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# Liver Transplantation With Grafts From Super Obese Donors

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**Background.** There are limited data on liver transplant (LT) outcomes with grafts from super obese donors. The present study aims to evaluate a unique cohort of recipients following LT using grafts from donors with body mass index (BMI)  $\geq 50$ . **Methods.** Patients receiving grafts from donors with BMI  $\geq 50$  and BMI  $< 50$  from 2010 to 2019 were identified. A 1:2 case-control match was conducted to compare outcomes between the groups. Survival was analyzed using the Kaplan-Meier curves. **Results.** Six hundred sixty-five adult LTs were performed in the study period. Eighteen patients receiving a graft from a donor with BMI  $\geq 50$  were identified and matched to 36 patients receiving a graft from a donor with BMI  $< 50$ . Grafts from male donors were significantly lower in the donor BMI  $\geq 50$  group when compared with the donor BMI  $< 50$  group (16.7% versus 66.7%,  $P = 0.001$ ). Liver biopsy was performed in 77.8% of grafts in the donor BMI  $\geq 50$  group, whereas only in 38.8% of the grafts in the donor BMI  $< 50$  group ( $P = 0.007$ ). Recipients in the donor BMI  $\geq 50$  group had a significantly higher diagnosis rate of hepatocellular carcinoma pretransplant versus the donor BMI  $< 50$  group (38.9% versus 8.3%, respectively;  $P = 0.006$ ). Major complications within 30 d did not differ statistically between groups. Biliary complications within the first 30 d were equal among groups (16.7%). Subanalysis comparing the super obese donor group versus the nonobese donor group showed no differences in terms of postoperative complications, readmission rate, graft rejection, or major complications including the need for reoperation, retransplantation, or mortality. Graft and patient survival at 1-, 3-, and 5-y graft were similar between the donor BMI  $\geq 50$  group versus donor BMI  $< 50$  group (94%/89%/89% versus 88%/88%/88%,  $P = 0.89$ , and 94%/94%/94% versus 88%/88%/88%,  $P = 0.48$ , respectively). **Conclusions.** LT with carefully selected grafts from super obese donors can be safely performed with outcomes comparable with non-super obese donor livers. Therefore, these types of grafts could represent a safe means to expand the donor pool.

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## INTRODUCTION

The shortage of transplantable liver grafts has been well established.<sup>1</sup> Marginal liver grafts—including those from elderly donors, donation after circulatory death, steatotic grafts, split grafts, donors with increased risk of disease transmission such as hepatitis C virus (HCV) and hepatitis B virus, and grafts with prolonged cold ischemia time

(CIT)—represent a novel strategy to expand the donor pool and provide lifesaving transplantation to those with end-stage liver disease who may not otherwise have access to organs.<sup>2,3</sup> Not surprisingly, inferior outcomes for graft and patient survival have been observed after transplantation with marginal livers<sup>4</sup>; however, outcomes are generally acceptable with careful donor and recipient selection.

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The impact of donor body mass index (BMI) on clinical outcomes after liver transplantation (LT) remains poorly understood. Obesity rates continue to rise in the United States, with the most recent National Center for Health Statistics Data Brief showing an alarming rise in the prevalence of obesity among US adults, from 31% in 1999–2000 to 42% in 2017–2018.<sup>5,6</sup> Adults aged 20–59 y represent half of the deceased donor pool in the United States and among these groups, the obesity prevalence is 40% and 45% for adults aged 20–39 and 40–59, respectively.<sup>7</sup> As a consequence of this obesity epidemic, the donor pool will likely be populated by an increasing proportion of obese individuals with higher probability of high steatotic grafts.

Concerns exist regarding the safe use of these “imperfect” liver grafts for transplantation as they are used to help ameliorate the well-known organ shortage crisis. Recent evidence suggests that grafts from obese donors with BMI >30 kg/m<sup>2</sup> can be safely transplanted without a negative impact on the long-term patient outcome after LT.<sup>8</sup> However, there is still a necessity for more conclusive and validating results. We aim to extend these results by characterizing the outcomes following LT in a unique cohort of recipients undergoing LT at our center using grafts from super obese donors (BMI ≥50 kg/m<sup>2</sup>).

## MATERIALS AND METHODS

### Study Design

Electronic medical records of all consecutive LT recipients at our institution between January 2010 and November 2019 were reviewed. Pediatric transplants, recipients who underwent retransplantation, multiorgan transplants, split LTs, living donor LTs, and LT with donation after circulatory death were excluded. The remaining cases were analyzed.

A matched case–control study using a random matching algorithm analysis was conducted. Patients with grafts from donors with BMI ≥50 were matched in a 1:2 ratio to patients with grafts from donors with BMI <50. In an attempt to reduce confounders as much as possible, primary diagnosis and macrosteatosis percentage on the donor graft were initially considered as parameters for matching criteria. However, no suitable matches could be found when applying those variables and, therefore, were not included. Decision was made to match the super obese donor group based on recipient age (±5 y), donor age (±10 y), and recipient model for end-stage liver disease (MELD) at transplant (±5 points). Demographic variables, surgical variables, postoperative outcomes, and long-term complications in the 2 groups of patients were compared.

BMI categories were defined following the previously established Centers for Disease Control and Prevention classification: normal BMI (18.5–<25), overweight (BMI 25–<30), obesity class 1 (BMI 30–<35), obesity class 2 (BMI 35–40), and obesity class 3 or severe obesity (BMI >40).<sup>9</sup> In addition, to further assess the impact on extremely high BMI donors, we categorize those individuals with BMI ≥50 as “super obese” and limited the obesity class 3 category to those with BMI between 40 and <50.

To further assess the outcomes after using a graft from a super obese donor, a subgroup analysis was performed among the cohort to compare outcomes between adults receiving a graft from nonobese donors (BMI <30) versus those receiving a graft from super obese donors. In addition, a subgroup analysis was performed between the study group and matched cohort according to donor BMI categories.

Because of the retrospective nature of the study, the University of Virginia Institutional Review Board for Health Science Research granted a waiver of Health Insurance Portability and Accountability Act authorization for the present study.

### Donor and Graft Data

The following donor demographics were analyzed and compared between groups: age, gender, BMI, CIT, and warm ischemia time. Donor liver biopsies were obtained on the basis of either the donor or recipient surgeon request when deemed clinically necessary and the percentage of macrosteatosis or microsteatosis that was used for analysis was the one determined by the clinical pathologist used by the organ procurement organization. Macrosteatosis percent was classified as previously described.<sup>10</sup>

### Recipient Data

The following recipient data were collected for analysis: age at the time of LT, gender, primary diagnosis, hepatocellular carcinoma (HCC) diagnosis pretransplant, time on waiting list, recipient BMI, MELD score (lab-MELD and MELD at transplant [exception based]), history of portal vein thrombosis, history of transjugular intrahepatic portosystemic shunt, intraoperative variables, length of hospital stay, laboratory values pretransplant and posttransplant at 48 h, 7 d, 3 mo, 6 mo, and 12 mo; postoperative outcomes; and long-term complications.

### Postoperative Care and Follow-up

Postoperative complications were identified and classified using the Clavien-Dindo classification system for surgical complications.<sup>11</sup> Major complications were defined as grades 3a to 5. If >1 complication occurred in a patient, the more serious event was taken for grading. Graft function after transplantation was assessed clinically and through biochemical markers measured at 48 h, 7 d, 3 mo, 6 mo, and 12 mo after discharge.

Recipient surgical outcomes were analyzed by assessing the length of postoperative intensive care unit (ICU) and hospital stay, as well as the development of postoperative complications and readmission within 30 d following LT.

The overall incidence of acute cellular rejection (ACR) in the first year after transplantation was also identified. ACR was diagnosed by biopsy obtained for clinical indications and determined to be consistent with ACR changes based on Banff criteria parameters, including mixed portal inflammation, bile duct inflammation/damage, and subendothelial inflammation of portal veins or terminal hepatic venules.<sup>12,13</sup> After hospital discharge, all patients were followed in the LT outpatient clinic. Retransplantation rate and long-term outcomes were also analyzed by actuarial graft and patient survival.

### Statistical Analysis

The baseline characteristics of the patients were expressed as median (interquartile range) and mean (±SD) as appropriate for continuous variables and as frequencies with percentages for categorical variables. IBM SPSS Statistics Version 26 was used to analyze the data. For all analyses, 2-tailed  $P < 0.05$  was considered statistically significant. Continuous variables were compared using the Student  $t$  or Mann-Whitney  $U$  tests, as appropriate. Categorical variables were compared using the Pearson chi-square or Fisher exact test, as appropriate. A binary logistic regression model to determine the influence of study variables on major complications was conducted by

backward stepwise selection with 3 blocks including statistically significant variables after univariate analysis and those deemed to be clinically relevant. The first block included recipient's baseline characteristics, the second block included donor and graft's characteristics, and the third block included posttransplant liver function tests. Graft and patient survivals were calculated by the Kaplan-Meier method. Graft failure was defined as retransplantation or death. Outcome for patient survival was death at the moment of data collection.

## RESULTS

From January 2010 to November 2019, 665 consecutive patients underwent LT at our institution. Following the inclusion criteria, 468 cases were reviewed. After a 1:2 matching, 18 patients who received grafts from super obese donors (BMI  $\geq 50$ ) and 36 patients who received grafts from donors with BMI  $< 50$  were generated and compared with each other.

### Donor, Graft, and Perioperative Characteristics

Donor age was similar between groups. There was a significantly lower proportion of grafts from male donors in the donor BMI  $\geq 50$  group versus the donor BMI  $< 50$  group (3 [16.7%] versus 24 [66.7%], respectively;  $P=0.001$ ). By definition, median donor BMI was higher in the donor BMI  $\geq 50$  group compared with the donor BMI  $< 50$  group (55.8 versus 30.2, respectively;  $P\leq 0.001$ ). Among the donor BMI  $< 50$  group, 19.4% of the grafts were recovered from a normal BMI donor, 27.8% from an overweight donor, 33.3% from a donor with obesity class 1, 16.7% from a donor with obesity class 2, and 2.8% from a donor with obesity class 3. CIT and warm ischemia time were similar between groups (Table 1).

Although 77.8% (14/18 donors) of the grafts in the BMI  $\geq 50$  group were biopsied before the transplant by the organ

**TABLE 1.**  
Donor and graft characteristics according to donor BMI

Donor variables	Donor BMI $< 50$ group (n = 36)	Donor BMI $\geq 50$ group (n = 18)	P
Donor age <sup>a</sup>	49.5 (38.2–58.0)	49 (40–54.2)	0.6
Donor male gender (%)	24 (66.7)	3 (16.7)	0.001
Donor BMI <sup>a</sup>	30.2 (25.7–34.7)	55.8 (53.9–59.2)	$< 0.001$
Normal BMI	7 (19.4)	–	
Overweight	10 (27.8)	–	
Obesity class 1	12 (33.3)	–	
Obesity class 2	6 (16.7)	–	
Obesity class 3	1 (2.8)	–	
Cold ischemia time (min) <sup>a</sup>	413 (358–483)	406 (329–474)	0.92
Warm ischemia time (min) <sup>a</sup>	42 (36–48)	45 (38–63)	0.21
Liver biopsy	14 (38.8)	14 (77.8)	0.007
Microsteatosis	n = 7	n = 9	0.04
<5	1 (14.3)	5 (55.5)	
5%–33%	6 (85.7)	3 (33.3)	
34%–66%	0	0	
>66%	0	1 (11.1)	
Macrosteatosis	n = 10	n = 9	0.07
<5	4 (40)	3 (33.3)	
5%–33%	6 (60)	5 (55.5)	
34%–66%	0	1 (11.1)	
>66%	0	0	

<sup>a</sup>Median (interquartile range).  
BMI, body mass index.

procurement organization, only 38.8% (14/36 donors) of the grafts underwent a pretransplant liver biopsy in the donor BMI  $< 50$  group ( $P=0.007$ ). Between those, microsteatosis presence was significantly higher in the donor BMI  $\geq 50$  group, evidenced in 9 grafts versus 7 in the donor BMI  $< 50$  group ( $P=0.04$ ). In contrast, no statistical difference was found with regard to macrosteatosis presence between groups ( $P=0.07$ ). Nine grafts in the donor BMI  $\geq 50$  group and 10 in the BMI  $< 50$  group demonstrated some degree of macrosteatosis; the highest found was 35% in the donor BMI  $\geq 50$  group and 30% in the donor BMI  $< 50$  group. Macro and microsteatosis degrees are summarized in Table 1. Perioperative variables were similar between groups (Table S1, SDC, <http://links.lww.com/TXD/A367>).

### Recipient Preoperative Characteristics

Recipient characteristics such as age, gender, BMI at transplant, lab-MELD, MELD at transplant, and time on waitlist did not differ significantly between the 2 groups (Table 2). It is important to note that there was a higher proportion of overweight recipients in the donor BMI  $\geq 50$  group than in the donor BMI  $< 50$  group (8 [44.4%] versus 7 [19.4%], respectively,  $P=0.053$ ). Distribution of the remaining BMI categories among recipients is displayed in Table 2. Cause of liver disease was similar between groups ( $P=0.08$ ). Nonalcoholic steatohepatitis (NASH) (27.8%) and alcohol cirrhosis

**TABLE 2.**  
Preoperative characteristics of liver transplant recipients according to donor BMI

Recipient variables	Donor BMI $\geq 50$ (n = 36)	Donor BMI $< 50$ group (n = 18)	P
Age at transplant <sup>a</sup>	58 (53–61.5)	58.5 (50–61.2)	0.8
Male gender (%)	29 (80.6)	15 (83.3)	0.8
BMI at transplant <sup>a</sup>	30.3 (24.9–33.2)	28.7 (27.7–33.1)	0.58
Normal BMI	9 (25)	2 (11.1)	0.23
Overweight	7 (19.4)	8 (44.4)	0.053
Obesity I	17 (47.2)	5 (27.8)	0.17
Obesity II	2 (5.6)	2 (11.1)	0.46
Severe obesity	1 (2.8)	1 (5.6)	0.61
INR pretransplant <sup>a</sup>	1.55 (1.3–2.1)	1.5 (1.3–1.6)	0.26
Creatinine pretransplant <sup>a</sup>	1.1 (0.9–1.6)	0.8 (0.7–1.1)	0.03
Total bilirubin pretransplant <sup>a</sup>	3.3 (1.9–8.9)	2.0 (1.5–3.5)	0.11
Lab-MELD <sup>b</sup>	17.6 ( $\pm 8$ )	15.5 ( $\pm 6$ )	0.31
MELD at transplant <sup>bc</sup>	23.5 ( $\pm 6.16$ )	23.3 ( $\pm 5.66$ )	0.89
Time on waitlist (d) <sup>a</sup>	76.5 (14.5–287.7)	100.5 (44–602.2)	0.36
PVT history	7 (19.4)	5 (27.8)	0.48
TIPS	5 (13.9)	4 (22.2)	0.43
Primary diagnosis			0.08
NASH	11 (30.6)	5 (27.8)	
HCV cirrhosis	12 (33.3)	3 (16.6)	
Alcohol cirrhosis	5 (13.8)	4 (22.2)	
HBV cirrhosis	2 (5.6)	1 (5.6)	
Cryptogenic	1 (2.7)	3 (16.7)	
Other	5 (13.8)	2 (11.1)	
HCC diagnosis pre-LT	3 (8.3)	7 (38.9)	0.006

<sup>a</sup>Median (interquartile range).

<sup>b</sup>Mean (SD).

<sup>c</sup>MELD at transplant (exception based).

BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; LT, liver transplantation; NASH, nonalcoholic steatohepatitis; MELD, model of end-stage liver disease; PVT, portal vein thrombosis; SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt.

(22.2%) were the most common primary diagnosis in the donor BMI  $\geq 50$  group, whereas in the donor BMI  $< 50$  were HCV cirrhosis and NASH (33.3% and 30.6%, respectively). In contrast, a significantly higher proportion of recipients with HCC diagnosis were found in the donor BMI  $\geq 50$  group versus the donor BMI  $< 50$  group (7 (38.9%) versus 3 (8.3%), respectively,  $P = 0.006$ ). Preoperative workup and recipient's demographics are summarized in Table 2.

### Postoperative Outcomes

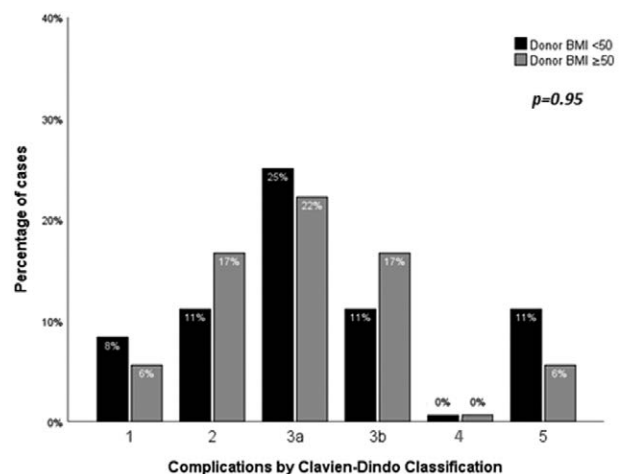
Postoperative liver function test showed improvement within the first week after transplantation and was similar between the 2 groups (Table S2, SDC, <http://links.lww.com/TXD/A367>). Early allograft dysfunction was observed in 1 (5.6%) patient in the donor BMI  $\geq 50$  group, whereas in none in the donor BMI  $< 50$  group ( $P = 0.15$ ). Although not significantly different, post-transplant ICU stay and length of hospital stay were slightly shorter in the donor BMI  $\geq 50$  group (Table 3). According to the Clavien-Dindo classification (Figure 1), there was no statistical difference between the overall complication rate among groups ( $P = 0.95$ ). In both groups, the most common type of postoperative complication was 3a. Although 4 (22.2%) patients experienced this type of complication in the donor BMI  $\geq 50$  group, 9 (25%) patients experienced type 3a complications in the donor BMI  $< 50$  group. All corresponded to patients who had biliary stenosis postoperative and underwent endoscopic retrograde cholangiopancreatography, except for 1 recipient in the donor BMI  $< 50$  group, who developed a large right pleural effusion requiring thoracentesis. The remaining biliary complication in the donor BMI  $< 50$  group corresponded to a bile leak in a patient with overall complication grading of 3b. Major complications within 30 d were diagnosed in 6 (33.3%) recipients in the donor BMI  $\geq 50$  group and in 9 (25%) recipients in the BMI  $< 50$  group ( $P = 0.51$ ). Mortality within 30 d was observed only in 1 (2.7%) recipient in the donor BMI  $< 50$  group. In this case, the patient developed primary nonfunction and died on the fourth postoperative day. Unfortunately, this graft was not biopsied preoperatively, but a postoperative biopsy of this graft showed the presence of 80% macrosteatosis on the graft; donor BMI was 28.7. Because of his complicated postoperative period and poor prognosis, the family decided against the possibility of retransplantation, and therefore, the patient was not relisted. In the donor BMI  $\geq 50$  group, overall mortality occurred in 1 recipient (5.6%) who developed intraoperative coagulopathy with a difficult posttransplant course complicated by development of portal vein thrombosis, early allograft dysfunction, recurrent gastrointestinal bleeding episodes, and a bronchoaspiration event. Despite aggressive management, the recipient died 2 mo after transplantation. This patient received a graft from a donor with BMI of 60.9, with no evidence of microsteatosis and 10% of macrosteatosis. The remaining 3 mortality causes in the donor BMI  $< 50$  group occurred within the first year and were attributed to graft versus host disease, multiple postoperative complications, and multiple organ failure due to widely metastatic high-grade neuroendocrine carcinoma on a patient with recently diagnosed cryptogenic cirrhosis, respectively. Of note, the neuroendocrine carcinoma was diagnosed on explant pathology, where it was found to have metastasis to lymph nodes. The biliary complication rate within the first 30 d posttransplant was not different between groups (BMI  $\geq 50$  group = 3 [16.7%] versus BMI  $< 50$  group = 6 [16.7%],  $P = 1.0$ ). Table 3 summarizes the postoperative outcomes.

**TABLE 3.** Postoperative outcomes of liver transplant recipients according to donor BMI

Postoperative outcomes	Donor BMI $< 50$ group (n = 36)	Donor BMI $\geq 50$ group (n = 18)	P
Overall complications (%)	17 (47.2)	10 (55.6)	0.56
Overall complication within 30 d (%)	20 (55.6)	7 (38.9)	0.24
Major complication within 30 d (%)	9 (25)	6 (33.3)	0.51
Readmission within 30 d	7 (19.4)	6 (33.3)	0.28
Mortality (%)	4 (11.1)	1 (5.6)	0.5
30 d mortality (%)	1 (2.7)	0	
Primary nonfunction (%)	1 (2.8)	0	0.45
Early allograft dysfunction	0	1 (5.6)	0.15
Posttransplant ICU stay (d) <sup>a</sup>	1.79 (1.16–3.53)	1.54 (0–2.3)	0.34
LOS from LT to discharge (d) <sup>a</sup>	7.5 (5–10.7)	7 (5.7–10)	0.67
Biliary complications within 30 d (%)	6 (16.7)	3 (16.7)	1.0
Biliary complications within 1 y (%)	9 (25)	6 (33.3)	0.51
Vascular complications (%)	3 (8.3)	5 (27.8)	0.058
Reoperation within 1 y (%)	5 (13.9)	1 (5.6)	0.35
ACR within 1 y (%)	7 (19.4)	3 (16.7)	0.8
NASH recurrence	4/11 (36.3)	2/5 (40)	0.88
Retransplant (%)	0	1 (5.6)	0.15
Follow-up time (d) <sup>a</sup>	738.5 (195.2–1775.7)	1689.5 (637.5–2323.2)	0.059
1-/3-/5-y graft survival (%)	88/88/88	94/89/89	0.89
1-/3-/5-y patient survival (%)	88/88/88	94/94/94	0.48

<sup>a</sup>Median (interquartile range).

ACR, acute cellular rejection; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; LT, liver transplant; NASH, nonalcoholic steatohepatitis.



**FIGURE 1.** Overall complications according to Clavien-Dindo classification for patients following liver transplantation with grafts from donors with BMI  $\geq 50$  vs donors with BMI  $< 50$ . BMI, body mass index.

Between the patients with pretransplant NASH diagnosis, NASH recurrence rate was similar among groups, seen in 2 of 5 (40%) patients in the donor BMI  $\geq 50$  group, and in 4 of 11 (36.3%) patients in the donor BMI  $< 50$  group ( $P = 0.88$ ). Only 2 patients had recurrence within the first year, both from the donor BMI  $< 50$  group.

A logistic regression model was performed to determine the effects of statistically significant and clinically relevant variables on the likelihood of recipients developing major complications. The first block in the model included age at transplant, pretransplant diagnosis of HCC, pretransplant diagnosis of HCV, albumin level pretransplant, and MELD score at transplant. The second block included donor gender, donor BMI, and ischemic times. Finally, the third block included peak bilirubin and creatinine level within 7 d. The model showed no associations on any of the included variables with the development of major complications (Table 4).

Although recipients in the donor BMI  $\geq 50$  group versus donor BMI  $< 50$  group had higher 1-, 3-, and 5-y graft survival (94%, 89%, and 89% versus 88% for all time periods, respectively,  $P = 0.89$ , log rank [Mantel-Cox]), the difference was not statistically significant. Likewise, patient survival at 1-, 3-, and 5-y was higher in the donor BMI  $\geq 50$  group versus donor BMI  $< 50$  group (94%, 94%, and 94% versus 88%, 88%, and 88%,  $P = 0.48$  log rank [Mantel-Cox]) without reaching statistical significance. Figure 2A and B depict the survival curves obtained for graft and recipients from each donor group, respectively. Overall graft survival among the entire ( $N = 468$ ) non-super obese cohort was 98%, 94%, and 75% at 1-, 3-, and 5-y, respectively, with patient survival rates at 1-, 3-, and 5-y of 99%, 95%, and 77%, respectively. Graft and patient survival did not differ significantly among the entire non-super obese cohort versus the super obese donor group. The lower graft and patient survival rate seen in the donor BMI  $< 50$  group can be attributed to random matching selection of recipients in the control group not reflecting the entire cohort as shown in the overall graft and patient survival rates for the non-super obese cohort.

**TABLE 4.**

**Logistic regression model to determine the effects of statistically significant variables on the likelihood of recipients developing major complications**

Variables in the equation	P	Exp (B)	95% CI	
			Lower	Upper
Age at transplant	0.33	0.88	0.68	1.13
HCV <sup>a</sup>	0.70	0.53	0.02	13.95
HCC diagnosis pretransplant	0.98	0.97	0.07	12.81
Albumin level pre-LT (g/dL) <sup>a</sup>	0.13	17.8	0.39	804.4
MELD score at transplant	0.94	1.0	0.82	1.22
Donor gender <sup>a</sup>	0.11	0.91	0.005	1.81
Donor BMI	0.93	0.99	0.89	1.10
Cold ischemia time	0.31	0.98	0.96	1.01
Warm ischemia time	0.64	1.03	0.89	1.20
Peak bilirubin level within 7 d posttransplant <sup>a</sup>	0.45	1.16	0.78	1.71
Peak creatinine level within 7 d posttransplant <sup>a</sup>	0.82	1.11	0.42	2.91

<sup>a</sup>Variables statistically significant after univariate analysis.

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; MELD, model of end-stage liver disease.

## Subgroup Analyses

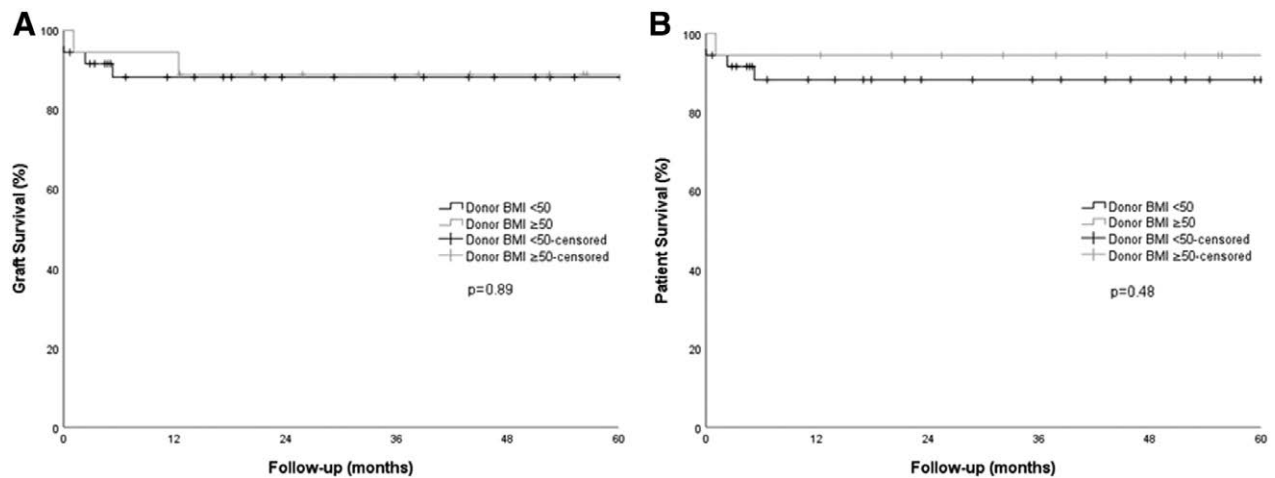
As the control group also included donors with some degree of obesity, a subgroup analysis was performed among the cohort to compare outcomes between adults receiving a graft from nonobese donors (BMI  $< 30$ ,  $n = 17$ ) versus those receiving a graft from a super obese donors ( $n = 18$ ). When the subgroup analysis was performed, no differences between groups were found regarding recipient baseline characteristics including age, gender, BMI, lab-MELD, and MELD score at transplant or time on waitlist. Also, no differences were found between groups in terms of postoperative complications, readmission rate, graft rejection, or major complications including the need for reoperation, liver retransplantation, or mortality. The early major complication rate was 29.4% in the nonobese group and 33.3% in the super obese group, but no statistically significant differences were found. In addition, to further assess the outcomes between the recipients in the donor BMI  $\geq 50$  group versus those receiving a graft from non-super obese donors, a subgroup analysis was performed between the study group and matched cohort ( $n = 54$ ) according to donor BMI categories, results from this subset analysis can be found in Table S3 (SDC, <https://links.lww.com/TXD/A367>).

## DISCUSSION

In the present study, outcomes following LT using grafts from super obese donors (BMI  $\geq 50$ ) were evaluated and compared with grafts from donors with BMI  $< 50$ . Major complications and biliary complications were low and not different between groups. In addition, no significant differences in graft and patient survival following LT were found between using grafts from super obese donors versus non-super obese donors. We found a significantly higher rate of HCC diagnosis pretransplant between the recipients in the donor BMI  $\geq 50$  group, as well as a predominance of female donors in this group.

Obesity rates have been trending up among adults in the United States over the past 2 decades.<sup>5,6</sup> Although the importance of donor BMI in LT outcomes is commonly mentioned, its role as an independent factor is not well characterized. Molina Raya et al<sup>14</sup> conducted a study with the aim to analyze LT outcomes according to donor BMI comparing recipients receiving a graft from an obese donor (BMI  $\geq 30$ ) versus those from a nonobese donor (BMI  $\leq 30$ ). The authors found no differences in survival or posttransplant complications among groups, with the exception of a longer, but not clinically relevant, ICU stay. Similarly, our study, which included a much higher donor BMI group, did not find significant differences in outcomes between the study groups.

Regarding the use of marginal livers, one of the most studied criteria is the presence of steatosis in the donor graft. Steatosis is found frequently in liver biopsies from obese patients, and previous studies suggest an association between the degree of steatosis and the incidence of serious postoperative complications such as initial poor function and primary nonfunction.<sup>15-17</sup> In a recent analysis of the Organ Procurement and Transplantation Network/United Network for Organ Sharing database, Northup et al<sup>17</sup> found that a high macrosteatosis graft paired with a high BMI recipient increases mortality risk up to 1 y after transplant for a LT recipient. The combination of both a high macrosteatosis graft and a high BMI recipient yielded the worst outcomes, whereas a low macrosteatosis graft into a normal BMI recipient gave the best survival. In



**FIGURE 2.** Kaplan-Meier curves for graft and patient survival following liver transplantation with grafts from donors with BMI  $\geq 50$  vs donors with BMI  $< 50$ . A, Graft survival,  $P=0.89$ , log rank (Mantel-Cox). B, Patient survival,  $P=0.48$ , log rank (Mantel-Cox). BMI, body mass index.

our study, a subgroup analysis of the obese recipients (BMI  $> 30$ ) receiving a graft from a super obese donor (BMI  $\geq 50$ ) showed no significant association between the presence of macrosteatosis and pairing of an obese recipient with a super obese donor in the development of major complications within the first year ( $P=0.23$ ; Table S4, SDC, <http://links.lww.com/TXD/A367>). Out of the 8 recipients in this subgroup, only 1 (12.5%) had a major complication. As only 1 graft among that subgroup had evidence of high macrosteatosis, we were not able to truly find an association between high macrosteatosis and the development of complications among obese recipients–super obese donors pairing. The deleterious effects of using a high macrosteatosis graft in an obese recipient reported in larger series should be taken into account when deciding to use these types of graft–recipient matching scenarios.<sup>17</sup> In regards to microsteatosis, previous studies have not found an association with microsteatosis degree and post-transplant outcomes.<sup>17</sup> In our study, microsteatosis was found to be significantly more prevalent in the donor BMI  $\geq 50$  than in the donor BMI  $< 50$  group; however, the percentage of biopsied grafts was less than half in both groups, limiting our ability to draw strong conclusions on microsteatosis role.

Based on the fact that there is significant inter and intra-observer variability when quantifying steatosis in a donor liver biopsy, which is aggravated by frozen section artifacts, Sun et al developed a deep learning convolutional neural network (CNN) that generates a steatosis probability map from a whole slide image and calculates the percent of steatosis. The authors analyzed 96 whole slide images from 91 individual donors evaluated by their institutional transplant pathology service during a 20-mo period. Only annotations on macrovesicular steatosis were included. Interobserver agreement was analyzed and compared with CNN predictions finding that the model has superior performance in steatosis estimation compared with the on-service pathology at the time of transplant evaluation. Although the deep learning model was found to have lower sensitivity than the on-service pathology for identifying a case with  $> 30\%$  steatosis, it had higher specificity (71.4% versus 80.9% and 97.3% versus 85.3%, respectively). The authors found that the model incorrectly classified 2 slides as  $> 30\%$  compared with 11 by the on-service pathologist, meaning that if a 30% steatosis cutoff were used as a threshold for not using an organ, the CNN model would result in 9% fewer organs

being discarded.<sup>18</sup> These findings demonstrate the important role of donor biopsy to make an adequate decision to use or decline a graft for transplantation. In our cohort, a significant amount of donors did not undergo a biopsy, even in the super obese donor group. More donor liver biopsies should be done and standardization of steatosis assessment among transplant centers should be pursued. Therefore, uniformity of degree of steatosis assessment/read among transplant centers is necessary to improve decision making regarding organ utilization. We suggest that to safely expand the donor pool, the decision to decline donor grafts should not be made solely based on BMI and instead a liver biopsy should be performed before declining a liver offer from obese donors.

Interestingly, we found a significantly higher proportion of female donors in the donor BMI  $\geq 50$  group when compared with the donor BMI  $< 50$  group. This could be explained by the important role of gender in the distribution among subcutaneous adipose tissue and visceral adipose tissue (omental and mesenteric). Different factors play a role in this distribution disparity, such as sex steroids and genetic determinants.<sup>19</sup> Overall, at comparable levels of total body adiposity, women tend to have lower intra-abdominal/visceral fat mass when compared with men and more subcutaneous white adipose tissue deposits in the abdominal and gluteofemoral area.<sup>19</sup> This could explain the reason why, despite the high BMI in these female donors, the macroscopic liver aspect and microscopic characteristics were still under criteria to be transplanted. Further evaluation of outcomes of grafts recovered from super obese female donors is needed.

Although at the moment we do not have an established protocol on the use of liver graft from super obese donors in our institution, as observed in the results, we tend to use these grafts on lower-risk patients who are in need of transplantation but have poor access to it. In general, we try to allocate these grafts to patients without previous abdominal surgery, with lower lab-MELD scores, and low BMI if possible so that recipient hepatectomy is easier, with less bleeding and therefore have a higher chance of keeping CIT as short as possible. In addition, further considerations need to be taken into account to reduce potential overexpenses of resources that comes with the recovery of these super obese donors' grafts, especially in the present era, in which the increasing demand of organs has forced to increased use of extended criteria donors for graft retrieval.<sup>20</sup>

The present study has several limitations. Its retrospective nature and small sample size could potentially result in confounding factors that favor the use of super obese donor grafts. Additionally, there is inherent selection bias, which we seek to minimize by the matching approach. Including primary diagnosis and macrosteatosis degree on the matching criteria could have provided more representative results. However, 1:2 ratio for indication for transplant was not possible for 2 of the patients in the donor BMI  $\geq 50$  group, and because of the high percentage of grafts not being biopsied in the control group and the absence of macrosteatosis in half of the study group, we were not able to include it in the matching algorithm. Having this in mind, the results proposed in this article should be interpreted with caution. Further investigations with a larger number of patients would be warranted to minimize type II error. Despite these limitations, given the fact that there is scarce knowledge regarding the implications of super obese donor graft use, this study provides a starting point in characterizing outcomes following LT with high BMI donors.

In conclusion, based on our findings, LT with grafts from super obese donors can be performed with acceptable recipient outcomes in well-selected donor and candidate populations. Congruent outcomes as those of donors with BMI within normal or overweight range can be achieved, contributing to the expansion of the liver organ pool. Particular consideration should be taken into account when facing an offer from a super obese female donor as these grafts could have suitable characteristics despite the donor's BMI. Particular consideration should be taken into account when facing an offer from a super obese female donor as these grafts could have suitable characteristics despite the donor's BMI. Consideration to use these grafts should be made as well in more stable recipients, such as those with lower native-MELD and pretransplant MELD driven by exception points (HCC). Therefore, livers from donors with high BMI should not be routinely declined out of hand but instead be considered for donor biopsy and possibly transplanted to carefully selected adult candidates after complete assessment.

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