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Liver Transplantation in Recipients With Class III Obesity: Posttransplant Outcomes and Weight Gain

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Background. There has been a dramatic increase in obesity in the United States. Several studies have reported conflicting results for the impact of obesity on outcomes of liver transplantation (LT). This study aims to assess the impact of obesity on LT and changes in body mass index (BMI) after transplantation. **Methods.** All adult LTs performed at Indiana University between 2001 and 2018 were reviewed. BMIs of recipients were subdivided into 6 categories. Survival outcomes were compared across the subgroup. BMI was followed up in a cohort of patients from 2008 to 2018. **Results.** Among 2024 patients, 25% were in class I obesity, 9.3% were in class II obesity, and 1.1% were in class III obesity. There was no significant difference in patient and graft survival at 10-y follow-up with respect to BMI. Among 1004 patients in the subgroup, BMI of all groups except the underweight group declined in the first 3 mo postoperatively; however, the BMI of all groups except the class III obesity group returned to the pre-LT level by 2 y and reached a plateau by 5 y. In the class III obesity group, there was a significant increase in body weight at 5 y. **Conclusions.** Class III obesity was not associated with higher mortality in our cohort. Because our cohort is small, it may be underpowered to detect a smaller difference in outcome. From our observation, obesity should not be considered a contraindication for LT. Post-LT interventions are required to prevent significant weight gain for the class III obesity group.

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Over the past decades, there has been a dramatic increase in obesity in the United States. In 2015 to 2016, the prevalence of obesity was 39.8% in adults and 18.5% in youth.[1]

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By 2030, estimates suggest that >50% of the US population will have a body mass index (BMI) ≥30 kg/m^2.[2] Because of an increase in the prevalence of obesity, the number of obese patients undergoing liver transplantation (LT) and candidates awaiting LT is rising rapidly in the United States. The proportion of candidates with BMI ≥40 kg/m^2 continues to increase, and approximately 1 in 6 candidates (17%) are with BMI ≥35 kg/m^2.[3]

Several studies have reported conflicting results on the impact of severe obesity on outcomes of LT.[4-15] Some centers and insurance payers have set a cutoff for BMI to list candidates at BMI >40 kg/m^2. Currently, the American Association for the Study of Liver Disease considers morbid obesity (BMI ≥40 kg/m^2) as a relative contraindication for LT because these patients are at higher risk of posttransplant complications and mortality.[16] Practice guidelines of the European Association for the Study of the Liver also recommend that a multidisciplinary team should carefully evaluate patients with a BMI ≥35 kg/m^2 before listing[17]; however, morbidly obese patients have higher waitlist mortality rates, and morbid obesity is an independent risk factor for acute-on-chronic liver failure.[12,18,19] Based on this fact, some centers offer LT to carefully selected patients with morbid obesity.

Currently, the suitability of patients with morbid obesity for LT remains controversial. Furthermore, the post-LT course of body weight in obese patients is not well characterized. The purpose of this study is to assess the impact of pre-LT BMI on postoperative outcomes, including graft survival, patient survival, and change in body weight post-LT.

MATERIALS AND METHODS

Study Population

This was a single-center retrospective study. All adult LTs, which were performed at Indiana University Health University Hospital between July 2001 and December 2018, were reviewed. Retrospective analysis of patient data from the transplant center database was approved by the institutional review board. Pediatric recipients (<18 y), retransplant candidates, and combined liver-kidney transplant recipients were excluded. Recipients were subdivided into 6 groups based on BMI at transplant: underweight, normal, overweight, class I obesity, class II obesity, and class III obesity (<18.5, 18.5–24.9, 25–29.9, 30–34.9, 35–39.9, ≥40 kg/m^2, respectively). Posttransplant BMI was monitored in a subgroup of patients receiving LT from January 2008 to December 2018. BMI was not adjusted for ascites because the volume of ascites drained at the time of transplant did not differ significantly between groups.

Listing and Preoperative Management

Recipient listing for LT was according to standard criteria and protocols as established by our center and the United Network for Organ Sharing. In our program, surgeons evaluate pretransplant patients carefully based on the body habitus and feasibility of LT from a surgical standpoint. Obese patients are considered to have higher cardiovascular risk. Patients at risk for coronary artery disease undergo a coronary angiogram and stress test.[20] In the case of ≥50% stenosis in a major coronary artery (left anterior descending artery or right coronary artery) or critical disease defined as stenosis ≥70% in at least moderate-sized branch vessels, percutaneous coronary intervention was performed before LT.[20]

Surgical Procedure

Organ procurements for brain-dead donors were performed using standard surgical techniques and cold preservations. The technique and optimization protocol of donor after circulatory death liver procurement was previously described.[21,22] The detail of recipient operation was described previously.[23] Briefly, our center applied the piggyback technique to preserve native vena cava without using a venovenous bypass.[24] Before reperfusion, the liver grafts were routinely flushed with 3 L of albumin solution at room temperature through the portal vein. Hepatic artery anastomosis was performed after reperfusion of the portal vein. Coagulopathy was corrected as directed by thromboelastogram. These patients were routinely sent to a closed transplant intensive care unit.

Statistical Analysis and Endpoints

The primary endpoints were long-term patient survival and graft survival after LT. The secondary outcomes were short-term outcomes, including 90-d graft and patient survival, operative components, and complications. The Kaplan-Meier method was used to estimate the graft and patient survival in each group. The log-rank test was used to analyze the differences in survival across groups. The association between BMI categories and patient survival and graft survival was assessed using multivariate Cox regression analysis. The multivariate Cox regression analysis included the potential confounding factors in the model (donor age, model for end-stage liver disease score, donor after circulatory death, and year of transplant). The hazard ratio and its 95% confidence interval from both univariate and multivariate Cox proportional regression analyses are summarized and plotted. The Mann-Whitney U test was used to analyze secondary outcomes between the class III obesity group and others. The Wilcoxon-Mann-Whitney test and the Friedman test were used to compare the BMI changes among groups. *P* values were reported as statistically significant at <0.05 for all analyses. *P* values approximating 0.1 were described as a trend. All statistical analyses were conducted with SPSS MacOS version 26 (SPSS, Inc; Chicago, IL).

RESULTS

Study Population

A total of 2024 patients who underwent LT were included in the study. The percentages of patients in each BMI category were as follow: 1.9% underweight, 24.5% normal, 32.6% overweight, 25% class I obesity, 9.3% class II obesity, and 1.1% class III obesity. The median age was 55 y, 66.7% were male, and the patients diagnosed with chronic hepatitis C, nonalcoholic steatohepatitis (NASH), and hepatocellular carcinoma were 37%, 17%, and 20.5%, respectively. The median follow-up period was 5.5 y. The median length on the waitlist was 41 d. Demographics and clinical characteristics of patients at transplant are summarized in Table 1.

Impact of Morbid Obesity on the Outcome of LT

Primary outcomes are summarized in Table 2. Patient and graft survival for recipients with class III obesity were comparable with other groups (log-rank $P = 0.35$ and 0.21, respectively) (Figure 1). Numerically, the patient survival for recipients with class III obesity was 97.0%, 92.1%, 87.0%, and 79.8% at 1, 3, 5, and 10 y. The graft survival for recipients with class III obesity was 94.4%, 85.1%, 79.8%, and 72.5% at 1, 3, 5, and 10 y. By Cox regression analysis, there was no significant difference in patient and graft survival in each BMI group. Secondary outcomes are summarized in Table 3. The class III obesity group had similar short-term outcomes, including operative components and complications, with other BMI groups.

Post-LT Weight Gain

A total of 1004 patients were included in the subgroup analysis. The BMI follow-up data (Figure 2) showed that all groups' mean BMIs except for the underweight group decreased significantly in the first 3 mo after LT. After this initial 3-mo period, all groups' BMIs except the class III obesity group returned to the pre-LT level within 2 y and reached a plateau at 3 to 5 y. In patients with class III obesity, there was a significant increase in BMI at long-term follow-up with BMI of 45.51 kg/m^2 from pre-LT BMI of 41.3 kg/m^2 ($P = 0.04$).

DISCUSSION

In this single-center study, we found out that morbid obesity is not associated with inferior post-LT survival outcomes when compared with nonobese patients. The 10-y patient survival for recipients with the class III obesity group was 80%. Our study is the largest single-center study in the United States with long-term follow-up. Contrary to our findings, Conzen et al[9] reported that recipients with BMI of >40 kg/m^2 had significantly inferior 5-y graft (49.0% versus 75.8%; $P < 0.02$) and patient (51.3% versus 78.8%; $P < 0.01$) survival.[9] Their BMI of >40 kg/m^2 cohort includes 26 patients consisting of 3.3% of their entire cohorts. Giorgakis et al reported mean graft

TABLE 1.

Demographics and clinical characteristics of recipients

	BMI <18.5 (n = 38; 1.9%)	BMI 18.5–24.9 (n = 496; 24.5%)	BMI 25–29.9 (n = 660; 32.6%)	BMI 30–34.9 (n = 507; 25%)	BMI 35–39.9 (n = 188; 9.3%)	BMI ≥40 (n = 23; 1.1%)
Age (y)	47	52	54	55	54	55
Male	19 (50%)	313 (63.1%)	467(70.8%)	342 (67.5%)	124 (66%)	8 (34.8%)
MELD	20	19	19	19	19	20
Cause						
HCV	9 (23.7%)	173 (34.9%)	286 (42.1%)	172 (33.9%)	68 (36.2%)	5 (21.7%)
NASH	1 (2.6%)	43 (9.7%)	82 (12.4%)	127 (25%)	73 (38.8%)	10 (43.5%)
HCC	9 (23.7%)	95 (19.2%)	143 (21.7%)	106 (20.9%)	39 (20.7%)	4 (17.4%)
Comorbidity						
DM	4 (10.5%)	74 (14.9%)	128 (31.2%)	126 (24.9%)	45 (23.9%)	9 (39.1%)
HTN	6 (15.8%)	69 (13.9%)	113 (27.6%)	117 (23.1%)	49 (26.1%)	8 (34.8%)
CKD	5 (13.2%)	55 (11.1%)	67 (16.3%)	64 (12.6%)	19 (10.1%)	2 (8.7%)
Graft type						
DBD	35 (92.1%)	432 (87.1%)	551 (83.5%)	424 (83.6%)	174 (92.6%)	22 (95.7%)
DCD	3 (7.9%)	64 (12.9%)	109 (16.5%)	83 (16.4%)	14 (7.4%)	1 (4.3%)
Follow-up, mo	88	73	74	72	61	77

Continuous variables were expressed as a median.
BMI, body mass index; CKD, chronic kidney disease; DBD, donor after brain death; DCD, donor after circulatory death; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, arterial hypertension; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis.

TABLE 2.

Patient and graft survival

	BMI <18.5	BMI 18.5–24.9	BMI 25–29.9	BMI 30–34.9	BMI 35–39.5	BMI ≥40
Graft survival, %						
1 y	86.8	87.3	89.9	88.8	89.4	94.4
3 y	81.2	81.3	82.0	83.0	81.0	85.1
5 y	78.2	75.0	74.2	80.5	77.1	79.8
10 y	71.4	62.5	59.7	67.7	63.7	72.5
Patient survival, %						
1 y	92.1	88.7	90.9	89.7	90.3	97.0
3 y	86.5	82.7	83.4	84.4	81.8	92.1
5 y	80.1	77.2	76.1	82.1	78.5	87.0
10 y	76.6	66.8	61.4	70.0	66.5	79.8

Continuous variables were expressed as a median.
BMI, body mass index.

survival and patient survival of recipients with BMI <35 kg/m^2 and BMI ≥35 kg/m^2 were similar with 10-y follow-up; however, this study did not evaluate outcomes for recipients with BMI >40 kg/m^2.[25] Until now, many single-center studies and national database studies have evaluated the impact of obesity on outcomes after LT. Nevertheless, no other single-center study has evaluated the outcomes in recipients with class III obesity undergoing LT. Moreover, national database studies are not ideal for addressing this specific issue because of the heterogeneity in listing and transplantation practices in obese patients.

At our center, class III obese patients were carefully selected from a surgical standpoint. Surgeons examined the body habitus of patients with class III obesity for operative suitability. The feasibility of LT is assessed by surgeons with physical examination to assess the "upper abdominal domain" of the recipients, as well as careful assessment of the computed tomography scans, taking into consideration the size of the liver, intraabdominal mesenteric fat, etc. Finally, the feasibility of transplantation in obese patients is subjective and largely based on surgeons' surgical expertise, skills, and experience. We recognize that these operations can be complicated, and to achieve a high success rate, we use 2 attending surgeons and 1 transplant surgery trainee in these procedures. All obese patients were encouraged to lose weight through dietary modifications and exercise. Transplant dieticians followed all obese and malnourished patients; however, a strict weight-loss criterion for candidacy was not used. In general, obese patients with portal vein thrombosis or with anticipated complicated surgery were considered high risk. These careful selection criteria in obese candidates could have contributed to better outcomes in our study. Therefore, a selection bias may be present by which obese patients with other adverse factors may have been excluded and never added to the waiting list. Such a bias would have the effect of reducing the measured differences in outcome among BMI categories. In addition to the stricter criteria for listing, our center adopted aggressive coronary artery disease screening with cardiac catheterization, which is associated with the low rate of myocardial infarction and cardiac mortality after LT.[20,26] Because coronary artery disease is an independent predictor of poor outcome after LT,[27] these center-specific valid patient screenings and interventions prior LT could have led to better outcomes in the class III obesity group.

Regarding post-LT weight gain, although we observed a BMI increase in our class III obesity group, long-term graft

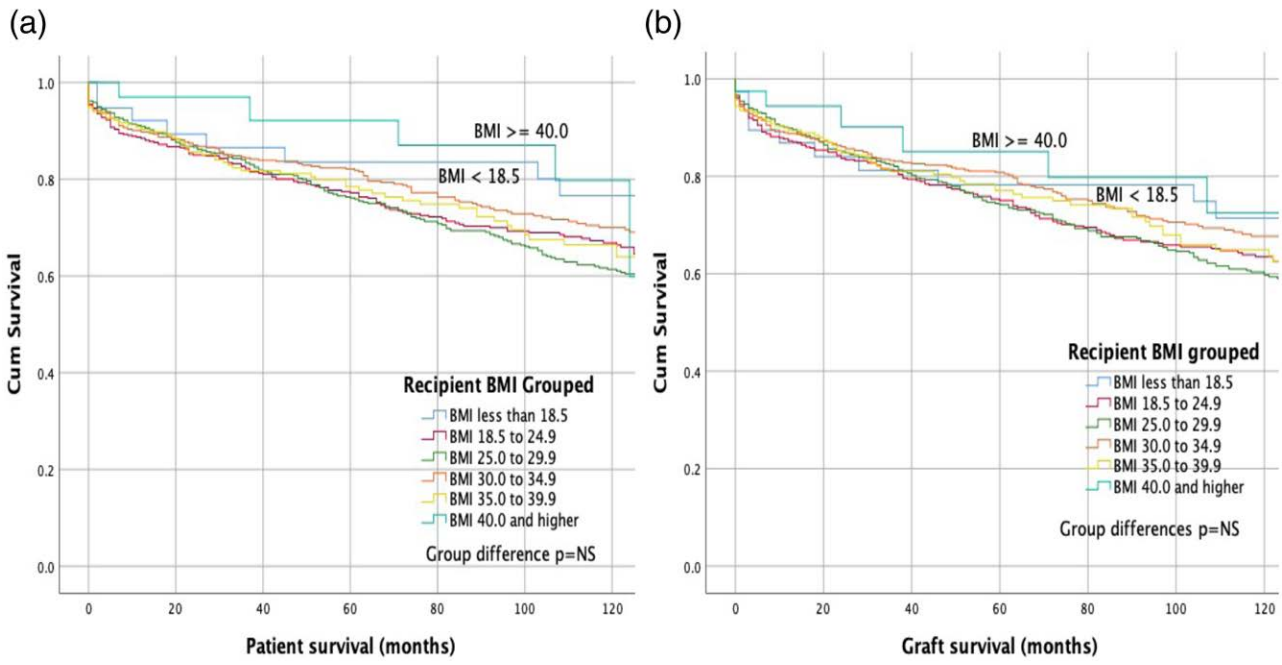

FIGURE 1. Overall patient survival at 10-y follow-up (A) and graft survival (B). BMI, body mass index; NS, not significant.

TABLE 3.

Short-term outcomes

	BMI <18.5	BMI 18.5–24.9	BMI 25–29.9	BMI 30–34.9	BMI 35–39.9	BMI ≥40	*P*
Procedural factors							
CIT, h	6.8	6.1	6.0	6.0	6.2	6.0	0.82
WIT, min	23	23	24	24	24	21	0.10
EBL, mL	1250	1000	800	1000	1000	675	0.45
Complication							
Myocardial infarction	0	1.9	2.3	3.0	2.0	0	0.56
Stroke	0	1.2	0.3	2.3	0	0	0.70
Wound infection	7.9	6.7	7.0	6.8	9.6	0	0.53
DVT	0	3.1	1.4	3.0	0	7.1	0.20
Short-term outcome							
EAD	39.5	28.4	27.6	29.1	31.9	40.9	0.22
ICU stay, d	4.0	3.0	3.0	4.0	4.0	6.5	0.13
Hospital stay, d	10.0	9.0	10.0	10.0	10.0	10.0	0.38
90-d graft survival	91.7	92.5	93.9	93.7	93.0	96.4	0.51
90-d patient survival	94.4	93.5	94.7	94.3	93.0	100	0.18

Continuous variables were expressed as a median.
BMI, body mass index; CIT, cold ischemia time; DVT, deep vein thrombosis; EAD, early allograft dysfunction; EBL, estimated blood loss; ICU, intensive care unit; WIT, warm ischemia time.

and patient survival were comparable with other groups. The cause of end-stage liver disease varied across the BMI groups. In our cohorts, NASH was dominant in the class III obese group. Lattanzi et al[28] reported that patients' BMIs transplanted for NASH increased progressively at 3 to 5 y after LT. In contrast, the BMI of patients transplanted for other causes reached the pre-LT level at 3 y and plateaued after that. Thus, the reason for remote BMI increase in our class III obesity group can be explained by the dominancy of NASH cause in this group. From previous studies, an increase of post-LT BMI in obese patients is associated with an inferior outcome. Patients with obesity tend to gain weight and develop metabolic syndrome after LT.[29] LT recipients who develop posttransplant metabolic syndrome have a higher risk of vascular-related morbidity and mortality.[30] The increased incidence of posttransplant diabetes mellitus is associated with a worse outcome of LT.[31] Currently, our institution manages post-LT obese patients with active weight-loss programs, including standard lifestyle advice, dietary modification, and physical therapy; however, emerging evidence showed that office-based lifestyle intervention was ineffective in achieving weight loss in LT recipients.[32] Thus, even our study showed the long-term graft and patient survival of the class III obesity group was comparable with other groups, we should consider more aggressive post-LT intervention to prevent long-term BMI increase for the class III obesity group.

This study has several limitations. First, this is a single-center study, and the number of recipients is small compared with national registry studies. It may be underpowered to detect smaller differences of outcome in each

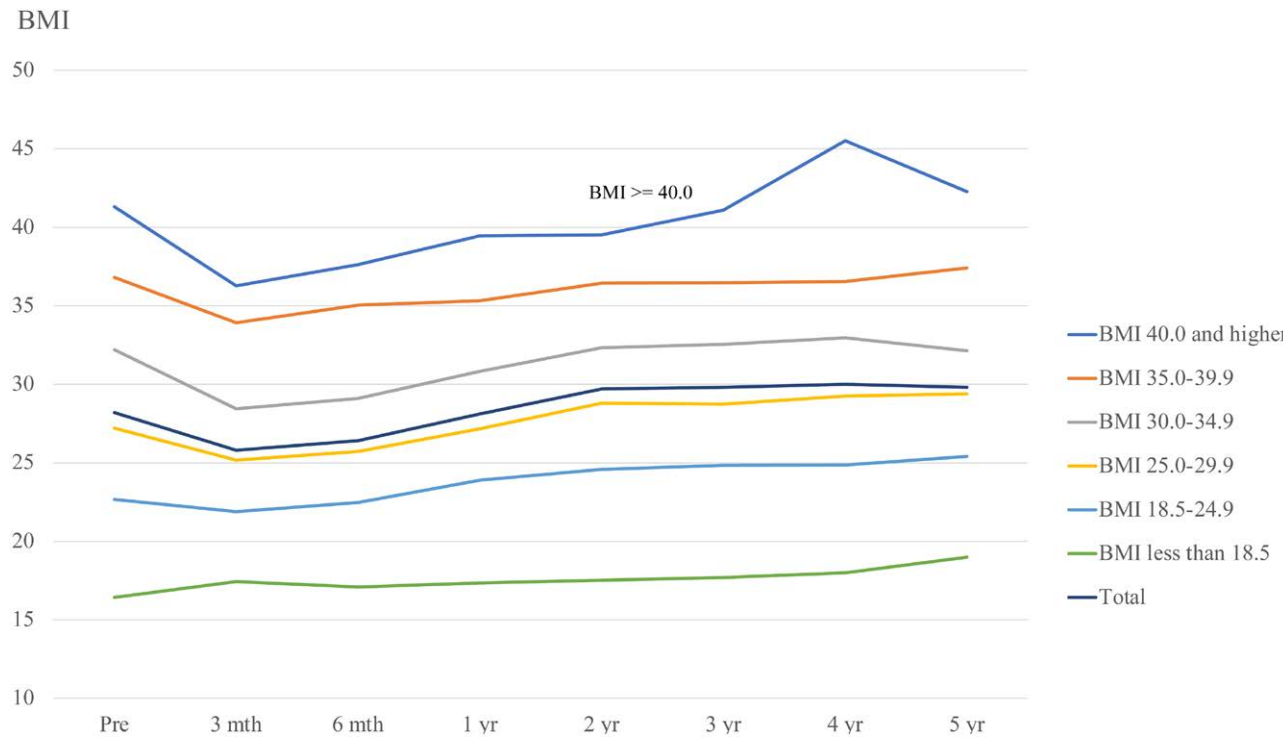

FIGURE 2. BMI trend after liver transplantation at 5-y follow-up. BMI, body mass index.

BMI group. These findings may also reflect our center-specific technique, management, and recipient selection process and may not be able to generalize to other centers. Second, we only studied recipients with BMI ≥40 kg/m^2 who were transplanted because we had to have the outcomes of these transplants, and, thus, our results may not generalize to every potential recipient with BMI ≥40 kg/m^2. Third, the number of patients with BMI ≥40 kg/m^2 in our cohort consists of only 1.1% of the whole cohort. Thus, the outcomes can be purely based on this bias. There is a tendency that might show poorer outcomes in morbidly obese recipients. To address this, we need more case volumes to analyze this tendency.

CONCLUSIONS

This study showed that morbid obesity in cirrhotic patients is not associated with higher posttransplantation mortality in our cohort. Because our cohort is small, it may be underpowered to detect a smaller difference in outcome. From our observation, obesity, including class III obesity, should not be considered to be a contraindication to LT in the absence of other risk factors.

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