



# Influence of Donor Obesity on Long-Term Liver Transplantation Outcomes

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## ABSTRACT

**Objective.** To analyze liver transplantation outcomes according to the body mass index (BMI) of donors.

**Material and Methods.** A retrospective descriptive study was conducted in patients transplanted at our center between January 2006 and December 2014, comparing outcomes between grafts from obese (body mass index [BMI]  $\geq 30$ ) and nonobese (BMI  $\leq 30$ ) donors.

We analyzed the reasons for transplantation, the morbidity-mortality related variables, and survival after a minimum follow-up of 24 months. A multivariate logistic model was constructed to predict the mortality. Survival was analyzed with the Kaplan-Meier method, and survival curves were compared using the log-rank test.

**Results.** The study included 50 obese and 175 nonobese donors. A significant difference between the groups was found in the pre-extraction intensive care unit (ICU) stay of the donors ( $P = .006$ ) but not in the post-transplantation complications or survival of the respective recipients ( $P > .05$ ).

In the multivariate analysis, mortality was significantly associated with the presence of the hepatitis C virus (HCV) ( $P = .001$ ) in the recipient and with the age of the donor ( $P = .043$ ), finding the risk of death to be 2.87-fold higher in patients with HCV versus without HCV (95% confidence interval [1.641–5.043]) and 1.7% higher with every additional year of donor age (odds ratio 1.017, 95% confidence interval [1–1.034]).

**Conclusions.** A significantly longer pre-extraction ICU stay was observed in obese (BMI  $\geq 30$ ) versus nonobese (BMI  $< 30$ ) donors, but no significant between-group difference was found in the post-transplant complications or survival of the respective recipients. The mortality risk was higher in HCV-positive recipients and in those receiving grafts from older donors.

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**T**HE RISING demand for transplantations and decrease in donations has increased the importance of extended criteria donors (ECDs) as a means to extend the organ pool. According to the German Medical Association [1], ECDs are defined by age  $\geq 65$  years, body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, intensive care unit (ICU) stay  $\geq 7$  days, histologically confirmed steatohepatitis  $> 40\%$ , serum sodium  $\geq 165$  mmol/L, total bilirubin  $\geq 3$  mg/dL, or transaminases  $\geq 150$  U/L [1].

Grafts from ECDs have been associated with worse outcomes [2]. It has been reported that the ECD features with

the greatest influence on post-transplant outcomes are donor age, degree of steatohepatitis, and cold ischemia time, while the effects of donor obesity remain unclear [3–5].

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With this background, the objective of this study was to investigate the influence of donor obesity on post-transplantation complications and long-term survival.

## MATERIAL AND METHODS

A single-center, observational, and retrospective study was conducted in patients undergoing a liver transplantation between January 2006 and December 2014 at the Virgen de las Nieves Hospital of Granada (Spain). Donors were classified as obese (BMI  $\geq 30$  kg/m<sup>2</sup>) or nonobese (BMI  $< 30$  kg/m<sup>2</sup>) based on their weight and height measured immediately before graft extraction (BMI = weight [kg]/height [m<sup>2</sup>]) [6].

Data were gathered on the age, sex, weight, height, BMI, donor type, medical history of interest, and blood group of donors. The same data were gathered on the recipients as well as the reason for transplantation, Child and Model for End-Stage Liver Disease (MELD) scores, and history of portal vein thrombosis. The study was approved by the hospital ethics committee.

Bivariate analyses of donor data included the aforementioned variables plus the need for vasoactive drugs, length of ICU stay, serology data, ultrasound findings, and pre-extraction analytical results. Additional recipient variables considered in bivariate analyses were the intraoperative need for blood products; onset of postreperfusion syndrome; post-transplantation biliary, arterial, or portal complications; need for reintervention or retransplantation; graft rejection; and onset of ischemic cholangiopathy. Survival was compared between recipients of grafts from obese versus nonobese donors, and the influence of study variables on recipient mortality was analyzed in both groups.

Follow-up ultrasound studies to detect complications were carried out on days 1, 7, and 14 post-transplantation or more frequently when indicated. The minimum follow-up for recipients in this study was 24 months (until death, retransplantation, or end of study period [December 2016]).

Quantitative variables were expressed as means with standard deviation and qualitative variables as percentages. In bivariate analyses, Pearson's  $\chi^2$  test and Fisher's tests were used for qualitative variables and the Student's *t*-test or Mann-Whitney U test for quantitative variables. A multivariate logistic regression model to predict mortality was constructed by backward stepwise selection. Survival was analyzed by the Kaplan-Meier method, using the log-rank test to compare survival curves.  $P < .05$  was considered significant. IBM SPSS Statistics 19 (IBM Corporation, Armonk, NY, United States) was used for statistical analyses.

## RESULTS

Out of 225 patients undergoing liver transplantation between January 2006 and December 2014, 175 received grafts from nonobese donors (BMI  $< 30$  kg/m<sup>2</sup>) and 50 from obese donors (BMI  $\geq 30$  kg/m<sup>2</sup>).

Tables 1 and 2 report the findings for donor and recipient variables and the results of comparative analysis as a function of donor BMI.

The only significant between-group difference was in the mean length of Intensive Care Unit (ICU) stay ( $P = .006$ ), which was longer for recipients of grafts from obese ( $5.33 \pm 4.15$  days) versus nonobese ( $4.24 \pm 4.47$  days) donors. Borderline significant differences were observed in the presence of high blood pressure in donors (16% of

**Table 1. Descriptive and Comparative Analysis of Donor Variable**

Donors	Nonobese Donors (BMI $< 30$ ) n = 175 (77.78%)	Obese Donors (BMI $\geq 30$ ) n = 50 (22.22%)	P
BMI	26.06 $\pm$ 2.80	32.52 $\pm$ 2.25	<b>&lt;.01</b>
Age	57.3 $\pm$ 1.27	63.3 $\pm$ 2.26	<b>.025</b>
Age $\leq 59$	89 (50.9%)	19 (38%)	<b>.031</b>
60–69	39 (22.3%)	7 (14%)	
70–79	37 (21.1%)	17 (34%)	
$\geq 80$	10 (5.7%)	7 (14%)	
Sex			
Female	60 (34.5%)	21 (42%)	.419
Male	114 (65.5%)	29 (58%)	
Cardiovascular Disease	16 (9.1%)	6 (12%)	.590
Diabetes	17 (9.7%)	3 (6%)	.576
High Blood Pressure	28 (16.0%)	14 (28.0%)	<b>.086</b>
Noradrenalin	74 (44.1%)	24 (48%)	1
Dopamine	13 (7.7%)	2 (4%)	.529
Dobutamine	2 (1.2%)	1 (2%)	.544
Bilirubin	1.22 $\pm$ 1.55	0.904 $\pm$ 0.660	.814
Sodium	144.48 $\pm$ 7.37	143.9 $\pm$ 6.30	.676
HCV-Positive	2 (1.2%)	1 (2%)	.544
HBV-Positive	30 (18.3%)	9 (19.6%)	1
CMV-Positive	84 (66.7%)	22 (61.1%)	.675
ICU Stay (days)	2.80 $\pm$ 3.72	2.09 $\pm$ 2.04	.362
Donor Type:			-
Brain Death	165 (94.3%)	47 (94%)	
Maastrich IIa	6 (3.4%)	1 (2%)	
Maastrich IIb	1 (0.6%)	0 (0%)	
Maastrich III	3 (1.7%)	2 (4%)	
Ultrasound:			-
Not Performed	24 (13.8%)	6 (12.2%)	
Normal	116 (66.7%)	33 (67.3%)	
Moderate Steatosis	26 (14.9%)	8 (16.3%)	
Cysts	7 (4%)	2 (4.2%)	
Steatosis + Cysts	1 (0.6%)	0 (0%)	

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; ICU, intensive care unit.

Bold values in table indicate significance.

nonobese donors vs 28% of obese donors;  $P = .086$ ) and post-transplantation biliary complications (16% of recipients with grafts from nonobese donors vs 28% from obese donors;  $P = .086$ ).

Pretransplantation biopsies were only conducted in livers from 2 obese donors and 5 nonobese donors due to the good macroscopic appearance of the liver in the remaining cases. Moderate steatosis was reported in 1 of the obese cases; and mild cholestasis, steatosis, and chronic portal vein inflammation in the other. In the 5 nonobese cases, 50% steatosis was found in 1, but findings were normal in the other 4.

Mortality-related variables were analyzed, finding that donor age ( $P = .043$ ) and the hepatitis C virus (HCV) positivity of the recipients ( $P = .001$ ) were significantly associated with mortality. A borderline association with mortality was observed for post-transplantation biliary leak ( $P = .062$ ) and donor history of cardiovascular disease ( $P = .078$ ). Donor BMI was not associated with mortality ( $P = .631$ ).

**Table 2. Descriptive and Comparative Analysis of Recipient Variables**

Recipients	Nonobese Donors (BMI <30) n = 175 (77.78%)	Obese Donors (BMI ≥30) n = 50 (22.22%)	P
HCV-Positive	56 (32.0%)	16 (32.0%)	.1
Hepatocellular Carcinoma	36 (20.6%)	14 (28.0%)	.357
Sex			.004
Female	36 (20.6%)	1 (2.0%)	
Male	139 (79.4%)	49 (98.0%)	
BMI	27.33 ± 4.45	29.10 ± 4.49	<b>.014</b>
Age	53.61 ± 9.22	53.32 ± 7.48	.513
Child	7.53 ± 1.73	8.02 ± 1.76	.51
MELD	18.33 ± 5.45	18.22 ± 5.25	.761
Intraoperative Blood Products:			
Red Blood Cell Concentrates	4.18 ± 3.57	18.22 ± 5.25	.753
Platelets	2.31 ± 4.15	3.83 ± 6.10	.115
Fresh Plasma	1129.84 ± 1097.42	1133.68 ± 863.69	.413
Previous Portal Vein Thrombosis	38 (21.7%)	10 (20.0%)	.290
Postreperfusion Syndrome	31 (17.9%)	8 (16.3%)	.963
Complications:			
Biliary	28 (16.0%)	14 (28.0%)	<b>.086</b>
Arterial	24 (13.71%)	4 (8%)	.755
Portal	10 (5.71%)	4 (8%)	.1
Ischemic Cholangiopathy	12 (6.9%)	3 (6.0%)	.1
Rejection:			
Acute	48 (27.4%)	14 (28.0%)	
Chronic	4 (2.3%)	1 (2.0%)	
Retransplant	6 (3.4%)	3 (6.0%)	.420
Deep Vein Thrombosis	0	1 (2%)	.222
Pulmonary Thromboembolism	1 (0.6%)	1 (2%)	.396
ICU Stay	4.24 ± 4.470	5.33 ± 4.150	<b>.006</b>
Hospital Stay	29.84 ± 23.513	30.10 ± 21.523	.779

Abbreviations: BMI, body mass index; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease.  
Bold values in table indicate significance.

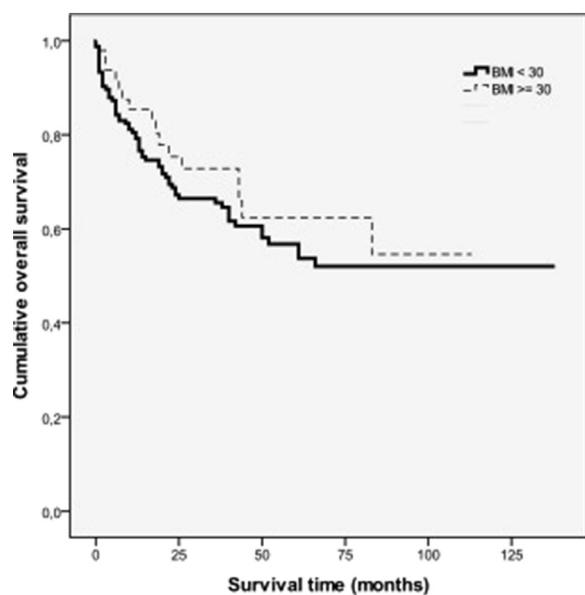
Finally, a multivariate analysis including all variables showed that mortality was influenced by HCV positivity in recipients and by donor age, finding the risk of death to be 2.87-fold higher in recipients with HCV (95% confidence interval [1.641–5.043]) and 1.7% higher with each additional year of donor age (odds ratio 1.017, 95% confidence interval [1–1.034]).

The mean recipient survival was 69.83 ± 4.09 months in those with grafts from nonobese donors and 74.45 ± 7.33 months in those with grafts from obese donors, while the mean graft survival was 82.33 ± 5.32 months for those from nonobese donors versus 76.03 ± 7.29 months for those from obese donors. Figs 1 and 2 depict the survival curves obtained for recipients and grafts from obese and nonobese donors, respectively.

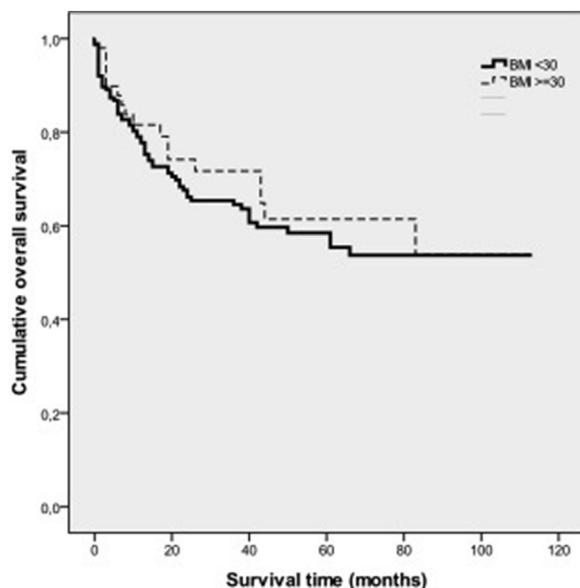
Actuarial post-transplant survival rates were 79.2% at 1 year, 65.5% at 3 years, and 59.3% at 5 years in obese donor recipients versus 85.4% at 1 year, 72.8% at 3 years, and 62.4% at 5 years in nonobese donor recipients ( $P = .502$ , log-rank test). Graft survival rates were 77.7% at 1 year, 64.5% at 3 years, and 58.5% at 5 years in those from nonobese donors versus 81.6% at 1 year, 71.7% at 3 years, and 61.4% at 5 years in those from obese donors ( $P = .440$ , log-rank test).

The main causes of death overall (both groups) were post-transplantation onset of infection (25 cases, 29.1%), and other medical causes (23%-26.7%), followed by the

onset of de novo tumors (15%-17.4%), viral reinfection (7%-8.1%), arterial complications (6%-7%), and recurrence of liver carcinoma (6%-7%).



**Fig 1.** Kaplan-Meier survival curve for recipients.



**Fig 2.** Kaplan-Meier survival curve for grafts.

## DISCUSSION

The need to augment the pool of liver donors has led to the increased use of ECDs. One of the characteristics of these donors is a BMI  $\geq 30$  kg/m<sup>2</sup>, and the influence of this factor was investigated in the present study. Other defining characteristics of ECDs, that is, age, serum bilirubin, and/or sodium levels, and ICU stay, were all below ECD threshold values in this series of obese donors (Table 1).

It has been reported that the degree of histologically demonstrated liver steatosis is a more reliable indicator of graft suitability in comparison to donor BMI [3–5], which is frequently used as a criterion due to its greater reproducibility and accessibility; however, the BMI is not necessarily related to biopsy findings on the degree of steatosis, and the latter are observer dependent and nonreproducible [7].

Researchers have associated donor obesity with lack of primary graft function, early primary graft dysfunction, need for early retransplantation, and higher risk of renal failure [7–10]. In the present study, however, no difference was found in the frequency of arterial or portal vein complications, graft rejection, need for retransplantation, need for intraoperative blood products, or postreperfusion syndrome between the recipients of grafts from obese and nonobese donors. Borderline significant between-group differences were observed in biliary complications, which were almost 2-fold more frequent in recipients of grafts from obese donors (28% vs 16%), although within the range of frequencies reported in the literature (up to 30%) [11]. Based on the present findings, it is not possible to establish whether this higher rate of biliary complications was related to donor obesity per se. The only significant difference between these groups was in the length of ICU stay, but the slightly longer mean stay in recipients of grafts

from obese donors ( $5.33 \pm 4.15$  vs  $4.24 \pm 4.470$  days) cannot be considered clinically relevant.

Finally, an increased risk of death was observed in HCV-positive recipients, as previously reported [12,13], which may prove to be a modifiable risk factor with new HCV treatments. We also observed that the risk of death was higher with older donor age in our series, although there have been numerous reports of good outcomes after the transplantation of liver grafts from elderly donors [14].

The lack of significant differences in post-transplantation complications or survival between the recipients of grafts from obese and nonobese donors is in agreement with previous findings and confirms that the transplantation of liver grafts from donors with BMI  $\geq 30$  kg/m<sup>2</sup> is a safe procedure [7,15].

## CONCLUSIONS

We found no significant differences in survival or post-transplant complications except for a slightly longer ICU stay in recipients of grafts from obese versus nonobese donors.

When liver grafts from obese donors are used, the risk of death is higher with older donor age and in HCV-positive recipients.

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