DCD organs over time, the rates of DCD use were similar in transplants for NASH and non-NASH indications (OR 1.53 (0.21-11.11), *P*=0.677; Supplementary Table 2). Subgroup analyses divided by patients with and without HCC identified similar recipient and donor differences between NASH and non-NASH groups (Supplementary Table 3).

Patient survival outcomes after liver transplantation

There was no significant difference in post-LT patient survival between NASH and non-NASH recipients (Figure 4), either for recipients without (HR 1.10, 95% CI 0.99-1.22, Table 2) or with HCC (HR 1.09, 95% CI 0.97-1.23, Supplementary Table 4). Amongst those without HCC, recipients with NASH (N=1,667) had equivalent post-LT survival to patients with ARLD (N=17,505, HR 0.95, 95% CI 0.85-1.06) and better survival than those with HCV (N=9,007, HR 1.27 (1.14-1.42), *P*<0.001) (Table 2, Figure 3 panel A). For those with HCC, survival in recipients with NASH (N=1,073) was marginally worse than ARLD (N=4,715, HR 0.87 (0.76-0.99), *P*=0.034), but was similar to HCV (N=7,114, HR 1.07, 95% CI0.94-1.21) and CC (N=3,229, HR 0.93, 95% CI 0.81-1.06) (Supplementary Table 4, Figure 3 panel B).

On multivariable Cox regression, several recipient and donor characteristics were found to be significantly associated with post-LT survival (Table 2, Supplementary Table 4). Upon adjusting for these factors, NASH was not found to be a significant independent predictor of patient survival, either in patients without (HR 0.97, 95% CI 0.86-1.09) or with (HR 1.10, 95% CI 0.97-1.24) HCC. Combining the HCC groups to analyze the cohort as a whole returned similar results (HR 1.02, 95% CI 0.93-1.11) (Supplementary Figure 2 panel A, Supplementary Table 5).

Graft survival outcomes after liver transplantation

On univariable analysis, post-LT graft survival (overall allograft survival) for recipients with NASH was comparable to those with non-NASH indications amongst patients without (HR 1.06, 95% CI 0.96-1.17) and with HCC (HR 1.02, 95% CI 0.91-1.15) (Figure 5, Supplementary Table 6). Analyzing the cohort as a whole returned consistent results (HR 1.06, 95% CI 0.98-1.14) (Supplementary Figure 2, Supplementary Table 5).

Upon adjusting for significant determinants in multivariable Cox regression analyses (Supplementary Table 5, Supplementary Table 6), NASH was not found to be a significant independent predictor of graft survival, either in patients without (HR 0.98, 95% CI 0.88-1.09), with (HR 1.02, 95% CI 0.90-1.15), or independent of HCC (HR 0.99, 95% CI 0.91-1.08).

Causes of death after liver transplantation

Of patients who died after LT for NASH (N=631) and non-NASH (N=16,989) indications, a significant proportion died from unknown causes (NASH: N=266, 42.2%; non-NASH: N=4,799, 28.2%; overall = 28.7%).

In recipients without HCC (Supplementary Table 7), infection (N=86, 24.0%), and cardio/cerebrovascular complications (N=19, 5.3%) comprised the top two known causes of death in patients transplanted for NASH. Infection (N=2,512, 21.6%; HR 1.15 (0.92-1.42), *P*=0.216) and cardio/cerebrovascular complications (N=937, 8.1%; HR 0.70 (0.44-1.10), *P*=0.123) were also major causes of death in recipients transplanted for non-NASH

indications, occurring at similar rates to those observed in NASH. There was a notable excess of death from extrahepatic (non-HCC) solid organ malignancy in those transplanted for ARLD (N=603, 12.9% vs. N=9, 2.5%), and recurrent disease in those transplanted for HCV (N=651, 21.5% vs. N=2, 0.6%), compared to NASH recipients. These are reflected in the considerably lower risk of death from extrahepatic malignancy (HR 0.41 (0.21-0.79), *P*=0.008) and recurrent primary liver disease (HR 0.08 (0.02-0.33), *P*<0.001) in NASH than in pooled non-NASH recipients.

Amongst patients with concomitant HCC (Supplementary Table 8), recurrent HCC (N=53, 19.5%), infection (N=28, 10.3%) and extrahepatic solid organ (non-HCC) malignancy (N=18, 6.6%) were the top three causes of death in patients transplanted for NASH. All three were also prominent causes of death in those transplanted for other indications, although there was again a notable excess risk of death from recurrence of primary (non-malignant) liver pathology in those transplanted for HCV (N=468, 20.8%) and ARLD (N=85, 6.9%) compared to NASH recipients (N=6, 2.2%; *P*<0.001).

Factors that influence overall survival in patients who are transplanted for NASH

For patients transplanted for NASH in the absence of HCC, a number of recipient (age, sex, blood group, BMI, MELD) and donor (blood group) characteristics were found to be associated with post-LT survival (Table 3). Subsequent multivariable Cox regression modeling revealed that older recipient age (61-65 years: HR 2.07 (1.39-3.08); >65 years: HR 1.72 (1.10-2.71); relative to ≤45 years), and MELD score >23 (HR 1.48 (1.04-2.30);

relative to ≤11) carried an increased risk of post-LT mortality. In addition, eccentric recipient BMI was also associated with poorer post-LT survival; an effect that was more pronounced at the extremes (≤18.5 $kg.m^{-2}$: HR 4.29 (1.01-18.21); 18.5-25 $kg.m^{-2}$: HR 2.24 (1.27-3.96); >40 $kg.m^{-2}$: HR 1.96 (1.16-3.32); relative to 25-30 $kg.m^{-2}$). Male recipient gender (HR 0.79 (0.63-0.98); *P*=0.031), and blood group B donor organs (HR 0.37 (0.22-0.63); relative to blood group A) offered a comparative survival advantage.

For patients with NASH and concomitant HCC, none of the available variables were found to be significantly associated with survival on either univariable or multivariable analyses (Supplementary Table 9).

Discussion

This study finds the proportion of transplants for patients with NASH has risen to now account for 8.4% of annual transplants in Europe, and reflects rates published from national datasets[18,19]. The trends are in keeping with those seen in the US where NASH accounts for more than 18% of transplants[8,10,20,21]. The magnitude of the impact of NASH on transplant services in the US may forecast the future burden in Europe in heed of the projected rise of obesity across the continent[1,2,22]. However, wide intra-continental variations in risk factor profiles may limit the local applicability of pan-European data[23,24]. Further to the effect of risk-factors, a greater awareness of NASH, and greater confidence amongst transplant physicians to make a diagnosis based on phenotypic associations may also contribute to the greater proportion of transplants[25]. However, the effects of ascertainment bias in our study are unlikely to be significant in the absence of a commensurate decrease in transplants performed for CC.

There remains controversy in the way large databases establish diagnoses of NASH and CC[25]. In keeping with other large database studies, and to facilitate meaningful comparisons between datasets, we have chosen CC patients with a BMI>30kg.m^{-2} as our presumed NASH cohort[8–10,15,16]. We acknowledge that ascites and edema contribute to the BMI and are not corrected for in the ELTR, though this is also a limitation of using other large registry databases[8]. 57.3% of our NASH study cohort were “presumed NASH” which is comparable to data from the US; between 45.2%[8] and 67.5%[9] of the NASH cohorts using the UNOS database were “presumed NASH”. However, the differences in the characteristics and outcomes between pure and presumed NASH (Supplementary

Table 10, Supplementary Figure 3, 4 and 5) highlight that NASH patients are still a heterogeneous population and systematically identifying high and low risk subsets based on recipient and donor characteristics as highlighted in Table 3, is of critical importance.

A greater proportion of recipients with NASH were transplanted for HCC than non-NASH recipients (Table 1). Our findings were in keeping with a recent analysis of the US Scientific Registry of Transplant Recipients database[26], in which the authors describe an 7.7-fold increase in the prevalence of NASH in patients transplanted for HCC between 2002 and 2016. A number of studies have suggested that patients with NASH are at greater risk of developing HCC[16,21,27], owing partly to the risks associated with obesity and insulin resistance[28–30]. NASH-related HCC is major worldwide concern and left unchecked may offset the anticipated declines in primary liver cancer through the control of HBV and HCV[31].

Amongst the NASH cases, there was a difference in the rates of HCC between the pure NASH (28.5%) and presumed NASH (47.1%) cohorts (Supplementary Table 10), due to incorporating the orphan E1 ELTR code (Cancers – Hepatocellular carcinoma, cirrhosis; no secondary diagnosis) in to the cryptogenic cohort[8]. The rate of HCC in CC (at the exclusion of obese patients) was 46.1% (Supplementary Table 11).

As with other registry studies, readers of our data should be mindful of the potential influence of missing data points, despite the vast number of cases included in the study. As described in our Methods, a significant proportion of cases in our dataset had missing

data for one of MELD, recipient BMI or donor BMI. There were statistically significant differences in patient characteristics between cases with and without missing data points (Supplementary Table 12). We utilized a "missing-indicator" method to maximally utilize the available cases and minimize any loss of statistical power in our multivariable analyses. We compared patient survival in those with available data against those with missing data. The cases with a missing recipient BMI did not confer a bias to overall patient survival (univariable Cox regression; HR 1.01, 95% CI 0.98-1.04, *P*=0.485) compared to cases with available values. Cases with missing MELD (HR 0.93, 95% CI 0.90-0.96, *P*<0.001) and donor BMI (HR 0.90, 95% CI 0.87-0.93, *P*<0.001) did carry a weighted risk, although the effect was small. Moreover, we compared multivariable models using the missing-indicator method and an "available case analysis" method whereby only cases without missing observations are included, and found no significant differences to key outcomes (Supplementary Table 13 & 14). The influence of the incomplete data is a recurrent limitation of registry database studies and although different statistical methods to account for the effect of missing data are widely used, they each carry an inherent bias. Best practice on the statistical methods should be incorporated across registries and ideally stated in the standard operating procedures of registries.

There were no significant differences in post-LT deaths due to infection and cardio/cerebrovascular events between NASH and non-NASH recipients without HCC. Conclusions drawn from these data should be tempered in knowledge of the 28.7% of cases in which the causes of death were unknown. However, the loss of data quality with

duration of follow up is pervasive to large databases; an analysis of the United Network of Organ Sharing (UNOS) database noted that 24% of deaths that occurred 5 years or later after transplantation were from unknown causes[32]. The size of the database cohorts may allow for a higher tolerability towards missing data points, but it remains a limitation. By comparison, a recent meta-analysis of six single- and two-center studies demonstrated an excess of deaths from sepsis (OR 1.71) and cardiovascular causes (OR 1.65) in the NASH cohort[20].

NASH was not found to be an independent predictor of patient or graft survival. These results add to a growing body of evidence that suggest current practice in patient selection and peri-operative care results in acceptable outcomes for such patients, and reflect good utility of donor organs[6,10,20]. Nevertheless, our findings demand scrutiny of assessing transplant risk based on recipient age and BMI. The risk attributed to older recipients is particularly pertinent as a growing proportion of transplants are being performed on elderly recipients in both the US and Europe[33]. Moreover, the risk carried by recipients with lower BMI may reflect the independent effects of a catabolic and sarcopenic phenotype[34]. However, the associations at both extremes of BMI are based on relatively few patients (N=77 for BMI ≤25 $kg.m^{-2}$; N=92 for BMI >40 $kg.m^{-2}$, cp. N=233 for BMI 25-30 $kg.m^{-2}$). Critical variables including pre-LT comorbidities, and in particular components of metabolic syndrome, may have influenced prognostic determinants in our analysis and significantly added to the power of our model[11,35]. None of our measured variables were found to be associated with post-LT mortality in recipients with HCC, which suggests that HCC-specific factors that reflect the burden of disease are likely to have a critical influence

on post-transplant outcomes[36]. Tumor specific factors have only been collected by the ELTR since 2007, and a dedicated study exploring the influence of these factors on post-transplant outcomes has recently been published[37].

Large databases such as ELTR and UNOS were designed to facilitate research but have to compromise between the practicalities of ensuring data collection and the desire to capture relevant data fields. Technological developments to optimize data collection and periodic review of collected fields in response to evolving knowledge comprise potential solutions. Moreover, harmonization of data fields across different registries would allow meaningful comparisons between datasets.

In summary, we report a year-on-year increase of LTs done for NASH in the ELTR region since 2002. The proportion of transplants done for NASH with concomitant HCC is rising, and reflects the widely acknowledged association of NASH with HCC. NASH was not an independent predictor of post-LT patient and graft survival. Nevertheless, careful assessment and selection of patients will be critical to maintain acceptable survival in those transplanted for NASH, with specific scrutiny of female patients, recipients over the age of 60, those with advanced liver disease (MELD>23) and particularly patients with extreme high or low BMI.

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Author names in bold designate shared co-first authorship

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Tables

	NASH N=2,741	**Non-NASH** N=66,209
RECIPIENT CHARACTERISTICS		
Age; years; *median (IQR)***	60 (54-64)	55 (48-61)
Sex: male; *%*	71.1	72.1
Blood group; *%*		
A	43.6	43.6
AB	5.8	5.6
B	13.0	12.7
O	37.6	38.1
BMI; kg.m^{-2}; *mean (SD)***	32.6 (4.6)	25.8 (4.4)
MELD; *median (IQR)*	16 (12-21)	16 (12-22)
HCC; *%* **	39.1	28.9
DONOR CHARACTERISTICS		
Age; *median (IQR)**	53 (39-61)	52 (37-64)
Sex: male; *%***	62.3	57.6
Blood group; *%*		
A	41.8	42.7
AB	4.5	4.2
B	11.2	11.7
O	42.5	41.4
BMI; kg.m^{-2}; *mean (SD)***	26.9 (4.8)	25.5 (4.3)
Type of donor; *%* **		
DBD	84.6	90.4
DCD	6.6	2.6
Domino	0.8	1.0
Living	8.0	6.1

Table 1

Comparison of donor and recipient factors in patients transplanted for NASH and non-NASH indications. **P*<0.05; ***P*<0.001

	Univariable	Multivariable
	HR (95% CI)	
RECIPIENT CHARACTERISTICS		
NASH (vs non-NASH)	*1.10 (0.99-1.22)*	*0.97 (0.86-1.09)*
Cirrhosis aetiology	**Overall****	n/a
NASH	1.00	
ARLD	0.95 (0.85-1.06)	
HCV	**1.27 (1.14-1.42)****	
AiLD	**0.62 (0.56-0.70)****	
HBV	**0.68 (0.60-0.77)****	
CC	1.01 (0.90-1.14)	
Other	**0.70 (0.62-0.80)****	
Age (years)	**Overall****	**Overall****
</=45	1.00	1.00
46-55	**1.24 (1.18-1.31)****	**1.24 (1.18-1.31)****
56-60	**1.46 (1.38-1.55)****	**1.49 (1.41-1.59)****
61-65	**1.74 (1.64-1.85)****	**1.78 (1.67-1.89)****
>65	**1.94 (1.80-2.09)****	**2.04 (1.89-2.20)****
Sex: male	**1.12 (1.07-1.16)****	**1.11 (1.06-1.15)****
MELD	**Overall****	**Overall****
≤11	1.00	1.00
>11, ≤14	0.97 (0.89-1.07)	0.98 (0.89-1.07)
>14, ≤18	0.99 (0.91-1.07)	1.02 (0.94-1.11)
>18, ≤23	1.00 (0.92-1.09)	1.05 (0.96-1.15)
>23	1.48 (1.37-1.60)	**1.52 (1.40-1.64)****
Missing value	1.15 (1.07-1.24)	**1.22 (1.12-1.33)****
Blood group	Overall	**Overall***
A	1.00	1.00
AB	0.98 (0.90-1.06)	**1.18 (1.01-1.38)***
B	0.99 (0.94-1.05)	1.12 (0.95-1.31)
O	1.00 (0.96-1.04)	0.94 (0.84-1.07)
BMI ($kg.m^{-2}$)	**Overall****	**Overall****
≤18.5	**1.20 (1.06-1.36)***	**1.34 (1.18-1.52)****
>18.5, ≤25.0	1.00	1.00
>25.0, ≤30.0	1.00 (0.95-1.06)	0.95 (0.90-1.01)
>30.0, ≤35.0	**1.09 (1.02-1.17)***	1.04 (0.97-1.12)
>35.0, ≤40.0	1.09 (0.96-1.23)	1.06 (0.93-1.21)
>40.0	**1.35 (1.10-1.67)***	**1.35 (1.09-1.67)***
Missing value	1.02 (0.97-1.07)	1.04 (0.98-1.11)
DONOR CHARACTERISTICS		
Age (years)	**Overall****	**Overall****
</=34	1.00	1.00
35-47	**1.19 (1.13-1.27)****	**1.16 (1.09-1.23)****
48-57	**1.30 (1.22-1.37)****	**1.25 (1.18-1.33)****

58-67	**1.45 (1.37-1.54)****	**1.38 (1.29-1.47)****
>68	**1.63 (1.54-1.73)****	**1.52 (1.43-1.62)****
Sex: male	0.99 (0.95-1.03)	not in final model
Blood group	Overall	**Overall***
A	1.00	1.00
AB	0.91 (0.83-1.00)	**0.82 (0.68-0.97)***
B	0.96 (0.91-1.02)	0.90 (0.76-1.06)
O	1.02 (0.98-1.06)	1.07 (0.95-1.21)
BMI (kg.m^{-2})	**Overall****	**Overall****
≤18.5	0.92 (0.80-1.06)	0.91 (0.79-1.06)
>18.5, ≤25.0	1.00	1.00
>25.0, ≤30.0	**1.10 (1.05-1.15)****	1.02 (0.97-1.07)
>30.0, ≤35.0	**1.09 (1.01-1.18)***	1.02 (0.94-1.11)
>35.0, ≤40.0	1.10 (0.95-1.28)	1.02 (0.88-1.19)
>40.0	0.89 (0.69-1.15)	0.85 (0.66-1.10)
Missing value	0.92 (0.88-0.96)	**0.85 (0.80-0.90)****
Type of donor	**Overall****	**Overall****
DBD	1.00	1.00
DCD	**0.68 (0.59-0.79)****	**0.73 (0.62-0.85)****
Domino	1.20 (1.00-1.23)	1.20 (0.99-1.45)
Living	**1.14 (1.05-1.23)****	**1.43 (1.31-1.56)****
OTHER VARIABLES		
Re-transplant	**1.76 (1.67-1.86)****	**1.80 (1.71-1.91)****
Era of transplant	**Overall****	**Overall****
2002-2004	1.00	1.00
2005-2007	1.05 (0.99-1.10)	1.03 (0.98-1.09)
2008-2010	**1.13 (1.07-1.19)****	**1.07 (1.00-1.13)***
2011-2013	1.00 (0.94-1.06)	**0.93 (0.87-0.99)***
2014-2016	**0.87 (0.80-0.93)****	**0.81 (0.75-0.89)****

Table 2

Recipient and donor factors that influence patient survival in transplant recipients without HCC. The final multivariable models based on 47,040 patients. **P*<0.05; ***P*<0.001

	Univariable	Multivariable
	HR (95% CI)	
RECIPIENT CHARACTERISTICS		
Age (years)	**Overall***	**Overall****
≤45	1.00	1.00
46-55	1.17 (0.79-1.76)	1.31 (0.87-1.98)
56-60	1.08 (0.71-1.62)	1.23 (0.81-1.87)
61-65	**1.71 (1.16-2.52)***	**2.07 (1.39-3.08)****
>65	1.50 (0.96-2.33)	**1.72 (1.10-2.71)***
Sex: male	**0.74 (0.60-0.92)***	**0.79 (0.63-0.98)***
MELD	**Overall****	**Overall****
≤11	1.00	1.00
>11, ≤14	0.96 (0.63-1.48)	1.03 (0.66-1.62)
>14, ≤18	**0.65 (0.43-0.98)***	0.66 (0.44-1.06)
>18, ≤23	0.68 (0.44-1.05)	0.71 (0.47-1.15)
>23	1.41 (0.97-2.05)	**1.48 (1.04-2.30)***
Missing value	0.83 (0.52-1.32)	0.93 (0.57-1.51)
Blood group	**Overall***	not in final model
A	1.00	
AB	0.84 (0.53-1.33)	
B	0.56 (0.37-0.85)*	
O	1.02 (0.82-1.27)	
BMI (kg.m^{-2})	**Overall***	**Overall***
≤18.5	2.58 (0.62-10.72)	**4.29 (1.01-18.21)***
>18.5, ≤25.0	**1.98 (1.13-3.47)***	**2.24 (1.27-3.96)***
>25.0, ≤30.0	1.00	1.00
>30.0, ≤35.0	1.22 (0.85-1.74)	1.38 (0.95-2.01)
>35.0, ≤40.0	1.38 (0.92-2.08)	1.43 (0.93-2.18)
>40.0	**1.92 (1.15-3.18)***	**1.96 (1.16-3.32)***
Missing value	0.89 (0.41-1.92)	1.13 (0.49-2.63)
DONOR CHARACTERISTICS		
Age (years)	Overall	not in final model
≤45	1.00	
46-55	1.15 (0.82-1.62)	
56-60	1.15 (0.83-1.59)	
61-65	1.20 (0.85-1.69)	
>65	1.28 (0.88-1.84)	
Sex: male	0.97 (0.78-1.20)	not in final model
Blood group	**Overall***	**Overall***
A	1.00	1.00
AB	0.83 (0.49-1.41)	0.99 (0.58-1.70)
B	**0.39 (0.23-0.65)****	**0.37 (0.22-0.63)****
O	1.05 (0.85-1.31)	1.06 (0.85-1.32)
BMI (kg.m^{-2})		not in final model
≤18.5	1.85 (0.59-5.83)	
>18.5, ≤25.0	1.13 (0.89-1.43)	

>25.0, ≤30.0	1.00	
>30.0, ≤35.0	0.98 (0.70-1.36)	
>35.0, ≤40.0	0.69 (0.34-1.40)	
>40.0	1.15 (0.54-2.45)	
Missing value	0.73 (0.44-1.20)	
Type of donor	Overall	
DBD	1.00	
DCD	0.79 (0.47-1.33)	not in final model
Domino	1.16 (0.29-4.64)	
Living	1.45 (1.02-2.05)	
OTHER VARIABLES		
Era of transplant	Overall	
2002-2004	1.00	
2005-2007	0.90 (0.59-1.37)	
2008-2010	1.18 (0.79-1.76)	n/a
2011-2013	1.09 (0.72-1.63)	
2014-2016	1.13 (0.74-1.71)	

Table 3

Recipient and donor factors that significantly affect post-transplant survival in patients transplanted for NASH without HCC. The final multivariable models based on 1,628 patients. *P<0.05; **P<0.001

Figure Legends

Figure 1

Flow chart of case selection from the ELTR database.

Figure 2

Trends of annual primary LTs performed for different indications in the ELTR region.

Figure 3

Survival analysis for patients undergoing primary liver transplantation for different indications. Kaplan-Meier curves of patient survival for cases without (A), and with (B) HCC (log-rank: *P*<0.001 for both).

Figure 4

Survival analysis for patients with and without HCC undergoing primary LT for NASH and non-NASH indications. Kaplan Meier analysis demonstrated no significant survival differences between patients transplanted for NASH and non-NASH indications amongst those without HCC (log-rank: *P*=0.081) or with HCC (log-rank: *P*=0.155). There is a significant difference between patients transplanted with and without HCC overall (log-rank: *P*<0.001).

Figure 5

Overall allograft survival analysis for patients undergoing primary liver transplantation for different indications. Kaplan-Meier curves of overall allograft survival for cases without (A), and with HCC (B) (log-rank: $P<0.001$ for both).

Figure 1

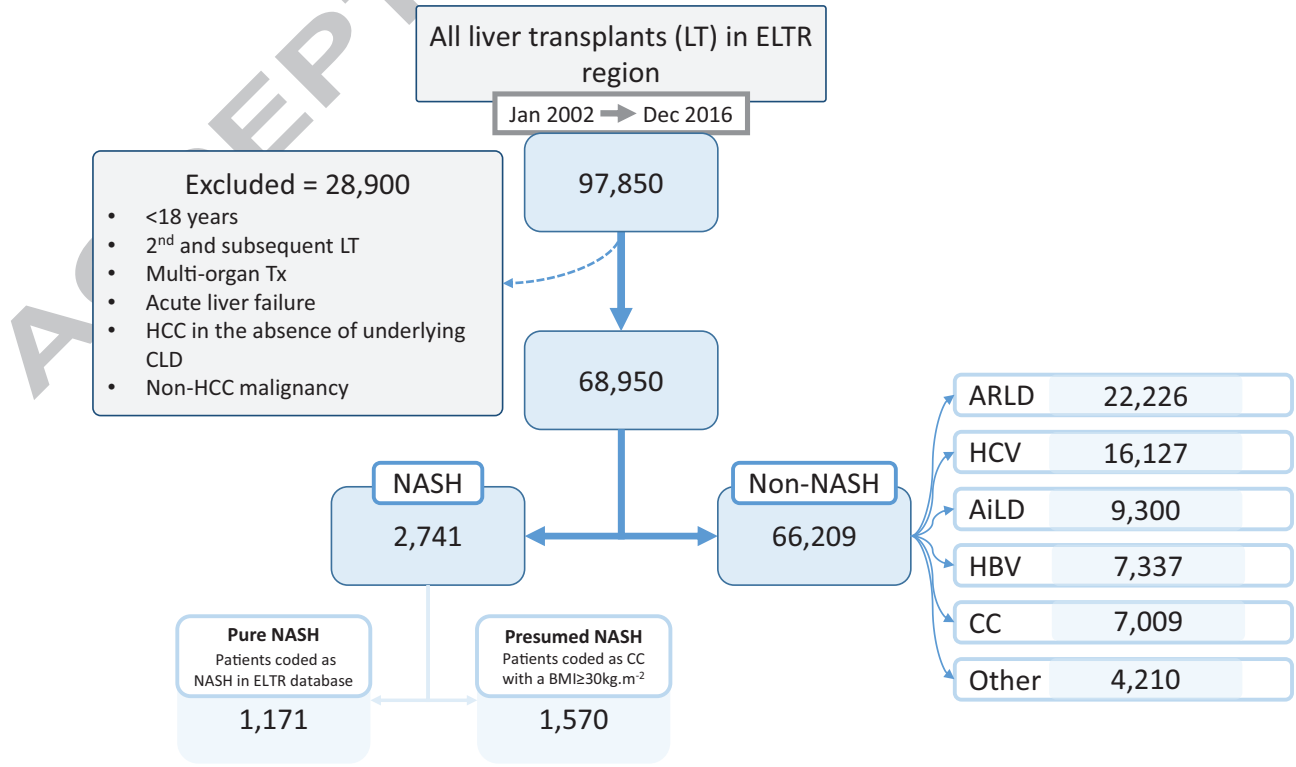


Figure 2

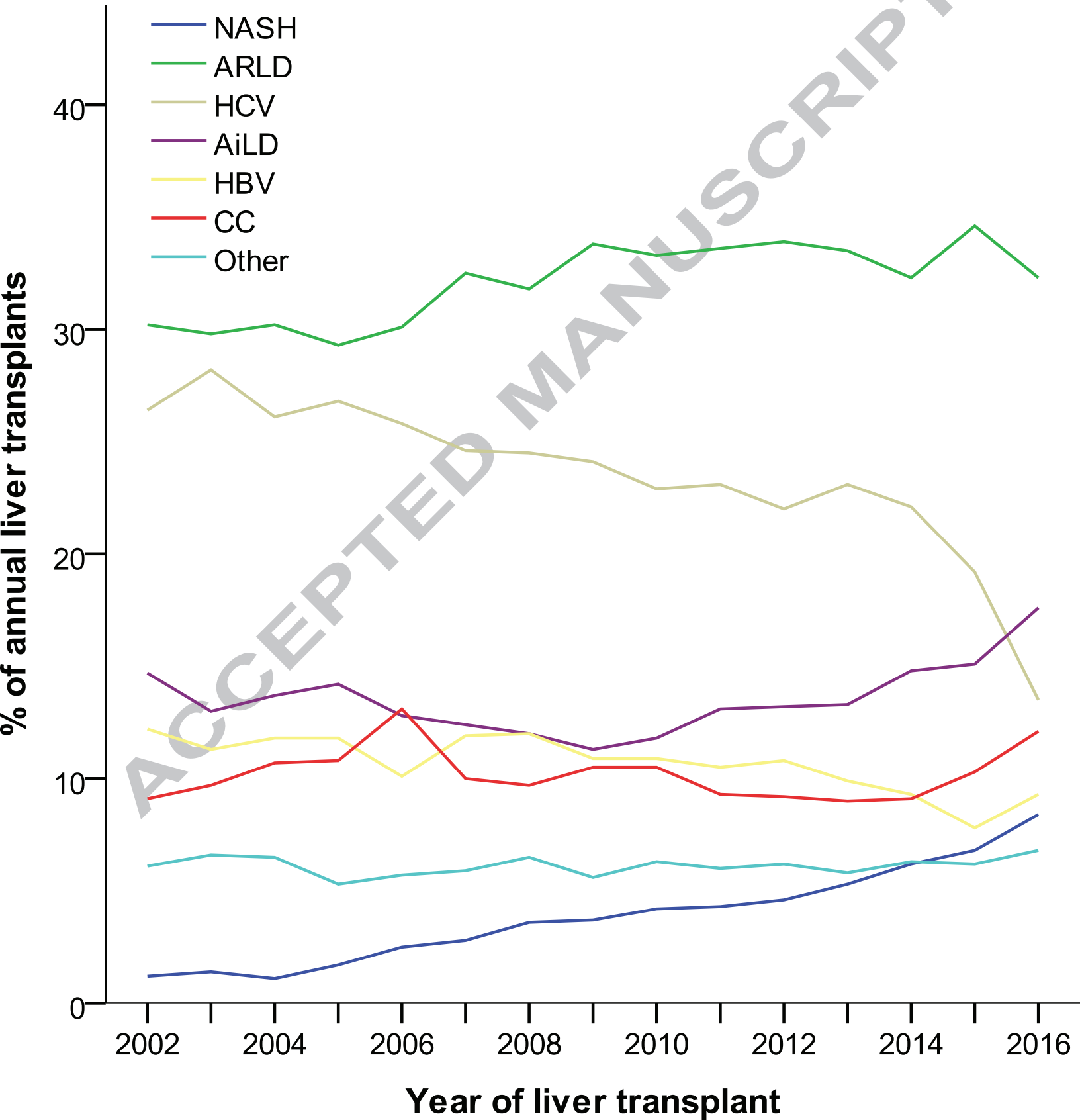
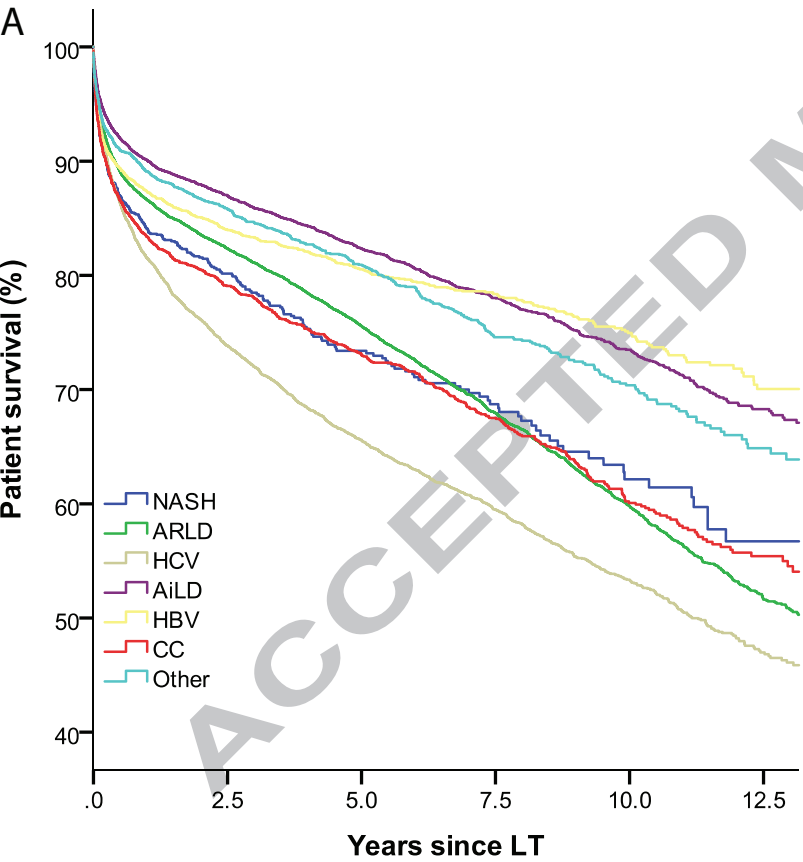
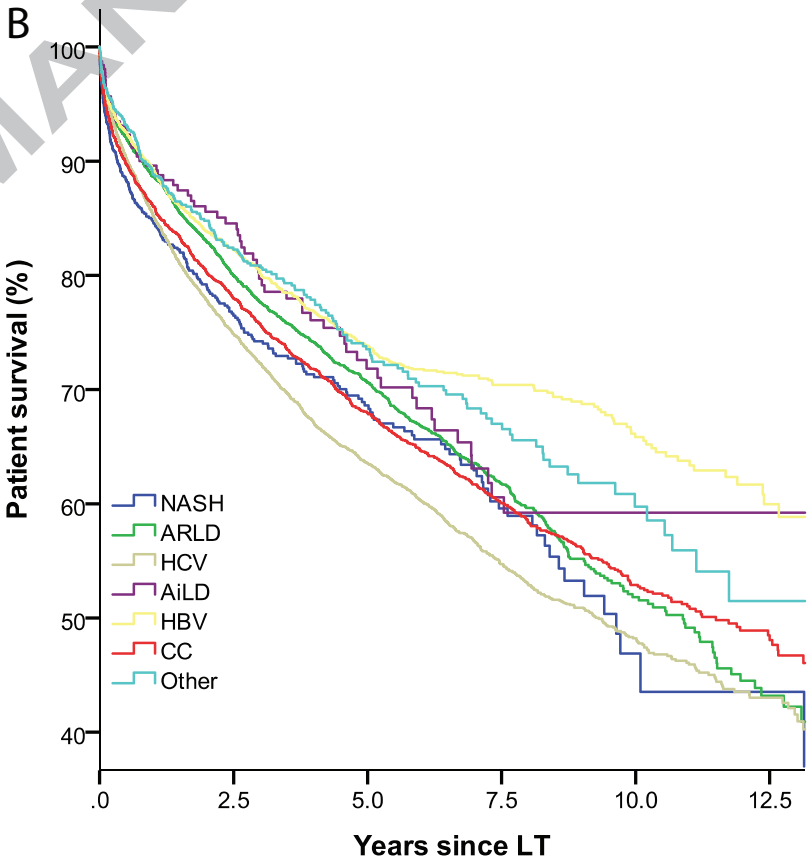


Figure 3

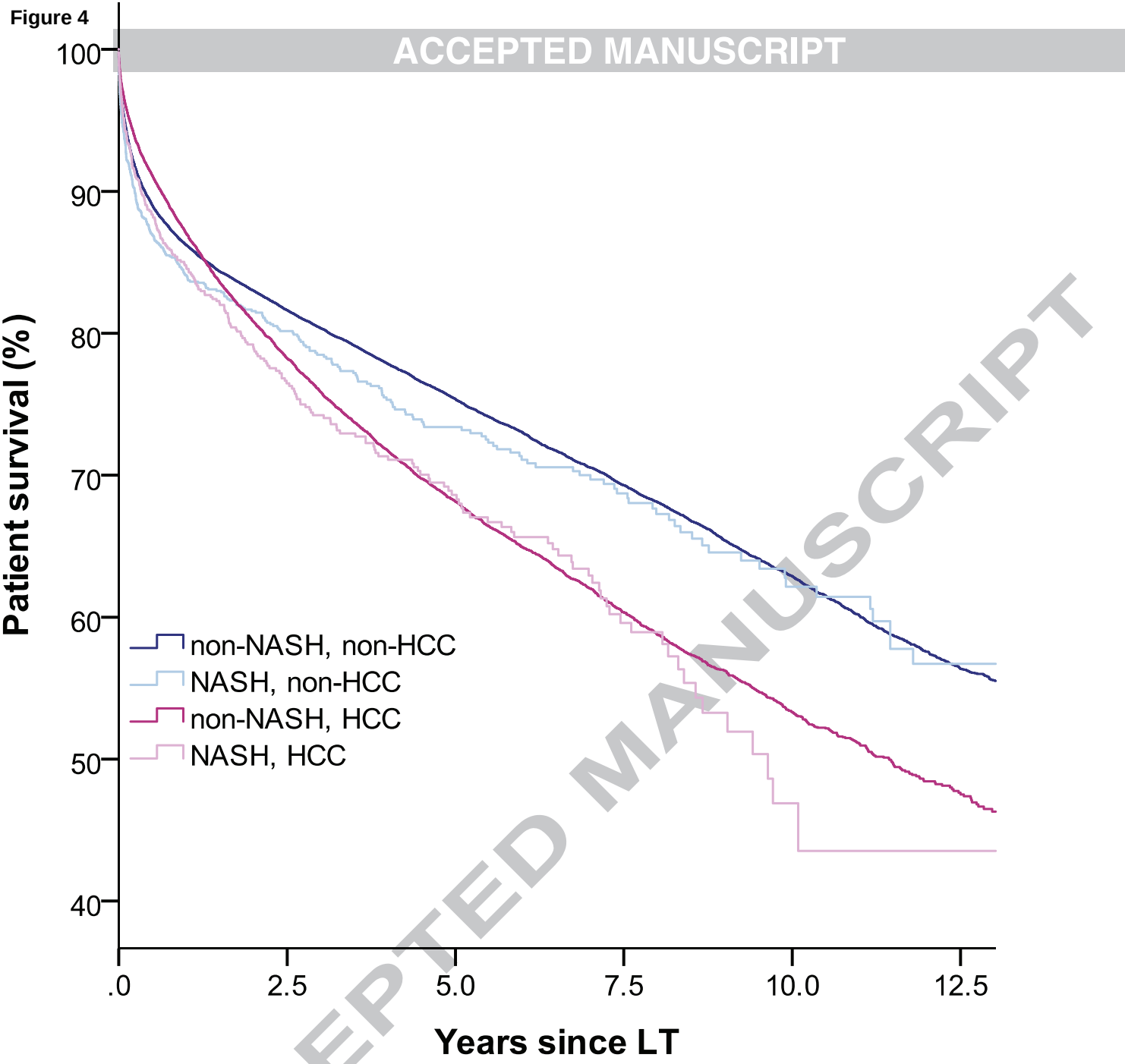




		Patient survival; %			
		Years since transplant			
	At risk; N	1.0	2.5	5.0	10.0
NASH	1667	84.1	78.5	73.4	62.1
ARLD	17505	86.6	82.3	75.5	59.8
HCV	9007	81.5	73.8	65.6	53.3
AiLD	8971	90.1	87.0	82.3	73.5
HBV	4471	87.3	84.0	80.5	75.0
CC	4475	83.4	79.1	73.1	60.1
Other	3777	89.1	85.8	80.9	70.4

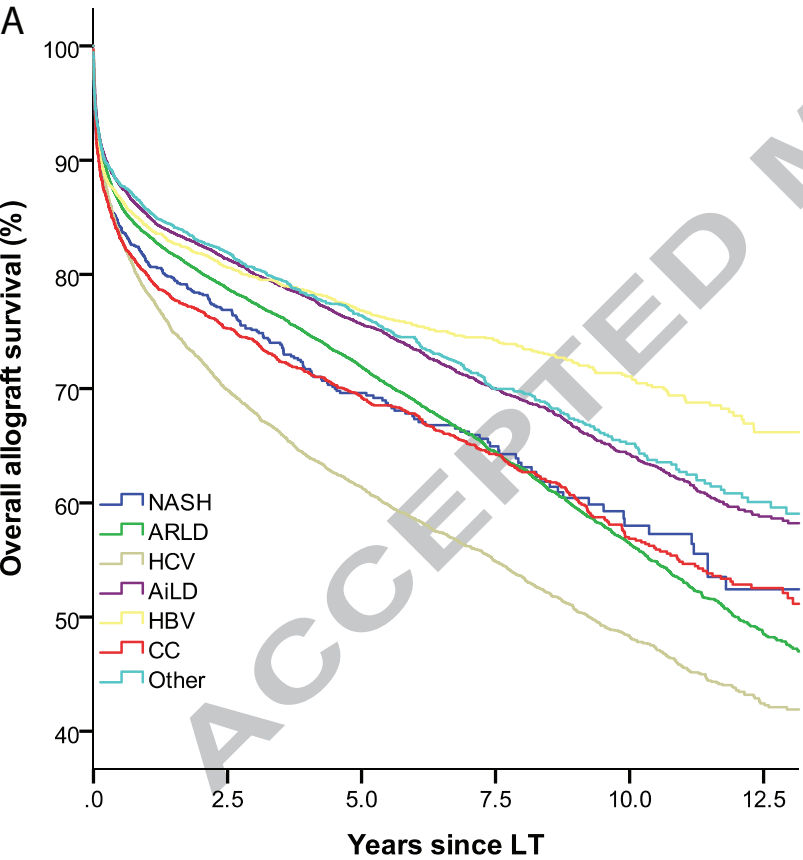
		Patient survival; %			
		Years since transplant			
	At risk; N	1.0	2.5	5.0	10.0
NASH	1073	84.7	76.5	68.6	46.9
ARLD	4715	88.7	80.0	70.6	51.8
HCV	7114	85.2	74.9	63.5	48.2
AiLD	320	89.6	84.6	71.8	59.2
HBV	2855	89.2	82.3	73.8	65.8
CC	3229	86.0	78.0	68.0	52.9
Other	881	88.8	82.3	73.5	59.8

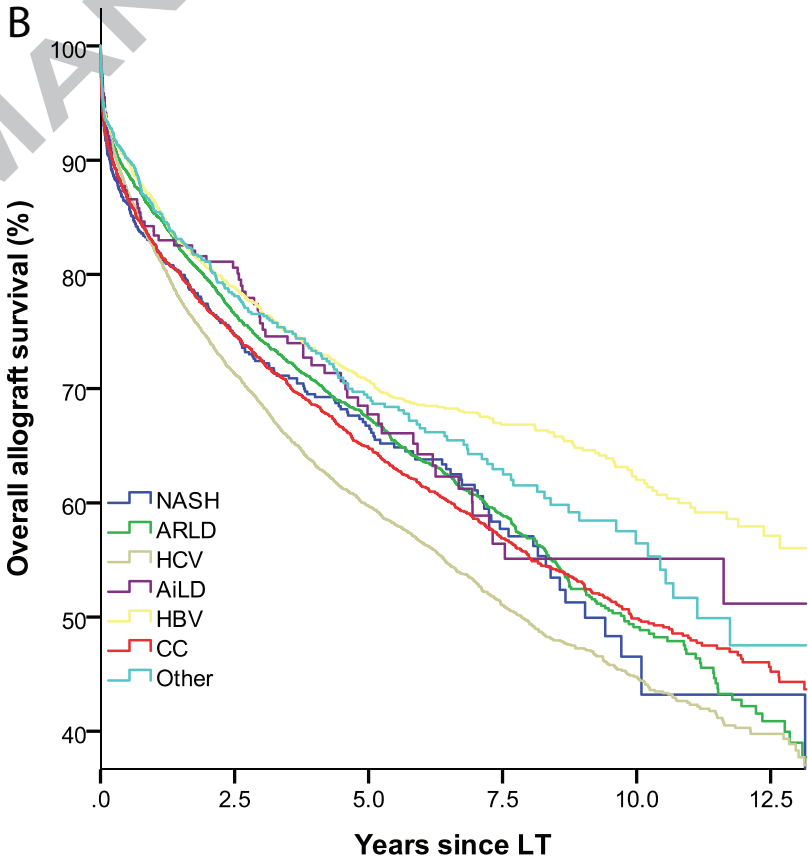
Figure 4



		Patient survival; %			
		Years since transplant			
	At risk; N	1.0	2.5	5.0	10.0
Non-NASH; non-HCC	47063	86.2	81.6	75.4	62.9
NASH; non-HCC	1667	84.1	80.2	73.4	62.1
Non-NASH; HCC	19114	87.0	78.2	68.1	53.3
NASH; HCC	1073	84.7	76.5	68.6	46.9

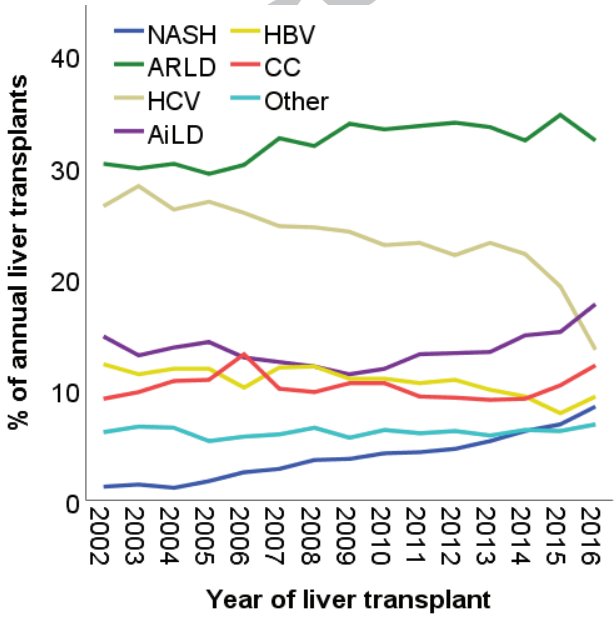
Figure 5

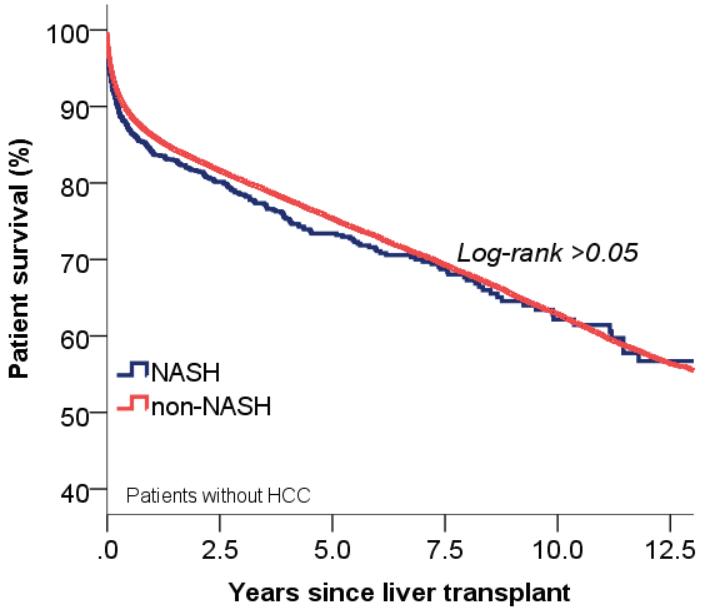




		Patient survival; %			
		Years since transplant			
	At risk; N	1.0	2.5	5.0	10.0
NASH	1667	83.0	72.9	70.0	56.0
ARLD	17505	86.2	81.3	73.6	55.2
HCV	9007	81.1	73.1	63.5	47.9
AiLD	8971	89.1	84.8	77.8	64.2
HBV	4471	86.7	82.6	78.1	59.63
CC	4475	82.8	77.6	70.5	55.5
Other	3777	88.5	84.3	77.7	64.4

		Patient survival; %			
		Years since transplant			
	At risk; N	1.0	2.5	5.0	10.0
NASH	1073	84.5	75.6	66.1	41.4
ARLD	4715	88.1	78.4	68.0	46.5
HCV	7114	84.6	73.6	61.1	42.5
AiLD	320	89.0	82.6	69.5	50.9
HBV	2855	89.0	81.1	71.2	59.4
CC	3229	85.6	77.2	66.3	49.2
Other	881	88.0	80.9	70.5	52.7





Highlights:

- An increasing proportion of patients are being transplanted for NASH in Europe.
- Hepatocellular carcinoma was more common in patients transplanted with NASH.
- Survival in recipients with NASH is comparable to that of other disease indications.
- Age, BMI, and advanced liver disease predicted poorer outcomes in NASH recipients.