

Retrospective Cohort Study

Impact of body mass index on outcomes of 48281 patients undergoing first time cadaveric liver transplantation

Subhashini Ayloo, Scott Hurton, Matthew Cwinn, Michele Molinari

Subhashini Ayloo, Scott Hurton, Matthew Cwinn, Michele Molinari, Department of Surgery, Victoria General Hospital, Dalhousie University, Halifax, Nova Scotia B3H 2Y9, Canada

Michele Molinari, Department of Public Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia B3H 2Y9, Canada

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Correspondence to: Dr. Michele Molinari, Department of Surgery, Victoria General Hospital, Dalhousie University, 1276 South Park Street, Office, 6-302 Centennial Building, Halifax, Nova Scotia B3H 2Y9, Canada. michele.molinari@nshealth.ca
Telephone: +1-902-4737624
Fax: +1-902-4737639

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Abstract

AIM: To investigate possible disparities in perioperative morbidity and mortality among different body mass index (BMI) groups and to simulate the impact that these differences might have had on the cohort of patients undergoing cadaveric liver transplantation (LT).

METHODS: All adult recipients undergoing first time LT for benign conditions and receiving a whole graft from brain-dead donors were selected from the united network of organ sharing registry. From January 1994 to June 2013, 48281 patients satisfied the inclusion criteria and were stratified by their BMI. The hypothesis that abnormal BMIs were independent predictors of inferior outcomes was tested with univariate and multivariate regression analyses.

RESULTS: In comparison to normal weight recipients, underweight and morbidly obese recipients had increased 90-d mortality (adjusted OR = 1.737; 95%CI: 1.185-2.548, $P = 0.005$) (adjusted OR = 1.956; 95%CI: 1.473-2.597, $P = 0.000$) respectively and inferior patients' survivals (adjusted HR = 1.265; 95%CI: 1.096-1.461, $P = 0.000$) (adjusted HR = 1.157; 95%CI: 1.031-1.299, $P = 0.013$) respectively. Overall, patients' 5-year survival were 73.9% for normal-weight, 71.1% for underweight, 74.0% for overweight, 74.4% for class I obese, 75.0% for class II obese and 71.5% for class III obese recipients. Analysis of hypothetical exclusion of underweight and morbidly obese patients from the pool of potential LT candidates would have improved the overall survival of the entire cohort by

2.7% (95%CI: 2.5%-3.6%).

CONCLUSION: Selected morbidly obese patients undergoing LT for benign conditions had 5-year survival rates clinically comparable to normal weight recipients. Impact analysis showed that exclusion of high-risk recipients (underweight and morbid obese patients) would not significantly improve the overall survival of the entire cohort of patients requiring LT.

Key words: Obesity; Impact analysis; Survival; Liver transplantation; Body mass index

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Core tip: Obesity has become a prevalent condition in many part of the world. Yet, evaluation of its impact on patients requiring liver transplantation is limited. Analysis of united network of organ sharing data of 48281 patients undergoing first time cadaveric liver transplantation has shown that, 5-year survival rates for selected underweight and morbidly obese patients were clinically comparable to normal weight recipients as 5-year survival for class III obese recipients was 71.5% vs 73.9% for normal weight patients. Impact analysis showed that exclusion of morbidly obese and underweight recipients would not significantly improve the overall survival of the entire cohort of patients undergoing liver transplant.

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INTRODUCTION

Since 1980, the incidence of obesity in the adult population has more than doubled in many countries^[1,2]. Obesity might cause a spectrum of disorders such as non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH) that can lead to cirrhosis and hepatocellular carcinoma^[3]. Data from the United States have shown that during the last decade, the indication for liver transplantation (LT) for NASH has risen from 1.2% to 9.7%. Currently it represents the third most common cause of liver failure but it is expected to be the leading indication by year 2025 if the current trends of obesity remain unchanged^[4].

Some studies have reported that obese recipients have worse outcomes than normal weight counterparts^[4-7]. However, some other investigators did not find any significant differences^[8,9]. One of the shortcomings of these studies is the lack of adjustment for known effect modifiers such as coexisting comorbidities. Therefore,

the controversy around the issue whether obesity itself is an independent predictor of poorer outcomes after LT still remains. In vision of these conflicting results, we reviewed the outcomes of a large cohort of adult patients who underwent LT in the United States with the intent of assessing if abnormal body mass index (BMI) was an independent predictor for patients' and grafts' survival after adjusting for clinical and demographic characteristics selected a priori. Secondary outcomes of this study were to investigate possible disparities in perioperative morbidity and mortality among different BMI groups and to simulate the impact that these differences might have had on the cohort of patients undergoing LT.

MATERIALS AND METHODS

Data of this study were extracted from United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) Files that included socio-demographic and clinical variables of every donor and recipient of solid organ transplants performed in the United States during the period between January 1, 1994 and June 30, 2013. For each recipient, BMI was calculated using the formula: Weight (kg)/height (m)². The World Health Organization definitions were used to classify recipients in six categories: Underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), class I obese (BMI 30-34.9), class II obese (BMI 35-39.9) and class III obese patients (BMI ≥ 40)^[10]. Data for different BMI classes were not adjusted for ascites because the volume of peritoneal fluid drained during LT was not recorded in the STAR Files.

Every adult (age ≥ 18 years) undergoing a LT was considered a potential candidate without restriction of race, citizenship or UNOS region where surgery was performed. Recipients who underwent LT for known primary or secondary liver malignancies (*e.g.*, hepatocellular carcinoma, cholangiocarcinoma, neuroendocrine metastases, *etc.*) and recipients who had a malignancy found in their explanted livers were excluded to avoid confounders related to the neoplastic nature of their disease. Other exclusion criteria were transplants using grafts harvested from living or non-heart beating donors, split grafts, multivisceral or redo transplants and transplant performed across ABO incompatible blood groups as those recipients had increased risk of non-functioning grafts, perioperative morbidity and mortality. Additional exclusion criteria were missing data on recipients' weight or height, lack of records on short and long-term outcomes, or the presence of variables that were deemed implausible for an adult recipient^[11]. Cutoffs for these variables were: Recipient height ≤ 120 cm or ≥ 240 cm, recipient weight ≤ 30 kg or ≥ 250 kg, BMI ≤ 13 or ≥ 80, cold ischemia time ≤ 1 h or ≥ 24 h and warm ischemia time ≤ 10 min or ≥ 120 min. No imputations of missing data were performed and recipients who had more than 10% of omitted information were excluded.

For the purpose of this study, variables included in the final analysis were recipients' age at the time of transplant, sex, ethnicity, primary cause of liver disease, height and weight or BMI when available, presence of renal failure requiring hemodialysis before surgery, history of diabetes (type I or II), presence of chronic obstructive pulmonary disease (COPD), hypertension, model for end-stage liver disease score after its implementation in 2002 and beforehand when serum creatinine, bilirubin and INR were available for calculation, perioperative complications, perioperative mortality and overall patients' and grafts' survival. Donors' variables included age, gender, height and weight or BMI if available, primary cause of death and ethnicity. Intraoperative variables included warm ischemia time measured in minutes and cold ischemia times measured in hours.

Recipient overall survival was estimated by calculating the difference between the date of transplantation and the date of death from any cause. Censoring was used for recipients who were still alive at the end of the time interval of this study or who were alive at the time of their last available follow-up or at the time of retransplantation.

Graft survival was calculated by the difference between the date of transplantation and the date of recipient death or the first date that recorded graft failure or the date when the recipient underwent a redo LT. Perioperative adverse events leading to death were grouped in the following categories: Hemorrhagic (*e.g.*, intraoperative or postoperative bleeding), vascular (either arterial or venous thrombosis), biliary (anastomotic strictures or leaks), infections, acute cellular rejection, cerebrovascular complications (ischemic or hemorrhagic strokes) and primary graft non function defined as irreversible graft function requiring emergency liver replacement within the first 2 wk after LT. The remaining less common complications were categorized as others or unknown if the cause of death was not reported in the UNOS files.

Primary outcomes of this study included patient and graft survival, and secondary outcomes were perioperative causes of morbidity and mortality stratified by recipients' BMI groups.

Late causes of death (≥ 12 mo after LT) were grouped in the following categories: Infections, cardiopulmonary (*e.g.*, ischemic cardiomyopathy, embolism, insufficiency), renal failure, cerebrovascular events (ischemic or hemorrhagic strokes), malignancies (any type of cancer), graft failure (*e.g.*, recurrent disease or chronic rejection), and hemorrhagic (any cause). The remaining infrequent causes of death were grouped together under the category named "other", and if there was no recorded cause of death, patients were entered in the group named "unknown". This study was conducted and reported according to recommendations from the STROBE statement^[12] and did not require approval by the local ethic review board.

Statistical analysis

Sample size of this retrospective analysis was fixed. All variables of first time cadaveric LTs performed over a 19-year period in the United States had been captured in an electronic healthcare database prospectively maintained by UNOS and provided to the authors upon their request.

The cohort was described using estimates of central tendency (means, medians) and spread (standard deviation, interquartile range) for continuous data and frequency and percentages for categorical data.

Etiologies of end stage liver disease (ESLD) were grouped as follows: Hepatitis C virus (HCV), alcohol, alcohol and HCV, other viral hepatitis in combination with HCV, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), congenital or metabolic diseases (*e.g.*, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, hemochromatosis, polycystic liver disease, *etc.*), NASH, hepatitis B virus (HBV), autoimmune, acute liver failure and other rare conditions.

The primary end points were overall patient and graft survivals stratified by recipients' BMI at time of transplant. Kaplan-Meier method was used to calculate survival estimates and analyzed with two-sided log-rank test, with the hazard ratio and two-sided 95% CIs. All hazard ratios (HR) and adjusted HR (AHR) involving patients' and grafts' survivals are reported with normal weight recipients as the reference group. The median follow-up time for both patients' and grafts' survival were estimated by means and medians of the reverse Kaplan-Meier method. Multiple clinically relevant two-way interactions were evaluated in the multivariable Cox model and included in the final model if significant at a *P*-value < 0.05. The proportional hazard assumption of the final adjusted model was tested visually by plotting the scaled Schoenfeld residuals of time and BMI, the main predictor of interest. Departure from linearity was assessed by plotting scatterplot smooth curves through residuals^[13,14]. Time-dependent covariates such as recipients' age, which allowed for a change in the hazard ratio over time, were considered and used in the model when appropriate.

To account for the cohort effects, all analyses were adjusted for year of transplantation. Univariate and multivariate Cox regression analyses were performed to test the null hypothesis that recipients' BMI was a predictor of patients' and graft survival. Only pre-transplant characteristics were used in the models and all confounders entered in the regression models were selected a priori as they had been shown to be correlated with patients' and grafts' survival in earlier studies: Year of transplantation, patients' and recipients' characteristics (age, gender, BMI), recipients' comorbidities (renal insufficiency, diabetes, COPD, hypertension), primary indication for LT, warm and cold ischemia times.

Secondary outcomes were perioperative morbidity and mortality. For these analyses, proportions were compared using the χ^2 test and continuous variables

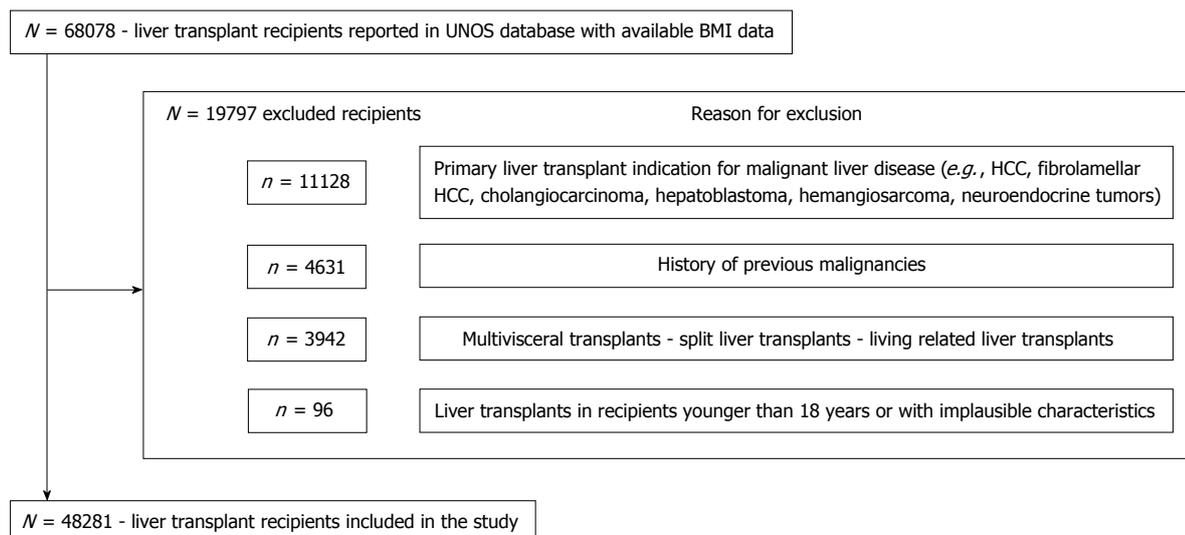


Figure 1 Flowchart of all the include and exclude patients in this study. BMI: Body mass index; UNOS: United Network for Organ Sharing; HCC: Hepatocellular carcinoma.

were compared using ANOVA test across multiple BMI groups. Perioperative mortality was calculated during the index admission, at 30, 60 and 90 d and at 1-year post LT. Unadjusted and adjusted risk estimates of perioperative mortality were calculated as odds ratios (OR) and adjusted OR (AOR) with 95%CI using logistic regression analysis. Risk estimates were adjusted for patients' and donors' BMI (six categories: Underweight, normal weight, overweight, class I obese, class II obese and class III obese), recipients' and donors' age (six categories: 18-45, 46-55, 56-65, 66-75, ≥ 76), recipients' and donors' sex, year of transplantation, recipients' comorbidities (four categories: Renal insufficiency requiring dialysis, diabetes type I and II, COPD, hypertension), warm and cold ischemia time, and primary indication for LT (twelve categories: HCV, Alcohol and HCV, HCV and other viral hepatitis, Alcohol, HBV, PSC, NASH, autoimmune, acute liver failure, congenital or metabolic disease, other).

All statistical analyses were performed using IBM SPSS Statistics version 20 (SPSS Inc. Chicago, IL, United States). Statistical significance was identified by two-tailed *P*-values of less than 0.05 and 95%CI.

Impact analysis of the potential benefit of allocating grafts to patients with BMIs that had the longest survival and lowest perioperative mortality risk was performed using estimates of central tendency and 95%CI. Microsoft® excel 2008 was used to calculate the overall number and 95%CI of preventable perioperative deaths and the number and 95%CI of life-years that could have been saved by allocation grafts to low-risk recipients.

RESULTS

Donors and recipients characteristics

Among 68078 LT recipients recorded in the UNOS registry, a total of 48281 (70.9%) met eligibility criteria

(Figure 1). Of these, 914 (1.89%) were underweight, 14529 (30%) had normal BMI, 16724 (34.6%) were overweight and 16114 were obese (33.3%). Within the group of obese recipients, 9944 (61.7%) were class I obese, 4438 (27.5%) class II and 1732 (10.3%) satisfied class III criteria (Table 1). Demographic and clinical characteristics of the donors are summarized in Table 2.

Primary outcomes

Overall survival: During the study period, 16689 patients (34.6%) died while 31539 were alive or censored. Median overall survival for the entire cohort was 12.7 years (95%CI: 12.5-12.9). Normal weight patients had the longest median survival (13.1 years; 95%CI: 12.6-13.6 years) while the shortest survival was observed in class III obese recipients (11.3 years; 95%CI: 10.3-12.3) and underweight patients (11.5 years; 95%CI: 10.4-12.7) (Table 3).

Kaplan-Meier functions, stratified by recipients' BMI, are reported in Figure 2. Logrank test showed a significant survival difference across BMI groups ($P = 0.004$) and pairwise comparisons showed that underweight ($P = 0.034$) and class III obese patients ($P = 0.001$) experienced significant lower survivals compared to normal weight counterparts.

At multivariate cox regression analysis, after adjusting for recipients' and donors' characteristics (age, gender, BMI, primary cause of end-stage liver disease, comorbidities), cold and warm ischemia times and year of transplantation, underweight status (AHR = 1.265; 95%CI: 1.096-1.461; $P = 0.001$) and class III obesity (AHR = 1.157; 95%CI: 1.031-1.299; $P = 0.013$) remained significant predictors for shorter survival in comparison to normal weight recipients (Table 4). On the other hand, being overweight appeared to have modest protective effect (AHR = 0.908; 95%CI: 0.864-0.954; $P = 0.000$).

Table 1 Demographic and clinical characteristics of the study population

Variable	Total number of patients (n = 48281) (100%)	WHO BMI classification				P value
		Underweight (n = 914) (1.9%)	Normal weight (n = 14529) (30.0%)	Overweight (n = 16724) (34.6%)	Class I (n = 9944) (20.5%) Class II (n = 4438) (9.2%) Class III (n = 1732) (3.5%)	
Age in years, median (25 th , 75 th)	53 (46, 59)	50 (40, 57.2)	52 (44, 58)	53 (46, 58)	53 (46, 58)	0.000
Gender, n (%)						
Male	30250 (62.7)	407 (44.5)	8573 (59.0)	11336 (67.8)	6489 (65.3)	0.000
Female	18,031 (37.3)	507 (55.5)	5956 (41.0)	5388 (32.2)	3455 (34.7)	896 (51.7)
Recipient living status, n (%)						
Alive	27552 (57.1)	496 (54.3)	8040 (55.4)	9534 (57.1)	5825 (58.6)	0.000
Dead	16689 (34.6)	346 (37.9)	5123 (35.3)	5804 (34.7)	3344 (33.7)	601 (34.7)
Lost at follow-up	3987 (8.3)	72 (7.9)	1348 (9.3)	1370 (8.2)	765 (7.7)	115 (6.6)
Race, n (%)						
Non-hispanic white	36809 (76.2)	664 (72.6)	10850 (74.7)	12820 (76.7)	7687 (77.3)	0.000
Non-hispanic black	3962 (8.2)	92 (10.1)	1237 (8.5)	1277 (7.6)	815 (8.2)	170 (9.8)
Hispanic	5535 (11.5)	73 (8.0)	1534 (10.6)	2020 (12.1)	1191 (12.0)	217 (12.5)
Asian	1446 (3.0)	78 (8.5)	782 (5.4)	415 (2.5)	131 (1.3)	10 (0.6)
Other	529 (1.1)	7 (0.7)	126 (0.8)	192 (1.1)	120 (1.2)	22 (1.2)
Recipient BMI, median (25 th , 75 th)	27.05 (23.8, 31.1)	17.63 (17.0, 18.1)	22.73 (21.2, 23.9)	27.26 (26.0, 28.5)	32.01 (30.3, 33.3)	42.24 (41.1, 44.2)
Primary indication for liver transplantation, n (%)						
HCV	13838 (28.7)	176 (19.3)	3538 (24.4)	5248 (31.4)	3101 (31.2)	0.000
Alcohol	8111 (16.8)	163 (17.8)	2543 (17.5)	2909 (17.4)	1686 (17.0)	188 (10.9)
Idiopathic	5073 (10.5)	77 (8.4)	1179 (8.1)	1656 (9.9)	1270 (12.8)	263 (15.2)
Alcohol + HCV	3601 (7.5)	44 (4.8)	1033 (7.1)	1370 (8.2)	762 (7.7)	82 (4.7)
PSC	2799 (5.8)	101 (11.1)	1396 (9.6)	903 (5.4)	282 (2.8)	25 (1.4)
Congenital/metabolic disease	2567 (5.3)	80 (8.8)	870 (6.0)	826 (4.9)	455 (4.6)	121 (7.0)
PBC	2485 (5.1)	92 (10.1)	1122 (7.7)	765 (4.6)	342 (3.4)	48 (2.8)
NASH	2247 (4.7)	13 (1.4)	226 (1.6)	585 (3.5)	660 (6.6)	241 (13.9)
HBV	1896 (3.9)	33 (3.6)	798 (5.5)	646 (3.9)	291 (2.9)	36 (2.1)
Other	5664 (11.7)	135 (14.7)	1824 (12.5)	1816 (10.8)	1095 (11.0)	291 (14.7)
MELD score, median (25 th , 75 th)	21 (16, 28)	22 (16, 28)	21 (16, 29)	20 (15, 28)	21 (16, 28)	22 (16, 31)
Cold ischemia time, hours, median (25 th , 75 th)	7.0 (5.4, 9.2)	7.1 (5.3, 9.1)	7.0 (5.3, 9.1)	7.0 (5.3, 9.1)	7.1 (5.4, 9.2)	7.3 (5.7, 9.4)
Warm ischemia time, minutes, median (25 th , 75 th)	44 (34, 55)	44 (35, 55)	43 (34, 55)	44 (35, 55)	44 (35, 56)	41 (31, 50)
Waiting time, days (including days on hold), median (25 th , 75 th)	120 (27, 335)	91 (21, 286)	106 (24, 308)	124 (28, 336)	131 (30, 358)	86 (12, 314)
Hospital stay after liver transplant, days, median (25 th , 75 th)	11 (8, 19)	13 (7, 23)	11 (8, 19)	11 (8, 18)	11 (8, 18)	13 (9, 22)
Preoperative comorbidities, n (%)						
Diabetes type I	536 (1.1)	9 (1.7)	108 (0.8)	181 (1.1)	155 (1.6)	23 (1.3)
Diabetes type II	8541 (18.0)	81 (9.1)	1827 (12.9)	2896 (17.6)	2179 (22.2)	453 (26.6)
Dialysis	3538 (7.3)	80 (8.8)	1059 (7.3)	1160 (6.9)	693 (7.0)	180 (5.1)
Hypertension	4124 (8.5)	54 (5.9)	989 (6.8)	1424 (8.5)	990 (10.0)	186 (10.7)
Chronic obstructive pulmonary disease	447 (0.9)	13 (1.4)	133 (0.9)	153 (0.9)	86 (0.9)	17 (1.0)

HCV: Hepatitis C virus; HBV: Hepatitis B virus; PSC: Primary sclerosing cholangitis; NASH: Non-alcoholic steatohepatitis; BMI: Body mass index; WHO: World Health Organization; MELD: Model for End-Stage Liver Disease; PBC: Primary biliary cirrhosis.

Table 2 Donor demographic and clinical characteristics

Donor variable	WHO recipients' BMI				P value
	Total number of donors (n = 48281) (100%)	Underweight (n = 914) (1.9%)	Normal weight (n = 14529) (30.0%)	Overweight (n = 16724) (34.6%)	
Age in years, median (25 th , 75 th)	40 (24, 53)	37 (20, 52)	39 (22, 53)	40 (24, 53)	41 (25, 54)
BMI, median (25 th , 75 th)	25.2 (22.3, 29.0)	23.6 (20.7, 27.1)	24.6 (21.7, 28.2)	25.3 (22.3, 29.0)	25.8 (22.8, 30.0)
Gender, n (%)					
Male	29034 (60.1)	486 (53.2)	8171 (56.2)	10219 (61.1)	2801 (63.1)
Female	19247 (39.8)	428 (46.8)	6358 (43.8)	6505 (38.9)	1637 (36.9)
Primary cause of death, n (%)					
Anoxia	6895 (14.3)	163 (17.8)	2004 (13.8)	2337 (33.9)	675 (15.2)
Cerebrovascular	19840 (41.1)	355 (38.8)	5980 (41.2)	6869 (41.1)	1826 (41.1)
Head trauma	20273 (42.0)	372 (40.7)	6161 (42.4)	7098 (42.5)	1831 (41.3)
Central nervous system tumor	357 (0.7)	8 (0.9)	107 (0.7)	116 (0.7)	24 (0.5)
Other	892 (1.8)	16 (1.8)	272 (1.9)	292 (1.7)	82 (1.8)
Race, n (%)					
Non-hispanic white	34907 (72.3)	639 (69.9)	10488 (72.2)	12078 (72.2)	3264 (73.5)
Non-hispanic black	6758 (14.0)	127 (13.9)	1938 (13.3)	2334 (14.0)	640 (14.4)
Hispanic	5118 (10.6)	109 (11.9)	1623 (11.2)	1790 (10.7)	427 (9.6)
Asian	885 (1.8)	28 (3.1)	299 (2.1)	309 (1.8)	55 (1.2)
Other	673 (1.3)	11 (1.2)	241 (1.6)	213 (1.2)	52 (1.1)

BMI: Body mass index; WHO: World Health Organization.

Graft survival: During the study period, 20207 grafts failed (41.9%) and median graft survival was 11.8 years (95%CI: 11.6-12.0) (Table 5).

Figure 3 represents Kaplan-Meier probability functions for graft failure stratified by recipients' BMI. Underweight (11.1 years; 95%CI: 10.1-12.1, $P = 0.034$) and class III obese patients (10.7 years; 95%CI: 9.7-11.7, $P = 0.001$) had significant shorter median survivals when compared to normal weight recipients (12.0 years; 95%CI: 11.6-12.5).

The most frequent causes of graft failure were recipients' death (60.9%), recurrent disease (4.9%), primary graft non-function (3.5%), infections (3.5%), and unknown reasons (23.2%) (Table 6).

Cox-regression multivariate analysis showed that underweight status (AHR = 1.315; 95%CI: 1.129-1.531; $P = 0.000$) and class III obesity (AHR = 1.156; 95%CI: 1.021-1.309; $P = 0.022$) remained significant predictors for shorter graft survival in comparison to normal weight recipients after adjusting for both recipients' and donors' characteristics (age, gender, BMI, primary cause of end-stage liver disease, comorbidities), cold and warm ischemia times and year of transplantation. On the other hand, grafts transplanted in overweight recipients had lower risk of failure with AHR of 0.931 (95%CI: 0.882-0.981; $P = 0.008$) in comparison to normal weight recipients.

Secondary outcomes

Perioperative mortality: Statistical significant differences in perioperative mortality were identified between normal weight and class II and III obese patients at 30, 60, 90-d and at 1-year after LT (Figure 4).

Analysis of the most common causes of perioperative deaths during the index admission is summarized in Table 7. Overall, in hospital mortality was observed in 4.6% of the entire cohort and sepsis and multiorgan failure represented 31.9% of all causes of death. Comparison across BMI categories showed that only cardiovascular ischemic or embolic events were significantly higher in class II obese patients vs normal weight recipients (0.2% vs 0.05%).

Table 3 Mean and median overall survival by recipients' body mass index class

Recipient's BMI	Means and medians for survival time (yr)							
	Estimate	Std. error	Mean ¹		Estimate	Std. error	Median	
			Lower bound	Upper bound			Lower bound	Upper bound
Underweight	10.8	0.3	10.2	11.4	11.5	0.6	10.4	12.7
Normal	11.6	0.1	11.4	11.7	13.1	0.2	12.6	13.6
Overweight	11.5	0.1	11.4	11.7	12.8	0.2	12.5	13.2
Obese-class I	11.3	0.1	11.2	11.5	12.4	0.2	11.9	12.8
Obese-class II	11.1	0.1	10.8	11.4	12.2	0.3	11.6	12.9
Obese-class III	10.7	0.2	10.2	11.1	11.3	0.5	10.3	12.3
Overall	11.5	0.0	11.4	11.5	12.7	0.1	12.5	12.9

¹Estimation is limited to the largest survival time if it is censored. BMI: Body mass index.

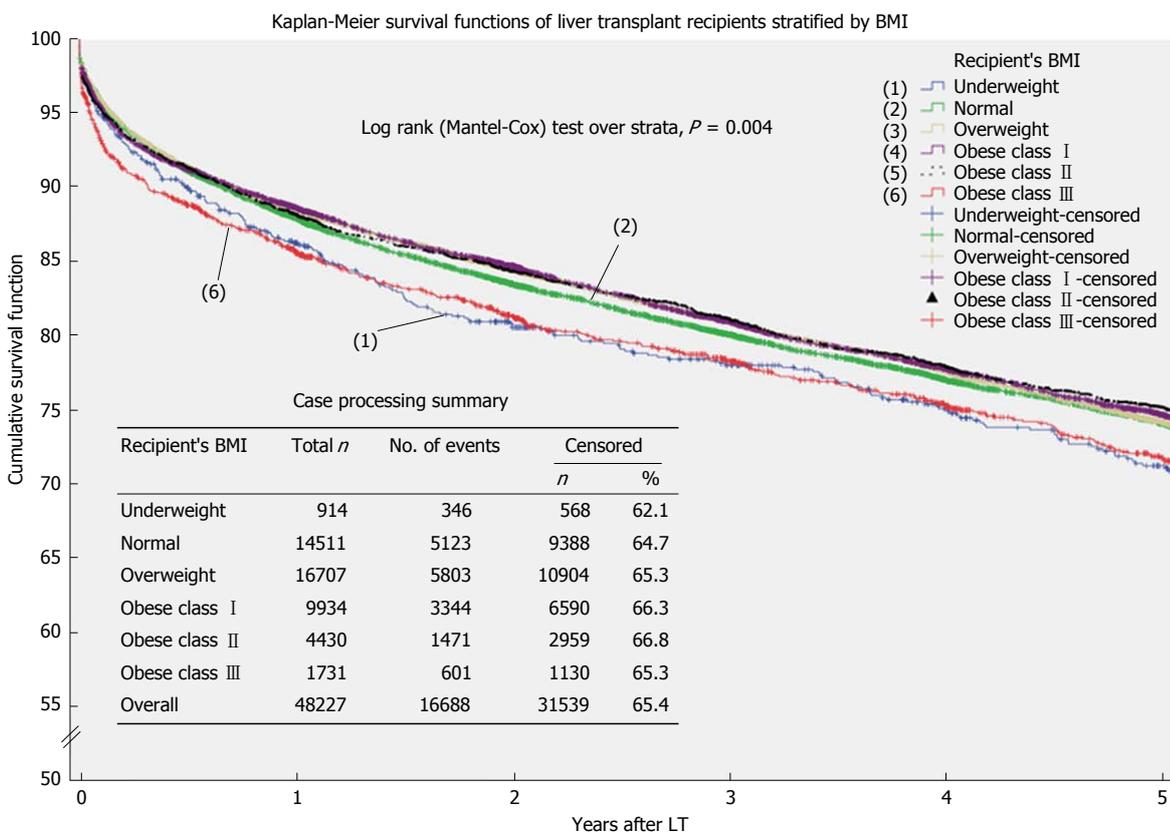


Figure 2 Kaplan-Meier overall survival functions of liver transplant recipients during the first 5 years stratified by their body mass index. Log rank (Mantel-Cox) test over strata showed significant survival difference ($P = 0.004$). In comparison to normal weight recipients, underweight recipients ($P = 0.034$) and class III obese patients ($P = 0.001$) experienced significant lower probability of overall survival. BMI: Body mass index; LT: Liver transplantation.

At multivariate logistic regression analysis, recipients' BMI category remained a significant predictor for in-hospital, 90 d and 1 year mortality after adjusting for cold and warm ischemia time, donors' characteristics, primary indication for LT and recipients' comorbidities (Table 8). Specifically, when compared to normal weight recipients, class III obesity was a predictor for in-hospital mortality (AOR = 1.749; 95%CI: 1.276-2.397; $P = 0.001$), 90 d mortality (AOR = 1.956; 95%CI: 1.473-2.597; $P = 0.000$) and 1 year mortality (AOR = 1.458; 95%CI: 1.154-1.842; $P = 0.002$). Also, being underweight was a risk factor for 90 d mortality (AOR = 1.737; 95%CI: 1.185-2.548; $P = 0.005$) and 1-year

mortality (AOR = 1.505; 95%CI: 1.105-2.048; $P = 0.009$) while being overweight was protective (AOR = 0.886 at 1-year post LT; 95%CI: 0.792-0.992; $P = 0.036$).

All causes of death: Analysis of all primary causes of mortality after LT is reported in Figure 5. Infections were responsible for 21.1% of all deaths, cardiopulmonary complications for 14.9%, and graft failure for 10.9%. Other main causes of mortality were malignant diseases (9.4%), unknown causes (8.3%) and other less common causes that represented 27.3% of all deaths when grouped together (Figure 5A).

Table 4 Univariate and multivariate Cox analysis of predictors of overall survival

Variable	Univariate analysis		Multivariate analysis	
	Hazard rate (95%CI)	P value	Hazard rate (95%CI)	P value
Recipient BMI		0.003		0.000
Normal weight (reference)	1		1	
Underweight	1.125 (1.009-1.255)	0.034	1.265 (1.096-1.461)	0.001
Overweight	1.005 (0.968-1.043)	0.807	0.908 (0.864-0.954)	0.000
Obese class I	1.024 (0.980-1.070)	0.284	0.947 (0.893-1.004)	0.067
Obese class II	1.042 (0.983-1.104)	0.169	0.971 (0.898-1.051)	0.470
Obese class III	1.163 (1.069-1.266)	0.000	1.157 (1.031-1.299)	0.013
Donor BMI		0.001		0.000
Normal weight (reference)	1		1	
Underweight	0.962 (0.897-1.033)	0.288	1.017 (0.928-1.114)	0.716
Overweight	1.060 (1.023-1.098)	0.001	1.009 (0.962-1.057)	0.717
Obese class I	1.049 (0.998-1.102)	0.059	0.986 (0.921-1.057)	0.695
Obese class II	1.129 (1.045-1.220)	0.002	1.020 (0.912-1.140)	0.729
Obese class III	0.988 (0.999-1.112)	0.988	0.889 (0.765-1.034)	0.128
Recipient age		0.000		0.000
18-45 (reference)	1		1	
46-55	1.264 (1.212-1.319)	0.000	1.207 (1.143-1.276)	0.000
56-65	1.536 (1.471-1.603)	0.000	1.490 (1.405-1.580)	0.000
66-75	2.005 (1.887-2.130)	0.000	2.069 (1.904-2.247)	0.000
≥ 76	3.224 (2.099-4.951)	0.000	2.476 (1.462-4.194)	0.001
Donor age		0.000		0.000
0-17 (reference)	1		1	
18-45	1.107 (1.050-1.166)	0.000	1.066 (0.996-1.141)	0.066
46-55	1.297 (1.223-1.376)	0.000	1.266 (1.170-1.370)	0.000
56-65	1.502 (1.411-1.598)	0.000	1.413 (1.300-1.537)	0.000
66-75	1.706 (1.583-1.840)	0.000	1.609 (1.453-1.782)	0.000
≥ 76	1.661 (1.448-1.883)	0.000	1.609 (1.340-1.932)	0.000
Recipient sex (male)	1.063 (1.030-1.097)	0.000	1.025 (0.979-1.073)	0.297
Donor sex (male)	0.951 (0.922-0.980)	0.001	0.967 (0.926-1.008)	0.967
Cold ischemia time (h)	1.010 (1.006-1.013)	0.000	1.008 (1.003-1.013)	0.001
Warm ischemia time (min)	1.002 (1.001-1.003)	0.000	1.002 (1.001-1.003)	0.000
Year of transplantation	0.996 (0.992-0.999)	0.017	0.987 (0.980-0.993)	0.000
Dialysis	1.507 (1.422-1.598)	0.000	1.492 (1.367-1.629)	0.000
Diabetes	1.406 (1.355-1.460)	0.000	1.314 (1.248-1.383)	0.000
COPD	1.384 (1.218-1.573)	0.000	1.250 (1.075-1.454)	0.004
Hypertension	1.207 (1.150-1.267)	0.000	1.057 (0.998-1.120)	0.059
Primary indication		0.000		0.000
HCV	1.356 (1.313-1.400)	0.000	1.429 (1.335-1.530)	0.000
Alcohol + HCV	1.214 (1.152-1.281)	0.000	1.477 (1.351-1.616)	0.000
HCV + other viral hepatitis	1.093 (0.932-1.283)	0.274	1.342 (1.098-1.638)	0.004
Other	1.020 (0.951-1.094)	0.583	1.111 (0.993-1.244)	0.067
Alcohol	1.060 (1.018-1.103)	0.005	1.188 (1.102-1.282)	0.000
HBV	0.669 (0.613-0.729)	0.000	0.782 (0.691-0.883)	0.000
PSC	0.597 (0.554-0.644)	0.000	0.709 (0.634-0.792)	0.000
PBC	0.670 (0.623-0.721)	0.000	0.715 (0.641-0.797)	0.000
NASH	0.906 (0.821-1.001)	0.051	0.953 (0.783-1.160)	0.630
Autoimmune	0.807 (0.742-0.878)	0.000	0.916 (0.810-1.036)	0.164
Acute liver failure	0.801 (0.689-0.931)	0.004	1.049 (0.822-1.339)	0.701
Congenital or metabolic disease	0.758 (0.703-0.817)	0.000	0.825 (0.736-0.926)	0.001

At multivariate analysis, after adjusting for patients' and donors' characteristics, primary indication for liver transplantation, comorbidities, year of transplantation and warm and cold ischemia times, class III obesity and underweight status remained independent factors associated with lower survival. HCV: Hepatitis C virus; HBV: Hepatitis B virus; PSC: Primary sclerosing cholangitis; NASH: Non-alcoholic steatohepatitis; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; PBC: Primary biliary cirrhosis.

Compared to other BMI groups, class III obese patients died more frequently from infections and cardio-pulmonary complications. On the other hand, normal weight and overweight patients experienced a higher rate of malignant diseases (Figure 5B).

Impact analysis

Analysis of the hypothetical number of lives that could

have been saved within one-year post LT by allocating grafts only to low risk groups (normal weight, overweight and obese class I recipients) was performed using observed values and ranges of this study. If no transplants had been performed for class III obese patients, 55 deaths could have been avoided, 38 if no transplants had been done for class II obese and 18 if no transplants had been done for underweight

Table 5 Mean and median graft survival by recipients' body mass index class

Recipient's BMI	Means and medians for graft survival time (yr)							
	Mean ¹				Median			
	Estimate	Std. error	95%CI		Estimate	Std. error	95%CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Underweight	10.4	0.3	9.8	11	11.1	0.4	10.1	12.1
Normal	11.1	0.07	10.9	11.3	12	0.2	11.6	12.5
Overweight	11.1	0.07	11	11.3	12	0.1	11.6	12.4
Obese-class I	11	0.09	10.8	11.2	11.7	0.2	11.3	12.1
Obese-class II	10.8	0.14	10.5	11.1	11.7	0.3	11.1	12.3
Obese-class III	10.3	0.24	9.8	10.8	10.7	0.5	9.7	11.7
Overall	11	0.04	11	11.1	11.8	0.1	11.6	12

¹Estimation is limited to the largest survival time if it is censored. BMI: Body mass index.

Table 6 Summary of the primary causes of graft loss stratified by recipients' body mass index n (%)

Primary cause of graft failure	All recipients (n = 16715)	WHO recipients' BMI class						P value
		Underweight (n = 346) (I)	Normal weight (n = 5129) (II)	Overweight (n = 5813) (III)	Obese recipients			
					Class I (n = 3351) (IV)	Class II (n = 1473) (V)	Class III (n = 603) (VI)	
Primary graft non-function	603 (3.6)	11 (3.2)	178 (3.5)	221 (3.8)	128 (3.8)	48 (3.3)	17 (2.8)	≥ 0.05
Biliary complications	89 (0.5)	2 (0.6)	18 (0.4)	34 (0.6)	23 (0.7)	6 (0.4)	6 (1.0)	≥ 0.05
Vascular thrombosis	119 (0.7)	2 (0.6)	45 (0.9)	39 (0.7)	16 (0.5)	11 (0.7)	6 (1.0)	≥ 0.05
Recurrent disease	829 (4.9)	14 (4.0)	240 (4.6)	306 (5.2)	172 (5.1)	75 (5.0)	22 (3.6)	≥ 0.05
Acute rejection	158 (0.9)	2 (0.6)	57 (1.1)	55 (0.9)	27 (0.8)	10 (0.7)	7 (1.2)	≥ 0.05
Chronic rejection	270 (1.6)	7 (2.0)	104 (2.0)	82 (1.4)	50 (1.5)	17 (1.1)	10 (1.6)	≥ 0.05
Infection	589 (3.5)	11 (3.2)	163 (3.2)	216 (3.7)	119 (3.6)	53 (3.6)	27 (4.5)	≥ 0.05
Recipient death	10172 (60.9)	224 (64.7)	3107 (60.6)	3480 (59.9)	2037 (60.8)	945 (64.2)	379 (62.9)	≥ 0.05
Unknown	3886 (23.2)	73 (21.1)	1217 (23.7)	1380 (23.7)	779 (23.2)	308 (20.9)	129 (21.4)	≥ 0.05

WHO: World Health Organization; BMI: Body mass index.

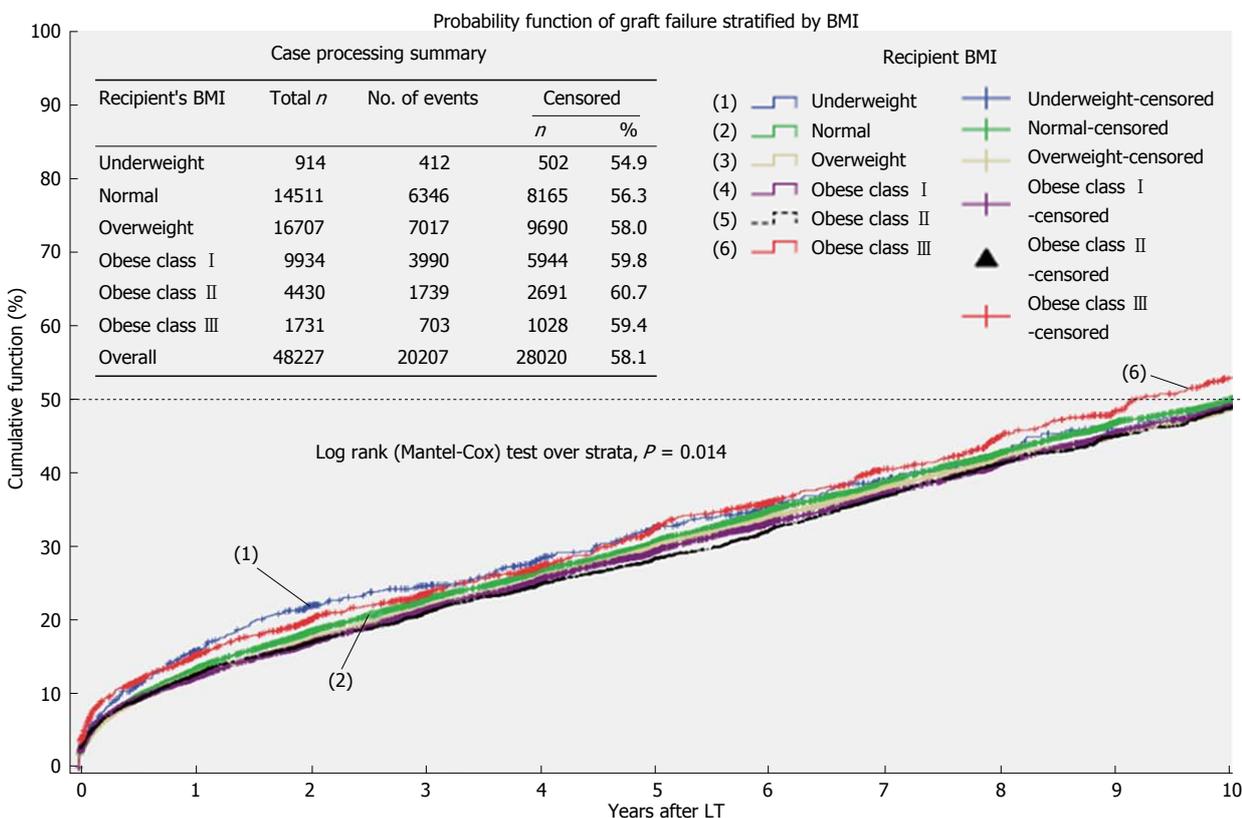


Figure 3 Kaplan-Meier functions of graft survival stratified by recipients' body mass index. BMI: Body mass index; LT: Liver transplantation.

Table 7 Summary of the primary causes mortality during the index admission for liver transplantation stratified by recipients body mass index *n* (%)

Primary cause of perioperative mortality	All recipients (<i>n</i> = 48281)	WHO recipients' MBI class						Group comparisons	<i>P</i> value
		Underweight (<i>n</i> = 914) (I)	Normal weight (<i>n</i> = 14529) (II)	Overweight (<i>n</i> = 16724) (III)	Obese recipients				
					Class I (<i>n</i> = 9944) (IV)	Class II (<i>n</i> = 4438) (V)	Class III (<i>n</i> = 1732) (VI)		
Infections or multiorgan failure	718 (1.4)	22 (2.4)	202 (1.3)	229 (1.3)	155 (1.5)	67 (1.5)	43 (2.4)	≥ 0.05	
Cerebrovascular complication	155 (0.3)	4 (0.4)	47 (0.3)	60 (0.3)	25 (0.2)	14 (0.3)	5 (0.2)	≥ 0.05	
Hemorrhagic	128 (0.2)	3 (0.3)	38 (0.2)	41 (0.2)	32 (0.3)	11 (0.2)	3 (0.1)	≥ 0.05	
Single organ failure	102 (0.2)	1 (0.1)	25 (0.1)	35 (0.2)	21 (0.2)	13 (0.2)	7 (0.4)	≥ 0.05	
Intraoperative complications	75 (0.1)	2 (0.2)	30 (0.2)	21 (0.1)	12 (0.1)	4 (0.09)	6 (0.3)	≥ 0.05	
Cardiovascular or embolic event	53 (0.1)	1 (0.1)	8 (0.05)	16 (0.09)	13 (0.13)	12 (0.2)	3 (0.17)	(II vs V) ≤ 0.05	
Vascular thrombosis	22 (0.04)	0	5 (0.03)	9 (0.05)	2 (0.02)	4 (0.09)	2 (0.1)	≥ 0.05	
Biliary complication	2 (0.004)	0	0	1 (0.005)	1 (0.01)	0	0	≥ 0.05	
Primary graft non-function	62 (0.12)	1 (0.1)	11 (0.07)	27 (0.16)	12 (0.12)	5 (0.1)	6 (0.3)	≥ 0.05	
Rejection	9 (0.01)	0	3 (0.02)	3 (0.01)	2 (0.02)	1 (0.02)	0	≥ 0.05	
Other causes	751 (1.5)	12 (1.3)	203 (1.3)	235 (1.4)	177 (1.7)	91 (2.0)	33 (1.9)	≥ 0.05	
Unknown	172 (0.3)	1 (0.1)	57 (0.3)	61 (0.3)	32 (0.3)	13 (0.2)	8 (0.4)	≥ 0.05	
Total	2249 (4.6)	47 (5.1)	629 (4.3)	738 (4.4)	484 (4.8)	235 (5.2)	116 (6.6)		

WHO: World Health Organization; BMI: Body mass index.

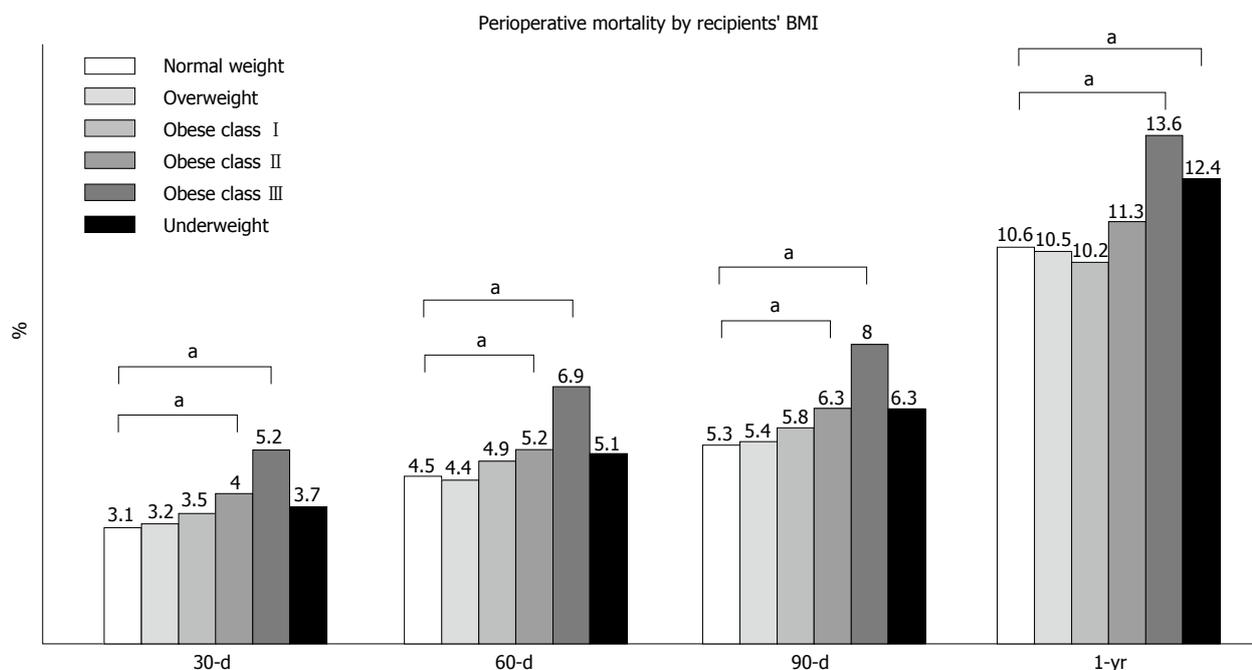


Figure 4 Graphical representation of perioperative and 1-year mortality stratified by recipients' body mass index. Statistical significant difference in perioperative mortality at 30 d, 60 d and 90 d post liver transplantation was found between normal weight recipients and class II and class III obese patients. At 1 year after surgery, a statistical significant difference in mortality was noted between normal weight recipient and class III obese patients. ^a*P* ≤ 0.05. BMI: Body mass index.

recipients. These results were equivalent to 2.38% of deaths for the entire cohort.

Analysis of the long-term impact of allocating grafts to underweight recipients showed a potential loss of 1009 life-years (95%CI: 390-1627 years), equivalent to 80 grafts (95%CI: 29-133 grafts). Allocation of grafts to obese class II recipients resulted in a potential loss of 2311 life-years (95%CI: 1690-2932 years) or equivalent to 183 grafts (95%CI: 129-240 grafts). Allocation of grafts to obese class III recipients resulted in a potential loss of 2056 life-years (95%CI: 1319-2793

years) or equivalent to 163 grafts (95%CI: 101-229 grafts). Overall, we estimated that avoiding LT for the two highest risk BMI groups (underweight and class III obese recipients) would have saved 3065 life-years (95%CI: 1710-4421 years) that were equivalent to 243 extra grafts (95%CI: 131-363 grafts).

In the best hypothetical scenario where all the extra-grafts were allocated to patients with the longest median survival (normal weight recipients), the net gain for the entire cohort was 15921 life-years (95%CI: 15375-22754 life-years) that corresponded to a 2.7%

Table 8 Multivariate logistic analysis of in hospital, 90-d and 1-year mortality stratified by recipients' body mass index at the time of liver transplantation

Variable	Multivariate analysis: In hospital mortality		Multivariate analysis: 90-d mortality		Multivariate analysis: 1-yr mortality	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
Recipient BMI						
Normal weight	1		1		1	
Underweight	1.359 (0.865-2.135)	0.184	1.737 (1.185-2.548)	0.005	1.505 (1.105-2.048)	0.009
Overweight	0.942 (0.798-1.112)	0.481	0.995 (0.856-1.157)	0.950	0.886 (0.792-0.992)	0.036
Obese class I	1.171 (0.974-1.408)	0.094	1.185 (1.000-1.430)	0.050	0.900 (0.792-1.028)	0.120
Obese class II	1.135 (0.889-1.450)	0.309	1.197 (0.959-1.495)	0.112	1.004 (0.846-1.193)	0.960
Obese class III	1.749 (1.276-2.397)	0.001	1.956 (1.473-2.597)	0.000	1.458 (1.154-1.842)	0.002
Donor BMI						
Normal weight	1		1		1	
Underweight	1.581 (1.214-2.060)	0.001	1.449 (1.131-1.857)	0.003	1.200 (0.978-1.472)	0.080
Overweight	1.025 (0.881-1.194)	0.746	1.008 (0.878-1.158)	0.907	1.025 (0.922-1.140)	0.647
Obese class I	0.983 (0.788-1.226)	0.878	1.016 (0.832-1.239)	0.879	1.061 (0.913-1.233)	0.437
Obese class II	1.217 (0.878-1.686)	0.239	1.189 (0.880-1.606)	0.259	1.223 (0.973-1.536)	0.996
Obese class III	1.013 (0.647-1.585)	0.955	0.952 (0.626-1.448)	0.817	0.999 (0.731-1.365)	0.996
Recipient age						
18-45	1		1		1	
46-55	1.305 (1.089-1.563)	0.004	1.324 (1.122-1.583)	0.001	1.302 (1.146-1.479)	0.000
56-65	1.563 (1.292-1.891)	0.000	1.719 (1.447-2.041)	0.000	1.650 (1.443-1.888)	0.000
66-75	2.251 (1.737-2.917)	0.000	2.451 (1.941-3.094)	0.000	2.570 (2.146-3.078)	0.000
≥ 76	5.081 (1.410-18.316)	0.013	6.345 (2.060-20.105)	0.001	2.694 (0.871-8.328)	0.344
Donor age						
0-17	1		1		1	
18-45	1.207 (0.961-1.516)	0.106	1.216 (0.988-1.496)	0.065	1.138 (0.968-1.337)	0.118
46-55	1.492 (1.154-1.929)	0.002	1.411 (1.117-1.784)	0.004	1.464 (1.221-1.755)	0.000
56-65	1.357 (1.027-1.793)	0.032	1.388 (1.079-1.785)	0.011	1.365 (1.123-1.660)	0.002
66-75	1.308 (0.929-1.843)	0.124	1.379 (1.014-1.875)	0.041	1.550 (1.230-1.954)	0.000
≥ 76	0.639 (0.291-1.403)	0.265	0.864 (0.456-1.638)	0.654	1.527 (1.034-2.253)	0.033
Recipient sex (male)	0.909 (0.787-1.050)	0.194	0.966 (0.847-1.102)	0.608	1.051 (0.948-1.164)	0.344
Donor sex (male)	1.017 (0.888-1.164)	0.807	1.009 (0.892-1.142)	0.888	0.993 (0.904-1.092)	0.888
Cold ischemia time (h)	1.033 (1.019-1.047)	0.000	1.021 (1.007-1.035)	0.003	1.024 (1.013-1.035)	0.000
Warm ischemia time (min)	1.008 (1.005-1.011)	0.000	1.007 (1.005-1.010)	0.000	1.006 (1.004-1.008)	0.000
Year of transplantation	0.987 (0.968-1.006)	0.182	0.970 (0.953-0.987)	0.000	1.003 (0.989-1.016)	0.686
Dialysis	2.922 (2.378-3.590)	0.000	2.824 (2.326-3.429)	0.000	2.436 (2.071-2.865)	0.000
Diabetes	1.165 (0.990-1.371)	0.065	1.149 (0.992-1.331)	0.063	1.226 (1.095-1.374)	0.000
COPD	1.276 (0.803-2.027)	0.303	1.155 (0.996-1.341)	0.057	1.233 (0.883-1.720)	0.219
Hypertension	0.957 (0.796-1.151)	0.642	0.959 (0.810-1.135)	0.624	1.027 (0.905-1.166)	0.680
Primary indication for transplant						
HCV	1.369 (1.114-1.682)	0.003	1.215 (1.049-1.408)	0.009	0.980 (0.847-1.135)	0.791
Alcohol + HCV	1.307 (0.976-1.752)	0.073	1.038 (0.808-1.332)	0.772	0.961 (0.788-1.173)	0.698
HCV + Other viral hepatitis	1.307 (0.976-1.752)	0.073	0.895 (0.509-1.575)	0.701	0.876 (0.564-1.362)	0.558
Other	0.730 (0.549-0.970)	0.030	0.693 (0.544-0.883)	0.003	0.843 (0.677-1.050)	0.128
Alcohol	1.380 (1.095-1.740)	0.006	1.172 (0.988-1.391)	0.068	1.366 (1.153-1.618)	0.000
HBV	1.230 (0.871-1.737)	0.239	1.263 (0.912-1.747)	0.159	1.326 (1.023-1.719)	0.033
PSC	1.749 (1.229-2.489)	0.002	1.608 (1.190-2.172)	0.002	1.777 (1.377-2.293)	0.000
PBC	1.989 (1.394-2.837)	0.000	1.834 (1.352-2.487)	0.000	1.754 (1.365-2.252)	0.000
NASH	1.564 (0.899-2.722)	0.113	1.043 (0.660-1.649)	0.857	1.298 (0.902-1.869)	0.160
Autoimmune	1.179 (0.825-1.686)	0.365	0.879 (0.648-1.191)	0.405	1.027 (0.794-1.329)	0.840
Acute liver failure	0.839 (0.462-1.522)	0.839	0.797 (0.450-1.410)	0.435	1.183 (0.712-1.964)	0.517
Congenital or metabolic disease	1.139 (0.832-1.522)	0.563	1.094 (0.821-1.458)	0.540	1.162 (0.919-1.469)	0.211

HCV: Hepatitis C virus; HBV: Hepatitis B virus; PSC: Primary sclerosing cholangitis; NASH: Non-alcoholic steatohepatitis; COPD: Chronic obstructive pulmonary disease; PBC: Primary biliary cirrhosis.

(95%CI: 2.5%-3.6%) improvement in overall survival for the entire cohort.

DISCUSSION

The main findings of this study were that class III obesity and underweight status were associated with higher perioperative mortality and inferior patient and graft survival in comparison to normal weight recipients.

To our knowledge, this is the largest multicentric retrospective observational study on the impact of BMI in LT recipients. One of its strengths is the fact that its sample size allowed us to adjust the analysis of primary and secondary outcomes for several confounders. Our study corroborated the results of several other investigators^[4,15-19] but it went against the findings of other groups^[8,9,18,20,21] including a recent meta-analysis^[9] of 13 studies involving 76620 LT recipients that found

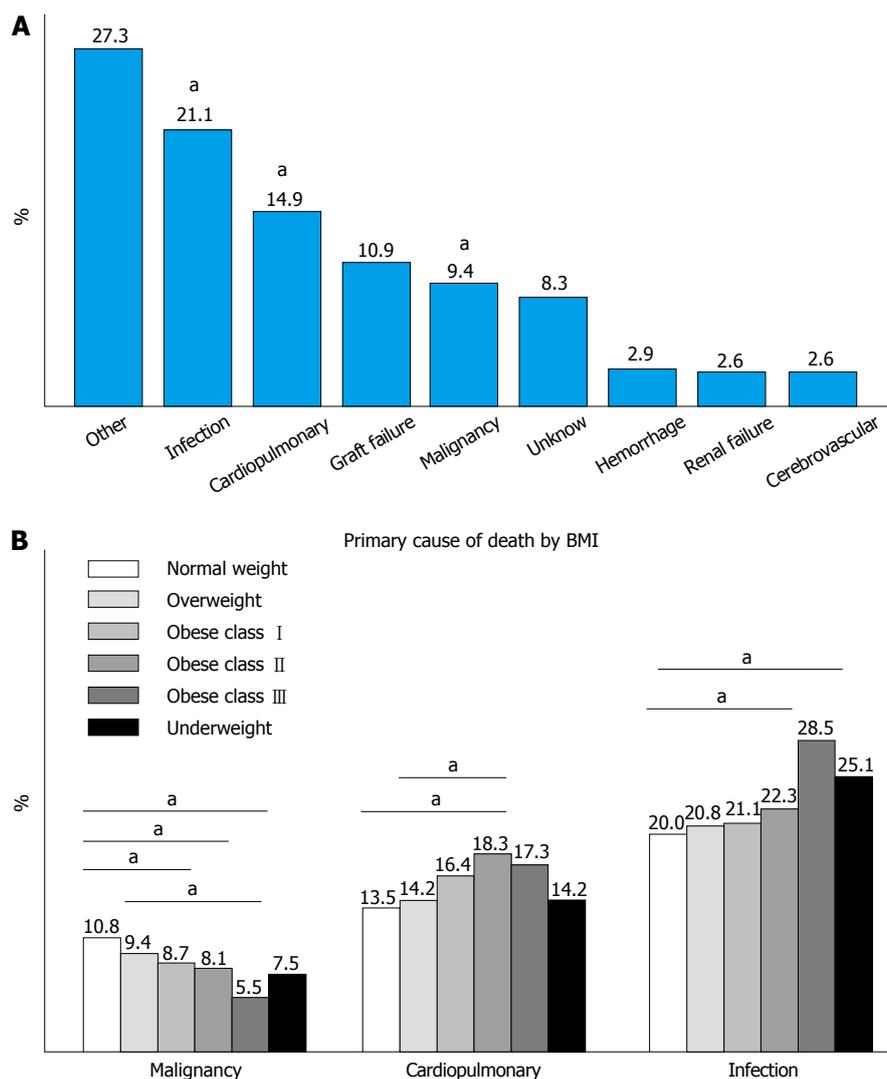


Figure 5 All causes of deaths after liver transplantation. A "a" represent statistical significant differences among recipients' BMI categories (A). Infections were more frequently observed in class II and class III obese recipients in comparison to normal weight patients. Similarly, deaths caused by cardiopulmonary complications were more frequent in class II obese patients vs normal weight or overweight recipients. On the other hand, deaths caused by malignancies were more frequent in normal weight and overweight recipients in comparison to other BMI categories (B). $^aP \leq 0.05$. BMI: Body mass index.

that obesity did not impact survival of patients undergoing LT.

In 2008, Segev *et al.*^[22] found that in the United States, obese and morbidly obese patients were more likely turned down for a LT in comparison to normal weight candidates. A possible explanation for this is finding that LTs for obese patients can be challenging and require more resources in comparison to recipients with lower BMI indices^[6,7,23]. Yet, transplant centers are dealing with obese patients with increasing frequency because obesity is prevalent in many countries^[24] and in the contest of insufficient number of grafts, this creates a unique ethical dilemma^[25,26]. One of the possible strategies is to deny LT to certain groups of high risk patients based on the utilitarian principle of maximizing results by transplanting only patients who have the best potential outcomes, and to accept the fact that patients who do not receive a LT would have significant shorter lives. In our study, 5-year survival for class III obese recipients was 71.5% vs 73.9% for normal

weight patients. Although statistically significant, the absolute difference was clinically irrelevant. Therefore, the exclusion of patients based only on their BMI might be unethical in vision of the fact that 5-year survival of obese and underweight LT recipients was higher than 50% conventionally considered the minimum survival benefit to justify allocation of liver grafts to patients with ESLD^[27,28].

One of the most pressing questions we wanted to address in this study was to quantify the impact of abnormal BMIs on the overall survival of the entire cohort of patients waiting for a LT. Therefore, we simulated clinical scenarios where different graft allocation policies were implemented. By excluding underweight and morbidly obese recipients (the two highest-risk categories for perioperative mortality but representing only 5.4% of the entire cohort), an extra 243 grafts (95%CI: 131-363) could have been used to transplant low risk patients. This strategy would result in an overall 5-year survival improvement of 0.5% (95%CI:

0.27%-0.75%) for the entire cohort. The main reasons for this marginal increase were the fact that underweight and class III obese patients represented only a very small percentage of the cohort, and the fact that the absolute difference in median survival between normal weight recipients and class III obese and underweight patients was only 1.8 and 1.6 years respectively. These relatively small differences are most likely due to the fact that LT recipients undergo rigorous cardiopulmonary testing prior to listing, and only the healthiest of the morbidly obese patients are cleared for transplantation with overall acceptable results.

Our study has several limitations. One of the most important is its retrospective design. Therefore, confounders like immunosuppression protocols, surgical skills and pre and postoperative care provided by so many transplant centers could not be controlled in the final analysis. Another main finding of this study was that the proportion of patients who died from malignant diseases was inversely correlated with their BMI. This phenomenon was observed also by Valentijn *et al.*^[29] in patients undergoing non-transplant related surgeries where 52% of underweight patients died of cancer-related deaths in comparison to 24% for class III obese. This might be due to different factors (*e.g.*, smoking habits), or to the fact that obese patients might have lower risk of developing cancer^[30]. Further investigations are needed to test if obesity is indeed a protective condition against malignancies after transplantation as one of the most important limitations of this study is its retrospective design.

Another limitation was our inability to adjust for the amount of ascites that often affects patients with ESLD. Therefore, the true incidence of obesity might have been overestimated. In addition, we intentionally included recipients transplanted over a long period of time to increase the study population. The advantage of having a large number of patients had to be weighed against the fact that over the study period, there have been significant changes such as immunosuppression protocols, perioperative care and patient selection with significant decrease in morbidity and mortality for obese patients undergoing LT during the last ten years. These improvements might have decreased our ability to detect any clinically significant differences in overall survivals across different BMI categories.

Despite these limitations, our study has the strength of including a very large number of patients that allowed us to perform multivariate analyses to test if selected obese patients have significant worse outcomes than normal weight patients after LT. The results suggested that even for very selected class III obese and underweight recipients, perioperative morbidity and mortality are higher than normal-weight recipients. However, these differences are clinically inconsequential as these patients have good long-term outcomes and their exclusion has a minimal survival benefit for the entire cohort of patients waiting for LT. These findings might be of some help to clinicians and policy makers

who deal with the ethical dilemma of allocating liver grafts to recipients with abnormal BMI. The biggest challenge ahead of transplant programs remains the selection of those recipients who, despite their abnormal BMI, will have good outcomes and long-term benefit from LT.

COMMENTS

Background

Liver transplantation (LT) is the only treatment that can save patients' lives in the presence of irreversible liver failure. There has been a persistent discrepancy between the number of patients who are waiting for a liver transplant and the number of available livers. Several strategies have been used to increase the number of donors, but despite all the best efforts, a significant proportion of patients affected by end-stage liver disease still die while waiting for a suitable organ. Since organs are limited, the transplant community has used some criteria to prioritize the allocation of livers grafts to patients who are in urgent need of a transplant. The main reason for these criteria is to maximize the benefits and minimize the potential risks associated with such extensive surgeries. One of the emerging controversies in the field of transplantation is the allocation of livers to patients who are obese as they are considered at high risk of developing serious complications that can lead to death after LT. Therefore, there is evidence that obesity might be a negative factor that disadvantages some groups of patients who have lower probabilities of being selected for LT.

Research frontiers

The authors' group analyzed a very large database containing data prospectively collected from patients who underwent LT in the United States to assess if abnormal body mass index (BMI) was a negative predictor for survival after LT. Previous studies, using different databases, had conflicting results and controversy regarding LT, especially for obese patients, still persists.

Innovations and breakthroughs

This paper found that, although underweight and morbid obese patients had increased risks for perioperative complications and lower long term survival in comparison to normal weight recipients of liver transplants, the absolute differences were clinically negligible. In addition, impact analysis revealed that exclusion of high risk patients from undergoing LT did not improve the overall results for the entire group of patients who needed a LT.

Applications

Selected obese and underweight patients affected by end-stage liver disease should not be excluded from LT as their overall outcomes are clinically comparable to normal weight patients.

Terminology

BMI is the ratio between a person's stature and respective weight. In most cases, the higher is the BMI, the higher is the concentration of fat in the body. Persons with BMI higher than 30 are considered obese and individuals with BMI higher than 40 are considered morbidly obese. Obesity is associated with increased risks for metabolic derangements such as diabetes, hypertension, hypercholesterolemia and atherosclerotic diseases. Because of this association, obese patients are considered at higher risk of developing cardiopulmonary complications after LT and they absorb more resources when undergoing complex surgical interventions like LT.

Peer-review

This is a large retrospective study to attempt to answer if BMI affect outcomes of liver transplant patients. The study is well designed, performed, and written.

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