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Liver transplantation for NASH cirrhosis is not performed at the expense of major post-operative morbidity

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ABSTRACT

Background: Non-alcoholic steatohepatitis (NASH) is an emerging indication for liver transplantation (LT) and coexists with multiple comorbidities. Obese and cirrhotic patients experience more perioperative complications. Limited data exist about short-term complications after LT for NASH cirrhosis.
Aim: Investigate short-term complications in patients transplanted for NASH cirrhosis.
Methods: Single center retrospective cohort study including patients >18 years who underwent LT between 2009–2015. Exclusion criteria were LT for acute liver failure and non-cirrhotic disease. Post-operative complications and severity within 90-days were classified using the Clavien–Dindo classification of surgical complications and comprehensive complication index (CCI). $P<0.05$ was significant.
Results: Out of 169 eligible patients, 34 patients (20.1%) were transplanted for NASH cirrhosis. These patients were significantly older (59.2 *vs.* 54.8 years, $P=0.01$), more obese (61.8% *vs.* 8.1%, $P<0.01$), had more diabetes mellitus (73.5% *vs.* 20%, $P<0.01$), metabolic syndrome (83.3% *vs.* 37.8%, $P<0.01$) and cardiovascular disease (29.4% *vs.* 11.1%, $P<0.01$). More grade 1 complications (OR 1.64, 95%CI 1.03–2.63, $P=0.04$) and more grade 2 urogenital infections (OR 3.4, 95%CI 1.1–10.6, $P=0.03$) were found. Major complications, CCI, 90-day mortality and graft survival were similar.
Conclusion: Despite significantly increased comorbidities in patients transplanted for NASH cirrhosis, major morbidity, mortality and graft survival after 90 days were comparable to patients transplanted for other indications.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis without excessive alcohol consumption. The spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and ultimately cirrhosis [1]. As a result of the obesity epidemic, NAFLD is an increasingly relevant public health concern and is emerging as the most common cause of chronic liver disease in Western countries. The prevalence of hepatic steatosis is rising and already estimated to be 22% in the Western-European population [2]. The prevalence of NASH was found in 69% of NAFLD patients with an indication for liver biopsy [3]. Progression to fibrosis occurs in 41% of patients with NASH [3] and up to 26% will eventually develop cirrhosis [1,4].

NAFLD is considered to be the hepatic component of the metabolic syndrome (MetS) [5]. As a consequence, these patients suffer from significant cardiovascular disease (CVD) with progressive atherosclerosis [6], and have a substantial increased risk of early morbidity and mortality [3,7]. It is well-known that surgery in obese patients results in more complications; wound infections, sepsis, renal failure and prolonged mechanical ventilation [8,9]. Patients with hepatic steatosis who undergo major hepatic surgery have significantly increased risk of post-operative complications, including death [10]. Furthermore, cirrhosis is an independent major risk factor for in-hospital mortality and prolonged length of hospital stay after elective surgery [11]. The combination of obesity, hepatic steatosis and cirrhotic liver disease may tremendously increase the perioperative risk in patients with NASH cirrhosis.

Due to the rising incidence of obesity, cirrhosis secondary to NASH is expected to become the most important indication for

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liver transplantation (LT) in the near future. Illustrative, an increase of 170% of waitlist registrants with NASH has already been found in the past 10 years [12]. Long-term patient and graft survival of patients transplanted for NASH cirrhosis are comparable to other indications for LT [13–16]. However, limited data and conflicting results exist about the short-term and procedure related complications after LT for NASH cirrhosis [17]. There are indications that patients transplanted for NASH have more short-term complications such as sepsis [13,14], CVD [14,18–21] and hepatic artery thrombosis (HAT) [18]. There is however no universal consensus on short-term post-operative outcomes of patients transplanted for NASH cirrhosis [17]. This is due to heterogeneous studies with different baseline characteristics, methods and relatively small cohort sizes.

Due to the global obesity epidemic it is of great importance to evaluate the impact of NASH cirrhosis on post-operative complications following LT since NASH coexists with numerous comorbidities and risk factors that may affect patient and graft survival. Only few studies have investigated these short-term complications with conflicting results and mainly focus on mortality. Thus, our aim was to investigate whether patients transplanted for NASH cirrhosis are at increased risk for short-term post-operative complications after LT.

2. Materials and methods

2.1. Design and participants

A single center retrospective analysis was performed in all patients undergoing LT at the University Medical Center Groningen, the Netherlands, between January 2009 and December 2015. All procedures were performed in accordance with the 2000 Declaration of Helsinki. Inclusion criteria were patients older than 18 years at time of LT. Exclusion criteria were LT for acute hepatic failure and for non-cirrhotic liver diseases (Fig. 1). Patients aged 70 years and up are not accepted for LT in the Netherlands. Acceptance for LT is addressed at an individual patient level, where comorbid diseases and body mass index (BMI) are taken into account, and discussed in the multidisciplinary transplantation group where the transplant surgeon, anesthesiologist, radiologist and hepatologist make a shared decision.

2.2. Data collection

All medical records of transplanted patients between 2009–2015 were reviewed. Data was retrieved from electronic patient records, including medical (discharge) letters, operation-, anesthesiology- and intensive care unit (ICU) reports, pre-transplant and explant histology reports and biochemical testing results. Recipient and donor characteristics and per- and post-operative variables were collected within a follow-up period of 90-days after LT. The following patient and biochemical characteristics were collected and analyzed; age, sex, weight, height, waist circumference, blood pressure, underlying disease, presence of hepatocellular carcinoma (HCC), renal replacement therapy (RRT), medical history and history of smoking, alcohol and medication use. Operative variables analyzed were transplant year, cold ischemic time, amount of drained ascites, estimated blood loss and transfusion of red blood cells (RBC), fresh frozen plasma (FFP) and platelets. Furthermore, post-operative complications, HAT, primary non-function (PNF), duration of post-transplant ICU stay, total post-transplant length of stay (LOS) and re-transplantation within 90-days were registered. Donor characteristics were also collected; age, sex, weight, height, BMI, cause of death, donation after brain death (DBD) and donation after cardiac death (DCD), length of ICU stay, anti-Hepatitis B core (HBc) status, Epstein–Barr virus (EBV) and cytomegalovirus (CMV) status. Venous blood samples were collected pre- en post-LT. Total bilirubin, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, sodium, fasting glucose, platelets, international normalized ratio (INR), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), CMV and 24 h urine protein and creatinine clearance were analyzed with standardized laboratory measurements and quality assessment control at the Department of Laboratory Medicine of the University Medical Center Groningen, the Netherlands.

2.3. Definition of NASH

NASH was defined by: (1) exclusion of other liver disease, (2) histological evidence of NASH based on liver biopsy before LT or on explant histology after LT, (3) pre-cirrhotic imaging demonstrating hepatic steatosis. When histology was unavailable an international accepted phenotypic diagnosis of NASH was made based on the presence of the following criteria; (4) the presence of MetS [15] or the combination of BMI $\geq$30 kg/m^2 and diagnosis of type 2 diabetes mellitus (T2DM). Patients with other liver diseases causing steatosis (*i.e.* patients with hepatitis or alcoholic liver disease) were classified separately (Fig. 1). To distinguish NASH from alcoholic steatohepatitis excessive alcohol consumption (males >2 and females >1 alcoholic drinks per day [22]) was documented. In the event of any uncertainty about diagnosis of NASH, consensus was obtained by two independent transplant hepatologists.

2.4. Definition of comorbid diseases

Obesity was classified as BMI $\geq$30 kg/m^2. Hypertension was defined as systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg and/or medication use for hypertension. All patients received a cardiovascular assessment according to the 2014 ESC/ESA guidelines on non-cardiac surgery, in which electrocardiography and echocardiography (including contrast enhanced echocardiography for presence of a patent foramen ovale) is advised [23]. The revised cardiac risk index was used to estimate the risk on ischemic heart disease. When there was a high-risk on ischemic heart disease a myocardial perfusion scan was performed. Patients with ischemic heart disease were treated before acceptance for LT, and if not possible, not accepted for liver transplantation. The diagnosis of CVD was confirmed if a patient had myocardial infarction, coronary artery disease, angina pectoris, congestive heart failure, atrial fibrillation, stroke or transient ischemic attack in their pre-transplant medical history. The diagnosis of T2DM was confirmed when a subject had a history of T2DM, used glucose lowering medication or had a HbA1c $\geq$47 mmol/mol. MetS was defined by the revised diagnostic criteria from the American Heart Association by the National Cholesterol Education Program Adult Treatment Panel III [24].

2.5. Calculations, assessment and grading of complications

The model for end-stage liver disease (MELD) was calculated by serum bilirubin, creatinine and INR [25]. The Child-Pugh-Turcotte (CPT) score was calculated by total bilirubin, serum albumin, INR, ascites and hepatic encephalopathy [26].

Complications were defined using the complete and commonly applicable National Cancer Institute's Common Terminology Criteria for Adverse Events, 4.0 [27]. Post-operative complications up to 90-days post LT were classified according to the validated modified classification of surgical complications by Dindo et al. [28]. Crosschecking of complications and grading every complication

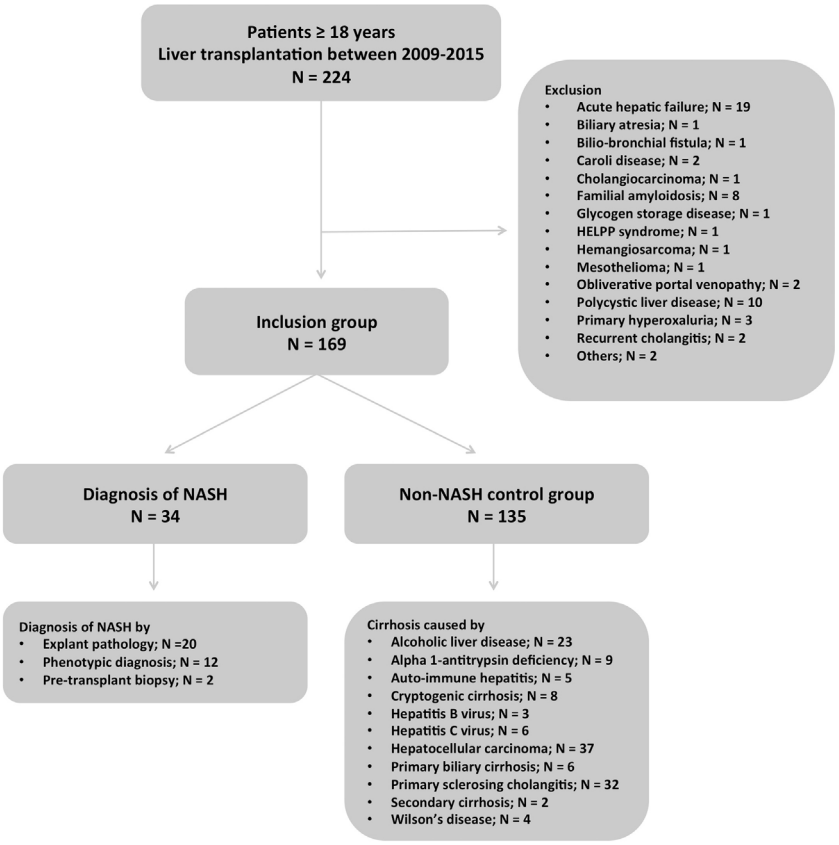

Fig. 1. Flow chart of the study population.

according to the Clavien–Dindo classification was performed by author RD and validated by author VM. Using the Clavien–Dindo classification the comprehensive complication index (CCI) was calculated for each individual patient. This complication index assesses the actual burden of complications on the whole postoperative course [29]. To calculate the CCI, all complications following LT were summarized and computed through the operation risk index approach at www.assessurgery.com. The final index yields a score from 0 (no complication) to 100 (death) [29]. To investigate a potential time-effect in occurrence of complications, an additional analysis, as previously described, was performed with all post-operative complications in total LOS post LT.

2.6. Statistical analysis

Statistical analysis was performed with SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). Normality of distribution was assessed and checked for skewness. Continuous data are expressed in medians with interquartile ranges (IQR) and categorical variables in numbers with percentages. Variables were compared between NASH and non-NASH groups using the Mann–Whitney *U* test, Chi-square test and Fisher's Exact test. Missing values were labeled as user-missing values and excluded from statistical analysis by pairwise deletion. Multivariate binary logistic regression analysis was performed to disclose independent association of NASH on complications and was adjusted for age, sex, transplant year and donor characteristics. Results are presented by odds ratios (OR) with 95% confidence intervals (CI). A Kaplan–Meier survival curve with log-rank test was used for 90-day graft survival after LT. Patients were censored at time of re-transplantation. A *P*-value of <0.05 was considered statistically significant.

3. Results

Between 2009–2015 a total of 224 patients older than 18 years were transplanted. After applying exclusion criteria, the final study group consisted of 169 eligible patients (Fig. 1). The median age of the study group at time of LT was 56.9 years, with a median BMI of 25.9 kg/m^2 and was predominantly male (69.8%). Out of 169 patients, 34 patients (20.1%) were transplanted for NASH cirrhosis. Median MELD score was lower in the NASH group, though not significantly different (14.5 *vs.* 17.0, $P = 0.09$). CPT scores and number of HCC were also not significantly different between groups. Patients transplanted for NASH cirrhosis were older (59.2 *vs.* 54.8 years, $P = 0.01$), more obese (61.8% *vs.* 8.1%, $P < 0.01$), had more T2DM (73.5% *vs.* 20%, $P < 0.01$), hypertension (60.6% *vs.* 30.0%, $P < 0.01$, blood pressure available in 95.2% of patients), MetS (83.3% *vs.* 37.8%, $P < 0.01$, waist circumference available in 69.8% of patients) and CVD (29.4% *vs.* 11.1%, $P < 0.01$). Consequently, in NASH patients antihypertensive medication, statins and glucose lowering medication were more prescribed. Patient characteristics are presented in Table 1. Immunosuppressive regimens were not significantly different between NASH and non-NASH patients (Table 1). There was a trend towards less prednisone use in the NASH group (45.2% *vs.* 65.0%, $P = 0.05$), although this was not significantly different when adjusted for in multivariate analyses ($P = 0.16$). Transplant year was not different between groups (all $P > 0.17$).

More patients in the non-NASH group received livers from DBD donors (68.9% *vs.* 55.9%), although not statistically significant ($P = 0.15$) (Table 2). Donor age, sex, height, BMI, cause of death, length of ICU stay, anti-HBc status, EBV and CMV status were not significantly different between groups (Table 2). Operative characteristics concerning cold ischemic time, drained ascites, blood loss and amount of transfusion of RBC, FFP and platelets during LT were

Table 1
Baseline characteristics.

	NASH (N = 34)	Non-NASH (N = 135)	*P*-value
Baseline characteristics			
Sex: males, *n* (%)	22 (64.7)	96 (71.1)	0.47
Age (years), *median (IQR)*	59.2 (53.5–63.2)	54.8 (47.6–61.2)	0.01
MELD score, *median (IQR)*	14.5 (11.8–17.3)	17.0 (12.0–22.0)	0.09
CPT score, *median (IQR)*	8.0 (7.0–9.3)	9.0 (7.0–10.0)	0.19
Concurrent HCC, *n* (%)	10 (29.4)	37 (27.4)	0.82
BMI (kg/m^2), *median (IQR)*	31.5 (28.6–36.4)	25.3 (23.4–28.1)	<0.01
BMI <20 kg/m^2, *n* (%)	1 (2.9)	6 (4.4)	1.00
BMI ≥30 kg/m^2, *n* (%)	21 (61.8)	11 (8.1)	<0.01
Waist circumference (cm), *median (IQR)*	113.5 (107.0–124.3)	97.0 (87.0–103.0)	<0.01
• Male, *median (IQR)*	114.0 (110.0–122.0	100.0 (90.0–105.0)	<0.01
• Female, *median (IQR)*	109.0 (103.0–129.0)	90.0 (82.0–100.0)	<0.01
Systolic blood pressure (mmHg), *median (IQR)*	130 (110–140)	120 (110–130)	0.18
Diastolic blood pressure (mmHg), *median (IQR)*	68 (60–77)	70 (60–80)	0.53
RRT pre-operative, *n* (%)	1 (2.9)	6 (4.4)	1.00
Smoking, *n* (%)	4 (12.1)	38 (29.7)	0.04
Laboratory tests			
ALT (U/L), *median (IQR)*	28.0 (18.8–43.8)	49.0 (28.0–105.0)	<0.01
AST (U/L), *median (IQR)*	49.0 (33.8–72.5)	82.0 (46.0–144.0)	<0.01
GGT (U/L), *median (IQR)*	58.0 (38.8–96.5)	68.0 (45.0–142.0)	0.21
ALP (U/L), *median (IQR)*	107.0 (97.8–142.3)	148.0 (103.0–226.0)	<0.01
Total bilirubin (μmol/L), *median (IQR)*	31.5 (25.0–58.8)	55.0 (29.0–167.0)	0.02
Albumin (g/L), *median (IQR)*	33.0 (29.8–36.00)	31.0 (27.0–36.0)	0.15
Platelets (×10^9/L), *median (IQR)*	90.5 (75.8–140.8)	90.0 (62.0–139.0)	0.73
INR, *median (IQR)*	1.4 (1.2–1.6)	1.4 (1.2–2.0)	0.34
Sodium (mmol/L), *median (IQR)*	136.5 (134.0–140.3)	137.0 (134.0–140.0)	0.92
Fasting glucose (mmol/L), *median (IQR)*	6.9 (5.8–9.1)	6.0 (5.2–7.3)	<0.01
HDL cholesterol (mmol/L), *median (IQR)*	1.9 (1.1–2.4)	1.0 (0.6–1.3)	0.54
LDL cholesterol (mmol/L), *median (IQR)*	6.9 (5.8–9.1)	2.0 (1.4–2.7)	0.22
Triglycerides (mmol/L), *median (IQR)*	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.60
Total cholesterol (mmol/L), *median (IQR)*	3.0 (2.1–3.9)	3.5 (2.5–4.6)	0.05
24-h urine			
• Proteins (g/24u), *median (IQR)*	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.87
• Creatinine clearance (mL/min), *median (IQR)*	73.0 (29.1–103.0)	72.0 (42.0–114.0)	0.30
Comorbidities			
Type 2 diabetes mellitus, *n* (%)	25 (73.5)	27 (20.0)	<0.01
Hypertension, *n* (%)	20 (60.6)	39 (30.0)	<0.01
Metabolic syndrome, *n* (%)	25 (83.3)	42 (37.8)	<0.01
CVD, *n* (%)	10 (29.4)	15 (11.1)	<0.01
Medication use			
Antihypertensive medication, *n* (%)	6 (17.6)	3 (2.2)	<0.01
Beta-blockers, *n* (%)	6 (17.6)	9 (6.7)	0.08
Statins, *n* (%)	7 (20.6)	4 (3.0)	<0.01
Insulin, *n* (%)	15 (44.1)	13 (9.6)	<0.01
Oral glucose-lowering medication, *n* (%)	11 (32.4)	12 (8.9)	<0.01
Post-operative immunosuppressive regimen			
Tacrolimus, *n* (%)	28 (90.3)	95 (75.4)	0.09
Cellcept, *n* (%)	10 (32.3)	62 (49.2)	0.09
Prednisone, *n* (%)	14 (45.2)	76 (65.0)	0.05
Cyclosporine, *n* (%)	1 (3.2)	15 (11.9)	0.20
Azathioprine, *n* (%)	3 (9.7)	10 (7.9)	0.72
Sirolimus, *n* (%)	5 (16.7)	16 (12.8)	0.56

Data are given in number with percentages (%) or median with interquartile ranges (IQR). For comparison between two groups Mann–Whitney *U* test were used for continuous variables and for binary variables Chi square or Fisher's exact test were used. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. *Abbreviations*: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CVD, cardiovascular disease; CPT, Child-Pugh-Turcotte; GGT, gamma-glutamytransferase; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; RRT, renal replacement therapy, TG, triglycerides.

not significantly different between the NASH and non-NASH group (Table 2).

When looking at complications up to 90-days post-operative (Table 3), patients transplanted for NASH cirrhosis suffered from more grade 1 complications compared with patients in the non-NASH group (47 *vs.* 124 total events, patients with events 76.5% *vs.* 58.5%, $P = 0.02$) and remained significant after adjustment for age, sex, transplant year and donor characteristics (age, sex, BMI, DBD or DCD donor, cause of death, length of ICU stay) in multivariate analysis (OR 1.64, 95%CI 1.03–2.63, $P = 0.04$). Grade 1 complications included: persisting ascites after surgery, pleural effusion and peripheral oedema (requiring diuretics), dyspnea due to pulmonary oedema or atelectasis, albumin administration, non-infectious diarrhea, constipation requiring laxatives or enemas, fever and/or elevated C-reactive protein levels on expectative management, electrolyte disturbances requiring correction, wound infections opened at bedside and/or requiring daily flushing and re-admissions for abnormal liver enzymes or electrolyte disturbances. Grade 2-5 complications were not significantly different between groups. Consequently, CCI (46.1 *vs.* 45.7, $P = 0.61$) was also not significantly different between groups (Table 3). Analysis of subcategorized infections and complications (Table 4) revealed that patients transplanted for NASH cirrhosis were more prone to have urogenital tract infections (grade 2 complication) after

Table 2
Liver transplantation related characteristics.

	NASH (N = 34)	Non-NASH (N = 135)	*P*-value
Donor			
DBD donor, *n* (%)	19 (55.9)	93 (68.9)	0.15
Age (years), *median (IQR)*	54.0 (42.5–62.3)	51.5 (40.8–60)	0.52
Sex: males, *n* (%)	22 (64.7)	78 (57.8)	0.58
Height (m), *median (IQR)*	1.76 (1.70–1.85)	1.75 (1.70–1.85)	0.90
Weight (kg), *median (IQR)*	80.0 (66.3–90.0)	80.0 (70.0–90.0)	0.91
BMI (kg/m^2), *median (IQR)*	24.9 (22.5–27.8)	24.9 (22.8–27.6)	0.76
Cause of death			
• Cerebrovascular accident, *n* (%)	23 (67.6)	81 (60.0)	0.57
• Trauma, *n* (%)	4 (11.8)	26 (19.3)	0.33
• Circulation, *n* (%)	2 (5.9)	10 (7.4)	1.00
• Respiratory, *n* (%)	1 (2.9)	2 (1.5)	0.50
• Meningitis, *n* (%)	1 (2.9)	0 (0.0)	0.21
• Other disorders of the brain, *n* (%)	2 (5.9)	4 (3.0)	0.61
• Domino liver, *n* (%)	0 (0.0)	1 (0.7)	1.00
• Euthanasia, *n* (%)	1 (2.9)	3 (3.0)	1.00
• Suicide, *n* (%)	0 (0.0)	2 (1.5)	1.00
Length of ICU stay (days), *median (IQR)*	2 (1–4)	2 (2–5)	0.21
Anti-HBc positive donor, *n* (%)	0 (0.0)	2 (1.5)	0.47
CMV positive donor, *n* (%)	13 (38.2)	61 (45.9)	0.42
EBV positive donor, *n* (%)	11 (32.4)	30 (22.2)	0.40
Operative			
Cold ischemic time (min), *median (IQR)*	452.5 (421.0–514.3)	432.0 (375.0–506.0)	0.15
Drained ascites (mL), *median (IQR)*	2000 (0–7000)	475 (0–4000)	0.19
Blood loss (mL), *median (IQR)*	3400 (1900–6525)	3000 (2000–5800)	0.80
RBC transfusion (units), *median (IQR)*	3 (1–8)	3 (0–8)	0.65
FFP transfusion (units), *median (IQR)*	0 (0–4)	0 (0–4)	0.42
Platelets transfusion (units), *median (IQR)*	0 (0–0)	0 (0–0)	0.07
Post-operative			
Length of ICU stay (days), *median (IQR)*	3 (1–5)	2 (1–4)	0.34
Post-transplant LOS (days), *median (IQR)*	24.5 (20.0–34.3)	23.0 (16.0–38.0)	0.56

Data are given in number with percentages (%) or median with interquartile ranges (IQR). For comparison between two groups, Mann–Whitney *U* test were used for continuous variables and for binary variables Chi square or Fisher's exact test were used. test were used. *Abbreviations*: BMI, body mass index; CMV, cytomegalovirus; DBD, donation after brain death; EBV, Epstein-Barr virus; FFP, fresh frozen plasma; HBc, Hepatitis B core; ICU, intensive care unit; LOS, length of stay; NASH, non-alcoholic steatohepatitis; RBC, red blood cells.

Table 3
Complications according to the modified Clavien–Dindo classification and comprehensive complication index up to 90-days after liver transplantation.

Clavien–Dindo classification Grade		NASH (N = 34)	Non-NASH (N = 135)	*P*-value
1	Total events	47	124	0.02
	Patients with events, *n* (%)	26 (76.5)	79 (58.5)	0.06
2	Total events	64	253	0.96
	Patients with events, *n* (%)	27 (79.4)	105 (77.8)	0.84
3a	Total events	17	119	0.14
	Patients with events, *n* (%)	12 (35.3)	64 (47.4)	0.20
3b	Total events	7	42	0.35
	Patients with events, *n* (%)	6 (17.6)	34 (25.2)	0.36
4a	Total events	11	44	0.73
	Patients with events, *n* (%)	10 (29.4)	34 (25.2)	0.62
4b	Total events	1	2	0.57
	Patients with events, *n* (%)	1 (2.9)	2 (1.5)	0.49
5	Total events	1	4	1.00
	Patients with events, *n* (%)	1 (2.9)	4 (3)	1.00
Comprehensive complication index				
CCI, *median (IQR)*		46.1 (29.6–57.0)	45.7 (33.5–58.6)	0.61

Modified Clavien–Dindo classification [28] and comprehensive complication index (CCI) [29] was used for grading of complications. CCI was calculated on www.assesssurgery.com. Data are given in total events, patient events with percentages (%) or median with interquartile ranges (IQR). For comparison between two groups, Mann–Whitney *U* test, Chi-square and Fisher's exact test were used. *Abbreviations*: CCI, comprehensive complication index; NASH, non-alcoholic steatohepatitis.

LT (47.1% *vs.* 20.0%, $P < 0.01$), and this remained significant after adjustment for age, sex, transplant year and donor characteristics in multivariate analysis (OR 3.4, 95%CI 1.1-10.6, $P = 0.03$). No differences were found in infections of other etiologies. In addition, there was no difference between the NASH and non-NASH group in the need for re-laparotomies, the occurrence of biopsy proven acute cellular rejection, PNF, development of HAT or re-transplantation within the first 90-days after LT (Table 4). When complications were divided in minor (grade 1–3a) and major (grade 3b–5) complications, 94.1% of patients transplanted for NASH cirrhosis and 89.6% for non-NASH cirrhosis had minor complications and 41.2% *vs.* 42.4% major complications (not significantly differ-

Table 4
Subcategorized post-operative complications up to 90-days after liver transplantation.

	NASH (N = 34)	Non-NASH (N = 135)	*P*-value
Urogenital tract infection, *n* (%)	16 (47.1)	27 (20.0)	<0.01
Respiratory infection, *n* (%)	3 (8.8)	15 (11.1)	1.00
Gastro-intestinal infection, *n* (%)	8 (23.5)	48 (35.6)	0.18
Skin infection, *n* (%)	4 (11.8)	16 (11.9)	1.00
Fever of unknown origin, *n* (%)	6 (17.6)	19 (14.1)	0.60
Sepsis, *n* (%)	4 (11.8)	17 (12.6)	1.00
RRT post-operative, *n* (%)	4 (11.8)	16 (11.9)	1.00
Biopsy proven acute cellular rejection, *n* (%)	1 (2.9)	10 (7.4)	0.70
HAT, *n* (%)	0 (0)	9 (6.7)	0.21
PNF, *n* (%)	0 (0.0)	2 (1.6)	1.00
Re-laparotomy, *n* (%)	5 (14.7)	33 (24.4)	0.22
Re-transplantation, *n* (%)	2 (5.9)	14 (7.4)	0.53

Data are given in numbers with percentages (%). For comparison between two groups Chi-square and Fisher's exact test were used. *Abbreviations*: HAT, hepatic artery thrombosis; NASH, non-alcoholic steatohepatitis; PNF, primary non-function; RRT, renal replacement therapy.

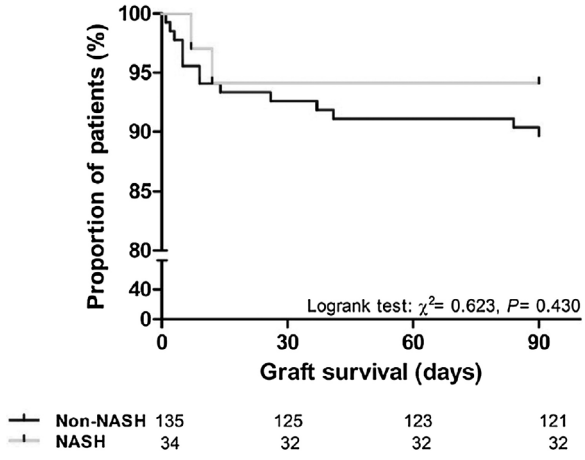

Fig. 2. 90-Day graft survival after liver transplantation for patients with NASH, compared to those transplanted for other reasons (non-NASH).

ent). Post-operative ICU and total LOS (24.5 *vs.* 23 days) were also not significantly different between groups (Table 2). Graft survival 90-days post LT (94.1% *vs.* 89.6%, *P* = 0.43) (Fig. 2) and mortality rate (2.9% *vs.* 3%, *P* = 1.00) were similar for patients with NASH and non-NASH.

An additional sensitivity analysis in which complications of total post-operative LOS (NASH IQR 20–34 days *vs.* non-NASH IQR 16–38 days) were evaluated, demonstrated similar results. In patients transplanted for NASH cirrhosis, post-operative major morbidity and mortality rates in LOS were similar (Supplementary Tables 1 and 2).

4. Discussion

In this study we demonstrate that patients transplanted for NASH cirrhosis are older, more obese, have more T2DM, MetS and CVD. However, despite the presence of increased comorbidities in NASH cirrhosis, major complications, CCI, mortality and graft survival after 90 days were similar with those transplanted for non-NASH cirrhosis.

Our findings that patients transplanted for NASH cirrhosis are older, more obese and have more T2DM, CVD and MetS have been confirmed by previous studies [13,15,30]. Median MELD score of 14.5 for patients transplanted for NASH cirrhosis was lower when compared to previous studies showing a MELD score ranging from 13 to 33 [13–16,18,19]. This difference may be explained by relatively preserved kidney functions within the study group at time of LT, with median creatinine clearance of 73 mL/min, only 2.9% of NASH patients with renal replacement therapy and 1.2% simultaneous liver–kidney transplantation. Other studies reported pre-transplant hemodialysis in 45% of NASH patients [15] and simultaneous liver-kidney transplantation in 28% [19], both resulting in substantial higher creatinine levels and MELD scores. Secondly, MELD scores in our study are probably lower since they were calculated by serum bilirubin, creatinine and INR levels at time of transplantation and exceptional MELD points were not included in the final calculation.

AST, ALT, bilirubin and ALP were significantly higher in the non-NASH group and GGT was, though not statistically significant, increased in the NASH group. This discrepancy could be explained by the origin of liver disease. NASH patients often show replacement of accumulated hepatic fat and inflammation by fibrotic tissue caused by a number of cell death pathways. Apoptosis, autophagic cell death, necrosis, necroptosis and pyroptosis are activated during NASH development and have redundant roles in triggering liver damage and fibrosis [31] and consequential result in less elevated transaminase levels. Moreover, in up to 60% of NASH patients with advanced fibrosis normal ALT levels are found [32]. Additionally, GGT can be elevated in hepatic steatosis [33], whereas GGT and ALP are both elevated in cholestatic liver disease [34].

Donor characteristics; type (DBD *vs.* DCD), age, sex, height, BMI, cause of death, length of ICU stay, anti-HBc status, EBV and CMV status, cold ischemic time, operative blood loss and requirement of transfusion products were not significantly different between patients transplanted for NASH and non-NASH cirrhosis, which is supported by previous studies [13,14]. Agopian et al. reported a significant increase in transfusion of RBC (18 *vs.*14 units) in NASH patients, although an absolute number of blood loss was not described [15]. In our study, median blood loss during transplantation of NASH patients was 3400 mL compared to 3000 mL in the non-NASH group, with a similar median amount of transfused RBC units of 3 per patient. This discrepancy can be explained by the severity of illness of NASH patients prior to transplantation demonstrated by Agopian et al. with higher MELD scores, more pre-transplant hemodialysis (45%), vasopressin use (17%) and mechanical ventilation (16%) before LT and longer post-operative ICU and total LOS [15]. Post-operative ICU stay and total LOS in patients transplanted for NASH cirrhosis in our cohort was not prolonged, which is consistent with previous literature [13,14,19].

Only one other study described post-LT complications using the modified Clavien–Dindo classification. Dare et al. showed that obesity with concomitant T2DM was a strong predictor for post-operative event rate, however NASH was not an independent risk factor. They found similar rates of grade 1 and 2 complications with more wound infections, bacteremia and pneumonias in patients transplanted for NASH cirrhosis [35]. In our study the occurrence of grade 1 complications and urogenital tract infections were significantly increased in patients with NASH cirrhosis. Looking at grade

1 complications into detail, persisting ascites after surgery was one of them. A possible explanation is the higher pre-transplant amount of ascites in the NASH group of 2000 mL (IQR 0–7000 mL) *vs.* 475 mL (IQR 0–4000 mL), $P = 0.19$. However, the number of patients with pre-transplant ascites was similar between the NASH and non-NASH group (71.0% *vs.* 68.3%, $P = 0.77$). Constipation, requiring laxatives or enemas, was also more present in the NASH group. The presence of T2DM and autonomic neuropathy of the enteric nervous system could be a potential cause [36]. A higher rate of urogenital tract infections in the NASH group could also be explained by the presence of T2DM. Poor control of diabetes, impaired renal function due to diabetic glomerulosclerosis, impaired neutrophil function in the presence of urinary glucose and increased residual urine secondary to diabetic neuropathy, are thought to increase the susceptibility of urogenital tract infections [37].

Major morbidity was not significantly different between the NASH and non-NASH group. Recent data on 56,995 adult LT patients, using the United Network for Organ Sharing-Standard Transplant Analysis and Research dataset, was reviewed where similar risk of all-cause and cardiovascular-related mortality was described after adjusting for BMI and diabetes mellitus [38]. Heuer et al. reported that 15% of patients transplanted for NASH cirrhosis required a re-laparotomy due to bleeding or biliary complications, which is similar to our findings of 14.7% [39]. In contrast to Heuer et al. our study also focused on graft survival and mortality rates in patients transplanted for other indications. These numbers are similar in both groups which was confirmed by recent other studies [13,15,19,35].

Additionally, the CCI was calculated and showed no difference between post-operative burden of morbidity for patients transplanted for NASH cirrhosis compared with patients transplanted for other indications. The CCI has been recently developed and accounts for all post-operative complications to better assess the actual burden of complications on the whole post-operative course. Recording complications individually and reporting only the most severe one, as usually done in most studies fails to provide information about the cumulative (overall) morbidity. The CCI informs on all complications balancing their weight by severity. This sensitive and clinically relevant endpoint seems key in enabling longitudinal assessment of cumulative morbidity [40]. Hence, CCI better reflects the burden of all combined post-operative complications in surgical patients than the Clavien–Dindo classification score alone, which incorporates only the most severe complication [29].

Our study has several strengths. This study is the first in its kind describing short-term complications and graft survival after LT for NASH cirrhosis and other indications in a detailed fashion. The complications have been precisely scored by using the modified Clavien–Dindo classification of surgical complications providing a comprehensive analysis of complications based on therapeutic consequences of complications. In combination with the CCI, it constitutes an objective approach for the assessment of surgical outcomes.

However, some limitations need to be taken into consideration. First, this is a cross-sectional analysis of a cohort study, thus cause-effect relationships cannot be established with certainty. Second, the retrospective design comes with well-known limitations such as missing values and inaccurate registration of complications. Dindo et al. previously examined that surgical residents only report 80% of complications in the first post-operative period [41]. In our study, this potential bias was diminished because data were extracted from medical discharge letters from the consultant transplant hepatologist and intensivist. In addition, a well-trained independent researcher scored all reported complications which is known to have higher sensitivity scores of 97% with identification of complications [41], and subsequently, these scores were double-checked by an independent transplant surgeon. Finally, due to missing values for liver histology there might be some misclassification regarding the underlying etiology of cirrhosis. In case of missing histological diagnosis (liver biopsy before LT or explant histology after LT), NASH was defined by a phenotypic diagnosis by the presence of MetS as was previously used [15]. In cases with missing waist circumference, a BMI $\geq 30\ kg/m^2$ and concomitant T2DM was accepted as defining NASH. We believe that this effect is of limited influence on presented results.

In conclusion, this study has demonstrated that in patients transplanted for NASH cirrhosis post-operative major morbidity and mortality rates are comparable with patients transplanted for other indications, despite increased (minor) grade 1 post-operative complications and urogenital tract infections. These results are comforting considering the expected increase of patients with NASH cirrhosis in the near future. Future analysis regarding the recurrence of NAFLD, development of long-term complications, long-term graft patency and occurrence of comorbid diseases after LT is mandatory to better understand the natural history and risk profile of NASH patients and to prevent and treat its complications.

Disclosure statement

The authors have nothing to disclose.

Conflict of interest

None declared.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2017.08.022.

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