Liver transplantation in recipients with class III obesity: post-transplant outcomes and weight gain

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Abstract

Background

Over the past decades, 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 severe obesity's impact on LT outcomes and changes in body mass index (BMI) after transplantation.

Methods

All adult LT performed at Indiana University Health University Hospital between July 2001 and December 2018 were reviewed. A retrospective analysis for identified 2024 patients was conducted. BMI of recipients is subdivided into 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/m², respectively). Survival outcomes were compared between each group. Post-transplant BMI was followed up in a sub-group of patients receiving LT from January 2008 to December 2018. A retrospective analysis for identified 1004 patients was conducted.

Results

Among 2024 patients in the analytic cohort, 1.9% were underweight, 24.5% were normal, 32.6% were overweight, 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-year follow-up with respect to recipient obesity. The 1, 3, 5, and 10-year graft and patient survivals in class I obesity group were 97.0%, 92.1%, 87.0%, and 79.8% for patient survival and 94.4%, 85.1%, 79.8%, and 72.5% for graft survival.

Among 1004 patients identified in the sub-group, BMI of all groups except the underweight group declined in the first three months postoperatively. After the three months, the BMI of all groups except the class I obesity group returned to the pre LT level by two years and reached a plateau by five years. In patients with class I obesity, there was a significant increase in body weight after long-term follow-up.

Conclusion

In this study, class I obesity is not associated with higher mortality. Obesity, including class I obesity, should not be considered a contraindication to LT in the absence of other contraindications. Post-LT interventions are required to prevent significant weight gain in recipients with class I obesity after transplantation.

Background

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

By 2030, estimates suggest that >50% of the US population will have a body mass index (BMI) ≥ 30 kg/m².² Due to 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/m² continued to increase, and approximately one in six candidates (17%) are with BMI ≥ 35 kg/m².³

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/m². Currently, the American Association for the Study of Liver Disease considers morbid obesity (BMI ≥ 40 kg/m²) as a relative contraindication for liver transplantation since these patients are at higher risk of post-transplant complications and mortality.¹⁶ The European Association for the Study of the Liver practice guidelines also recommends that a multidisciplinary team should carefully evaluate patients with a BMI ≥ 35 kg/m² before listing.¹⁷ However, morbid obesity 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 aggressive 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 and patient survival and change in body weight post LT.

Method

Study population

This study was a single-center retrospective study. All adult LT, 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 approved by the institutional review board. Pediatric recipients (<18 years), re-transplant candidates, and combined liver-kidney transplant recipients were excluded. Recipients were subdivided into six 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/m², respectively). Post-transplant BMI was monitored in a sub-group 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 United Network for Organ Sharing. In our program, surgeons always evaluate pre-transplant patients carefully based on the body habitus and feasibility of liver transplantation from a surgical

standpoint. Since obese patients have a higher risk of morbidity and mortality for the vascular disease after LT, all listed obese patients get coronary angiogram and stress test. In case of $\geq 50\%$ stenosis in a major vessel (left anterior descending artery or right coronary artery) or critical disease defined as stenosis $\geq 70\%$ in at least moderate-sized branch vessels, percutaneous coronary intervention was performed before LT.²⁰

Surgical procedure

Organ procurements for brain dead donor were performed using standard surgical techniques and cold preservations. The technique and optimization protocol of donor after cardiac death (DCD) 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 During operation, we tried to maintain a central venous pressure less than 10mmHg. 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. When the risk of coagulopathy was estimated to be high, or the sign of coagulopathy was seen during operation, aminocaproic acid (Amicar, 25mg/kg, 1-hour infusion) infusion was used²⁵ These patients were routinely sent to closed transplant intensive care unit (ICU).

Statistical analysis and endpoints

The primary endpoints were patient survival and graft survival after LT. The secondary outcomes were lengths of hospital and ICU stay. Kaplan-Meier method was used to estimate the graft and patient survival in each group. 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 (MELD) score, DCD, and year of transplant). The hazard ratio and its 95% confidence interval from both univariate and multivariate Cox proportional regression analysis are summarized and plotted. Mann-Whitney U test was used to analyze secondary outcomes between the class $\geq$ obesity group and others. Wilcoxon-Mann-Whitney test and 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 liver transplantation were included in the study. The percentages of patients in each BMI category were: 1.9% underweight, 24.5% normal, 32.6% overweight, 25% class $\geq$ obesity, 9.3% class $\geq$ obesity, and 1.1% class $\geq$ obesity. The median age was 55 years, 66.7 % were male, and the patients diagnosed with chronic hepatitis C, nonalcoholic steatohepatitis (NASH), and

hepatocellular carcinoma (HCC) were 37%, 17%, and 20.5%. The median follow-up period was 5.5 years. The median length on the waitlist was 41 days. Demographics and clinical characteristics of patients at transplant are summarized in Table 1.

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%)	All n=2024
Age	47	52	54	55	54	55	55
Male	19(50%)	313(63.1%)	467(70.8%)	342(67.5%)	124(66%)	8(34.8%)	1349(66.7%)
MELD	20	19	19	19	19	20	18
Etiology							
HCV	9(23.7%)	173(34.9%)	286(42.1%)	172(33.9%)	68(36.2%)	5(21.7%)	748(37%)
NASH	1(2.6%)	43(9.7%)	82(12.4%)	127(25%)	73(38.8%)	10(43.5%)	344(17%)
HCC	9(23.7%)	95(19.2%)	143(21.7%)	106(20.9%)	39(20.7%)	4(17.4%)	415(20.5%)
Comorbidity							
DM	4(10.5%)	74(14.9%)	128(31.2%)	126(24.9%)	45(23.9%)	9(39.1%)	400(19.8%)
HT	6(15.8%)	69(13.9%)	113(27.6%)	117(23.1%)	49(26.1%)	8(34.8%)	384(19.1%)
CKD	5(13.2%)	55(11.1%)	67(16.3%)	64(12.6%)	19(10.1%)	2(8.7%)	233(11.5%)
Graft type							
DBD	35(92.1%)	432(87.1%)	551(83.5%)	424(83.6%)	174(92.6%)	22(95.7%)	1743(86.1%)
DCD	3(7.9%)	64(12.9%)	109(16.5%)	83(16.4%)	14(7.4%)	1(4.3%)	277(13.7%)
Follow-up(month)	88	73	74	72	61	77	65.5

Legend

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

Impact of morbid obesity on the outcome of LT

Primary and secondary outcomes are summarized in Table 2. Patient and graft survival for recipients with class 3 obesity were comparable with other groups (log-rank $P=0.35$ & 0.21 , respectively). (Figure 1) Numerically, the patient survival for recipients with class 3 obesity was 97.0%, 92.1%, 87.0%, and 79.8% at 1, 3, 5, and 10 years. The graft survival for recipients with class 3 obesity was 94.4%, 85.1%, 79.8%, and 72.5% at 1, 3, 5, and 10 years. By Cox regression analysis, there was no significant difference in patient and graft survival in each BMI group. The class 3 obesity group had a similar length of hospital and ICU stay with other BMI groups (Man-Whitney U, Length of hospital stay: $P=0.38$, Length of ICU stay: $P=0.13$).

Table 2 Patient and graft survival

	BMI <18.5	BMI 18.5-24.9	BMI 25-29.9	BMI 30-34.9	BMI 35-39.9	BMI ≥ 40	All	
Graft survival (%)								
1 year	86.8	87.3	89.9	88.8	89.4	94.4	89.1	
3 years	81.2	81.3	82.0	83.0	81.0	85.1	82.3	
5 years	78.2	75.0	74.2	80.5	77.1	79.8	77.1	
10 years	71.4	62.5	59.7	67.7	63.7	72.5	64.0	
Patient survival (%)								
1 year	92.1	88.7	90.9	89.7	90.3	97.0	90.1	
3 years	86.5	82.7	83.4	84.4	81.8	92.1	84.0	
5 years	80.1	77.2	76.1	82.1	78.5	87.0	78.9	
10 years	76.6	66.8	61.4	70.0	66.5	79.8	66.5	
ICU stay (days)	4.0	3.0	3.0	4.0	4.0	6.5	4.0	p=0.13
Hospital stay (days)	10.0	9.0	10.0	10.0	10.0	10.0	10.0	p=0.38
Days on waitlist (days)	34	40	36	43	50	35	40.5	p=0.39

Legend

Continuous variables were expressed as a median. Abbreviations: BMI-body mass index; ICU-intensive care unit

Post LT weight gain

A total of 1004 patients were included in the sub-group analysis. The BMI follow-up data (Figure 2) showed that all groups' mean BMI except for the underweight group decreased significantly in the first three months after LT. After this initial three month period, all groups' BMI except the class Ⅲ obesity group returned to the pre LT level within two years and reached a plateau at 3 to 5 years. In patients with class Ⅲ obesity, there was a significant increase in the BMI at long-term follow up with BMI of 45.51 Kg/m² from pre LT BMI of 41.3 Kg/m²; *P*=0.04).

Discussion

In this single-center study, we found out that morbid obesity is not associated with inferior post-liver transplantation survival outcomes when compared with non-obese patients. The 10-year patient survival for recipients with the class Ⅲ obesity group was 80%. Our study is the largest single-center studies in the US with long-term follow up. Contrary to our findings, Conzen et al reported recipients with BMI of >40 kg/m² had significantly reduced 5-year 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/m² cohort includes 26 patients consisting of 3.3 % of their entire cohorts. Giorgakis et al. reported mean graft survival and patient survival of recipients with BMI <35 kg/m² and BMI 35≥ kg/m² were similar with 10-year follow-up. However, this study did not

evaluate outcomes for recipients with BMI >40 kg/m².²⁶ 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 3 obesity undergoing LT. Moreover, national database studies are not ideal for addressing this specific issue due to the heterogeneity in listing and transplantation practices in obese patients.

At our center, class 3 obese patients were carefully selected from a surgical standpoint. Surgeons examined the body habitus of patients with class 3 obesity for operative suitability. All obese patients were encouraged to lose weight through dietary modifications and exercise. Transplant dietitians saw 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. This 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 (CAD) screening with cardiac catheterization, which is associated with the low rate of myocardial infarction and cardiac mortality after LT.^{20,27} Since CAD is independent predictors of poor outcome after liver transplantation²⁸, these center specific valid patient screening and intervention prior LT could lead to a better outcome in class 3 obesity group.

About post LT weight gain, although we observed a BMI increase in our class 3 obesity group, long-term graft and patient survival were comparable with other groups. The etiology of ESLD varied across the BMI groups. In our cohorts, NASH was dominant in the class 3 obese group. Lattanzi et al. reported that patients' BMI transplanted for NASH increased progressively at 3-5 years after LT. On the other hand, the BMI of patients transplanted for other etiologies reached the pre-LT level at three years and plateaued after that.²⁹ Thus, the reason for remote BMI increase in our class 3 obesity group can be explained by the dominance of NASH etiology 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.³⁰ LT recipients who develop posttransplant metabolic syndrome have a higher risk of vascular-related morbidity and mortality.³¹ The increased incidence of posttransplant DM is associated with a worse outcome of LT.³² 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.³³ Thus, even our study showed the long-term graft and patient survival of the class 3 obesity group was comparable with other groups, we should consider more aggressive post LT intervention to prevent long-term BMI increase for the class 3 obesity group.

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

in each 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 BMI ≥ 40 Kg/m² recipients that were transplanted since we had to have the outcomes of these transplants, and thus our results may not generalize to every potential BMI ≥ 40 Kg/m² recipients. Third, the number of patients with BMI ≥ 40 Kg/m² in our cohort consists of only 1.1 % of the whole cohort. Thus, the outcomes can be purely based on this bias.

Conclusion

This study showed that morbid obesity in cirrhotic patients is not associated with higher post-transplantation mortality. Obesity, including class Ⅲ obesity, should not be considered to be a contraindication to liver transplantation in the absence of other risk factors.

Abbreviations

LT, Liver transplantation

BMI, Body mass index

DCD, Donor after cardiac death

ICU, Intensive care unit

MELD, Model for end-stage liver disease

NASH, Nonalcoholic steatohepatitis

HCC, Hepatocellular carcinoma

CAD, Coronary artery disease

Declarations

Ethics approval and consent to participate

The Institutional Review Boards of the Indiana University Health University Hospital approved the study with written informed consent. (Protocol #: 1011003619R007)

Consent for publication

Written informed consents were obtained from the patients for publication of this research article.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DS: Participated in data collection, data analysis, and writing of the manuscript.

RSM: Participated in data collection and data analysis.

YP: Participated in collecting references and writing of the manuscript.

CK: Participated in data collection, data analysis, and writing of the manuscript.

PM, BE, MG, NG, ML: Involved in interpreting data and critical revision of the manuscript for valuable intellectual contents.

All authors have read and approved the manuscript.

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Figures

Figure 1

Overall patient survival at10 years follow-up (A) and graft survival (B)

Figure 2

BMI trend after liver transplantation at 5 years follow-up

Supplementary Files

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