ORIGINAL ARTICLE

Comparable Graft and Patient Survival in Lean and Obese Liver Transplant Recipients

Silvia E. Perez-Protto,[1] Cristiano Quintini,[2] Luke F. Reynolds,[5] Jing You,[3] Jacek B. Cywinski,[1] Daniel I. Sessler,[4] and Charles Miller[2]

[1]Anesthesiology Institute and Departments of [2]General Surgery (Liver Transplant Center), [3]Quantitative Health Sciences, and [4]Outcomes Research, Cleveland Clinic, Cleveland OH; and [5]Division of Urology, Ottawa Hospital, Ottawa, Canada

Obesity is among the great health problems facing Americans today. More than 32% of the US population is considered obese on the basis of a body mass index (BMI) exceeding 30 kg/m^2. Obesity increases the risk for numerous perioperative complications, but how obesity affects the outcome of liver transplantation remains unclear. We compared graft/patient survival after orthotopic liver transplantation performed at the Cleveland Clinic between April 2005 and June 2011 in 2 groups: obese patients with a BMI $\geq$ 38 kg/m^2 and lean patients with a BMI between 20 and 26 kg/m^2. We included 47 obese patients and 183 lean patients, whose demographics and baseline characteristics were well balanced after weighting with the inverse propensity score. After we controlled for observed confounding, no significant differences were observed in graft/patient survival between obese and lean patients ($P = 0.30$). The estimated hazard ratio for obese patients to experience graft failure or death was 1.19 [95% confidence interval (CI) = 0.85-1.67]. There were 134 patients who had follow-up for more than 3 years, and they included 27 obese patients and 107 lean patients. Within this subset, the odds of having metabolic syndrome were significantly greater for obese patients (46%) versus lean patients (21%; odds ratio = 4.76, 99.5% CI = 1.66-13.7, $P < 0.001$). However, no significant association between obesity and any other long-term adverse outcomes was found. In conclusion, this study shows that transplant outcomes were comparable for lean and obese recipients. We thus recommend that even morbid obesity per se should not exclude patients from consideration for transplantation. ***Liver Transpl 19:907-915, 2013***. © **2013 AASLD.**

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Obesity is among the great health problems facing Americans today. More than 32% of the US population is considered obese on the basis of a body mass index (BMI) exceeding 30 kg/m^2, and the fraction is expected to increase.[1] A result of this national trend is that an increasing number of liver transplant candidates are obese.[2] According to Organ Procurement and Transplantation Network data as of January 24, 2013, 8.5% of the patients on the waiting list for orthotopic liver transplantation (OLT) in 1998 were morbidly obese, and the percentage rose to 10.8% by

Additional Supporting Information may be found in the online version of this article.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; ICU, intensive care unit; OLT, orthotopic liver transplantation; SBP, systolic blood pressure.

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Address reprint requests to Silvia E. Perez-Protto, M.D., Anesthesiology Institute, Cleveland Clinic, P77, 9500 Euclid Avenue, Cleveland OH 44195. Telephone: 216-445-5125; FAX: 216-444-6135; E-mail: perezs2@ccf.org

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2012; in both years, it seems likely that many more obese patients who might have benefited from liver transplantation were never listed.

Obesity decreases life expectancy[3,4] and increases the risk for cardiovascular disease, diabetes mellitus type 2, osteoarthritis, certain cancers, and nonalcoholic steatohepatitis.[5,6] Because obesity increases the risk for numerous perioperative complications such as cardiac events, adverse respiratory outcomes,[7] infections, and wound complications[8] as well as overall mortality,[9-12] an important issue is whether obese patients should be considered for liver transplantation in light of the profound shortage of organs.

How obesity affects outcomes following liver transplantation remains unclear. Nonetheless, some centers do not perform transplantation for obese patients because of concerns about perioperative complications.[13] Few centers even list severely and morbidly obese patients, and among those listed, a smaller fraction undergoes transplantation in comparison with a reference group.[14] More data are needed to guide transplant programs' decisions on organ allocation. Thus, our goal was to compare the outcomes of OLT for patients with a BMI $\geq$ 38 kg/m^2 and patients with a BMI between 20 and 26 kg/m^2 at the Cleveland Clinic.

PATIENTS AND METHODS

With institutional review board approval and an informed consent waiver, this retrospective study was based on the Unified Transplant Center database, the United Network for Organ Sharing database, and the Perioperative Health Documentation System at the main campus hospital of the Cleveland Clinic.

The patient population consisted of individuals undergoing primary cadaveric OLT between April 2005 and June 2011 at the Cleveland Clinic. We excluded patients who were <18 years old, had a BMI greater than 26 and less than 38 kg/m^2, or had missing data for the primary outcome and/or covariables. We also excluded patients with a BMI < 20 kg/m^2 because Rustgi et al.[15] reported that 1-year posttransplant survival was reduced in this population.

We divided our study population into (1) obese patients with a BMI $\geq$ 38 kg/m^2 and (2) lean patients with a BMI between 20 and 26 kg/m^2. We defined morbid obesity as a BMI of $\geq$38 kg/m^2 rather than 35 kg/m^2 because patients with chronic liver failure usually present with fluid overload, ascites, or both, which increase their body weight.

Our primary outcome—patient/graft survival—was defined as the time to the earliest occurrence of graft failure or mortality. We studied the relationship between obesity and patient and graft survival univariately with Kaplan-Meier estimation[16] and a log-rank test. Our primary analysis was a Cox proportional hazards regression model[17] in which we controlled confounding variables with the inverse propensity score weighting method (which is described in the next paragraph in more detail). In these analyses, patients who experienced graft failure or died or were censored were removed from the risk set at that time.

We used the inverse propensity score weighting method[18] to control for confounding observed between the obese group and the normal-BMI group. First, the propensity score (ie, the probability of being in the obese group) was estimated for each patient with a multivariate logistic regression model in which the outcome variable was the obese group and the independent variables were all available potentially confounding variables (Table 1). The outcomes of the obese group and the normal-BMI group were compared with a relevant model in which each observation was weighted by the inverse of the propensity score. In addition, any potentially confounding variables that remained imbalanced between the obese and normal-BMI groups after the inverse of the propensity score [absolute standardized difference $> 0.32 \left(1.96 \times \sqrt{\frac{1}{47} + \frac{1}{183}}\right)$] was weighted were included in the model as well.[19]

As secondary outcomes, we assessed the relationships between obesity and the time to intensive care unit (ICU) and hospital discharge with multivariate Cox proportional hazards regressions, for which the same covariate adjustment method used in the primary analysis was employed. Patients dying before the event were considered to be failures in the analysis and were censored at the time of the worst observation among patients who were discharged alive. Bonferroni correction was used to adjust for multiple testing. Thus, 97.5% confidence intervals (CIs) were reported, and the significance criterion for the 2 secondary analyses was $P < 0.025$ (ie, 0.05/2).

For informational purposes, we report intraoperative variables and postoperative labs for the obese group and the normal-BMI group. The intraoperative outcomes included the duration of surgery, airway difficulties, intubation devices, estimated blood loss, amounts of transfused blood products (red blood cells, fresh frozen plasma, cryoprecipitate, and platelets), amounts of fluids (crystalloids and colloids), use of vasopressors, and hemodynamics [including the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (BP), pulmonary artery BP, central venous pressure, and cardiac output from the time of induction to the time of incision and within 1 hour before the time of closing]. The postoperative labs included blood glucose, creatinine, international normalized ratio, alanine aminotransferase, aspartate aminotransferase, prothrombin time, and bilirubin. All the variables were univariately compared between the obese and normal-BMI groups with the Student *t* test, Wilcoxon rank-sum test, Pearson chi-square test, or Fisher's exact test as appropriate.

Finally, within the subset of patients who had follow-up for more than 3 years, we assessed metabolic syndrome, hyperlipidemia, endocrine diseases (diabetes and hypothyroidism), renal dysfunction, renal

TABLE 1. Demographics and Baseline Characteristics (n = 230)

Variable	Before Weighting With the Inverse Propensity Score			After Weighting With the Inverse Propensity Score		
	Obese (n = 47)	Normal BMI (n = 183)	Absolute Standardized Difference[§]	Obese (n = 47)	Normal BMI (n = 183)	Absolute Standardized Difference[§]
Age (years)[†]	55 ± 10	54 ± 11	0.03	55 ± 18	54 ± 11	0.05
Sex: female (%)	47	31	0.34	35	36	0.02
Race (%)			0.30			0.07
White	91	82		83	84	
Black	6	11		12	10	
Other	2	7		5	6	
Hypertension (%)	51	43	0.17	43	42	0.02
Diabetes (%)	53	38	0.31	45	39	0.13
Left-side heart failure (%)	0	1	0.11	0	0	0.09
Right-side heart failure (%)	2	2	0.04	2	2	0.04
Primary diagnosis (%)			0.66			0.23
Noncholestatic cirrhosis	68	42		55	49	
Cholestatic liver disease/cirrhosis	4	16		10	13	
Biliary atresia	0	1		0	0	
Acute hepatic necrosis	4	2		2	2	
Metabolic disease	2	2		1	1	
Malignant neoplasms	17	31		29	28	
Other	4	7		3	6	
Days on waiting list[‡]	28 (9-109)	62 (22-147)	0.27	42 (12-241)	70 (22-142)	0.04
Previous liver transplant (%)	2	4	0.13	1	4	0.16
On life support at transplant (%)	4	3	0.08	3	3	0.01
On ventilator at transplant (%)	4	3	0.08	3	3	0.01
Year of transplantation[†]	2008 ± 2	2008 ± 2	0.26	2008 ± 2	2008 ± 2	0.06
Creatinine (mg/dL)[‡]	1.4 (1.0-2.1)	1.0 (0.8-1.6)	0.52	1.2 (1.0-2.0)	1.1 (0.8-1.7)	0.01
Bilirubin (mg/dL)[‡]	3.9 (2.2-8.6)	3.5 (1.5-9.6)	0.26	3.4 (2.0-8.6)	4.3 (1.6-10)	0.04
International normalized ratio[‡]	1.5 (1.3-1.7)	1.3 (1.2-1.6)	0.50	1.4 (1.2-1.7)	1.4 (1.2-1.6)	0.02
Alanine aminotransferase (IU/L)[‡]	31 (22-46)	35 (21-62)	0.16	28 (22-46)	34 (19-62)	0.00
Aspartate aminotransferase (IU/L)[‡]	70 (47-93)	68 (42-117)	0.05	70 (45-91)	66 (40-114)	0.06
Prothrombin time (seconds)[‡]	16 (14-19)	15 (13-18)	0.49	15 (13-19)	15 (13-18)	0.02
High calculated Model for End-Stage Liver Disease score[‡]	20 (15-27)	18 (12-23)	0.41	16 (13-25)	19 (12-24)	0.04
Donor risk index[‡]	1.3 (1.2-1.6)	1.4 (1.1-1.6)	0.08	1.3 (1.1-1.6)	1.4 (1.1-1.6)	0.06
ABO match level (%)			0.51			0.19
Identical	85	96		95	92	
Compatible	15	2		5	6	
Incompatible	0	2		0	2	

*An imbalance is indicated if the absolute value of the absolute standardized difference (difference in the means or proportions divided by the pooled standard deviation) is >0.32 $\left(\text{ie, } \left(1.96\times\sqrt{\frac{1}{47}+\frac{1}{183}}\right)\right)$.

[†]The data are presented as means and standard deviations.

[‡]The data are presented as medians and interquartile ranges. Some sets of percentages do not add up to 100 because of rounding.

insufficiency or chronic dialysis, acute renal insufficiency (nonchronic dialysis), recurrent disease, rejection, infectious events (pneumonia, sepsis, hepatic abscess, and abdominal wall infection), cardiac events (arrhythmias, heart failure, and myocardial infarction), and respiratory events (respiratory insufficiency, pleural effusion, and pulmonary edema). These complications were extracted from our transplant database. A registered nurse examined the electronic medical records and entered the new diagnosis

and events into the database at the time of the United Network for Organ Sharing follow-up form submission yearly after transplantation. The transplant center called patients at least yearly when they came from another institution and recorded any new data in the electronic medical records. All outcomes were defined as occurring within the first 3 years after transplantation. We used the inverse propensity score weighting method to control for confounding observed between the obese group and the normal-BMI group. Bonferroni correction was used to adjust for multiple testing.

Using available data on the earliest occurrence of graft failure or mortality for patients with normal BMIs, we had more than 90% power at the 0.05 significance level to detect a hazard ratio of 2.5 or greater with 230 patients. SAS software (version 9.3, SAS Institute, Cary, NC) was used for all statistical analysis; R statistical software (version 2.12.2, R Foundation for Statistical Computing, Vienna, Austria) was used for graphics.

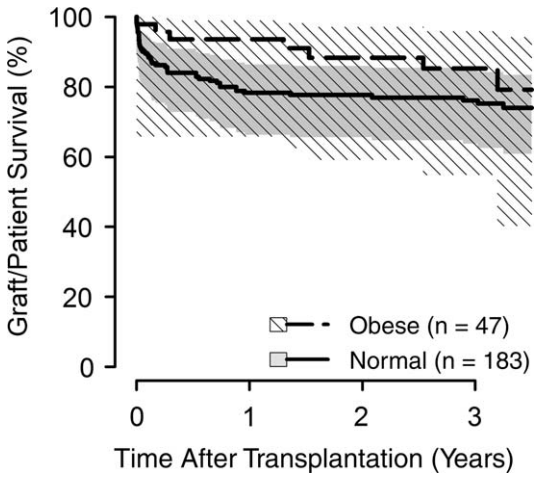

Figure 1. Kaplan-Meier estimates of graft/patient survival density functions for the obese group (n = 47) and the normal-BMI group (n = 183). Associated equal-precision 95% confidence bands are shown for the obese and normal-BMI groups with hash lines and shading, respectively. These univariate survival density estimates are not statistically different ($P = 0.64$, log-rank test).

RESULTS

Among the 230 adult patients who met the inclusion criteria and underwent OLT at the main campus of the Cleveland Clinic between April 2005 and June 2011, there were 47 obese patients (BMI $\geq$ 38 kg/m^2) and 183 lean patients (20 $\leq$ BMI $\leq$ 26 kg/m^2). The observed median BMIs were 41.6 kg/m^2 [interquartile range = 39.0-45.1 kg/m^2] and 24.0 kg/m^2 [interquartile range = 22.6-25.0 kg/m^2], respectively. Table 1 displays demographics and baseline characteristics as well as the corresponding absolute standardized differences between the 2 groups with and without weighting with the inverse propensity score (ie, the probability of being in the obese group).

All the variables were well balanced between the 2 groups after weighting with the inverse propensity score (absolute standardized difference < 0.32; Table 1). Thus, there was no need to adjust for any variable in addition to the weighting of the relevant inverse propensity score. The detailed causes of end-stage liver disease are reported in Supporting Table 1.

Univariately, there was no significant difference between obese and lean patients in patient/graft survival ($P = 0.64$, log-rank test). Kaplan-Meier estimates of patient/graft survival as a function of posttransplant times are provided in Fig. 1 and Table 2. Sixty-one patients experienced an outcome of interest (graft failure and/or death after liver transplantation), and they included 23 patients who experienced graft failure and 38 patients who died without graft failure. Fifteen of the 23 patients underwent retransplantation (11 survived, and 4 died), and 8 died without retransplantation. Detailed causes of death are reported in Supporting Table 2. The median follow-up time was 3.0 years (interquartile range = 1.0-4.0 years).

After we controlled for observed confounding, no significant differences were observed in graft/patient survival between obese patients and patients with normal BMIs ($P = 0.30$). The estimated hazard ratio for obese patients to experience the endpoint of graft failure or mortality in comparison with patients with normal BMIs at any given time after transplantation was 1.19 (95% CI = 0.85-1.67).

No significant association was found between obesity and the time to ICU discharge ($P = 0.29$) or the time to hospital discharge [$P = 0.035$ (which exceeded the significant criterion of 0.025); Table 3]. Additionally, summary statistics of intraoperative variables and postoperative labs are reported in Table 4.

There were 134 patients who had follow-up for more than 3 years, and they included 27 obese patients and 107 patients with normal BMIs. Within this subset, the odds of having metabolic syndrome were significantly greater for obese patients (46%) versus lean patients (21%; odds ratio = 4.76, 99.5% CI = 1.66-13.7, $P < 0.001$). However, no significant association between the obese group and any other long-term adverse outcomes was found (Table 5).

DISCUSSION

Our primary finding is that patient survival and graft survival were comparable in lean and morbidly obese transplant recipients after we controlled for potentially confounding variables. Our study is one of the largest single-center studies, and we included only patients from the last 7 years (ie, when treatment was relatively homogeneous).

We also used a sophisticated statistical analysis that enhanced the reliability and accuracy of our results. Our inverse propensity score weighting method controlled the potentially confounding factors observed for the obese group and the normal-BMI group very well. For example, the 2 groups presented with different indications for transplantation, which could have

TABLE 2. Primary Results: Comparison of Patient/Graft Failure in the Obese and Normal-BMI Groups (n = 230).

	Patient/Graft Survival (%)*		Death or Graft Failure/ Censored/Remaining†			
Time	Obese	Normal BMI	Obese	Normal BMI	Obese/Normal Hazard Ratio (95% CI)‡	*P* Value
At transplant	100 (100-100)	100 (100-100)	0/0/47	0/0/183	1.19 (0.85-1.67)	0.30
6 months	94 (87-100)	84 (79-89)	3/0/44	29/5/149		
1 year	94 (87-100)	78 (72-84)	3/2/42	39/9/135		
2 years	88 (79-98)	78 (72-84)	5/9/33	40/28/115		
3 years	85 (74-96)	76 (70-83)	6/18/23	42/50/91		
4 years	73 (55-91)	73 (66-80)	8/27/12	45/80/58		

*The data are presented as Kaplan-Meier survival density function estimates and their associated equal-precision 95% CIs.
†The number of patients who died or experienced graft failure, the number of patients who were censored, and the number of patients who remained at various time points after transplantation are presented.
‡Cox proportional hazards regressions were used, for which we controlled confounding variables with the inverse propensity score weighting method.

affected the outcomes. In particular, the lean group included higher numbers of patients with hepatocarcinoma (31% versus 17% in the obese group) and cholestatic liver disease (16% versus 4%), and both factors are associated with more favorable outcomes; however, they were well balanced after weighting with the inverse propensity score (28% versus 29% and 13% versus 10%, respectively). Although more obese patients with hepatocarcinoma were outside the Milan criteria (50% versus 35%), the patient and graft survival rates were still comparable for the lean and obese patients. Even though our obese population had a high proportion of recipients with nonalcoholic steatohepatitis (which has been associated with poor outcomes), it did not have the same impact in our population.[20] Indeed, the analysis was adjusted for all the aforementioned characteristics. Although our study was restricted to a single center, we had adequate power to identify obesity-related adverse transplant outcomes if they had been present.

Our results are consistent with previous work finding that obesity does not worsen mortality after liver transplantation.[21-24] Recent studies in liver transplant patients have similarly indicated that obesity is not associated with an increased length of stay in the ICU, ventilator support, or 2-year mortality after liver transplantation.[25,26] Sawyer et al.[21] did not find an increase in mortality, but they observed increased infection and multisystem organ failure rates in an acute setting in patients with a BMI > 35 kg/m^2. A Danish study reported that a BMI > 30 kg/m^2 increased mortality; however, the comparison groups in that analysis were poorly matched.[27] Nair et al.[28] found that morbid obesity (BMI > 40 kg/m^2) increased mortality in the short and long term, with cardiac complications being postulated as the mechanism.

TABLE 3. Secondary Results: Associations Between Obesity and the Time to ICU and Hospital Discharge (n = 230)

	Obese (n = 47)		Normal BMI (n = 183)			
Secondary Outcome	Discharged Alive [n (%)]	Days to Discharge*	Discharged Alive [n (%)]	Days to Discharge*	Obese/Normal Hazard Ratio (97.5% CI)†	*P* Value‡
Time to ICU discharge	44 (98)§	4 (2-5.5)	166 (97)¶	3 (2-5)	0.90 (0.71-1.13)	0.29
Time to hospital discharge	44 (97)§	10 (9-15.5)	169 (95)	10 (8-16)	1.25 (0.99-1.58)	0.035

*The summary statistics are presented as medians and interquartile ranges for patients who were discharged alive from the ICU or hospital.
†Cox proportional hazards regressions were used, for which we controlled confounding variables with the inverse propensity score weighting method. Patients dying before discharge were considered to be failures in the analysis and were censored at the time of the longest observation of any patient.
‡The significance criterion was $P < 0.025$ [ie, 0.05/2 (Bonferroni)] for each of the outcomes.
§Data for the length of the ICU stay were missing for 2 patients, and data for the length of the posttransplant hospital stay were missing for 1 patient.
¶Data for the length of the ICU stay were missing for 12 patients.

TABLE 4. Summary of the Intraoperative Variables and Postoperative Labs (n = 230)

Variables	Missing (n)	Obese (n = 47)	Missing (n)	Normal BMI (n = 183)	*P* Value*
Intraoperative					
Duration of surgery (hours)†		9.7 (8.1-11.3)		9.3 (8.1-10.8)	0.58
Intraoperative vasopressor [n (%)]		43 (91)		178 (97)	0.087‡
Intubation device [n/N (%)]	4		15		0.027‡
Laryngoscope		40/43 (93)		167/168 (99)	
GlideScope		2/43 (5)		1/168 (1)	
Fiber-optic bronchoscope		1/43 (2)		0/168 (0)	
Airway difficulty [n/N (%)]	4	1/43 (2)	28	2/155 (1)	0.12‡
Crystalloids (L)†		0 (0-0.9)		0 (0-1.0)	0.47
Colloids (L)†		2.0 (1.3-3.0)		1.8 (0.8-2.8)	0.14
Red blood cells (L)†		2.7 (1.6-3.7)		2.0 (1.1-3.6)	0.20
Fresh frozen plasma (L)†		1.5 (0.6-2.9)		1.4 (0.5-2.8)	0.62
Platelets (L)†		0.5 (0.5-1.0)		0.5 (0.0-1.3)	0.85
Cryoprecipitate (L)†		0 (0-0.2)		0 (0-0)	0.51
Estimated blood loss (L)†		6.2 (4.4-13.0)		5.0 (3.0-10.0)	0.072
From the time of induction to the time of incision§					
SBP (mm Hg)		112 ± 16		110 ± 16	0.42¶
DBP (mm Hg)		54 ± 10		55 ± 10	0.44¶
Mean BP (mm Hg)		72 ± 12		74 ± 12	0.38¶
Pulmonary artery SBP (mm Hg)	19	33 ± 5	102	28 ± 7	0.004¶
Pulmonary artery DBP (mm Hg)	19	17 ± 4	102	15 ± 4	0.018¶
Mean pulmonary artery BP (mm Hg)	19	24 ± 4	102	21 ± 5	0.003¶
Central venous pressure (mm Hg)	28	15.6 ± 5.4	90	11.9 ± 4.6	0.002¶
Cardiac output (L/minute)	24	10.5 ± 3.0	87	8.5 ± 2.8	0.003¶
Within 1 hour before the time of closing§					
SBP (mm Hg)		107 ± 13		106 ± 12	0.72¶
DBP (mm Hg)		49 ± 8		51 ± 7	0.089¶
Mean BP (mm Hg)		69 ± 10		71 ± 7	0.054¶
Pulmonary artery SBP (mm Hg)	19	34 ± 8	106	29 ± 6	0.003¶
Pulmonary artery DBP (mm Hg)	19	16 ± 5	106	15 ± 4	0.16¶
Mean pulmonary artery BP (mm Hg)	19	25 ± 5	106	22 ± 4	0.006¶
Central venous pressure (mm Hg)	28	12.8 ± 4.4	90	10.8 ± 3.6	0.033¶
Cardiac output (L/minute)	21	11.2 ± 2.5	77	9.9 ± 2.9	0.061¶
Postoperative labs†					
Blood glucose (mg/dL)	21	241 (208-265)	93	227 (185-269)	0.004
Creatinine (mg/dL)	26	1.4 (1.1-1.7)	101	1.0 (0.7-1.3)	0.31
International normalized ratio	21	1.5 (1.3-1.6)	96	1.5 (1.3-1.7)	0.98
Alanine aminotransferase (IU/L)	21	439 (305-720)	96	434 (253-816)	0.42
Aspartate aminotransferase (IU/L)	21	949 (479-1687)	96	1006 (607-1697)	0.91
Prothrombin time (seconds)	21	16.1 (14.5-17.5)	96	16.2 (13.6-18.0)	0.63
Bilirubin (mg/dL)	21	6.1 (4.2-8.3)	96	4.1 (2.7-6.9)	0.004

*Wilcoxon rank-sum test (unless otherwise specified).
†The data are presented as medians and interquartile ranges.
‡Fisher's exact test.
§The data are presented as means and standard deviations.
¶Student *t* test.

Hakeem et al.[29] just published a large database study showing longer ICU and hospital stays and increases in postoperative infective complications in an obese group. The main limitation of that report is the long study period because patient selection and surgical techniques changed substantially along the years. Furthermore, rather than analyzing mortality and graft failure separately, we analyzed them as a combined outcome to avoid the following 2 biases. First, mortality is a competing risk of graft failure. Second, assessing the effect on mortality alone would require the removal of the effect of retransplant interventions. Possible explanations for the discrepancies in the results of available studies include factors related to surgical techniques, preoperative evaluations, patient selection, perioperative medical care, statistical analysis approaches, and, perhaps most importantly, various obesity classifications.

There is no consensus on what is considered severe obesity in liver transplantation, and this makes it difficult to directly compare various studies. We defined our study group of interest with a higher BMI than usual because patients with chronic liver failure usually present with fluid overload, ascites, or both, which increase their body weight and lead to the inclusion of overweight patients in the obese category.

Although acute graft survival and patient survival are obviously critical, longer term outcomes are also important. Metabolic syndrome is among the more serious consequences of obesity and is defined by a constellation of interrelated risk factors, including abdominal obesity, impaired glucose tolerance, hypertension, and dyslipidemia. Unsurprisingly, obese transplant patients had a greater prevalence of metabolic syndrome after transplantation, and this finding is consistent with previous reports.[30] Previous work also suggests that metabolic syndrome directly promotes the development of atherosclerotic cardiovascular disease,[31] allograft failure, and the progression of fibrosis in patients with hepatitis C,[32] all of which are important sources of long-term morbidity and mortality in transplant recipients. Metabolic syndrome is also associated with major cardiovascular events and renal dysfunction.[33-35] No other longer term outcomes differed significantly. However, we had limited power for these outcomes, and some might well differ by clinically important amounts. For example, differences in cardiac morbidity and acute dialysis (both 15% for obese patients versus 6% for lean patients) are potentially important (Table 5). We believe that if risk factors in the obese population are not modified, longer follow-up times will allow the demonstration of a difference in survival mainly due to cardiac complications.

It is important to emphasize that our patient population had relatively low Model for End-Stage Liver Disease scores and relatively low donor risk indices as well. Better overall outcomes in the lean group would have been expected, but a selection bias could account for some of these differences. It is likely that surgically challenging obese patients (eg, severe portal vein thrombosis and multiple previous operations) may have been denied a transplant more easily in the setting of other significant comorbidities in comparison with lean patients. In our program, we do not have a specific protocol for obese patients, and our multidisciplinary transplant selection committee considers every case ad hoc. We think that the selection process for obese patients at our institution successfully identifies patients who have chances of success similar to those of lean patients.

Our short- and mid-term results both indicate that even substantial obesity does not worsen the outcomes of OLT if the patients are adequately evaluated and selected. This conclusion is clinically important because currently many centers either systematically or informally exclude morbidly obese patients from consideration or select obese patients less often.[14] Our results, in agreement with previous weaker evidence, indicate that the exclusion of obese recipients is unjustified and that these patients should be given the same access to transplantation as lean patients.[36] We want to emphasize that this conclusion may not apply to recipients with high Model for End-Stage Liver Disease scores. Although weight optimization of obese patients before transplantation is often challenged by significant

TABLE 5. Substudy Results: Comparison of Adverse Outcomes for Patients in the Obese and Normal-BMI Groups Who Had Follow-Up for More Than 3 Years (n = 134).

Adverse Outcome Within 3 Years After Transplantation	Obese (n = 27): n (%)	Normal BMI (n = 107): n (%)	Obese/Normal Odds Ratio (99.5% CI)*	*P* Value†
Metabolic syndrome‡	11 (46)	20 (21)	4.76 (1.66-13.7)	<0.001§
Cardiac	4 (15)	6 (6)	2.80 (0.66-12.0)	0.047
Chronic dialysis	1 (4)	4 (4)	0.55 (0.02-16.6)	0.62
Nonchronic dialysis	4 (15)	6 (6)	2.18 (0.47-10.1)	0.15
Hyperlipidemia	6 (22)	11 (10)	0.78 (0.25-2.48)	0.55
Endocrine	1 (4)	7 (7)	0.18 (0.01-3.29)	0.10
Infection	2 (7)	14 (13)	0.51 (0.11-2.48)	0.23
Recurrent disease	1 (4)	12 (11)	0.36 (0.08-1.59)	0.054
Rejection	0 (0)	0 (0)	—	—
Renal	5 (19)	17 (16)	1.90 (0.68-5.36)	0.08
Respiratory	2 (7)	6 (6)	0.62 (0.07-5.33)	0.54

*We used the inverse propensity score weighting method to control for confounding observed between the obese group and the normal-BMI group. Race and primary diagnosis (imbalanced after weighting by the inverse of the propensity score) were included in the models in addition to the weighting of the relevant inverse propensity score.
†The significance criterion was $P < 0.005$ for each of the outcomes [ie, 0.05/10 (Bonferroni)].
‡Values were missing for 3 patients in the obese group and for 13 patients in the normal-BMI group.
§Statistically significant.

fluid retention and metabolic derangement, posttransplant weight management has been an overlooked aspect of these patients both in our program and in the literature. The data show that the vast majority of patients drop a significant amount of weight within the first 6 months after surgery. It is likely that most of this weight loss comes from decreased fluid retention and caloric intake or a higher metabolism in the initial postoperative months.[30] After the first 6 months, there is a progressive weight increase, with a plateau reached approximately 2 years after transplantation (Supporting Fig. 1). On the basis of this information, we propose that obese patients could potentially benefit from a specifically designed weight control program taking place 1 year after surgery. It is important to point out that our institution does not have a program to help patients to modify risk factors after transplantation. As a result of this study, we have decided to focus on a postoperative wellness program that patients will be able to join if they desire.

In summary, our study shows that liver transplant outcomes were comparable in lean and obese recipients. The most likely explanation is that our obese patients were a select group of obese patients most likely to do well. Our data do not support—nor do we claim—that all morbidly obese patients should undergo transplantation. Instead, we specify that even morbid obesity per se should not exclude patients from consideration for transplantation. We thus recommend that efforts should be focused on posttransplant behavioral changes with a multidisciplinary approach in order to decrease the incidence of metabolic syndrome, which may influence long-term outcomes in this population.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010;303:235-241.
2. Pelletier SJ, Schaubel DE, Wei G, Englesbe MJ, Punch JD, Wolfe RA, et al. Effect of body mass index on the survival benefit of liver transplantation. Liver Transpl 2007; 13:1678-1683.
3. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, et al. Body weight and mortality among women. N Engl J Med 1995;333:677-685.
4. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097-1105.
5. Haslam DW, James WP. Obesity. Lancet 2005;366:1197-1209.
6. Jiang J, Torok N. Nonalcoholic steatohepatitis and the metabolic syndrome. Metab Syndr Relat Disord 2008;6:1-7.
7. Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. Crit Care Med 2008;36:151-158.
8. Schaeffer DF, Yoshida EM, Buczkowski AK, Chung SW, Steinbrecher UP, Erb SE, Scudamore CH. Surgical morbidity in severely obese liver transplant recipients—a single Canadian centre experience. Ann Hepatol 2009;8:38-40.
9. Choban PS, Flancbaum L. The impact of obesity on surgical outcomes: a review. J Am Coll Surg 1997;185:593-603.
10. Choban PS, Heckler R, Burge JC, Flancbaum L. Increased incidence of nosocomial infections in obese surgical patients. Am Surg 1995;61:1001-1005.
11. Thuluvath PJ, Yoo HY, Thompson RE. A model to predict survival at one month, one year, and five years after liver transplantation based on pretransplant clinical characteristics. Liver Transpl 2003;9:527-532.
12. Thuluvath PJ. Morbid obesity with one or more other serious comorbidities should be a contraindication for liver transplantation. Liver Transpl 2007;13:1627-1629.
13. Fujikawa T, Fujita S, Mizuno S, Shenkman E, Vogel B, Lipori P, et al. Clinical and financial impact of obesity on the outcome of liver transplantation. Transplant Proc 2006;38:3612-3614.
14. Segev DL, Thompson RE, Locke JE, Simpkins CE, Thuluvath PJ, Montgomery RA, Maley WR. Prolonged waiting times for liver transplantation in obese patients. Ann Surg 2008;248:863-870.
15. Rustgi VK, Marino G, Rustgi S, Halpern MT, Johnson LB, Tolleris C, Taddei TH. Impact of body mass index on graft failure and overall survival following liver transplant. Clin Transplant 2004;18:634-637.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
17. Cox DR. Regression models and life-tables. J R Stat Soc Ser B 1972;34:187-220.
18. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. Med Care 2007;45(suppl 2): S103-S107.
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28: 3083-3107.
20. Agopian VG, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, et al. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. Ann Surg 2012;256:624-633.
21. Sawyer RG, Pelletier SJ, Pruett TL. Increased early morbidity and mortality with acceptable long-term function in severely obese patients undergoing liver transplantation. Clin Transplant 1999;13(pt 2):126-130.
22. Braunfeld MY, Chan S, Pregler J, Neelakanta G, Sopher MJ, Busuttil RW, Csete M. Liver transplantation in the morbidly obese. J Clin Anesth 1996;8:585-590.
23. Keeffe EB, Gettys C, Esquivel CO. Liver transplantation in patients with severe obesity. Transplantation 1994;57: 309-311.
24. LaMattina JC, Foley DP, Fernandez LA, Pirsch JD, Musat AI, D'Alessandro AM, Mezrich JD. Complications associated with liver transplantation in the obese recipient. Clin Transplant 2012;26:910-918.
25. Werneck M, Afonso RC, Coelho GR, Sboarini C, Coelho MP, Thomé T, et al. Obese and nonobese recipients had similar need for ventilatory support after liver transplantation. Transplant Proc 2011;43:165-169.
26. Boin IF, Almeida LV, Udo EY, Stucchi RS, Cardoso AR, Caruy CA, et al. Survival analysis of obese patients undergoing liver transplantation. Transplant Proc 2007; 39:3225-3227.
27. Hillingsø JG, Wettergren A, Hyoudo M, Kirkegaard P. Obesity increases mortality in liver transplantation—the Danish experience. Transpl Int 2005;18:1231-1235.
28. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology 2002;35:105-109.
29. Hakeem AR, Cockbain AJ, Raza SS, Pollard SG, Toogood GJ, Attia MA, et al. Increased morbidity in overweight

and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. Liver Transpl 2013;19:551-562.

30. Kallwitz ER. Metabolic syndrome after liver transplantation: preventable illness or common consequence? World J Gastroenterol 2012;18:3627-3634.
31. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al.; for American Heart Association and National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112: 2735-2752.
32. Hanouneh IA, Feldstein AE, McCullough AJ, Miller C, Aucejo F, Yerian L, et al. The significance of metabolic syndrome in the setting of recurrent hepatitis C after liver transplantation. Liver Transpl 2008;14:1287-1293.
33. Charlton M. Obesity, hyperlipidemia, and metabolic syndrome. Liver Transpl 2009;15(suppl 2):S83-S89.
34. Hanouneh IA, Zein NN. Metabolic syndrome and liver transplantation. Minerva Gastroenterol Dietol 2010;56: 297-304.
35. Albeldawi M, Aggarwal A, Madhwal S, Cywinski J, Lopez R, Eghtesad B, Zein NN. Cumulative risk of cardiovascular events after orthotopic liver transplantation. Liver Transpl 2012;18:370-375.
36. Pelletier SJ, Maraschio MA, Schaubel DE, Dykstra DM, Punch JD, Wolfe RA, et al. Survival benefit of kidney and liver transplantation for obese patients on the waiting list. Clin Transpl 2003:77-88.