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

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**Research article**

**Keywords:** Liver transplantation outcome, body mass index, class Ⅲ obesity

**Posted Date:** August 28th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-52924/v1



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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 the impact of severe obesity on outcomes of LT and change in body mass index (BMI) after transplantation.

Methods

All adult LT performed between July 2001 and December 2018 were reviewed. A retrospective analysis was conducted. BMI of recipients is subdivided into six categories: 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.

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 Ⅲ 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.

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

Conclusion

In this study, class Ⅲ obesity is not associated with higher mortality. Obesity, including class Ⅲ obesity, should not be considered to be a contraindication to LT in the absence of other contraindications. Post-LT interventions are required to prevent significant weight gain in recipients with class Ⅲ 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.[3] 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.[4]

Several studies have reported conflicting results on the impact of severe obesity on outcomes of LT.[5–16] Some centers and insurance payers have set a cutoff for BMI to list candidates. Currently, the American Association for the Study of Liver Disease, in accordance with the American Society of Transplantation, 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.[17] 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 before listing.[18] However, at the same time, morbid obesity patients have higher waitlist mortality rates.[13,19] 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 at best. 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

This study was a single-center retrospective study. All adult LT performed 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 □ obesity, class □ obesity, and class □ 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. 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 the 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, donor after cardiac death (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. 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 (SPSS, Inc., Chicago, IL).

## Results

# Study population

A total of 2024 patients who performed 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 Ⅰ obesity, 9.3% class Ⅱ obesity, and 1.1% class Ⅲ 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% respectively. 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 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 to the outcome of LT

Primary and secondary outcomes are summarized in Table 2. Patient and graft survival for recipients with class Ⅲ obesity were comparable with other groups (log-rank $P = 0.35$ & 0.21, respectively). (Fig. 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 years respectively. And 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 respectively. By Cox regression analysis, there was no significant difference in patient and graft survival in each BMI group. The class Ⅲ obesity group had a similar length of hospital and ICU stay compared to other BMI groups (Length of hospital stay: $P = 0.18$, Length of ICU stay: $P = 0.51$).

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 | P-value |
|---|---|---|---|---|---|---|---|---|
| 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=0.51 |
| Hospital stay (days) | 10.0 | 9.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | p=0.18 |
| Days on waitlist (days) | 34 | 40 | 36 | 43 | 50 | 35 | 40.5 | p=0.17 |

# Legend

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

# Post LT weight gain

The BMI follow up data (Fig. 2) showed that the mean BMI of all groups except for the underweight group decreased significantly in the first three months after LT. After this initial three month period, BMI of all groups 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/m$^2$ from pre LT BMI of 41.3; $P = 0.04$).

## Discussion

In this single-center study, we found out that morbid obesity is not associated with worse 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 of such kind with long-term follow up. Contrary to our findings, Conzen et al reported recipients with BMI of > 40 kg/m$^2$ 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.[10] 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/m$^2$.[20] 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 due to 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. All obese patients were encouraged to lose weight through dietary modifications and exercise. Transplant dieticians 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.[21,22] Since CAD is independent predictors of poor outcome after liver transplantation[23], these center specific valid patient screening and intervention prior LT could lead to a better outcome in class 3 obesity group.

The etiology of ESLD varied across the BMI groups. In our study, NASH was dominant in the class Ⅲ obese group. Lattanzi et al. reported that the BMI of patients transplanted for NASH increased progressively at 3–5 years after LT[24]. On the other hand, the BMI of patients transplanted for other etiologies reached the pre-LT level at three years and plateaued after that.[24] From previous studies, a decrease in post-LT BMI is associated with a lower risk of patient death and graft loss. In our study, although we observed an increase in the BMI in our class Ⅲ obesity group, long-term graft and patient survival were comparable with other groups.

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. Also, these findings may 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 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 recipients.

## 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

ICU, Intensive care unit

MELD, Model for end-stage liver disease

DCD, Donor after cardiac death

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.

### Consent for publication

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

# 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.

# Funding

No funding was received for the preparation of this manuscript.

# Acknowledgments

Not applicable

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# Figures

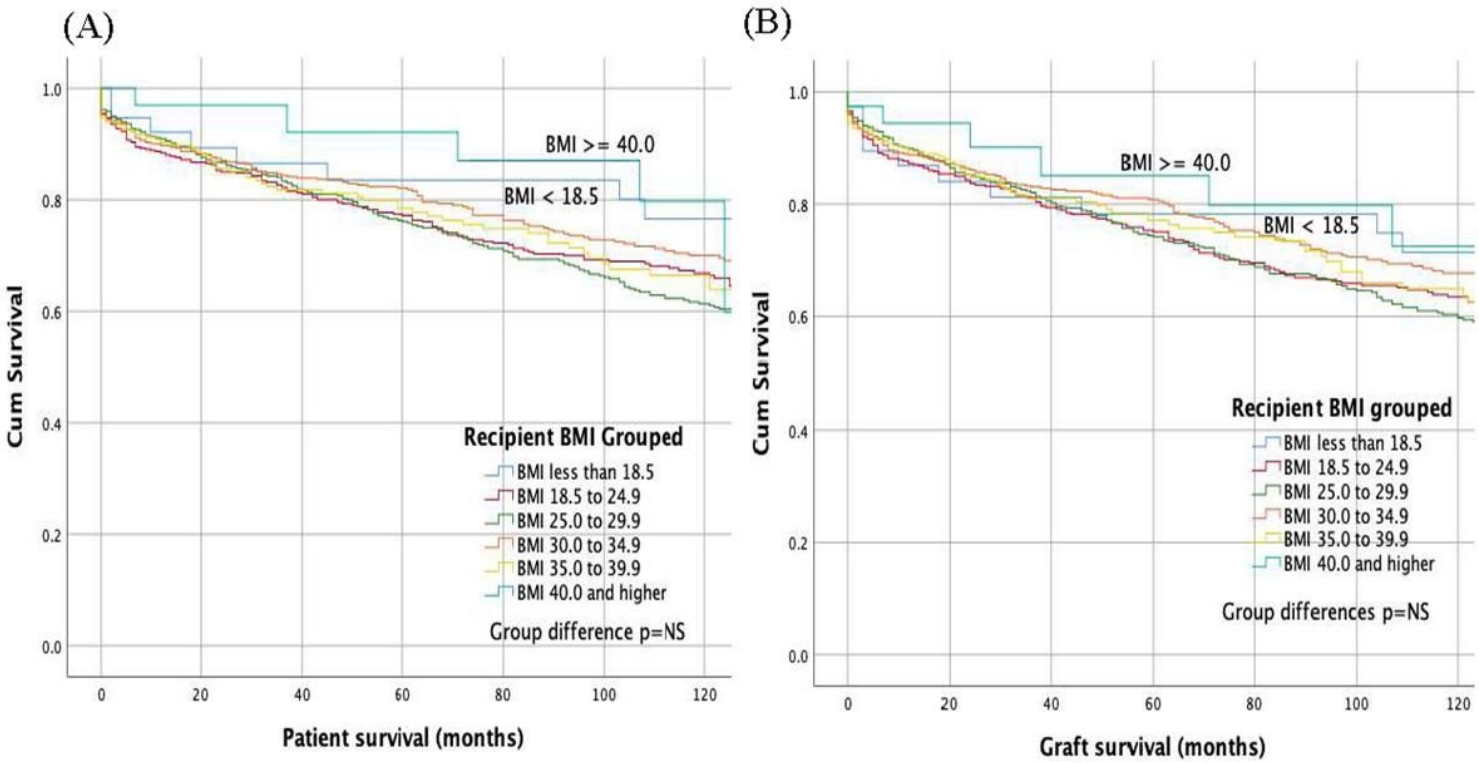
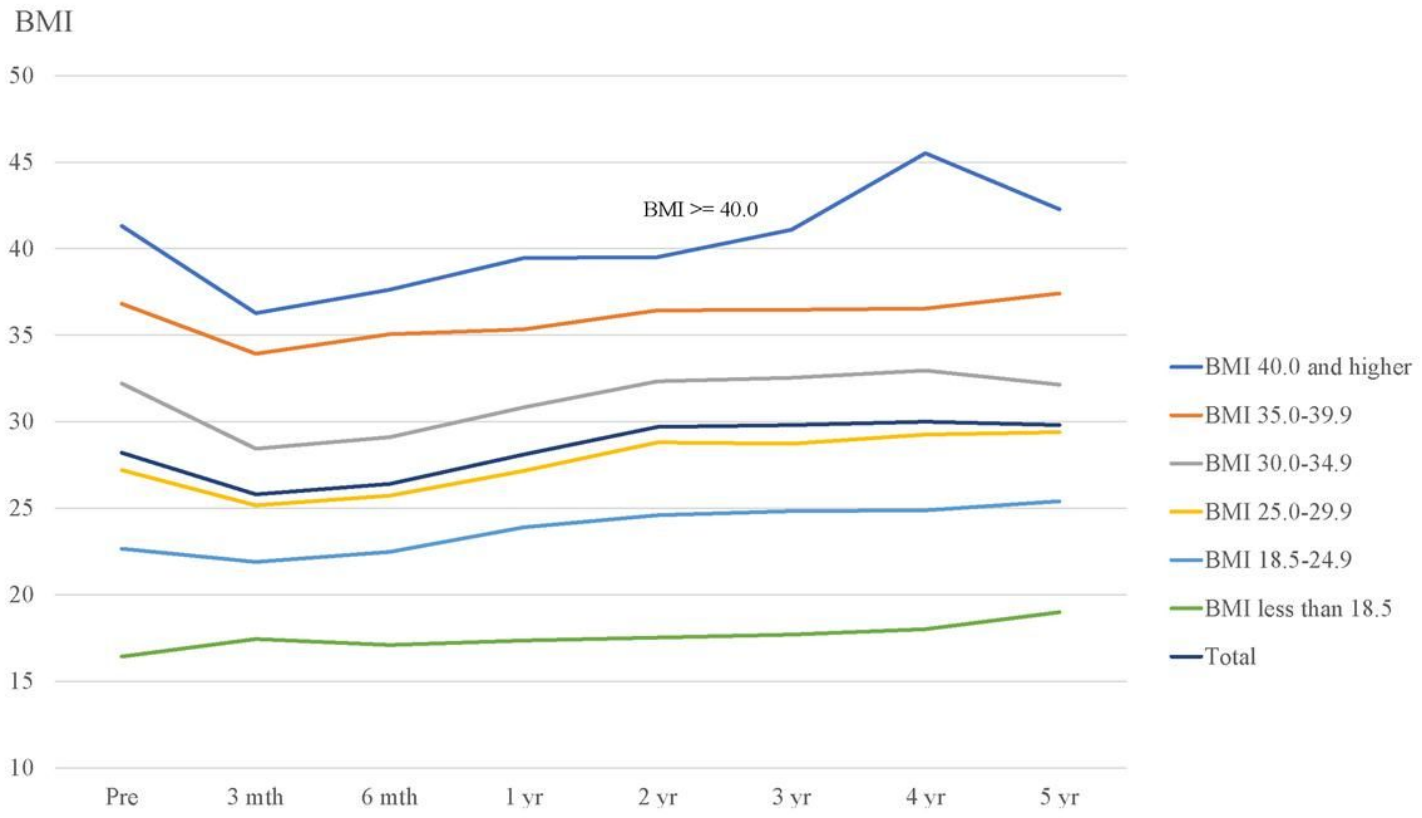



**Figure 1**

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




## Figure 2

BMI trend after liver transplantation at 5 years follow-up