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ORIGINAL ARTICLE

The impact of wait list body mass index changes on the outcome after liver transplantation

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We declare we have no conflict of interest.

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Summary

Obesity is associated with poor health outcomes in the general population, but the evidence surrounding the effect of body mass index (BMI) on postliver transplantation survival is contradictory. The aim of this study was to assess the impact of wait list BMI and BMI changes on the outcomes after liver transplantation. Using the Scientific Registry of Transplant Recipients, we compared survival among different BMI categories and examined the impact of wait list BMI changes on post-transplantation mortality for patients undergoing liver transplantation. Cox proportional hazards multivariate regression was carried out to adjust for confounding factors. Among 38 194 recipients, underweight patients had a poorer survival compared with normal weight (HR = 1.3, 95% CI: 1.13–1.49). Conversely, overweight and mildly obese men experienced better survival rates compared with their lean counterparts (HR = 0.9, 95% CI: 0.84–0.96, and HR = 0.86, 95% CI: 0.79–0.93 respectively). Female patients gaining weight over 18.5 kg/m^2 while on the wait list showed improving outcomes (HR = 0.46, (95% CI: 0.28–0.76)) compared with those remaining underweight. This study supports the harmful impact of underweight on postliver transplant survival, and highlights the need for a specific monitoring and management of candidates with BMIs close to 18.5 kg/m^2. Obesity does not constitute an absolute contraindication to liver transplantation.

Introduction

Overwhelming evidence associates obesity with poor health outcome, and obesity will probably be one of the most important public health challenges of the 21st century. In the surgical population, however, the adverse role of obesity has been challenged. Its impact appears clear on the increased risk of wound complications [1,2], but several reports show a reduced complication rate after cardiac [3,4] and noncardiac [5] surgery in obese patients. Because the burden of disease caused by obesity is largely related to the metabolic syndrome and its cardiovascular consequences, it is questionable whether obesity has a similar impact on thoroughly selected patients such as liver transplant candidates compared with the general population.

The body mass index (BMI) of liver transplant recipients has been evaluated as a post-transplant prognostic factor on several occasions, with contradictory results regarding the impact of obesity [6–11]. At the other end of the spectrum, the evidence regarding the hazardous effect of malnutrition and underweight on transplantation outcomes is more consistent [6,9,12]. The period extending between wait list inscription and liver transplantation represents a unique opportunity for improving patients' medical condition. Allowing candidates to ameliorate their metabolic status, through either weight loss or weight gain for obese and underweight patients, respectively, appears as an appealing strategy to improve liver transplant recipient outcomes. Moreover, no study evaluated the potential impact of BMI change of patients waiting for a liver transplantation.

The aim of this study was to assess the effect of wait list BMI changes on post-transplantation survival. We hypothesized that candidates' BMI normalization between wait list inscription and liver transplantation improved post-transplantation survival.

Materials and methods

Data source, study population and variables

We analysed data from the scientific registry of transplant recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates and transplant recipients in the United States of America (US), submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [13]. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides overview to the activities of the OPTN and SRTR contractors.

We included data from adult (>16 years) subjects receiving a liver transplantation from January, 2004 to February, 2011. Multiple organs transplants were excluded. Collected demographics included recipient age, gender, ethnicity and identity of transplant centre. Clinical characteristics of interest included indication for liver transplantation, model for end-stage liver disease (MELD) score, donor risk index (DRI) [14], medical history of hypertension, diabetes and/or chronic obstructive pulmonary disease (COPD), date of wait list inscription, date of transplantation, date of death, date of last follow-up visit and BMI. BMI was defined as patient's weight in kilograms divided by the square of his height in metres (kg/m^2). We excluded patients with a BMI over 70 kg/m^2 because of concerns regarding the potential of erroneous coding of height or weight (representing 95 (0.3%) patients) [7]. BMI change was calculated as the difference between candidate BMI at wait list inscription and recipient BMI at hospital admission on the day of transplantation. Two cut-offs (18.5 and 45 kg/m^2) were used to examine the impact of BMI change on the outcome after liver transplantation. These cut-off values were chosen to assess weight changes around the extremes, which may be more clinically relevant than variations close to the mean. We defined four groups describing BMI change around these cut-offs: (i) candidate and recipient BMI above 18.5 (or below 45) kg/m^2, (ii) candidate and recipient BMI below 18.5 (or above 45) kg/m^2, (iii) candidate BMI above 18.5 (or below 45) kg/m^2 and recipient BMI below 18.5 (or above 45) kg/m^2 and (iv) candidate BMI below 18.5 (or above 45) kg/m^2 and recipient BMI above 18.5 (or below 45) kg/m^2.

Statistical analysis

Categorical and continuous variables were analysed using the Pearson's chi-squared test and the Student *t*-test respectively. Data were stratified by gender. Overall survival was assessed according to the Kaplan–Meier survival function. We firstly explored the association between BMI at transplantation with postliver transplantation overall survival. We subsequently investigated survival differences according to wait list BMI change categories, as defined before. Overall survival was determined from the date of transplantation until the date of death from any cause. If no death was recorded, individuals were censored at last follow-up date, or on the 1st of April 2011. To compare survival among different BMI groups and BMI change categories, univariate analyses were performed using the log rank test. We carried out a multivariate regression using the Cox proportional hazards adjusted for selected clinically relevant confounding factors such as age, MELD score, indication for transplantation, DRI, date of transplantation and transplant centre. Of note, these confounding factors were all predicting the chance of post-transplant survival ($P < 0.0001$, log-rank or univariate Cox analysis). Statistical significance was set at the $P \leq 0.05$ level. Only two-tailed *P*-values are reported. All statistical analyses were computed using STATA 11® (StataCorp, College Station, TX, USA).

Results

Population characteristics

Patients' demographics and clinical characteristics are summarized in Table 1. The population comprised 38 194 adult ($\geq$16 years) liver transplant recipients. The mean recipient age at transplantation was 53 ± 10.5 years and 67% were men. The mean follow-up was 2.3 ± 1.9 years. A majority (82.7%) of recipients were on the wait list less than 1 year, with a mean waiting time of 7.94 ± 15.54 months (median: 2.20 months, interquartile range: 0.46–7.63). The mean MELD score was 20.1 ± 10.6 points. Hepatocellular carcinoma (HCC) was present in 14% of cases. Living donor or split liver was used in 5% of liver transplants, and 7.7% of subjects had a history of previous transplantation. A total of 2443 (5.9%) patients received a liver graft from donation after cardiac death (DCD).

At wait list inscription, approximately one-third (37.6%) of the studied population had a BMI over 30 kg/m^2. This is similar to the prevalence of obesity in the general population, as reported in the National Health and Nutrition Examination Survey (NHANES) 1999–2010 study [15]. Candidate obesity was associated with a history of diabetes ($P < 0.001$), hypertension ($P < 0.001$), coronary artery disease ($P < 0.001$) and drug-treated COPD ($P < 0.001$). Based on BMI at transplantation, there were 11 430 (30%) normal weight, 952 (2.5%) underweight, 13 354 (35%) overweight and 12 458 (32.5%) obese patients. Among obese subjects, 62.5%, 27% and 10.5%

Table 1. Patient characteristics.

Patients (*n*)	38 194
Mean age (years) ± SD (median)	53 ± 10.5 (54)
Gender (%)	
Female	12 484 (33)
Male	25 710 (67)
Ethnicity (%)	
White	25 876 (68)
African American	6145 (16)
Asian	872 (2)
Hispanic/Latino	4996 (13)
Others/multiethnic	307 (1)
Cause of liver disease (%)	
HCV	13 209 (34.5)
Alcohol	4937 (13)
HBV	985 (2.5)
Cryptogenic	2610 (7)
Autoimmune	951 (2.5)
Primary biliary cirrhosis	1219 (3)
Primary sclerosing cholangitis	1838 (5)
NASH	1866 (5)
Haemochromatosis	176 (0.5)
Alpha-1 antitrypsin deficiency	354 (1)
Metabolic disorder	293 (1)
Acute liver necrosis	1983 (5)
Others	7773 (20)
Presence of HCC (%)	5322 (14)
Mean candidate BMI (median)	28.4 ± 5.7 (28)
Mean recipient BMI (median)	28.1 ± 5.9 (27.4)
Mean MELD score ± SD (median)	20.1 ± 10.6 (18.5)
Mean DRI ± SD (median)	2.0 ± 0.5 (1.9)

BMI, body mass index (kg/m^2); DRI, donor risk index; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; NASH, nonalcoholic steato-hepatitis; MELD, model of end-stage liver disease; HCC, hepatocellular carcinoma; SD, standard deviation.

were further classified as obesity grade 1 (BMI = 30–34.9 kg/m^2), grade 2 (BMI = 35–39.9 kg/m^2) and grade 3 (BMI $\geq$40 kg/m^2).

Impact of BMI on survival after liver transplantation

Kaplan–Meier curves are shown in Fig. 1. A poorer survival for underweight patients was visible throughout follow-up in both gender groups (log rank test $P < 0.001$). The Cox proportional model for adjusted overall survival among BMI categories is summarized in Table 2. Male patients were first assessed. When assuming the proportional hazards, the covariate-adjusted HR for death was significantly higher for underweight male patients (HR = 1.3, 95% CI: 1.13–1.49, $P < 0.001$). Conversely, overweight (HR = 0.92, 95% CI: 0.87–0.97, $P = 0.003$) and grade 1 obesity (HR = 0.89, 95% CI: 0.84–0.95, $P = 0.001$) were associated with lower mortality rates compared with normal weight in male subjects. Among female patients, the risk of death was only increased in the underweight group (HR = 1.42, 95%

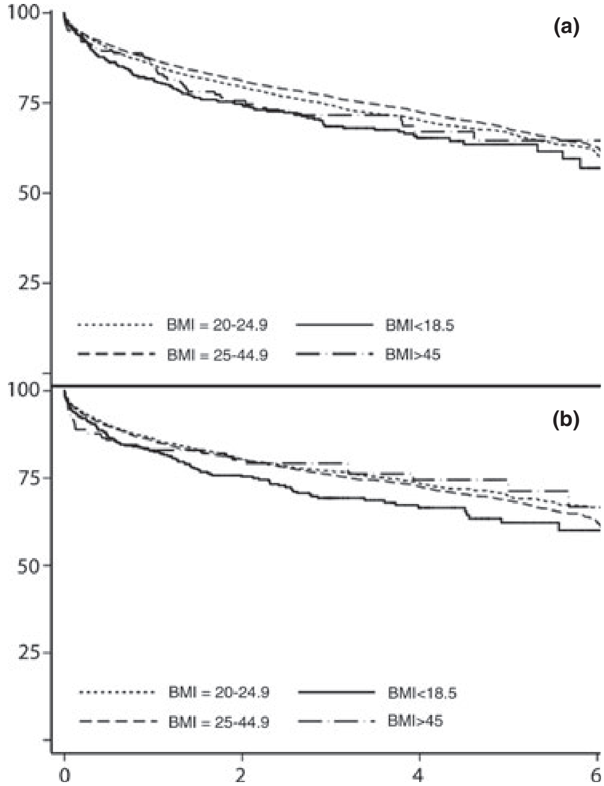

Figure 1 Kaplan–Meier curve, post-transplantation survival, according to body mass index (BMI) at transplantation. (a) Males, (b) Females.

Table 2. Covariate-adjusted survival, according to BMI category. Cox proportional hazards, adjusted for age at transplantation, indication for transplantation, MELD score, donor risk index, transplantation date, transplantation centre.

	n	HR	95% CI		*P*-value
Men	25 710				
Normal weight	7305	1 (ref.)	–	–	
Underweight	511	1.24	1.03	1.49	<0.001
Overweight	9698	0.90	0.84	0.96	0.003
BMI 30–34.9 kg/m^2	5400	0.86	0.79	0.93	0.001
BMI 35–39.9 kg/m^2	2110	0.92	0.82	1.03	0.32
BMI 40–44.9 kg/m^2	516	0.96	0.78	1.18	0.98
BMI $\geq$45 kg/m^2	170	0.98	0.71	1.35	0.83
Women	12 484				
Normal weight	4125	1 (ref)	–	–	
Underweight	441	1.42	1.15	1.75	0.001
Overweight	3656	0.96	0.86	1.06	0.40
BMI 30–34.9 kg/m^2	2397	0.99	0.88	1.11	0.86
BMI 35–39.9 kg/m^2	1238	1.02	0.88	1.18	0.80
BMI 40–44.9 kg/m^2	438	1.05	0.84	1.32	0.65
BMI $\geq$ 45 kg/m^2	189	0.95	0.67	1.36	0.79

BMI, body mass index; MELD, model for end-stage liver disease; HR, hazard ratio; CI, confidence interval.

CI: 1.1–1.75, $P = 0.001$). Overweight and obesity had no impact on adjusted post-transplant outcome (HR = 0.96, 95% CI: 0.86–1.06, $P = 0.4$, and HR = 0.99, 95% CI: 0.88–1.11, $P = 0.86$ respectively). To explore the potential confounding effect of ascites, an analysis was performed only using patients with a MELD score ≤ 15 (n = 13 825), which are less likely to have ascites. In this subgroup of patients, underweight recipients had a reduced survival (HR = 1.49, 95% CI: 1.18–1.88, $P = 0.001$). Patients with overweight (BMI = 25–30 kg/m^2) and moderate obesity (BMI = 30–35 kg/m^2) had a lower risk of death (HR = 0.89, 95% CI: 0.81–0.99, $P = 0.024$, and HR = 0.90, 95% CI: 0.80–1.01, $P = 0.064$ respectively).

When analysing the population with at least 5 years follow-up ($n = 4138$), patients with a BMI ≥ 35 kg/m^2 did not show a significantly poorer survival compared with normal weight recipients (HR = 0.83, 95% CI: 0.54–1.27, $P = 0.384$), and this result was not modified after gender stratification (men: HR = 0.88, 95% CI: 0.50–1.57, $P = 0.678$, women: HR = 0.79, 95% CI: 0.38–1.65, $P = 0.533$).

Table 3. Patients mean wait list BMI change (kg/m^2), stratified by baseline BMI category.

	n	Mean BMI change	95% CI
Underweight wait-listing	686	+2.6	2.18–2.96
Normal weight at wait-listing	9298	+0.39	0.34–0.45
Overweight at wait-listing	13 845	−0.25	−0.3; −0.21
BMI 30–34.9 kg/m^2 at wait-listing	8909	−0.68	−0.75; −0.62
BMI 35–39.9 kg/m^2 at wait-listing	3970	−1.31	−1.43; −1.19
BMI 40–44.9 kg/m^2 at wait-listing	1094	−1.69	−1.95; −1.43
BMI $\geq$45 kg/m^2 at wait-listing	392	−4.37	−5.32; −3.42

BMI, body mass index; CI, confidence interval.

Impact of wait list BMI changes on survival after liver transplantation

BMI changes while on the liver transplant wait list are shown in Table 3. When stratifying by baseline BMI category, BMI change tended to be more pronounced among patients with BMIs approaching upper and lower percentiles.

The adjusted effects of wait list BMI changes around the cut-offs of 18.5 and 45 kg/m^2 are shown in Table 4 for both male and female patients. Provided the proportional hazard assumption is correct, the HR associated with underweight on both occasions of wait list inscription and liver transplantation was 1.62, 95% CI: 1.34–1.96, $P < 0.001$, with similar effects in both gender groups, and using patients with BMI continuously over 18.5 kg/m^2 as controls. A wait list loss of weight below the threshold of 18.5 kg/m^2 was associated with a trend towards an increased risk of death after transplantation (HR = 1.2, 95% CI: 0.99–1.44, $P = 0.057$; men: HR = 1.22, 95% CI: 0.97–1.53, $P = 0.09$; women HR = 1.2, 95% CI: 0.88–1.65, $P = 0.249$). Conversely, an improving weight ($\geq$18.5 kg/m^2 at transplant) in female patients corrected the increased risk of death observed in the underweight group, with an improved survival compared with female patients with BMI continuously below 18.5 kg/m^2 (HR = 0.46, 95% CI: 0.28–0.76, $P = 0.003$), and similar outcomes as those maintaining a BMI above 18.5 kg/m^2 ($P = 0.198$). Of note, the protective effect of weight gain among underweight listed candidates was not present in the male group (HR remained at 0.97, 95% CI: 0.63–1.50, $P = 0.897$).

The HR associated with conservation of a BMI over 45 kg/m^2 from wait list inscription to liver transplantation was 1.52, 95% CI: 1.03–2.24, $P = 0.035$, and 0.99, 95% CI: 0.65–1.5, $P = 0.96$ for males and females respectively. BMI changes around the 45 kg/m^2 did not alter the observed post-transplant outcomes in both gender groups.

Table 4. Covariate-adjusted survival, according to wait list BMI change. Cox proportional hazards, adjusted for age at transplantation, indication for transplantation, MELD score, donor risk index, transplantation date, transplantation centre.

	Men				Women			
	n	HR	95% CI	*P*-value	*n*	HR	95% CI	*P*-value
Candidate and recipient BMI $\geq$18.5 kg/m^2	25 067	1 (ref.)			11 913	1 (ref.)		
Candidate and recipient BMI <18.5 kg/m^2	186	1.60	1.20–2.14	0.02	238	1.63	1.25–2.12	<0.001
Candidate BMI $\geq$18.5 and recipient BMI <18.5 kg/m^2	325	1.22	0.97–1.53	0.09	203	1.20	0.88–1.65	0.249
Candidate BMI < 18.5 and recipient BMI $\geq$18.5 kg/m^2	132	1.55	1.12–2.16	0.009	130	0.75	0.48–1.16	0.198
Candidate and recipient BMI <45 kg/m^2	25 450	1 (ref.)			12 211	1 (ref.)		
Candidate and recipient BMI $\geq$45 kg/m^2	91	1.52	1.03–2.24	0.035	127	0.99	0.65–1.50	0.963
Candidate BMI <45 and recipient BMI $\geq$45 kg/m^2	79	0.67	0.40–1.14	0.143	62	0.88	0.47–1.65	0.699
Candidate BMI $\geq$45 and recipient BMI <45 kg/m^2	90	1.06	0.66–1.71	0.8	84	1.17	0.75–1.18	0.493

BMI, body mass index; MELD, model for end-stage liver disease; HR, hazard ratio; CI, confidence interval.

When analysing wait list weight change as a continuous variable, a one-unit change of BMI (± 1 kg/m^2) was not associated with an improved or reduced survival, in both the BMI > 35 group (HR = 0.99, 95% CI: 0.98–1.01, $P = 0.670$), and BMI <18.5 group (HR = 0.98, 95% CI: 0.95–1.01, $P = 0.156$). In contrast, in the BMI = 18.5–35 kg/m^2 group, each increase in 1 kg/m^2 was associated with a 2% reduction of the hazard ratio for death (HR = 0.98, 95% CI: 0.98–0.99, $P = 0.013$).

Discussion

This study demonstrates that underweight liver transplant recipients of both genders have poorer outcomes than normal weight recipients. Patients with low BMIs should be specifically monitored and managed as a weight gain on the list over 18.5 kg/m^2 is associated with better survival in females, and a loss of weight below 18.5 kg/m^2 leads to poorer outcomes. In the studied population of transplant recipients, obesity has no clear negative impact on post-transplant survival, and appears even protective in male recipients with BMIs between 25 and 35 kg/m^2. These observations provide new insights to the debate of liver transplant candidates' weight management. In fact, a protective effect of overweight has never been described in liver transplantation so far, and to the best of our knowledge, this is the first study providing a dynamic analysis of wait list BMI variations.

Underweight has been repeatedly shown to be a marker of poor prognosis after liver transplantation [9,12,16,17], and this association has been confirmed herein. Our study went one step further, analysing the adjusted impact of wait list BMI changes on survival after liver transplantation. It showed a trend towards poorer survivals in patients with decreasing BMIs <18.5 kg/m^2, and improved outcomes in female patients gaining weight over 18.5 kg/m^2. This observation supports the need for a specific monitoring and management of liver transplant candidates with low BMIs close to 18.5 kg/m^2. Along this line, enteral feeding during the wait list period has been tested in a randomized controlled trial, and was associated to a trend towards better post-transplant survival [18]. One pilot study tested the effect of pre- and postliver transplantation immunonutrition on nutritional markers and clinical outcomes [19]. Although hampered by a small sample size ($n = 32$) and a low methodological rigour, the authors found a significant increase of total body protein content, and a statistical trend supporting lower infection rates in patients receiving immunonutrition. An *a priori* powered randomized, double-blind controlled trial (the PROUD trial, NCT00495859) testing long-term preliver transplant immunonutrition is currently ongoing, and albeit sponsored by the industry, it should provide evidence regarding the potential effectiveness of long-term immunonutrition [20].

The effect of candidate obesity after liver transplantation has been investigated on several occasions [7–12]. Some studies have observed increased rates of early postoperative complication and death, longer hospital stay and higher cost, but an acceptable long-term survival [8,21]. Other studies have demonstrated an improved survival benefit, compared with obese patients remaining on the list [9,11]. In this study of highly selected liver transplant candidates, obesity had no clear impact on post-transplant outcome, and high BMI should not be seen as a formal contraindication for liver transplantation. Our findings even suggest that after allowing for confounding factors, liver transplant recipients benefit from moderate body-weight excess (BMI 25–35 kg/m^2), as reflected by the lower covariate-adjusted HR for death in overweight and grade 1 obese male patients. These findings constitute a reverse epidemiological association, in which moderate excess weight appears as a protective factor. High BMI has been repeatedly reported to be protective in patients undergoing haemodialysis for end-stage renal disease [22–26]. Over the past decade, the "obesity paradox" has been mentioned in the cardiac [3,4] and noncardiac [5] surgical settings, as well as in other fields of medicine, such as acute and chronic heart failure [27–29], coronary artery disease [30, 31], cerebral stroke [32], critical care [33,34] and acute exacerbations of COPD [35]. These observations may be related to higher metabolic reserves in patients with moderately increased BMIs [36–38].

Unlike male patients, female recipients were not protected by a moderately increased BMI of 25–35 kg/m^2. Body fat distribution varies by gender, with men and women tending to store excess fat in the visceral or subcutaneous compartments respectively [39]. Owing to its harmful metabolic effects and cardiovascular impact, visceral adiposity has been consistently showed to be a predictor of poorer outcome outside the transplantation field [40]. Because male gender is an additional independent risk factor for cardiovascular disease, one can speculate that, after careful patient selection, a mildly elevated BMI in men may correspond to a condition of favourable metabolic reserve.

The strengths of this analysis include the large sample size, the availability of BMI values at both wait list inscription and transplantation, and the statistical adjustment for important confounders such as MELD score, DRI and transplant centre. However, our study has several shortcomings. First, because of incomplete or unavailable data, the role of ascites and smoking on BMI could not be assessed, while these variable have been shown to alter body fat composition, body weight and BMI [41]. However, we consider that both the large sample size and the fact that a vast majority of patients did not cross the cut-offs defined in our analysis made this potential selection bias largely diluted among population strata. Second, although the SRTR has repeatedly showed to be a powerful research tool, the retrospective nature of our analysis raises the possibility of measurement (data recording error) and selection biases.

In conclusion, in this large cohort of liver transplant patients, there was strong evidence supporting the overwhelming burden of disease caused by underweight, as represented by the poor survival of underweight patients failing to gain weight while on the wait list. Obesity is not a contraindication for liver transplantation. Our findings confirm the attention clinicians should devote to liver transplant candidates' weight management, especially in patients with low BMIs.

Authorship

LAO and CT: designed research, collected, analyzed and interpreted data, wrote manuscript. TB, PM and GM: interpreted data and wrote manuscript.

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