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# The Effect of Recipient Body Mass Index and Its Extremes on Survival and Graft Vascular and Biliary Complications After Liver Transplantation: A Single Center Retrospective Study

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Data Interpretation D
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**Background:** This is the largest UK-based study on the effect of recipient body mass index (BMI) and its extremes (BMI <18.5 and BMI ≥35 kg/m$^2$) on liver transplant (LT) outcomes. Its purpose was to analyze the BMI effect on post-LT mortality, graft loss, primary non-function (PNF), and graft vascular and biliary complications.

**Material/Methods:** Data were retrieved from a single-center LT database of 2,115 consecutive patients receiving first LT during period February 2004 to September 2015. Survivals were compared across the BMI groups; the effects of recipient BMI on survival, PNF, and graft vascular and biliary complications were analyzed via regression.

**Results:** Autoimmune disease and nonalcoholic steatohepatitis were prevalent among underweight and morbidly obese adults, respectively. Graft survival was similar across BMI classes at 30 days and in 1, 2, 5, and 10 years ($p$=0.75) and on obese versus non-obese ($p$=0.33). BMI <35 kg/m$^2$ versus BMI ≥35 kg/m$^2$ mean graft survival was similar ($p$=0.84). BMI <18.5 kg/m$^2$ recipients tended to have inferior mean graft and patient survivals; however, the difference was non-significant ($p$=0.09 and $p$=0.1 respectively). BMI <18.5 kg/m$^2$ recipients were at higher risk of hepatic artery thrombosis (HR, 1.73, 95% CI 1.73–3, $p$<0.05). Adult underweight status was an independent HAT risk factor (HR 3, 95% CI 1–8.6, $p$=0.046). BMI class did not affect ischemic cholangiopathy risk ($p$=0.84). However, the overall biliary complication risk increased by 3% for every 1 kg/m$^2$ BMI rise.

**Conclusions:** Post-LT survival is independent of recipient BMI. Underweight status is linked to higher HAT risk. Biliary complication risk increases with rising recipient BMI. After appropriate recipient selection, recipient BMI extremes are not a contraindication for LT.

**MeSH Keywords:** **Body Mass Index • Liver Transplantation • Obesity, Morbid**

**Abbreviations:** **AIH** – autoimmune hepatitis; **ALD** – alcoholic liver disease; **ANOVA** – analysis of variance; **CI** – confidence interval; **DBD** – donation after brain death; **DCD** – donation after cardiac death; **DM** – diabetes mellitus; **ESLD** – end-stage liver disease; **EWL** – excess weight loss; **HAT** – hepatic artery thrombosis; **HBV** – hepatitis B virus; **HCV** – hepatitis C virus; **HCC** – hepatocellular carcinoma; **KM** – Kaplan-Meier; **LD** – living donor; **LDLT** – living donor liver transplantation; **LT** – liver transplantation; **MELD** – model for end-stage liver disease; **NAFLD** – nonalcoholic fatty liver disease; **NASH** – nonalcoholic steatohepatitis; **NCLD** – non-cholestatic liver disease; **NIDDK** – National Institute of Diabetes and Digestive and Kidney Diseases; **PBC** – primary biliary cirrhosis; **PNF** – primary non-function; **PSC** – primary sclerosing cholangitis; **PVT** – portal vein thrombosis; **SRTR** – Scientific Registry of Transplant Recipients; **UNOS** – United Network for Organ Sharing; **WHO** – World Health Organization

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## Background

Obesity has reached epidemic dimensions. The World Health Organization (WHO) indicated that in 2014, over 28% of United Kingdom (UK) adults were obese [1]. Likewise, the obesity prevalence for the same period in the United States (US) was 32.6%, with two-thirds of Americans being classified as overweight or obese [1]. Nonalcoholic fatty liver disease (NAFLD) prevalence is estimated to be 46%, with nonalcoholic steatohepatitis (NASH) present in 12.2% of the US general population [2]. According to data from the Scientific Registry of Transplant Recipients (SRTR) and the United Network for Organ Sharing (UNOS), NALFD/NASH is currently the third most common indication for liver transplantation, following hepatitis C virus (HCV) infection and alcohol-related liver disease (ALD) [3]. Considering the worldwide rise in the severity and prevalence of obesity and the anticipated fall in HCV-related End-Stage Liver Disease (ESLD) over the next few decades, liver transplantation (LT) on obese patients and for the treatment of obesity-related ESLD will become increasingly common.

Despite the conventional wisdom that obese patients have higher peri-operative morbidity and mortality [4], the effect of obesity on LT outcomes remains unclear. Many transplant centers have specific weight criteria for transplant candidacy. This is mostly because of concerns raised over increased post-operative morbidity and mortality in this patient group. A landmark study, based on the UNOS database, reported increased early mortality rates in the morbidly obese and high five-year mortality in the severely and morbidly obese, attributed mostly to cardiovascular events [5]. A more recent US multi-center study using the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) LT Database observed that, after correction for ascites, BMI was not independently predictive of patient mortality or graft survival [6]. A UK-based study showed that BMI ≥25 kg/m$^2$ was associated with higher morbidity and prolonged hospital stay [7]. A Danish retrospective study of 365 consecutive patients showed that obese patients (BMI ≥30 kg/m$^2$) had significantly higher post-LT mortality, even though morbidity and length of hospital stay were comparable [8]. Nair et al. also reported that obese patients had prolonged hospital stays and increased overall transplantation costs [9], contrary to others [10].

This is the largest UK-based study to date on the effect of BMI on LT outcomes. The purpose of the study was to analyze the effect of BMI and the extremes of its spectrum on graft and patient survival (primary outcomes), as well as on PNF, and graft vascular and biliary complications (secondary outcomes).

## Material and Methods

The purpose of this study was to assess the effect of recipient BMI value on mortality and graft survival in patients undergoing LT and to explore the effect of BMI extremes i.e., BMI <18.5 and BMI ≥35 kg/m$^2$ on primary and secondary outcomes, using our institutional LT database. This database is being prospectively populated with data from patients undergoing LT at King's College Hospital.

The data retrieved was from February 29, 2004 to September 15, 2015. All consecutive LT recipients were included in the study, including transplantation for the treatment of acute liver failure (ALF). Exclusion criterion was re-transplantation (re-LT). Data collected included recipient age (pediatric if aged <16 years old) at the time of transplant, sex, height, weight (last recorded pre-transplant measurement of recipient weight), LT indication, malignancy at the time of transplant, cholestatic versus non-cholestatic liver disease (NCLD), HCV, pre-transplant diabetes mellitus (DM), LT waiting-list time, recipient status at the time of transplant (inpatient versus at home), model for end-stage liver disease (MELD) score, cold ischemia time (CIT), type of graft, primary non-function (PNF), post-LT hepatic artery thrombosis (HAT), post-transplant portal vein thrombosis (PVT), post-LT bile leak, biliary stricture requiring intervention, ischemic cholangiopathy (IC) or other significant graft biliary complications, post-LT mortality, graft loss, time-to-graft loss, time-to-patient death, duration of graft,and patient survival and length of follow-up. Liver disease etiology was categorized as ALD, hepatitis B cirrhosis (HBV), HCV, cholestatic (secondary biliary cirrhosis, extra hepatic biliary atresia, progressive familial intrahepatic cholestasis syndromes, Alagille syndrome), malignancy [hepatocellular carcinoma (HCC), hepatoblastoma], metabolic (a1-antitrypsin deficiency, Wilson's disease, hemochromatosis, amyloidosis, cystic fibrosis, propionic aciduria, citrullemia, glycogen storage disease, other inborn errors of metabolism), NASH/NAFLD, acute liver failure (other than metabolic/viral), autoimmune [primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH)], cryptogenic and 'other' (Budd Chiari, benign liver tumors and etiologies not falling in any of the aforementioned). Liver grafts were classified as donation after brain death (DBD), donation after cardiac death (DCD), living donor (LD), and domino liver allografts. Recipients were also classified according to age group (adult versus pediatric).

All recipients were stratified according to their pre-transplant BMI. The latter was calculated by weight in kilograms (using the last recorded pre-transplant measurement of recipient's weight), divided by height in meters squared (kg/m$^2$). The cohort was stratified into six BMI classes: BMI <18.5, BMI 18.5–24.9, BMI 25–29.9, BMI ≥30–34.9, BMI ≥35–39.9, and BMI ≥40 kg/m$^2$. In the adult population these classes were



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respectively called underweight (BMI <18.5 kg/m$^2$), normal weight (BMI 18.5–24.9 kg/m$^2$), overweight (BMI 25–29.9 kg/m$^2$), class I (BMI 30–34.9 kg/m$^2$), class II (BMI 35–39.9 kg/m$^2$) and class III obese (BMI ≥40 kg/m$^2$). In children these terms have historically been defined according to the child's BMI-for-age-and-gender percentile and are not reflective of a numeric BMI range. Therefore, for the sake of clarity, these terms will only refer to adults.

Primary outcomes included 30 days, one-, two-, five- and ten-years patient and graft survival. Secondary outcomes included the effect of BMI category on PNF and on graft HAT, PVT, and biliary complications.

**Statistical analysis**

Frequencies and percentiles described categorical data. Continuous data were described using estimates of central tendency and spread. For continuous variables, comparisons were performed via independent *t*-testing or one-way analysis of variance (ANOVA), followed by post-hoc Tukey testing, if a difference was identified within multiple groups. Categorical variables were compared via Pearson's $\chi^2$ testing of independence. The effect size was assessed via φ and Cramer's V testing. The effect of BMI and BMI categories on HAT, PVT, and biliary complications were also assessed via univariate logistic regression, which was followed by ad hoc analysis, if univariate regression revealed significant effects.

Chronic periods were represented in months and rounded up to the first decimal. Percentiles, $\chi^2$ values and risk ratios were rounded up to the first decimal. A *p* value was rounded up to the third decimal. Level of significance was set to a value of $p \leq 0.05$. A *p* value approximating 0.1 was described as a trend. All statistical analysis was performed with SPSS 22.0 for Windows (SPSS, Inc., Chicago, IL, USA).

## Results

The clinical characteristics of the recipients are summarized in Table 1. In all, 2,115 LT recipients were included in the study: 488 were children (23%, 48.6% male) and 1,627 were adults (76.9%, 61.3 male). Mean follow-up period was 55.2 ± 40 months (3–139 months); median follow-up was 49.7 months.

There were 388 patients (18.3%) who had BMI <18.5 kg/m$^2$, 845 patients (40%) who had BMI 18.5–24.9, 526 patients (24.9%) who had BMI 25–29.9, 279 patients (13.2%) who had BMI 30–34.9, 63 (3%) patients who had BMI 35–39.9, and 14 patients (0.7%) who had BMI ≥40 kg/m$^2$. Across all ages, 356 (16.8%) of the LT recipients had a BMI ≥30 kg/m. Mean recipient age was 39.07±22.6 years.

Adult obesity prevalence was 27.9%. Table 2 shows the BMI distribution among the adults (n=1,627). The majority of patients had a BMI between the BMI extremes: 44.5% of patients had normal BMI, whereas 31.7% where overweight and 16.2% were class I obese. 7.4% of patients belonged to the BMI extremes: 3.1% were underweight, 3.7% were class II obese, and 0.6% of adult recipients were class III obese. Among the adults, mean age varied across BMI groups (ANOVA, $p<0.001$), with underweights being significantly younger than BMI classes II and III ($p<0.001$ and $p=0.03$, respectively). Obese classes I/II tended to be older.

Table 3 shows the BMI distribution at the pediatric population (n=488). The majority of children (69.3%) had a BMI <18.5 kg/m$^2$; 4% had a BMI >30 kg/m$^2$; 1.2% (six children) had a BMI >35 kg/m$^2$, four of which (0.6%) had a BMI >40 kg/m$^2$.

As expected, LT indication differed among children and adults. In children, the most common indication was cholestatic liver disease (51.9%), followed by metabolic causes (15.8%). In adults, the most common etiologies were malignancy (19.4%), followed by autoimmune (19.3%), and ALD (17.4%). HCV cirrhosis as the primary LT indication accounted for 8.2% of the adult total. These calculations refer to the primary indication for transplant, meaning that patients with HCC and HCV or HCC and ALD were categorized under "malignancy" rather than "HCV" or "ALD"; this implies that the actual numbers of ALD and HCV cirrhotics were significantly higher: HCV cirrhosis was reported as the second diagnosis in 103 adult recipients, increasing the HCV cirrhosis prevalence to 14.6% of the adult cohort. Ninety adult recipients had ALD as a second diagnosis, increasing ALD prevalence to 22.9% of the adult population, making ALD the most common cause of underlying liver failure. NASH prevalence increased with higher BMI, with the mean BMI of patients with NASH being significantly higher than their counterparts (30±5.5 versus 26.3±5.2 respectively, $p<0.001$). The cross-tabulation of NASH with the BMI groups showed significant association between the two variables (Pearson $\chi^2=46.7$, $p<0.001$, φ and Cramer V=0.17, $p<0.001$).

LT indications varied across the adult BMI classes ($p<0.001$). First indication for LT at the adult underweight group was autoimmune disease. ALD and HCV/malignancy were the dominant diagnoses in patients with BMI values outside the extremes of the BMI spectrum. The dominant etiology in BMI ≥40 was NASH (28.6%). No NASH was reported in BMI <18.5.

Acute liver failure (ALF) prevalence as LT indication varied across groups: 44.3% of ALF recipients had normal weight, 19.1% were underweight, 19.4% were overweight, and 17.1% were obese (BMI ≥30 kg/m$^2$), of whom only 9 (2.9%) had a BMI ≥35 kg/m$^2$.



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**Table 1.** Clinical characteristics by BMI class and age group.

| | BMI <18.5 n=388** (18.3%) | BMI 18.5–24.9 n=845 (40%) | BMI 25–29.9 n=526 (24.9%) | BMI 30–34.9 n=279 (13.2%) | BMI 35–39.9 n=63 (3%) | BMI ≥40 n=14 (0.7%) | All n=2,115 | Pediatric (%) n=488 (23%) | Adult (%) n=1,627 (76.9%) |
|---|---|---|---|---|---|---|---|---|---|
| Age (year) | 8.1±14.1 | 40.9±19.7 | 51.6 (12.8) | 50.5±15 | 51.5±1.7 | 38.2±6.8 | 39.1±22.6 | 4±4.7 | 49.6± 13.2 |
| Male (%) | 190 (48.9) | 469 (55.5) | 349 (66.3) | 163 (58.4) | 47 (74.6) | 10 (71.4) | 1228 (58) | 48.6 | 61.3 |
| BMI* | 15.9±2.1 | 22.3±0.1 | 27.8±1.3 | 32.3±1.3 | 37±4.4 | 44.1± 4.1 | 24.3±0.1 | 17.8±4.8 | 23.3± 6.7 |
| ALD | 7 (1.8) | 103 (12.2) | 110 (20.9) | 44 (15.8) | 17 (27) | 1 (7.1) | 282 (13.4) | 0 | 282 (17.4) |
| HBV | 1 (0.3) | 15 (1.8) | 10 (1.9) | 5 (1.8) | 1 (1.6) | 0 | 32 (1.5) | 1 (0.2) | 31 (1.9) |
| HCV | 5 (1.3) | 52 (6.2) | 43 (8.2) | 39 (14) | 2(3.2) | 2 (14.3) | 143 (6.8) | 9 (1.9) | 134 (8.2) |
| Cholestatic | 187 (48.3) | 97 (11.5) | 29 (5.5) | 9 (3.2) | 1(1.6) | 2 (14.3) | 325 (15.4) | 252 (51.9) | 73 (4.5) |
| Malignancy | 39 (10.1) | 121 (14.3) | 126 (24) | 59 (21.1) | 17 (27) | 2 (14.3) | 364 (17.2) | 49 (10.1) | 315 (19.4) |
| Metabolic | 51 (13.1) | 51 (6) | 31 (5.9) | 20 (7.2) | 7 (11.1) | 0 | 160 (7.6) | 77 (15.8) | 83 (5.1) |
| NASH | 0 | 7 (0.8) | 13 (2.5) | 14 (5) | 3 (4.8) | 4 (28.6) | 41 (1.9) | 1 (0.2) | 40 (2.5) |
| ALF | 13 (3.4) | 83 (9.8) | 24 (4.6) | 14 (5) | 5 (7.9) | 1 (7.1) | 140 (6.6) | 18 (3.7) | 122 (7.5) |
| Autoimmune | 18 (4.6) | 202 (23.9) | 70 (13.3) | 24 (8.6) | 4 (6.3) | 2 (14.3) | 320 (15.2) | 6 (1.2) | 314 (19.3) |
| Cryptogenic | 3 (0.8) | 28 (3.3) | 23 (4.4) | 14 (5) | 3 (4.8) | 0 | 71 (3.4) | 3 (0.6) | 68 (4.2) |
| Other | 63 (17.8) | 86 (10.2) | 47 (8.9) | 34 (12.2) | 3 (4.8) | 0 | 233 (11) | 70 (14.3) | 163 (10) |
| MELD | 12.9±2.1 | 12.8±6.2 | 13.7 (±6.9) | 13.6±1.3 | 13.5±5.6 | 13± 1.4 | 13.2± 0.1 | 12.6± 3.5 | 13.3± 6.7 |
| Waiting time (days) | 123.4±7.2 | 192.8±24.1 | 171.9±10 | 185.7±19.6 | 256.7±53.6 | 219±46.7 | 175.7±10.3 | 132.5±195.2 | 189.1±13 |
| Graft type (%) | | | | | | | | | |
| DBD | 287 (73.8) | 680 (80.5) | 392 (74.5) | 199 (51.2) | 48 (76.2) | 12 (85.7) | 1618 (76.5) | 359 (73.6) | 1259 (77.4) |
| DCD | 19 (4.9) | 124 (14.7) | 117 (22.2) | 58 (14.9) | 10 (15.9) | 2 (14.3) | 330 (15.6) | 20 (4.1) | 310 (19) |
| LD | 83 (21.3) | 38 (4.5) | 11 (2.1) | 17 (4.4) | 2 (3.2) | 0 | 151 (7.1) | 109 (22.3) | 42 (2.6) |
| Domino | 0 | 2 (0.2) | 5 (1) | 5 (1.3) | 2 (3.2) | 0 | 14 (0.7) | 0 | 14 (0.9) |

Values reported are means ± standard deviation; BMI – units kg/m$^2$; ALD – alcohol liver disease; HBV – hepatitis B cirrhosis; HCV – hepatitis C cirrhosis; ALF – acute liver failure; NASH – nonalcoholic steatohepatitis; ALF – acute liver failure; MELD – model for end stage liver disease; DBD – donation after brain death; DCD – donation after cardiac death; LD – donation from living donor.

**Table 2.** BMI class distribution in adults (n=1,627).

| BMI class | <18.5 | 18.5–24.9 | 25–29.9 | 30–34.9 | 35–39.9 | ≥40 |
|---|---|---|---|---|---|---|
| N patients (%) | 50 (3.1) | 723 (44.5) | 516 (31.7) | 264 (16.2) | 61 (3.7) | 10 (0.6) |

BMI units kg/m$^2$. The majority of the adult patients (76.2%) had a BMI of 18.5–29.9 kg/m$^2$; 7.7% of patients were at the extremes of the BMI spectrum: 3.1% were underweight and 4.6% were morbidly or severely obese (BMI 35 kg/m$^2$).

**Table 3.** BMI class distribution in children (n=488).

| BMI class | <18.5 | 18.5–24.9 | 25–29.9 | 30–34.9 | 35–39.9 | ≥40 |
|---|---|---|---|---|---|---|
| N patients (%) | 338(69.3) | 121 (24.8) | 10 (2) | 15 (3.1) | 2 (0.4) | 4 (0.8) |

BMI units kg/m$^2$. The majority of the pediatric recipients (69.3%) had a BMI <18.5 kg/m$^2$. Despite a low BMI, the majority of these pediatric recipients were considered of healthy weight and not underweight, as long as their weight was above the fifth percentile for age-and-gender; 1.2% of the pediatric recipients had a BMI ≥35 kg/m$^2$.



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**Table 4.** The effect of BMI on primary outcomes: graft and patient survival distribution in 30 days, one, two, five and ten years across BMI groups (adult and pediatric population).

| | BMI <18.5 n=388 | BMI 18.5–24.9 n=845 | BMI 25–29.9 n=526 | BMI 30–34.9 n=279 | BMI ≥35 n=77 | Overall n=2,115 |
|---|---|---|---|---|---|---|
| Graft survival (%)[a] | | | | | | |
| 30 day | 95.5 | 95.2 | 96.0 | 95.2 | 97.3 | 95.8 |
| 1 year | 88.8 | 89.8 | 89.7 | 92.9 | 91.5 | 90.1 |
| 2 years | 87.6 | 87.8 | 87.0 | 89.5 | 91.5 | 88.1 |
| 5 years | 84.8 | 83.6 | 82.3 | 86.1 | 89.5 | 84.1 |
| 10 years | 81.4 | 78.8 | 76.4 | 81.6 | 65.3 | 78.7 |
| Patient survival (%)[b] | | | | | | |
| 30 day | 97.1 | 97.8 | 98.0 | 97.0 | 98.6 | 97.7 |
| 1 year | 92.8 | 93.1 | 92.3 | 94.7 | 92.8 | 93.0 |
| 2 years | 91.9 | 91.2 | 90.4 | 91.4 | 92.8 | 91.2 |
| 5 years | 89.1 | 87.8 | 85.7 | 87.4 | 90.9 | 87.6 |
| 10 years | 86.8 | 84.1 | 79.5 | 84.6 | 67.0 | 83.1 |

Graft and patient survival were similar in 30 days, one, two, five and 10 years. Log rank tested: [a] $\chi^2$=1.94, $p$=0.75; [b] $\chi^2$=2.85, $p$=0.58.

The average MELD score was 12.6±3.5 (without the addition of MELD exception points) and was similar across weight classes/age groups ($p$=0.44). Time on waiting list did not vary significantly among adult BMI classes, but was significantly shorter in children ($p$=0.02). 76.4% of all patients received grafts from DBD donors.

**The effect of BMI on primary outcomes**

The primary outcomes are summarized in Table 4. Irrespective of age group, the graft survival was similar across all BMI classes at 30 days and in one, two, five, and 10 years ($\chi^2$=1.94, $p$=0.75). For BMI 18.5–24.9 kg/m$^2$, one-, five- and 10-year survival rates were 89.8%, 83.6%, and 78.8%, respectively. For BMI 25–29.9 kg/m$^2$ it was 89.7%, 82.3%, and 76.4% respectively. For BMI 30–34.9 kg/m$^2$, it was 92.9%, 86.1%, and 81.6%, respectively. BMI ≥35 kg/m$^2$ graft survival rates were 91.5%, 89.5%, and 65.3% respectively. Likewise, overall patient survival rates were 93% in the first year, and 87.6% and 83.1% in post-transplantation years five and 10 respectively, and similar across weight groups ($\chi^2$=2.85, $p$=0.58).

Kaplan-Meier analysis showed that graft survival distribution was similar across BMI classes (Figure 1A). Mean graft survival time of recipients with BMI <30 kg/m$^2$ and BMI ≥30 kg/m$^2$ were similar ($\chi^2$=0.94, $p$=0.33). Mean graft survivals among BMI <35 kg/m$^2$ and BMI ≥35 kg/m$^2$ patients were also similar ($\chi^2$=0.042, $p$=0.84). Likewise, patient survival curves were similar among the BMI classes ($\chi^2$=2.85, $p$=0.58, Figure 1B) and between BMI <30 kg/m$^2$ versus BMI ≥30 kg/m$^2$ ($\chi^2$=0.18, $p$=0.67, Figure 1C).

Patients with BMI ≥35 kg/m$^2$ seemed to have shorter mean graft [95.8 months, 95% CI 109.4–114.7 versus 112 months, 95% CI 109.3–114.6] and patient survival (95.8 months, 95% CI 115.16–119.9 versus 117.478, 95% CI 115–119.9 months); however, log-rank comparison did not reach significance ($p$=0.28 and $p$=0.46 respectively, Figure 1D).

The underweight adults' mean graft survival was 98.3 months (range, 82–114.4 months), contrary to 112.7 months (range 110–115.3 months) in the rest of the adult recipients ($\chi^2$=3.57, $p$=0.06, Table 5, Figure 2A). The same trend, although less prominent, was observed for patient survival; the mean underweight patient survival was 106.7 months (range 99.2–121.3 months), as opposed to the mean survival of 118 months (range 115.6–121.3 months) for the rest of the adult recipients ($\chi^2$=2.6, $p$=0.1, Table 5, Figure 2B).

**The effect of BMI on secondary outcomes**

Table 6 shows the incidence of PNF and vascular and biliary complications across BMI groups.

On univariate analysis, BMI class did not affect PNF and therefore multivariate analysis was not warranted. PNF prevalence



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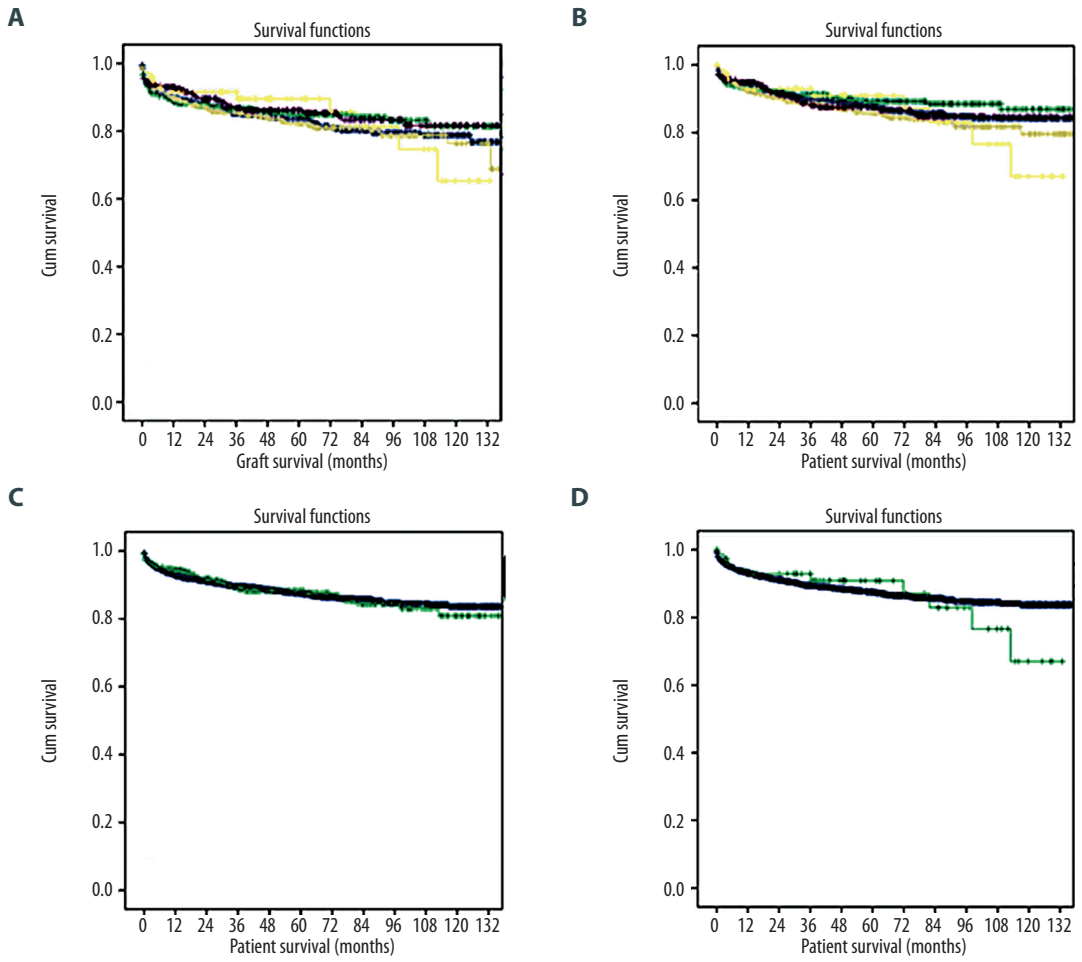


**Figure 1.** Kaplan-Meier curves of graft and patient survival (months). (**A**) Graft survival. (**B**) Patient survival: blue, BMI <18.5 kg/m$^2$; green, BMI 18.5–24.9 kg/m$^2$; brown, BMI 25–29.9 kg/m$^2$; purple, BMI 30–34.9 kg/m$^2$; yellow, BMI ≥35 kg/m$^2$. (**C**) Patient survival for BMI <30 kg/m$^2$ (blue) versus BMI ≥30 kg/m$^2$ (green). (**D**) Patient survival curve BMI <35 kg/m$^2$ (blue) versus BMI ≥35 kg/m$^2$ (green). Patient and graft survivals were similar on log-rank testing across BMI classes and across BMI <30 kg/m$^2$ versus BMI ≥30 kg/m$^2$. In (**A–C**) the BMI ≥35 kg/m$^2$ survival curve (illustrated as yellow, yellow and green respectively) crossed the survival curves of the rest of the subgroups after the fifth year, indicating that the survival risk for this patient group behaves differently in the long term, with the graft loss and patient death risk increasing in a higher rate compared to the rest of the BMI classes; however, log rank comparison did not reach significance.

was 1% (22 cases) and was equally uncommon across BMI classes/age groups. There was no recorded PNF in BMI ≥35 kg/m$^2$ (n=77).

Patients with BMI <18.5 kg/m$^2$ were at higher risk of post-LT graft HAT (1.73, 95% CI 1.73–3, $p$<0.05, Table 7). Likewise, pediatric recipients were at higher risk for developing HAT (HR 1.8, 95% CI 1.1–2.9, $p$=0.018) and PVT (HR 2.8, 95% CI 1.4–5.7, $p$=0.005), Table 8. Therefore, on univariate regression, low BMI and pediatric age were independent HAT risk factors. Ad hoc regression analysis of the effect of underweight status on the development of HAT in the adult subpopulation showed that underweight is an independent risk factor for the development of HAT among the adults (HR 3, 95% CI 1–8.6, $p$=0.046). The same did not apply for PVT risk ($p$=0.51, Table 9).

On univariate analysis, BMI class did not affect the risk of IC ($p$=0.84), biliary strictures ($p$=0.2), or other biliary complications ($p$=0.95); since univariate analysis did not reveal any significant effects, multivariate analysis on the effect of BMI class on biliary complications would be unrevealing and was therefore not pursued. When BMI was tested as a continuous variable, the overall biliary complication risk increased by 3% for every 1 kg/m$^2$ BMI rise (Table 6).



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**Table 5.** Comparison of mean graft and patient survival of underweight versus non-underweight adults (BMI <18.5 versus BMI ≥18.5 kg/m²).

| BMI (kg/m²) | <18.5 | ≥18.5 | $\chi^2$ | p |
|---|---|---|---|---|
| Mean graft survival (months) | 98.3 (82–114.4) | 112.7 (110–15.3) | 3.57 | 0.06 |
| Mean patient survival (months) | 106.7 (92.2–121.3) | 118 (115.6–121.3) | 2.6 | 0.1 |

Adult underweight patients tended to have inferior graft and patient survival, even though on cross-tabulation the finding did not reach statistical significance (log rank tested, $p$=0.09 and 0.1, respectively).

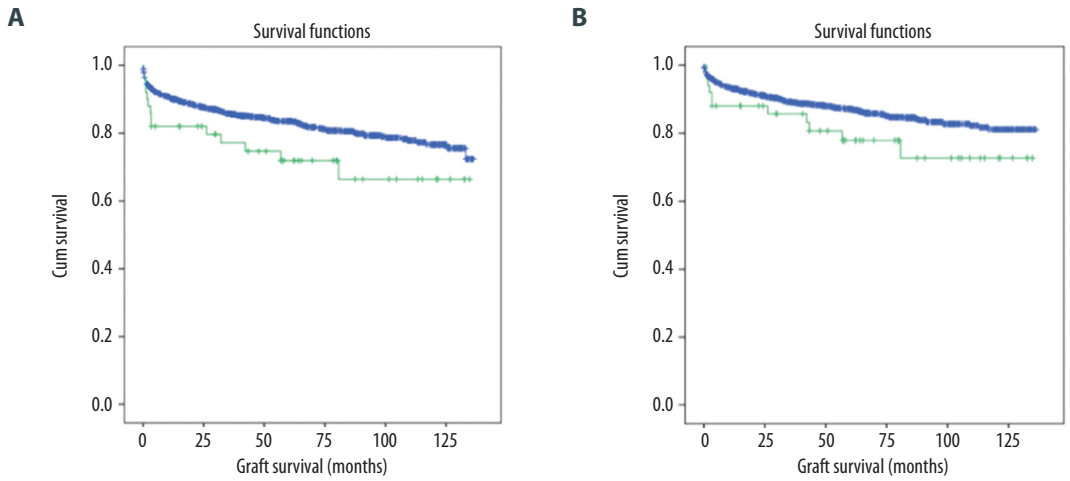


**Figure 2.** Kaplan-Meier curves of graft and patient survival, underweight versus non-underweight adults (months). (**A**) Graft survival. (**B**) Patient survival. Blue, non-underweight adults; green, underweight adults. Note: Cumulative survival was inferior in the adult underweight population at all times. However, log-rank testing did not reach significance ($p$ values 0.059 and 0.1 for curves **A** and **B** respectively). Gtsm – graft survival in months.

## Discussion

In a manner similar to defining cutoff BMI values in the preoperative assessment of various non-transplant operative procedures, it is imperative to investigate whether it would be appropriate to incorporate an acceptable BMI range in the pre-LT screening process.

To date, attention has been mostly directed to high BMI with inferior surgical outcomes having been described by various surgical disciplines [4]. Similar studies on post-LT outcomes have been conflicting. Nair et al. [5] observed inferior two- and five-year survival in morbidly obese patients, presumably due to their higher cardiovascular risk. However, LT does confer a survival benefit on the high BMI patients compared to those on the wait-list, an observation that needs to be kept in consideration [11].

Saab et al. [12] observed that BMI does not significantly impact post-LT patient survival. However, obese recipients had inferior survival if the cohorts in comparison had similar causes of liver disease. In our series, causes of liver failure varied between adult and pediatric patients and across BMI classes. Autoimmune disease was the most common indication among underweight adults, whereas ALD/HCC/HCV prevailed in the mid-BMI range adults, and NAFLD/NASH became increasingly common in the patients with higher BMIs. When adjusted for LT indication, obesity did not appear to confer inferior outcomes in our population. Rambha et al. [14] also observed that increased BMI was not associated with higher risk of graft loss or death. Singhal et al. [13] observed that BMI >40 kg/m² was not associated with higher mortality; however, their median follow-up was only two years, therefore potentially falsely unrevealing. Leonard et al. [6] observed that survival was not affected by BMI if the latter was corrected for ascites drained at the time of transplant.

In our cohort, K-M analysis of graft and patient survival revealed temporal variation of the BMI ≥35 kg/m² class death or graft loss risk (Figure 1D). Survival rates were 91.5% and 89.5% at two years and five years respectively, dropping to 65.3% at ten years, crossing the survival curves of the rest of the population


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**Table 6.** The effect of BMI on secondary outcomes (PNF, HAT, PVT, bile leak, biliary stricture, ischemic cholangiopathy, other biliary complications).

| | BMI <18.5 n=389 | BMI 18.5–24.9 n=845 | BMI 25–29.9 n=526 | BMI 30–34.9 n=279 | BMI 35–39.9 n=63 | BMI ≥40.1 n=14 | All n=2,115 | HR[a] | p |
|---|---|---|---|---|---|---|---|---|---|
| PNF (%) | 4 (1) | 7 (0.8) | 6 (1.1) | 5 (1.8) | 0 | 0 | 22 (1) | | NS |
| HAT (%) | 24 (6.2) | 31 (3.7) | 14 (2.7) | 6 (2.2) | 0 | 0 | 75 (3.5) | | **0.084** |
| PVT (%) | 13 (3.3) | 9 (1.1) | 7 (1.33) | 2 (0.7) | 0 | 0 | 31 (1.5) | | 0.877 |
| Bile leak (%) | 10 (2.6) | 48 (5.7) | 29 (5.5) | 23 (8.2) | 2 (3.2) | 0 | 112 (5.3) | **1.4[b] 95% CI: 1–1.8** | **0.045** |
| Biliary stricture (%) | 21 (5.4) | 45 (5.3) | 51 (9.7) | 26 (9.3) | 6 (9.5) | 0 | 149 (7) | | 0.2 |
| Other biliary complications (%) | 1 (0.3) | 5 (0.6) | 4 (0.8) | 1 (0.4) | 0 | 0 | 11 (0.5) | | 0.95 |
| Ischemic cholangiopathy (%) | 5 (1.3) | 14 (1.7) | 12 (2.28) | 7 (2.5) | 1 (1.6) | 0 | 39 (1.8) | | 0.84 |
| Total biliary complications (%) | 137 (9.5) | 112 (13.2) | 96 (18.3) | 57 (20.4) | 9 (14.3) | 0 | 311 (14.7) | **1.03[c]** | **0.019** |

PNF was uniformly uncommon. Even though HAT did not appear to be significantly affected by the BMI as a continuous variable, there was a tendency for higher incidence at the lower BMI recipients ($p$=0.084), which triggered ad hoc logistic regression on the effect of low BMI (<18.5 kg/m$^2$) on HAT and PVT risk. Low BMI appears to be protective of bile leak. Total biliary complications risk was positively correlated to BMI (HR 1.03, $p$=0.019).
[a] BMI was tested as a continuous variable; [b] $\chi^2$ analysis of HR of BMI ≥18.5 kg/m$^2$ versus BMI <18.5 kg/m$^2$; [c] i.e., risk of biliary complications increased by 3% for every 1 kg/m$^2$ increase of BMI. BMI – body mass index, kg/m$^2$; PNF – primary non-function; HAT – hepatic artery thrombosis; PVT – portal vein thrombosis.

**Table 7.** Effect of BMI and BMI class on HAT: comparison of BMI classes to the "normal" BMI class (BMI 18.5–24.9 kg/m$^2$).

| n=2,115 | HR | CI 95% | p |
|---|---|---|---|
| BMI (kg/m$^2$)[a] | | | 0.084 |
| **<18.5** | **1.7** | **1–3** | **0.05** |
| 25–29.9 | 0.7 | 0.4–1.4 | 0.31 |
| 30–34.9 | 0.6 | 0.2–1.4 | 0.22 |
| 35–39.9 | 0 | | 1 |
| ≥40 | 0 | | 1 |

BMI <18.5 kg/m$^2$ was associated with 1.73 HR of developing HAT ($p$=0.05). Since pediatric age was identified as an independent HAT risk factor (Table 8); the effect of low BMI on HAT risk was further tested separately on the adults (Table 9). [a] When BMI was tested as a continuous variable, there was a trend of higher HAT risk with decreasing BMI ($p$=0.084).

**Table 8.** Comparison of HAT/PVT risk in pediatric versus adult LT.

| | HR | CI 95% | *p* Value |
|---|---|---|---|
| HAT | 1.8 | 1.1–2.9 | **0.018** |
| PVT | 2.8 | 1.4–5.7 | **0.005** |

HR – hazard ratio; CT – confidence interval; HAT – hepatic artery thrombosis; PVT – portal vein thrombosis; LT – liver transplantation. Pediatric age was an independent risk factor for HAT/PVT.



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**Table 9.** Effect of underweight status in PVT/HAT (adults).

| | HR | CI 95% | *p* Value |
|---|---|---|---|
| HAT | 3 | 1–8.6 | **0.046** |
| PVT | 2 | 0.3–15.3 | 0.51 |

HR – hazard ratio; CT – confidence interval; HAT – hepatic artery thrombosis; PVT – portal vein thrombosis. Underweight status was an independent HAT risk factor after adult liver transplantation.

on the sixth through seventh year. Even after appropriate recipient selection, and despite excellent early outcomes, patient survival and censored-graft losses due to patients' death might be secondary to the inherent higher cardiovascular-specific death risk in the morbidly obese. It has to be noted that the comparison of these survival distributions might have been erroneously non-significant in our series due to the unequal sample sizes (only 3.7% of all recipients had BMI ≥35 kg/m$^2$).

Less is known about the effect of low BMI (BMI <18.5 kg/m$^2$) on LT outcomes. In our series, there was a trend of inferior mean graft (98.3 versus 112 months, $p$=0.059) and patient survival (106.7 versus 118 months, $p$=0.1, Table 5) among the underweight adults. Even though this finding did not reach significance, the K-M survival trends were clear (Figure 2A, 2B): underweight adults' expected graft and patient survival tended to be inferior at all time points. The failure of this observation to reach significance could be secondary to the small sample size of underweight adults (3.1%). It should be noted that this association of BMI <18.5 kg/m$^2$ to inferior outcomes was only observed in the adults. This perhaps indicates that BMI <18.5 kg/m$^2$ in adulthood indicates higher frailty, contrary to the pediatric population, where BMI <18.5 kg/m$^2$ is often considered healthy, for as long as BMI remains above the fifth BMI-percentile-for-age-and-gender. Therefore, a BMI <18.5 kg/m$^2$ in children is not necessarily linked to poorer outcome.

This link of low weight to higher post-LT mortality has recently been reported in a large scale UNOS-based analysis [14]. The increased mortality among patients who weigh less than average was well-recognized in a long-term follow-up series (the Framingham study) [15].

Recent studies have linked sarcopenia to increased post-LT mortality in the LDLT population [16]. Englesbe et al. [17] described the effect of sarcopenia on post-LT mortality, controlled for donor and recipient characteristics. Sarcopenia was quantified as the cross-sectional area of psoas muscle on computer tomography imaging. Sarcopenia was strongly associated to post-LT mortality (HR-3.7, $p$<0.001). It was suggested that sarcopenia should be considered an objective measure of patient frailty and should be included in the clinical decision making process. Sarcopenia was also an independent wait-list mortality predictor, especially among low MELD patients.

Sarcopenia has traditionally been linked to low BMIs; Tandon et al. correlated sarcopenia with increased mortality [18]. Low BMI LT candidates are often considered too frail to reach minimum listing criteria; and, if they do get transplanted, they do worse. It has been proposed that objective analytic morphomics of sarcopenia should be incorporated in the formal LT wait-list assessment [18,19]. Low BMI is an independent sarcopenia predictor [18]; and sarcopenia is a mortality predictor for those on the wait-list as well as post-LT [20,21].

The effect of BMI on post-LT morbidity has been variable [5–7,9,20]. Singhal et al. [13] observed than obese LT recipients were sicker at the time of transplant, as reflected by higher median MELD and longer hospital stay, resulting in higher hospital costs. In our cohort, average length of ICU stay did not significantly differ across weight groups, contrary to other reports [13,22]. MELD, inpatient status at the time of transplant, and time on wait-list did not significantly vary among the adults (pediatric candidates, however, did have significantly shorter wait-list times). Our analysis did not demonstrate increased sickness at the time of transplant and higher significant post-LT morbidity among the high BMI recipients.

The association of BMI <18.5 kg/m$^2$ with peri-LT thrombotic events has been recently reported by Bezinover et al. [23] in a large scale UNOS database analysis (65,646 patients). The authors observed that BMI <18.5 kg/m$^2$ and PSC, PBC, and AIC were associated with higher incidence of post-LT thrombotic episodes [23]. Likewise, in our cohort, we observed that patients with BMI <18.5 kg/m$^2$ had a triple risk of graft thrombotic events; and the most common LT indication for this BMI group was autoimmune disease (PSC, PBC, AIH).

A weakness of this study was its retrospective nature; recipient analytic morphomics, volume of ascites drained at the time of transplant, metabolic syndrome indicators, and post-LT BMI trends could not be systematically assessed. Also, BMI measurements were based on the last recorded pre-LT weight, which was not necessarily reflective of the dry weight at the time of transplant. Also, the authors' impression was that NASH/NAFLD prevalence was underestimated.

After appropriate transplant candidate selection and optimization, high BMI does not appear to confer higher LT-specific



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risk of death, graft loss, or post-LT morbidity, at least in the short-term. Albeit, survival curves of the morbidly obese seem to decline on an accelerated pace in the long-term. This trend of accelerated late death risk in the high BMI group might be attributable to the established higher cardiovascular-specific death hazard linked to obesity. Obesity is known to be strongly associated with DM, coronary artery disease, and cancer post-LT, and is a leading non-LT related mortality and morbidity cause [24]. In order to maximize post-LT survival benefit it is therefore important to minimize metabolic risk. Sustainable excess weight loss (EWL) after LT has been a matter of debate. Heimbach et al. observed that sleeve gastrectomy at the time of transplant confers sustainable EWL and protects from post-LT DM and steatosis, without additional death or graft loss risk [25]. A small French meta-analysis (n=56) observed that bariatric surgery is feasible and effective, resulting in acceptable EWL, and morbidity and mortality rates [26]. Lin et al. [27] reported on a series of nine morbidly obese patients who underwent sleeve gastrectomy after LT with no adverse effect on graft function. The same authors reported on a series of 26 morbidly obese patients who underwent sleeve gastrectomy prior to liver or kidney transplantation [28].

Even if the survival and cost-effectiveness of transplanting at the BMI extremes proved to be inferior to other BMI groups, the ethical imperative remains: since LT confers survival benefit [11] and there is currently no evidence supporting the contrary, these patients should be transplanted. The attention should therefore be turned into discovering means of identifying and correcting sarcopenic status and cardio-metabolic risk as these are flagged by the extreme BMI values. But until this is achieved, BMI extremes, after careful patient selection, should not constitute contraindication to LT.

## Conclusions

This single center retrospective study concluded that post-LT graft and patient survival were independent of recipient BMI. However, there was a trend of inferior long-terms survival at the BMI extremes. Similarly to the largest to-date UNOS series, adult underweight status was linked to higher HAT risk; and autoimmune disease was the most common LT indication among the underweight. Biliary complication risk increased with rising recipient BMI; however, ischemic cholangiopathy was not linked to BMI class. Overall, recipient BMI extremes are not a contraindication for LT after appropriate recipient selection.

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