Post-Transplant Obesity Impacts Long-Term Survival after Liver Transplantation

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Post-transplant obesity impacts long-term survival after liver transplantation

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ABSTRACT

Background: Short-term survival after orthotopic liver transplantation (OLT) has improved over the past decades, but long-term survival remains impaired. The effects of obesity on long-term survival after OLT are controversial. Because pre-transplant body mass index (BMI) can be confounded by ascites, we hypothesized that post-transplant BMI at 1 year could predict long-term survival.

Methods: A post-hoc analysis was performed of an observational cohort study consisting of adult recipients of a first OLT between 1993 and 2010. Baseline BMI was measured at 1-year post-transplantation to represent a stable condition. Recipients were stratified into normal weight (BMI < 25 kg/m^2), overweight (25 ≤ BMI ≤ 30 kg/m^2), and obese (BMI > 30 kg/m^2). Kaplan-Meier survival analyses were performed with log-rank testing, followed by multivariable Cox proportional hazards regression analysis.

Results: Out of 370 included recipients, 184 had normal weight, 136 were overweight, and 50 were obese at 1-year post-transplantation. After median follow-up for 12.3 years, 107 recipients had died, of whom 46 (25%) had normal weight, 39 (29%) were overweight, and 22 (44%) were obese (log-rank $P = 0.020$). Obese recipients had a significantly increased mortality risk compared to normal weight recipients (HR 2.00, 95% CI 1.08–3.68, $P = 0.027$). BMI was inversely associated with 15 years patient survival (HR 1.08, 95% CI 1.03–1.14, $P = 0.001$ per kg/m^2), independent of age, gender, muscle mass, transplant characteristics, cardiovascular risk factors, kidney- and liver function.

Conclusion: Obesity at 1-year post-transplantation conveys a 2-fold increased mortality risk, which may offer potential for interventional strategies (i.e. dietary advice, lifestyle modification, or bariatric surgery) to improve long-term survival after OLT.

1. Introduction

Orthotopic liver transplantation (OLT) is the life-saving treatment for patients suffering from end-stage liver disease [1]. Although short-term survival has improved over the past decades, long-term survival remains impaired. Overall 1- and 5-year survival rates after OLT are 90% and 70% respectively [2,3], whereas 20-year survival rate is approximately 50% [4]. This emphasizes the importance to identify risk factors for long-term outcomes in OLT recipients. Several risk factors have already been shown to impair long-term outcomes after OLT, such as primary liver disease [5,6], older recipient and donor age [5–7], as well as the livelong dependency on chronic immunosuppression therapy [8], which predisposes to the development of de novo malignancies [9], renal dysfunction [10,11], hypertension [2,12], new onset of diabetes mellitus [13,14], and hyperlipidaemia [12]. However, the effects of overweight and obesity on long-term survival after OLT remain contradictory [15].

Overweight and obesity are characterized by an abnormal or excessive fat accumulation that may impair health and is measured by the body mass index (BMI) [16]. In the general population, overweight and obesity are a major problem. Overall, in 2016, approximately 39% of the world's adult population was overweight, and 13% were obese [16]. Furthermore, the worldwide prevalence of obesity nearly tripled

Abbreviations: ALP, Alkaline Phosphatase; ALT, Alanine Transaminase; AST, Aspartate Transaminase; BMI, Body Mass Index; BSA, Body Surface Area; CER, Creatinine Excretion Rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, Diastolic Blood Pressure; eGFR, estimated Glomerular Filtration Rate; γ-GT, Gamma-Glutamyltransferase; HDL, High Density Lipoprotein; ICU, Intensive Care Unit; MELD, Model for End-stage Liver Disease; NASH, Non-alcoholic Steatohepatitis; OLT, Orthotopic Liver Transplantation; PSC, Primary Sclerosing Cholangitis; SBP, Systolic Blood Pressure.

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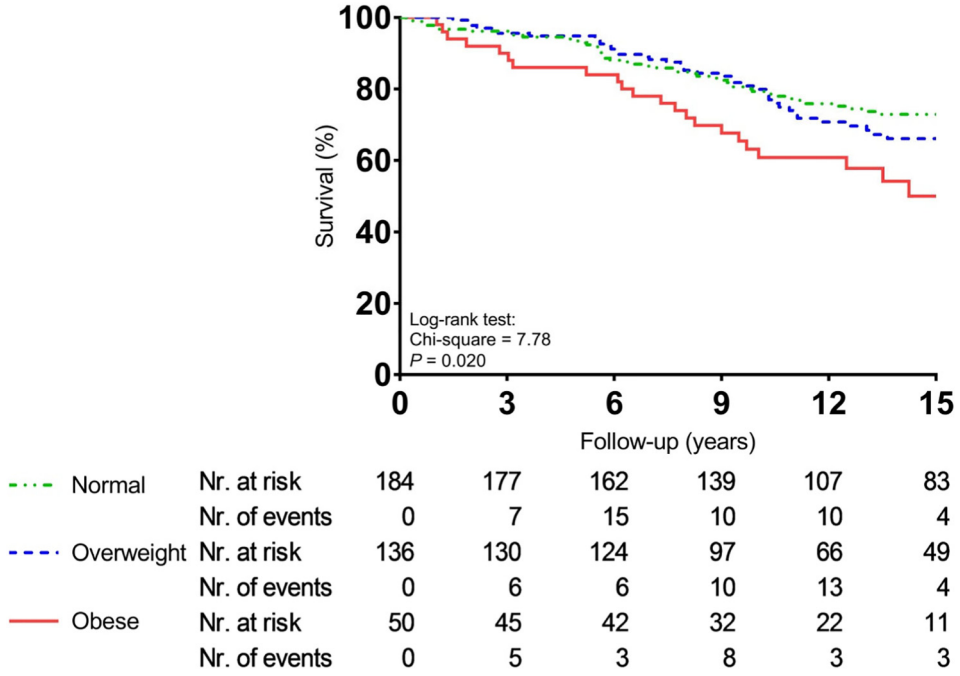
Table 1
Baseline characteristics of the overall OLT recipient population and according to BMI-stratified groups.

	Overall OLT recipients ($n = 370$)	Normal weight ($n = 184$)	Overweight ($n = 136$)	Obese ($n = 50$)	*P*-value
Men (%)	214 (57.8)	105 (57.1)	86 (63.2)	23 (46.0)	0.103
Demographics					
Age, y	48.5 ± 12.5	45.5 ± 13.0	51.4 ± 11.3	51.4 ± 10.9	<0.001
Current smoker, n (%)	50 (17.5)	27 (18.5)	18 (17.3)	5 (14.3)	0.839
Body composition					
Height, m	1.73 ± 0.10	1.75 ± 0.11	1.73 ± 0.09	1.69 ± 0.11	0.001
Weight, kg	77.0 ± 14.7	68.5 ± 10.0	81.2 ± 9.0	97.1 ± 17.3	<0.001
BMI, kg/m^2	25.7 ± 4.5	22.4 ± 2.0	27.0 ± 1.4	34.0 ± 3.7	<0.001
BSA, m^2	1.90 ± 0.21	1.82 ± 0.19	1.96 ± 0.16	2.06 ± 0.23	<0.001
Urinary CER (mmol/24 h) (m)	13.1 (10.7–15.4)	12.7 (10.5–14.8)	13.5 (11.3–16.3)	13.0 (10.7–17.0)	0.106
Urinary CER (mmol/24 h) (f)	9.2 (7.7–11.0)	8.8 (7.5–10.5)	9.6 (7.9–11.5)	10.1 (7.6–11.8)	0.274
Medical history					
Cardiovascular disease, n (%)	18 (4.9)	6 (3.3)	9 (6.6)	3 (6.0)	0.356
Hypertension, n (%)	225 (61.0)	90 (49.2)	93 (68.4)	42 (84.0)	<0.001
Circulation					
Heart rate, bpm	73.3 ± 9.8	73.1 ± 9.4	73.7 ± 10.3	72.9 ± 10.3	0.902
SBP, mmHg	133.0 ± 15.3	130.2 ± 14.7	134.9 ± 15.2	138.3 ± 16.0	0.001
DBP, mmHg	81.9 ± 9.1	80.4 ± 9.3	82.9 ± 8.7	84.5 ± 8.8	0.004
Renal function					
eGFR, ml/min per 1.73 m^2	69.7 ± 21.7	73.5 ± 24.0	65.9 ± 18.5	65.6 ± 18.2	0.003
Serum creatinine, μmol/L	104.6 ± 31.1	103.1 ± 36.3	107.0 ± 24.1	103.6 ± 27.0	0.520
Proteinuria, n (%)	39 (10.7)	17 (9.3)	14 (10.4)	8 (16.3)	0.368
Laboratory parameters					
Triglycerides, mmol/L	1.5 (1.2–2.2)	1.5 (1.0–1.9)	1.6 (1.2–2.3)	1.9 (1.3–2.5)	0.002
Total cholesterol, mmol/L	5.0 ± 1.4	4.9 ± 1.5	5.2 ± 1.3	5.1 ± 1.3	0.337
Glucose, mmol/L	5.7 (4.7–6.6)	5.4 (4.6–6.3)	5.8 (4.9–7.2)	6.3 (5.3–6.9)	0.001
Haemoglobin, mmol/L	8.0 ± 1.2	7.9 ± 1.3	8.1 ± 1.0	7.8 ± 0.9	0.084
Albumin, g/L	41.8 ± 4.5	41.6 ± 5.0	42.2 ± 4.0	41.1 ± 4.2	0.256
AST, U/L	26.5 (21.0–39.2)	26.3 (21.0–30.0)	26.8 (21.7–38.0)	26.6 (20.5–56.1)	0.926
ALT, U/L	28.2(19.0–49.1)	27.0 (18.1–49.4)	28.7 (20.8–47.5)	28.5 (20.8–58.0)	0.508
γ-GT, U/L	43.0 (22.0–126.5)	42.0 (20.3–122.7)	42.8 (22.5–133.2)	50.5 (24.5–144.5)	0.800
ALP, U/L	86.8 (64.9–126.1)	87.0 (62.5–137.5)	84.5 (65.0–113.5)	92.2 (66.7–126.3)	0.577
Bilirubin total, μmol/L	16.3 (11.5–23.4)	16.7 (11.5–26.9)	16.0 (11.3–21.0)	16.8 (11.8–23.2)	0.531
Bilirubin direct, μmol/L	5.8 (3.0–9.6)	6.0 (3.2–11.0)	5.0 (2.7–8.0)	5.5 (3.0–10.6)	0.075
Primary liver disease					<0.001
Acute liver failure, n (%)	21 (5.7)	13 (7.1)	6 (4.4)	2 (4.0)	
Viral hepatitis, n (%)	52 (14.1)	19 (10.3)	25 (18.4)	8 (16.0)	
Autoimmune hepatitis, n (%)	27 (7.3)	17 (9.2)	9 (6.6)	1 (2.0)	
Primary biliary cholangitis, n (%)	32 (8.6)	12 (6.5)	13 (9.6)	7 (14.0)	
Primary sclerosing cholangitis, n (%)	73 (19.7)	49 (26.6)	20 (14.7)	4 (8.0)	
Cryptogenic + NASH, n (%)	46 (12.4)	15 (8.2)	17 (12.5)	14 (28.0)	
Alcohol cirrhosis, n (%)	47 (12.7)	13 (7.1)	24 (17.6)	10 (20.0)	
Storage disorders, n (%)	21 (5.7)	9 (4.9)	9 (6.6)	3 (6.0)	
Other, n (%)	51 (13.8)	37 (20.1)	13 (9.6)	1 (2.0)	
Transplant characteristics					
Cold ischemia time, hours	8.1 (6.9–10.0)	8.1 (6.7–10.2)	8.2 (7.1–10.0)	7.9 (6.1–10.5)	0.473
Warm ischemia time, minutes	48.0 (41.5–57.0)	48.0 (41.8–57.0)	48.0 (42.0–57.0)	48.0 (41.0–57.0)	0.981
Age donor, years	43.7 ± 14.6	43.3 ± 14.8	43.5 ± 14.1	45.8 ± 14.9	0.544
Heart-beating donor, n (%)	331 (89.5)	166 (90.2)	122 (89.7)	43 (86.0)	0.685
Transplant era, n (%)					0.263
1993–1998	112 (30.3)	55 (29.9)	44 (32.4)	13 (26.0)	
1999–2004	131 (35.4)	74 (40.2)	41 (30.1)	16 (32.0)	
2005–2010	127 (34.3)	55 (29.9)	51 (37.5)	21 (42.0)	
Transplant complications					
Relaparotomy, n (%)	54 (14.6)	28 (15.2)	19 (14.0)	7 (14.0)	0.879
ICU stay, days	3.0 (1.0–7.0)	3.0 (1.0–7.5)	3.0 (2.0–7.0)	4.0 (2.0–8.0)	0.501
Pre-transplant MELD score	14.2 (10.0–20.8)	13.7 (8.7–20.0)	14.5 (10.0–21.4)	14.9 (11.5–23.2)	0.519
Pre-transplant ascites					0.049
None	173 (53.1)	91 (55.2)	60 (51.7)	22 (48.9)	
Mild	79 (24.2)	44 (26.7)	21 (18.1)	14 (31.1)	
Moderate	47 (14.4)	23 (13.9)	18 (15.5)	6 (13.3)	
Severe	27 (8.3)	7 (4.2)	17 (14.7)	3 (6.7)	
Medication					
Calcineurin inhibitor, n (%)					
Cyclosporine	157 (42.4)	74 (40.2)	61 (44.9)	22 (44.0)	0.689
Tacrolimus	194 (52.4)	98 (53.3)	68 (50.0)	28 (56.0)	0.730
Proliferation inhibitor, n (%)					
Azathioprine	165 (44.6)	85 (46.2)	58 (42.6)	22 (44.0)	0.816
Mycophenolate mofetil	58 (15.7)	26 (14.1)	20 (14.7)	12 (24.0)	0.218
Prednisolone, n (%)	317 (85.7)	162 (88.0)	114 (83.8)	41 (82.0)	0.412
Prednisolone dose, mg/day	10.0 (7.5–10.0)	10.0 (7.5–10.0)	10.0 (7.5–10.0)	10.0 (7.5–10.0)	0.273
Cumulative prednisolone dose, g	3.7 (1.8–4.6)	3.7 (2,0–5.5)	3.6 (1.1–4.0)	3.6 (0.5–4.2)	0.035
Antidiabetics, n (%)	75 (20.3)	25 (13.6)	31 (22.8)	19 (38.0)	<0.001
Antihypertensives, n (%)	183 (49.5)	67 (36.4)	80 (58.8)	36 (72.0)	<0.001
Statins, n (%)	32 (8.6)	5 (2.7)	18 (13.2)	9 (18.0)	<0.001



Normal	Nr. at risk	184	177	162	139	107	83
	Nr. of events	0	7	15	10	10	4
Overweight	Nr. at risk	136	130	124	97	66	49
	Nr. of events	0	6	6	10	13	4
Obese	Nr. at risk	50	45	42	32	22	11
	Nr. of events	0	5	3	8	3	3

Fig. 1. Actuarial survival for all-cause mortality according to BMI-stratified groups.

between 1975 and 2016. In the general population, high BMI is a risk factor for cardiovascular diseases, diabetes, musculoskeletal disorders, and cancer, resulting in increased morbidity and mortality [16].

Pre-transplantation overweight and obesity are very common in OLT recipients. The prevalence of overweight and obesity has been reported to be 41% and 28%, respectively [17]. Additionally, alcoholic liver disease, hepatocellular carcinoma, genetic factors, and male gender are risk factors for new-onset obesity after liver transplantation [18]. History of smoking and higher age are also associated with an increased incidence of obesity after OLT [19]. Because OLT recipients are prone to develop overweight or obesity post-transplantation [20], it is important to investigate the effects of overweight and obesity on long-term survival after OLT.

As pre-transplant body weight can be confounded by ascites, it is estimated that 11–20% of patients with large volume ascites are misclassified as being overweight or obese [21,22]. Furthermore, OLT recipients gain weight after transplantation, mainly during the first year after OLT [23]. Therefore, post-transplant body weight is likely to be more representative to calculate true BMI. In this study, we hypothesized that post-transplant BMI at 1 year after OLT is associated with long-term survival.

2. Methods

2.1. Study design and population

A post-hoc analysis of an observational cohort study (www.trialregister.nl – Trial NL6334) of adult (age ≥18 years) patients, who underwent a first OLT between 1993 and 2010, was performed. Baseline was set at 1 year post-transplantation to represent a stable condition and because most weight gain occurs within the first year after transplantation [23]. OLT recipients with missing baseline data on BMI, age, gender, or urinary creatinine excretion rate (CER) were excluded. Furthermore, those OLT recipients who died within 1 year after transplantation and those who were lost to follow-up were excluded. OLT recipients were stratified into normal weight (BMI < 25 kg/m^2), overweight ($25 \leq$ BMI ≤ 30 kg/m^2), and obese (BMI > 30 kg/m^2). This study was approved by the Medical Ethical Committee of our institute (METc 2014/77) and adhered to the Declaration of Helsinki and the Declaration of Istanbul.

2.2. Data collection

Gender, age, current smoking status, height, weight, primary liver disease, complications, and medication use were derived from patient records. Transplant characteristics were derived from the recipient's operative report. Donor characteristics were retrieved from the Eurotransplant database.

BMI was obtained by dividing a person's weight by the square of the person's height (kg/m^2). Body surface area (BSA) was calculated using the DuBois formula [24]. Cardiovascular disease history was defined as a previous myocardial infarction, cerebrovascular accident, and/or peripheral arterial disease. Hypertension was defined as a blood pressure of >140/90 mmHg and/or the use of antihypertensive medication.

Cumulative prednisolone dose was calculated as the daily prednisolone dose at baseline, multiplied by the number of days since transplantation, adding the dosage of prednisolone or methylprednisolone given for treatment of rejection. Methylprednisolone dosage was converted into prednisolone equivalents by multiplying methylprednisolone dosage by a factor of 1.25 [25]. To account for differences in immunosuppressive regimes, transplantation dates were stratified into 3 era's. During the first era (1993–1998), a combination of prednisolone

Note to Table 1:
Data are represented as mean ± SD, median (interquartile range) or n (%). Differences were tested by ANOVA or Kruskal-Wallis for continuous variables and with χ^2-test for categorical variables. BMI, body mass index; BSA, body surface area; CER; creatinine excretion rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyltransferase; ALP, alkaline phosphatase; NASH, non-alcoholic steatohepatitis; ICU, intensive care unit; MELD, model for end-stage liver disease.

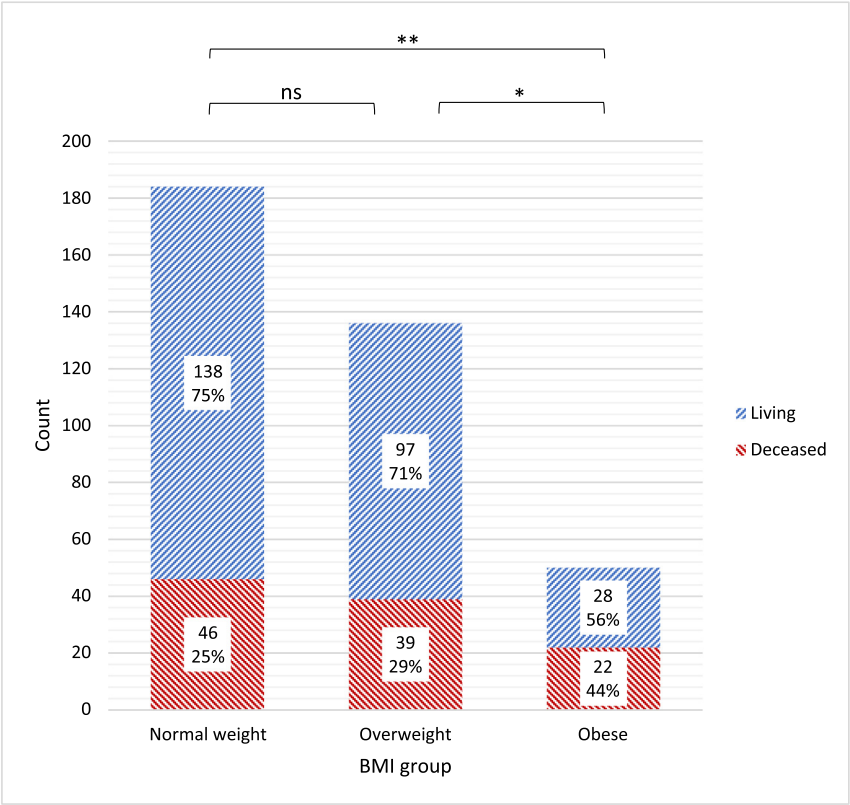


Fig. 2. Proportion of deceased OLT recipients according to BMI groups. Differences between groups assessed with χ^2-test; ns, not significant; $^{*}P < 0.05$; $^{**}P < 0.01$.

(10 mg/day), azathioprine (125 mg/day), and cyclosporin A (dosage resulting in trough blood levels of 100 μg/L) was given. During the second era (1999–2004), a combination of prednisolone and tacrolimus (dosage resulting in trough blood levels between 5 and 7 μg/L) could be given, as well as the combination of prednisolone, azathioprine, and cyclosporin A. Finally, during the third era (2005–2010), a combination of prednisolone, mycophenolate mofetil, and tacrolimus was given.

All serum and urine laboratory parameters were derived from our center's electronic laboratory system, using the median values between 9- and 15-months post-transplantation to minimize collection and measurement errors. OLT recipients were instructed to collect their urine according to a standardized protocol. For 24 subsequent hours, recipients collected urine, excluding the morning urine of the first day and including their morning urine of the second day. Kidney function was determined using the estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [26]. Proteinuria was defined as urinary protein excretion of >0.5 g/day. Muscle mass was estimated using urinary CER, obtained from 24 h urine samples [25].

Causes of death were derived from patient records or requested from general practitioners, and categorized into cardiovascular, infectious, malignant, and miscellaneous.

2.3. Outcome measures and follow-up

The primary outcome of this study was 15 years all-cause mortality. The secondary outcome was cause-specific mortality divided into four categories: cardiovascular, infectious, malignancy, and miscellaneous. Follow-up was recorded up to 15 years after baseline, or until December 31, 2018.

2.4. Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD) if normally distributed and as median (interquartile range [IQR]) if skewed. Categorical variables are presented as number (percentage). Differences across BMI stratified groups were compared using the one-way analysis of variance (ANOVA) for normally distributed variables, the Kruskal-Wallis test for skewed distributed variables, and chi-square test for categorical variables.

Kaplan-Meier analysis with the log-rank test was used for initial survival analysis. Subsequently, Schoenfeld residuals were investigated to test the proportionality of hazards. Cox proportional hazards regression analyses were performed for BMI as categorical variable as well as continuous variable. Data were presented as hazard ratios (HR) and 95% confidence intervals (CI). Potential interactions of BMI with age, gender,

Table 2
Causes of death of the overall OLT recipient population and according to BMI-stratified groups.

	Overall OLT recipients ($n = 107$)	Normal weight ($n = 46$)	Overweight ($n = 39$)	Obese ($n = 22$)	P value
Cardiovascular	24 (22.4)	14 (30.4)	8 (20.5)	2 (9.1)	0.184
Infectious	28 (26.2)	11 (23.9)	12 (30.8)	5 (22.7)	0.723
Malignant	33 (30.8)	11 (23.9)	15 (38.5)	7 (31.8)	0.337
Miscellaneous	22 (20.6)	10 (21.7)	4 (10.3)	8 (36.4)	0.046

Chi-square = 9.80; $P = 0.133$.

and urinary CER were checked. Cox proportional hazards models were constructed to adjust for potential confounders.

In model 1, we performed a crude Cox proportional hazards regression analysis. Subsequently, multivariable Cox proportional hazards regression analyses were performed. In model 2, we adjusted for body composition, using age, gender, and muscle mass as measured urinary CER. In model 3, we cumulatively adjusted for transplant related factors, including primary liver disease and transplantation era. In model 4 we cumulatively adjusted for independent cardiovascular risk factors, including cardiovascular disease history and smoking status. In model 5, we cumulatively adjusted for kidney function, using eGFR and the presence of proteinuria. Finally, in model 6, cumulative adjustments were made for liver function, using liver enzymes (AST, ALT, gamma-GT, ALP), direct bilirubin, and serum albumin. No adjustments were made for the use of calcineurin inhibitors and prednisolone, since transplantation eras are based on medication regimes. However, variations in the standard regimens were present and were related to side effects or treatment of allograft rejection [27,28]. Therefore, sensitivity analyses were performed, replacing transplantation era by the use of calcineurin inhibitors and/or prednisolone and/or cumulative prednisolone dose.

Additionally, univariable and multivariable Cox proportional hazards regression analyses were performed for all baseline variables, excluding variables with >10% missing values. Multivariable analysis was performed including all variables with $P < 0.1$ in the univariate analysis and gender. When variables were represented by other variables (e.g. serum creatinine and eGFR), the most significant variable was included in the multivariable analysis.

Cause-specific mortality was assessed using cox proportional hazards analysis and subsequently, predictors of cardiovascular mortality were assessed, using competing-risks regression models according to Fine and Gray [29].

To assess the effect of change in BMI in the first-year post-transplantation compared to pre-transplantation on all-cause mortality, additional analyses were performed using the models described above. Change in BMI was calculated as BMI 1-year post-transplantation minus BMI pre-transplantation. For BMI pre-transplantation the last documented BMI before transplantation was used. Because pre-transplant BMI is affected by ascites, we additionally performed analyses correcting for pre-transplant ascites in model 2, and excluding patients with pre-transplant ascites.

To visualize the relationship between BMI and all-cause mortality, a multivariable adjusted, restricted cubic spline with 3 knots positioned at the 10th, 50th, and 90th was made, based on model 6. Median BMI was used as reference.

P values are two-tailed and for all analyses a *P* value of <0.05 was considered to be statistically significant. Statistical analyses were performed, using IBM Statistics SPSS version 23.0 (IBM Inc. Chicago, IL), Stata/SE 14.2 (StataCorp LLC. College Station, TX), GraphPad Prism 7.02 (GraphPad Software, Inc. San Diego, CA), and R version 3.5.1 (R Foundation, Vienna, Austria).

3. Results

Between 1993 and 2010, a total of 393 adult patients underwent OLT. Nine OLT recipients died within the first year after transplantation and were excluded, as well as 13 OLT recipients with missing baseline data on BMI. Additionally, one recipient was lost to follow-up, resulting in 370 OLT recipients eligible for analysis. The majority of 184 (49.7%) OLT recipients had a normal weight, whereas 136 (36.8%) were overweight, and 50 (13.5%) were obese.

Baseline characteristics according to BMI categories are described in Table 1. Of all OLT recipients, 214 (57.8%) were male, with no significant differences between groups. Mean age was 48.3 ± 12.5 years, with normal-weight OLT recipients being significantly younger than those with a higher BMI classification. Mean BMI was 25.7 ± 4.5 kg/m^2. Concerning body composition, weight, BMI, and BSA, were significantly higher, whereas height was significantly lower in the obese group compared to lower BMI groups. However, no significant differences were found in urinary CER between groups. Hypertension was present in 225 (60.8%) OLT recipients and significantly higher in the obese group compared to lower BMI groups. Mean eGFR was 69.7 ± 21.6 ml/min/1.73m^2, with normal-weight OLT recipients having a significantly higher eGFR than overweight or obese OLT recipients. Serum triglycerides and glucose were significantly higher in the obese group compared to lower BMI groups, as well as the use of antidiabetics, antihypertensives, and statins.

Significant differences were seen between BMI groups and primary liver disease ($P < 0.001$). Primary sclerosing cholangitis (PSC) was most common in normal weight OLT recipients, viral hepatitis and alcohol cirrhosis were most common in overweight OLT recipients, and cryptogenic cirrhosis/non-alcoholic steatohepatitis (NASH) and alcohol cirrhosis were most common in obese OLT recipients.

Kaplan-Meier survival curves are depicted in Fig. 1. During a median follow-up of 12.3 years (IQR 8.4–15.0 years), 107 (28.9%) OLT recipients

Table 3
Association of BMI with all-cause mortality.

	Normal	Overweight		Obese		BMI continuous	
	Ref.	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
No. of events (%) ➔	46 (25.0)	39 (28.7)		22 (44.0)		107 (28.9)	
Model 1	1.00	1.19 (0.78–1.83)	0.421	2.04 (1.23–3.39)	0.006	1.08 (1.04–1.12)	<0.001
Model 2	1.00	0.99 (0.64–1.54)	0.974	1.80 (1.07–3.03)	0.026	1.07 (1.02–1.12)	0.002
Model 3	1.00	1.02 (0.64–1.62)	0.934	1.88 (1.07–3.32)	0.029	1.08 (1.03–1.13)	0.002
Model 4	1.00	1.05 (0.66–1.67)	0.829	2.00 (1.12–3.55)	0.019	1.08 (1.03–1.13)	0.002
Model 5	1.00	1.05 (0.65–1.68)	0.855	2.00 (1.10–3.63)	0.023	1.08 (1.03–1.13)	0.003
Model 6	1.00	1.09 (0.67–1.77)	0.730	2.00 (1.08–3.68)	0.027	1.08 (1.03–1.14)	0.001

Model 1: crude.
Model 2: adjustment for age, gender and urinary CER.
Model 3: model 2 + adjustment for primary liver disease and transplantation era.
Model 4: model 3 + adjustment for cardiovascular disease history and smoking status.
Model 5: model 4 + adjustment for eGFR and proteinuria.
Model 6: model 5 + adjustment for liver enzymes (AST, ALT, γ -GT, and ALP), direct bilirubin, and albumin.

Table 4
Predictors for 15 years all-cause mortality.

	Univariable analysis		Multivariable analysis	
BMI, per kg/m^2	1.08 (1.04–1.12)	<0.001	1.08 (1.03–1.14)	0.002
Gender, male/female	1.19 (0.80–1.75)	0.389	2.10 (1.20–3.66)	0.009
Age, per year	1.04 (1.03–1.06)	<0.001	1.03 (1.01–1.06)	0.009
Current smoking status, yes/no				
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	1.74 (1.07–2.82)	0.025	1.51 (0.88–2.58)	0.132
Unknown	0.93 (0.55–1.55)	0.769	0.83 (0.46–1.52)	0.556
Height, per m	0.70 (0.11–4.33)	0.700		
Weight, per kg	1.02 (1.01–1.03)	0.004		
BSA, per m^2	2.36 (0.95–5.90)	0.066		
Urinary CER, per mmol/24 h	0.62 (0.42–0.91)	0.015	0.57 (0.33–0.97)	0.040
Cardiovascular disease, yes/no	2.00 (1.02–3.96)	0.046	0.86 (0.40–1.82)	0.687
Hypertension, yes/no	1.29 (0.87–1.92)	0.210		
Heart rate, per bpm	0.99 (0.97–1.02)	0.580		
SBP, per mmHg	1.00 (0.99–1.01)	0.731		
DBP, per mmHg	0.99 (0.97–1.01)	0.427		
eGFR, per 10 ml/min per 1.73 m^2	0.90 (0.81–0.99)	0.024	0.98 (0.86–1.13)	0.798
Serum creatinine, per 10 μmol/L	1.06 (1.00–1.12)	0.035		
Proteinuria, yes/no	1.34 (0.76–2.35)	0.309		
Total cholesterol, per mmol/L	1.05 (0.92–1.21)	0.475		
Glucose, per mmol/L	1.09 (1.01–1.18)	0.030	1.02 (0.93–1.12)	0.683
Haemoglobin, per mmol/L	0.97 (0.82–1.15)	0.743		
Albumin, per g/L	0.92 (0.89–0.96)	<0.001	0.92 (0.88–0.97)	0.001
AST, per U/L	1.00 (1.00–1.00)	0.879		
ALT, per U/L	1.00 (1.00–1.00)	0.800		
γ-GT, per U/L	1.00 (1.00–1.00)	0.371		
ALP, per 10 U/L	1.01 (1.00–1.02)	0.050	0.99 (0.98–1.01)	0.501
Bilirubin total, per μmol/L	1.00 (0.99–1.01)	0.958		
Bilirubin direct, per μmol/L	1.00 (1.00–1.01)	0.254		
Primary liver disease, yes/no				
Acute liver failure	0.45 (0.10–1.98)	0.293	0.50 (0.11–2.26)	0.365
Viral hepatitis	1.67 (0.83–3.38)	0.153	0.72 (0.32–1.62)	0.421
Autoimmune hepatitis	1.97 (0.89–4.39)	0.096	2.39 (1.03–5.50)	0.041
Primary biliary cholangitis	1.23 (0.52–2.90)	0.636	0.88 (0.34–2.29)	0.792
Primary sclerosing cholangitis	1.00 (Ref.)		1.00 (Ref.)	
Cryptogenic + NASH	2.59 (1.32–5.11)	0.006	1.09 (0.48–2.48)	0.840
Alcohol cirrhosis	2.40 (1.22–4.74)	0.011	0.87 (0.40–1.89)	0.721
Storage disorders	0.68 (0.20–2.35)	0.545	0.42 (0.11–1.57)	0.196
Other	1.56 (0.76–3.19)	0.223	1.56 (0.73–3.34)	0.256
Age donor, per 10 years	1.21 (1.05–1.39)	0.008	1.06 (0.90–1.26)	0.458
Heart-beating donor, yes/no	0.56 (0.32–0.99)	0.044	0.90 (0.45–1.83)	0.780
Transplant era, yes/no				
1993–1998	1.00 (Ref.)		1.00 (Ref.)	
1999–2004	1.47 (0.92–2.34)	0.103	0.97 (0.55–1.71)	0.903
2005–2010	1.56 (0.93–2.61)	0.094	0.98 (0.45–2.14)	0.966
Cyclosporine, yes/no	0.68 (0.46–1.01)	0.055	0.68 (0.86–1.03)	0.208
Tacrolimus, yes/no	1.11 (0.76–1.62)	0.599		
Azathioprine, yes/no	0.90 (0.61–1.31)	0.576		
Mycophenolate mofetil, yes/no	1.21 (0.71–2.06)	0.489		
Prednisolone, yes/no	0.82 (0.47–1.42)	0.481		
Prednisolone dose, per mg/day	0.99 (0.94–1.04)	0.661		
Cumulative prednisolone dose, per g	0.91 (0.85–0.99)	0.020	0.94 (0.86–1.03)	0.208
Antidiabetics, yes/no	1.70 (1.10–2.61)	0.016	1.12 (0.65–1.95)	0.680
Antihypertensives, yes/no	1.21 (0.83–1.78)	0.316		
Statins, yes/no	2.01 (1.12–3.61)	0.020	1.05 (0.51–2.15)	0.899

Univariable and multivariable Cox proportional hazards regression analyses were performed for all variables with <10% missing values. Multivariable analysis was performed including all variables with P < 0.1 in the univariate analysis and gender. When variables were represented by other variables (e.g. serum creatinine and eGFR) the most significant variable was included in the multivariable analysis.

deceased. Forty-six (25.0%) OLT recipients in the normal weight group died, 39 (28.7%) OLT recipients in the overweight group died and 22 (44.0%) OLT recipients in the obese group died (Fig. 1, log-rank test: $P = 0.020$; Fig. 2). Twenty-four (22.4%) OLT recipients died as a result of cardiovascular causes, 28 (26.2%) OLT recipients died due to infectious causes, and for 33 (30.8%) OLT recipients their cause of death was malignant disease. Additionally, 22 (20.6%) OLT recipients died as a result of other causes, including recurring liver cirrhosis ($n = 8$), amyloidosis ($n = 6$), suicide or euthanasia ($n = 3$), neurologic causes ($n = 2$), graft failure ($n = 1$), lung emphysema (n = 1), and kidney failure due to azathioprine use (n = 1). No significant differences were found in causes of death between BMI groups (Table 2).

Results of Cox proportional hazards regression analyses are described in Tables 3 and 4. We found no evidence for interactions of BMI with age, gender, or urinary CER (all $P \geq 0.05$). Analyses according to BMI categories showed that obese OLT recipients had a significantly 2-fold higher risk of all-cause mortality (Table 3, model 1: HR = 2.04, 95% CI: 1.23–3.39, $P = 0.006$), when compared to normal weight OLT recipients. Multivariable adjustments for age, gender, urinary CER, primary liver disease, transplantation era, cardiovascular risk factors, kidney function, and liver function (Table 3, models 2–6) did not materially alter these results (Table 3, model 6: HR = 2.00, 95% CI: 1.08–3.68, $P = 0.027$). As a continuous variable, BMI was associated with higher all-cause mortality (Table 3, model 1 and Table 4, HR =

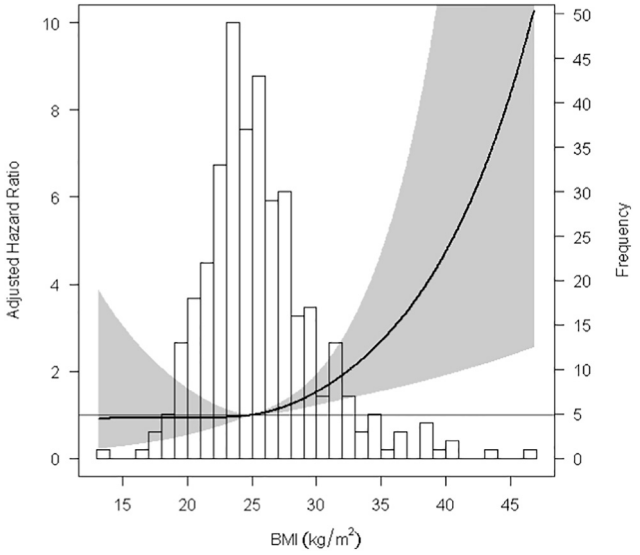


Fig. 3. Restricted cubic splines visualizing adjusted hazards ratio for BMI on all-cause mortality. Adjustments were made according to model 6. The black line represents the association of BMI on all-cause mortality. The gray area represents the 95% confidence interval.

1.08, 95% CI: 1.04–1.12, $P < 0.001$). Results remained similar independent of multivariable adjustments (Table 3, model 6: HR = 1.08, 95% CI: 1.03–1.14, $P = 0.001$; and Table 4, HR = 1.08, 95% CI: 1.03–1.14, $P = 0.002$). This association is graphically depicted in Fig. 3.

Table 5
Association of BMI with cause-specific mortality.

	BMI continuous	
	HR (95% CI)	P value
No. of events (%) cardiovascular	24 (6.5)	
Model 1	0.91 (0.81–1.01)	0.084
Model 2	0.94 (0.84–1.06)	0.327
Model 3	0.95 (0.84–1.08)	0.428
Model 4	0.99 (0.87–1.14)	0.933
Model 5	1.03 (0.90–1.18)	0.670
Model 6	1.04 (0.90–1.21)	0.559
No. of events (%) infectious	28 (7.6)	
Model 1	1.05 (0.97–1.14)	0.202
Model 2	1.09 (1.00–1.18)	0.043
Model 3	1.11 (1.01–1.22)	0.039
Model 4	1.09 (0.98–1.21)	0.123
Model 5	1.11 (1.00–1.23)	0.050
Model 6	1.12 (1.00–1.25)	0.046
No. of events (%) malignant	33 (8.9)	
Model 1	1.04 (0.96–1.12)	0.347
Model 2	1.03 (0.95–1.12)	0.523
Model 3	1.04 (0.94–1.14)	0.488
Model 4	1.06 (0.95–1.18)	0.275
Model 5	1.04 (0.93–1.17)	0.491
Model 6	1.07 (0.95–1.20)	0.243
No. of events (%) miscellaneous	22 (5.9)	
Model 1	1.06 (0.97–1.16)	0.176
Model 2	1.06 (0.97–1.17)	0.198
Model 3	1.09 (0.99–1.21)	0.072
Model 4	1.07 (0.96–1.19)	0.247
Model 5	a)	
Model 6	a)	

Model 1: crude.
Model 2: adjustment for age, gender and urinary CER.
Model 3: model 2 + adjustment for primary liver disease and transplantation era.
Model 4: model 3 + adjustment for cardiovascular disease history and smoking status.
Model 5: model 4 + adjustment for eGFR and proteinuria.
Model 6: model 5 + adjustment for liver enzymes (AST, ALT, γ-GT, and ALP), direct bilirubin, and albumin.
a) Not enough variables for reliable presentation.

Table 6
Change in BMI categories during the first year after OLT.

Pre-OLT \ Post-OLT	Normal weight	Overweight	Obese	Total
Unknown	24	20	6	*50*
Normal weight	129	44	3	*176*
Overweight	30	59	15	*104*
Obese	1	13	26	*40*
Total	*184*	*136*	*50*	*370*

Sensitivity analyses replacing transplantation era in model 3 by the use of calcineurin inhibitors and/or the use of prednisolone and/or cumulative prednisolone dose did not materially change the results for continuous and stratified analyses (Supplementary Table S1).

Additional Cox regression analyses were performed to investigate the association of BMI with cause-specific mortality (Table 5). A significant association of BMI with infectious mortality was found (Table 5, model 6: HR = 1.12, 95% CI: 1.00–1.25, $P = 0.046$). We found no statistically significant associations for BMI with cardiovascular, malignant, and miscellaneous mortality. Competing-risks regression models on cardiovascular mortality are described in Supplementary Table S2. Cardiovascular disease history (SHR = 4.33, 95% CI: 1.46–12.82, $P = 0.008$), current smoking status (SHR = 4.05, 95% CI: 1.69–9.71, $P = 0.002$), and low urinary CER (SHR = 0.32, 95% CI: 0.16–0.66, $P = 0.002$) were identified as the strongest predictors of cardiovascular mortality. Other risk factors for cardiovascular mortality were high age (SHR = 1.05, 95% CI: 1.01–1.10, $P = 0.028$), low eGFR (SHR = 0.74, 95% CI: 0.57–0.97 per 10 ml/min per 1.73 m^2, $P = 0.029$), low albumin (SHR = 0.88, 95% CI: 0.83–0.94, $P < 0.001$), high ALP (SHR = 1.02, 95% CI: 1.02–1.03 per 10 U/L, $P < 0.001$), high direct bilirubin (SHR = 1.02, 95% CI: 1.01–1.03, $P < 0.001$), and transplant era (SHR = 3.16, 95% CI: 1.05–9.54, $P = 0.041$).

Furthermore, change in BMI in the first-year post-transplantation compared to pre-transplantation, was analysed (Table 6). BMI pre-transplantation was measured at a median of 35.0 (IQR 8.5–80.0) days before transplantation. The vast majority of obese recipients 1-year post-transplantation were either overweight, or obese prior to transplantation. Normal-weight OLT recipients prior to transplantation rarely progressed to obesity after 1 year (Table 6). Change in BMI was not significantly associated with all-cause mortality (Supplementary Table S3). Results remained non-significant after correction for pre-transplant ascites (Supplementary Table S4). Analyses excluding OLT recipients with pre-transplant ascites, showed similar results (Supplementary Table S5).

4. Discussion

This study demonstrates that high BMI at 1 year after OLT is associated with increased risk of long-term all-cause mortality in OLT recipients. Furthermore, obese OLT recipients have a 2-fold increased risk of long-term all-cause mortality compared to normal weight OLT recipients. This underlines the importance of an adequate post-transplant BMI on long-term survival after OLT.

OLT recipients have approximately 20% reduced survival rates when compared to the general population [30]. In the current study, this survival rate was comparable for normal weight OLT recipients. Obese OLT recipients, however, had an additional 20% decrease in survival rate. Moreover, obese OLT recipients have a 2-fold higher risk of mortality compared to normal weight OLT recipients, which is substantially more than obese people in the general population when compared to normal weight people (HR = 1.18, 95% CI: 1.12–1.25) [31]. This emphasizes the importance of a healthy weight for OLT recipients.

In the general population, a high BMI is associated with the development of cardiovascular diseases, diabetes, musculoskeletal disorders and cancer, resulting in increased morbidity and mortality [16]. Obesity is the hallmark of metabolic syndrome, of which hypertension, hypertriglyceridemia, hyperglycaemia, and low serum high density lipoprotein (HDL) cholesterol are other components [32]. Our study reveals that

obese OLT recipients have indeed more often hypertension, higher serum triglycerides, and higher glucose levels, when compared to OLT recipients with normal weight at 1 year post-transplantation. Interestingly, we found no significant association of BMI with cardiovascular mortality. We hypothesize that cardiovascular mortality is at least partly prevented because OLT recipients are periodically screened for cardiovascular risk factors (e.g. blood-pressure, serum glucose and cholesterol) on follow-up and adequately treated if necessary, when compared to the general population [33].

In our study, BMI was different across categories of primary liver disease, indicating that primary liver disease is associated with BMI 1-year post-transplantation. However, as demonstrated in model 3, BMI remained significantly associated with mortality despite adjustment for primary liver disease, indicating that high post-transplant BMI is associated with long-term mortality, independent of primary liver disease.

In this study, a BMI ≥ 30 kg/m^2 was associated with a significantly higher mortality risk, but we did not stratify obese OLT recipients into further categories of obesity. Nevertheless, Fig. 3 depicts an exponential relation between BMI and all-cause mortality in OLT recipients. Thus, further research is warranted to investigate potential differences in mortality risk in OLT recipients with a BMI > 35 kg/m^2 and BMI > 40 kg/m^2 post-transplantation.

In the literature, associations between overweight and obesity on long-term survival after OLT are inconsistent [15]. Some studies revealed that high BMI was associated with higher mortality rates [30,34–39], whereas in other studies BMI was not identified as an independent predictor of patient survival [21,22,40–46]. Importantly, these studies have mainly focussed on pre-transplant BMI, while the effects of post-transplant BMI (i.e., the subject of this study) have been investigated only to a limited extent.

Previous studies demonstrated that time-dependent BMI or increase in BMI post-transplantation is associated with better patient survival, which is inconsistent with our study results [47,48]. This might be explained by differences in study design (e.g. change in BMI, time-dependent BMI, or BMI 1 year post-transplantation was used), differences in multivariable analyses, or the exclusion of patients with a BMI > 25 kg/m^2 in one study [48].

No significant differences were found in urinary CER between BMI groups. Therefore, in our study, weight gain after OLT was mostly due to an increase in fat mass, whereas muscle mass was independent of body weight. This increase in fat mass can be accelerated by poor lifestyle factors, including dietary intake, reduced physical activity, and immunosuppressive medication [20,23,49]. Although there is evidence that physical exercise improves long-term quality of life after OLT [50], studies on nutritional and physical-activity based interventions on long-term survival after OLT are currently lacking. Therefore, future studies concerning the effects of dietary advice and physical exercise on long-term survival are warranted. Furthermore, in selected patients, bariatric surgery, in particular sleeve gastrectomy, might be feasible and results in weight loss [51,52]. More research, however, is warranted to minimize risk of complications after bariatric surgery in OLT recipients. Optimal timing of bariatric surgery for obese recipients (i.e., before, during, or after OLT), remains to be defined [51,52].

This study has some valuable strengths. This study is characterized by an excellent follow-up. Median follow-up was 12,3 years (IQR 8.4–15.0 years) and only 1 OLT recipient was lost to follow-up. Additionally, only 13 OLT recipients (3%) were excluded because of missing baseline data on BMI or urinary CER. Furthermore, potential confounders were thoroughly addressed by using appropriate statistical analyses.

The current study has some limitations. The external validity of its findings is limited, due to the single-center cohort design. Furthermore, the post-hoc character of this study relies on adequate weight and height measurements performed by health care professionals, although we do not expect substantial variability among measurements.

In conclusion, post-transplant BMI is inversely associated with long-term survival after OLT. Moreover, obesity at 1-year post-transplantation conveys a 2-fold higher mortality risk, which may offer potential for interventional strategies (i.e. dietary advice, lifestyle modification, or bariatric surgery) to improve long-term survival of obese OLT recipients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154204.

CRediT authorship contribution statement

Jeffrey van Son: Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Suzanne P. Stam:** Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing. **Antonio W. Gomes-Neto:** Methodology, Validation, Formal analysis, Writing - review & editing, Visualization. **Maryse C.J. Osté:** Investigation, Writing - review & editing. **Hans Blokzijl:** Validation, Investigation, Writing - review & editing. **Aad P. van den Berg:** Validation, Investigation, Writing - review & editing. **Robert J. Porte:** Validation, Investigation, Writing - review & editing. **Stephan J.L. Bakker:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing, Supervision. **Vincent E. de Meijer:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing, Supervision.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose.

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The cohort on which this study was based is registered at http://www.trialregister.nl as “TransplantLines Historical Adult Liver Cohort (TxL-HALC)” [53].

References

[1] Haddad L, Cassenote AJF, Andraus W, et al. Factors associated with mortality and graft failure in liver transplants: a hierarchical approach. PLoS One 2015;10(8):e0134874. https://doi.org/10.1371/journal.pone.0134874.
[2] Watt KDS, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10(6):1420–7. https://doi.org/10.1111/j.1600-6143.2010.03126.x.
[3] Daniel KE, Eickhoff J, Lucey MR. Why do patients die after a liver transplantation? Clin Transpl 2017;31(3):e12906. https://doi.org/10.1111/ctr.12906.
[4] Schoening WN, Buescher N, Rademacher S, et al. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. Am J Transplant 2013;13(9):2384–94. https://doi.org/10.1111/ajt.12384.
[5] Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. Ann Surg 2005;241(6):905–18. https://doi.org/10.1097/01.sla.0000164077.77912.98.
[6] Filali Bouami S, Gwiasda J, Beneke J, et al. Prognostic factors for long-term survival after adult liver transplantation. Langenbecks Arch Surg 2018;403(4):495–508. https://doi.org/10.1007/s00423-018-1670-5.
[7] Gil E, Kim JM, Jeon K, et al. Recipient age and mortality after liver transplantation: a population-based cohort study. Transplantation 2018;102(12):2025–32. https://doi.org/10.1097/TP.0000000000002246.
[8] Geng L, Wang LD, Huang JJ, et al. Lower tacrolimus trough levels in the late period after living donor liver transplantation contribute to improvements in long-term clinical outcomes. Hepatobiliary Pancreat Dis Int 2018;17(3):204–9. https://doi.org/10.1016/j.hbpd.2018.05.001.
[9] Doycheva I, Amer S, Watt KD. De novo malignancies after transplantation: risk and surveillance strategies. Med Clin North Am 2016;100(3):551–67. https://doi.org/10.1016/j.mcna.2016.01.006.
[10] Reich DJ, Clavien PA, Hodge EE. Mycophenolate mofetil for renal dysfunction in liver transplant recipients on cyclosporine or tacrolimus: randomized, prospective, multicenter pilot study results. Transplantation 2005;80(1):18–25. https://doi.org/10.1097/01.TP.0000165118.00988.D7.
[11] Schlitt HJ, Barkmann A, Böker KHW, et al. Replacement of calcineurin inhibitors with mycophenolate mofetil in liver-transplant patients with renal dysfunction: a randomised controlled study. Lancet 2001;357(9256):587–91. https://doi.org/10.1016/S0140-6736(00)04055-1.
[12] Sharma P, Bari K. Chronic kidney disease and related long-term complications after liver transplantation. Adv Chronic Kidney Dis 2015;22(5):404–11. https://doi.org/10.1053/j.ackd.2015.06.001.

[13] Romagnoli J, Citterio F, Violi P, Cadeddu F, Nanni G, Castagneto M. Post-transplant diabetes mellitus: a case-control analysis of the risk factors. Transpl Int 2005;18(3):309–12. https://doi.org/10.1111/j.1432-2277.2004.00043.x.
[14] Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow up. Transplantation, vol 82. ; 2006. p. 1625–8. https://doi.org/10.1097/01.tp.0000250361.60415.96.
[15] Barone M, Viggiani MT, Avolio AW, Iannone A, Rendina M, Di Leo A. Obesity as predictor of postoperative outcomes in liver transplant candidates: review of the literature and future perspectives. Dig Liver Dis 2017;49(9):957–66. https://doi.org/10.1016/j.dld.2017.07.004.
[16] Abarca-Gómez L, Abdeen ZA, Hamid ZA, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017;390(10113):2627–42. https://doi.org/10.1016/s0140-6736(17)32129-3.
[17] Zaydfudim V, Feurer ID, Moore DE, Wisawatapnimit P, Wright JK, Wright Pinson C. The negative effect of pretransplant overweight and obesity on the rate of improvement in physical quality of life after liver transplantation. Surgery 2009;146(2):174–80. https://doi.org/10.1016/j.surg.2009.04.027.
[18] Beckmann S, Denhaerynck K, Stampf S, et al. New-onset obesity after liver transplantation—outcomes and risk factors: the Swiss Transplant Cohort Study. Transpl Int 2018;31(11):1254–67. https://doi.org/10.1111/tri.13308.
[19] Rezende Anastácio L, Garcia Ferreira L, Costa Liboredo J, et al. Overweight, obesity and weight gain up to three years after liver transplantation. Nutr Hosp 2012;27(4):1351–6. https://doi.org/10.3305/nh.2012.27.4.5768.
[20] Kallwitz ER, Loy V, Mettu P, Von Roenn N, Berkes J, Cotler SJ. Physical activity and metabolic syndrome in liver transplant recipients. Liver Transplant 2013;19(10):1125–31. https://doi.org/10.1002/lt.23710.
[21] Leonard J, Heimbach JK, Malinchoc M, Watt K, Charlton M. The impact of obesity on long-term outcomes in liver transplant recipients - results of the NIDDK liver transplant database. Am J Transplant 2008;8(3):667–72. https://doi.org/10.1111/j.1600-6143.2007.02100.x.
[22] Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology 2002;35(1):105–9. https://doi.org/10.1053/jhep.2002.30318.
[23] Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. Transpl Int 2005;18(4):461–6. https://doi.org/10.1111/j.1432-2277.2004.00067.x.
[24] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Nutrition 1916;5(5):303–11 [discussion 312-3].
[25] Stam SP, Osté MCJ, Eisenga MF, et al. Posttransplant muscle mass measured by urinary creatinine excretion rate predicts long-term outcomes after liver transplantation. Am J Transplant 2019;19(2):540–50. https://doi.org/10.1111/ajt.14926.
[26] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
[27] Haagsma EB, Van Den Berg AP, Kleibeuker JH, Slooff MJH, Dijkstra G. Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens. Aliment Pharmacol Ther 2003;18(1):33–44. https://doi.org/10.1046/j.1365-2036.2003.01613.x.
[28] Bijleveld CGE, Klompmaker IJ, Van den Berg AP, et al. Incidence, risk factors, and outcome of antithymocyte globulin treatment of steroid-resistant rejection after liver transplantation. Transpl Int 1996;9(6):570–5. https://doi.org/10.1007/BF00335557.
[29] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94(446):496–509. https://doi.org/10.1080/01621459.1999.10474144.
[30] Åberg F, Gissler M, Karlsen TH, et al. Differences in long-term survival among liver transplant recipients and the general population: a population-based nordic study. Hepatology 2015;61(2):668–77. https://doi.org/10.1002/hep.27538.
[31] Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories a systematic review and meta-analysis. JAMA - J Am Med Assoc 2013;309(1):71–82. https://doi.org/10.1001/jama.2012.113905.
[32] Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110(10):1245–50. https://doi.org/10.1161/01.CIR.0000140677.20606.0E.
[33] Afzali A, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. Liver Transplant 2012;18(1):29–37. https://doi.org/10.1002/lt.22435.
[34] Barone M, Viggiani MT, Losurdo G, Principi M, Leandro G, Di Leo A. Systematic review with meta-analysis: post-operative complications and mortality risk in liver transplant candidates with obesity. Aliment Pharmacol Ther 2017;46(3):236–45. https://doi.org/10.1111/apt.14139.
[35] Conzen KD, Vachharajani N, Collins KM, et al. Morbid obesity in liver transplant recipients adversely affects longterm graft and patient survival in a single-institution analysis. HPB 2015;17(3):251–7. https://doi.org/10.1111/hpb.12340.
[36] Saab S, Lalezari D, Pruthi P, Alper T, Tong MJ. The impact of obesity on patient survival in liver transplant recipients: a meta-analysis. Liver Int 2015;35(1):164–70. https://doi.org/10.1111/liv.12431.
[37] Hammad A, Kaido T, Hamaguchi Y, et al. Impact of sarcopenic overweight on the outcomes after living donor liver transplantation. HepatoBiliary Surg Nutr 2017;6(6):367–78. https://doi.org/10.21037/hbsn.2017.02.02.
[38] Dick AAS, Spitzer AL, Seifert CF, et al. Liver transplantation at the extremes of the body mass index. Liver Transplant 2009;15(8):968–77. https://doi.org/10.1002/lt.21785.
[39] Beckmann S, Drent G, Ruppar T, Nikolić N, De Geest S. Pre- and post-transplant factors associated with body weight parameters after liver transplantation – a systematic review and meta-analysis. Transplant Rev 2019;33(1):39–47. https://doi.org/10.1016/j.trre.2018.10.002.
[40] Fujikawa T, Fujita S, Mizuno S, et al. Clinical and financial impact of obesity on the outcome of liver transplantation. Transplant Proc 2006;38(10):3612–4. https://doi.org/10.1016/j.transproceed.2006.10.188.
[41] Giorgakis E, Tedeschi M, Bonaccorsi-Riani E, et al. The effect of recipient body mass index and its extremes on survival and graft vascular and biliary complications after liver transplantation: a single center retrospective study. Ann Transplant 2017;22:611–21. https://doi.org/10.12659/AOT.903475.
[42] Hakeem AR, Cockbain AJ, Raza SS, et al. Increased morbidity in overweight and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. Liver transplantation, vol 19. ; 2013. p. 551–62. https://doi.org/10.1002/lt.23618.
[43] Boin IFSF, Almeida LV, Udo EY, et al. Survival analysis of obese patients undergoing liver transplantation. Transplant Proc 2007;39(10):3225–7. https://doi.org/10.1016/j.transproceed.2007.08.101.
[44] Lamattina JC, Foley DP, Fernandez LA, et al. Complications associated with liver transplantation in the obese recipient. Clin Transpl 2012;26(6):910–8. https://doi.org/10.1111/j.1399-0012.2012.01669.x.
[45] Abdeen ZA, Hamid ZA, et al, NCD Risk Factor Collaboration (NCD-RisC) L. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet (London, England) 2017;390(10113):2627–42. https://doi.org/10.1016/S0140-6736(17)32129-3.
[46] Gunay Y, Guler N, Dayangac M, et al. Living donor liver transplantation for obese patients: challenges and outcomes. Liver Transplant 2014;20(3):311–22. https://doi.org/10.1002/lt.23794.
[47] Narayanan P, Mara K, Izzy M, et al. Recurrent or de novo allograft steatosis and long-term outcomes after liver transplantation. Transplantation 2019;103(1):E14–21. https://doi.org/10.1097/TP.0000000000002317.
[48] Martinez-Camacho A, Fortune BE, Gralla J, Bambha K. Early weight changes after liver transplantation significantly impact patient and graft survival. Eur J Gastroenterol Hepatol 2016;28(1):107–15. https://doi.org/10.1097/MEG.0000000000000490.
[49] Richardson RA, Garden OJ, Davidson HI. Reduction in energy expenditure after liver transplantation. Nutrition 2001;17(7–8):585–9. https://doi.org/10.1016/S0899-9007(01)00571-8.
[50] Yang LS, Shan LL, Saxena A, Morris DL. Liver transplantation: a systematic review of long-termquality of life. Liver Int 2014;34(9):1298–313. https://doi.org/10.1111/liv.12553.
[51] Diwan TS, Lee TC, Nagai S, et al. Obesity, transplantation, and bariatric surgery: an evolving solution for a growing epidemic; 2020. https://doi.org/10.1111/ajt.15784.
[52] Dziodzio T, Biebl M, Öllinger R, Pratschke J, Denecke C. The role of bariatric surgery in abdominal organ transplantation—the next big challenge? Obes Surg 2017;27(10):2696–706. https://doi.org/10.1007/s11695-017-2854-8.
[53] TransplantLines Historical Adult Liver Cohort (TxL-HALC). Trial register. https://www.trialregister.nl/trial/6334, Accessed date: 19 September 2019.