

S. Fujita^{1*}, T. Fujikawa^{1*}, S. Mizuno¹,
T. Matsumoto¹, E. Shenkman²,
B. Vogel², P. Lipori¹, A. W. Hemming¹,
D. Nelson³, R. J. Howard¹, R. D. Kim¹,
A. I. Reed¹

Effect of Obesity on Clinical and Financial Outcome in Patients Undergoing Liver Transplantation

Aim/Background: Liver transplantation may not be offered to some individuals at transplant programs because previous reports suggest that obese recipients have poorer outcomes. We assessed the influence of body mass index (BMI) on the outcome of liver transplantation in our liver transplant program.

Material/Methods: Patients receiving a liver transplant between 1990 and 2005 were divided according to BMI: group 1, BMI <25 kg/m²; group 2, BMI ≥ 25 and < 30; group 3, BMI ≥ 30 and <35; and group 4, BMI ≥ 35. The impact of BMI on graft survival, patient survival, postoperative complications, length of hospital stay, and overall costs were retrospectively investigated.

Results: BMI ranged from 15-42 (mean=26.7). Distribution into the groups was as follows: group 1, n=288 (41.1%); group 2, n=246 (35.1%); group 3, n=129 (18.4%); and group 4, n=37 (5.3%). We could not detect an effect of BMI on patient or graft survival, the incidence of acute graft rejection, or postoperative complications including cardiovascular complications. BMI was not related to length of hospital stay. There were no statistical differences between the three groups with respect to overall hospital cost in a generalized linear model, corrected for age, gender, calculated MELD score, re-transplant status, or return to the operating room.

Conclusions: Obesity did not influence either the costs or the clinical outcome following liver transplantation in our patient population.

Key words:

obesity, body mass index, liver transplantation, clinical outcome, cost analysis

¹Department of Surgery, ²Department of Epidemiology, Biostatistics and Health Policy Research, and ³Department of Medicine, University of Florida College of Medicine, Gainesville, FL, USA
* S.F. and T.F. are contributed equally to this work.

Auswirkungen von Übergewicht auf das klinische und finanzielle Ergebnis bei Patienten mit Lebertransplantation

Ziel/Hintergrund: Transplantationsprogramme bieten einigen Patienten keine Lebertransplantation an, da frühere Berichte nahe legen, dass übergewichtige Transplantatempfänger schlechtere Ergebnisse aufweisen. Wir untersuchten daher den Einfluss des body mass index (BMI) auf das Ergebnis nach Lebertransplantation im Rahmen unseres Lebertransplantationsprogrammes.

Material/Methoden: Patienten, die zwischen 1990 und 2005 ein Lebertransplantat erhielten, wurden entsprechend ihrem BMI in Gruppen unterteilt: Gruppe 1, BMI <25 kg/m²; Gruppe 2, BMI ≥

25 und < 30 ; Gruppe 3, BMI ≥ 30 und < 35 ; and Gruppe 4, BMI ≥ 35 . Der Einfluss des BMI auf das Transplantat- und Patientenüberleben, postoperative Komplikationen, Dauer des Krankenhausaufenthaltes sowie die Gesamtkosten wurden retrospektiv untersucht.

Ergebnisse: Der BMI lag im Bereich von 15-42 (Mittel=26.7). Die Verteilung auf die Gruppen war wie folgt: Gruppe 1, n=288 (41%); Gruppe 2, n=246 (35%); Gruppe 3, n=129 (19%) und Gruppe 4, n=37 (5%). Wir konnten keinen Einfluss des BMI auf das Patienten- oder Transplantatüberleben, die Inzidenz einer akuten Transplantatabstoßung oder postoperative Komplikationen einschließlich kardiovaskulären Komplikationen finden. Der BMI hatte keinen Bezug zur Dauer des Krankenhausaufenthaltes. Es gab keine statistischen Unterschiede zwischen den drei Gruppen hinsichtlich der Gesamtkosten des Krankenhausaufenthaltes in einem generalisierten linearen Modell, das für Alter, Geschlecht, kalkuliertem MELD Score, Re-Transplant-Status oder Rückkehr in den OP berichtigt war.

Schlussfolgerungen: Übergewicht hatte in unserer Patientenpopulation weder Einfluss auf die Kosten noch auf das klinische Ergebnis nach Lebertransplantation.

Schlüsselwörter:

Übergewicht, body mass index, Lebertransplantation, klinisches Ergebnis, Kostenanalyse

Abbreviations

| | |
|-------------|-----------------------------------|
| BMI: | body mass index |
| MELD score: | model for end-stage liver disease |
| LT: | liver transplantation |
| UNOS: | United Network for Organ Sharing |
| GLM: | General Linear Model |
| HR: | Hazard Ratio |
| CI: | confidential interval |
| LOS: | length of hospital stay |

Introduction

Age, gender, race, functional status, and socio-economic condition are considered to be risk factors that affect the outcome of liver transplantation (LT) (1, 2). In addition, obesity has been shown to be a potential risk factor in LT as well as in other organs such as the lung, heart, and kidney (3-8). Perioperative morbidity and mortality appears to be increased in obese patients after major surgical procedures because of concomitant diseases including coronary

artery disease, hyperlipidemia, and pulmonary dysfunction (9, 10).

Obesity is usually determined using body mass index (BMI; weight in kilograms/height in meters²). One is considered to be overweight when he or she has a BMI ≥ 25 kg/m² and obese when he or she has a BMI ≥ 30 (11). Obesity has been considered a relative contraindication for LT in some institutions (8, 12). Some transplant centers have placed an upper limit on the level of BMI at which obese patients were excluded from transplantation candidate. Recently, two large cohort studies have been reported using the United Network for Organ Sharing (UNOS) database (8, 13). These studies concluded that; (1) morbidly or severely obese patients (BMI ≥ 35) are associated with a significant increase in long-term mortality after LT, and (2) the major cause of death in obese patients was cardiovascular events. Although studies using large databases benefit from a large sample size, they also have limitations such as non-standardized patient selection criteria at each institution. We present

here our results of a single-center cohort to determine if obesity influences either the clinical outcome or overall hospital costs of transplantation in our adult LT population.

Patients and Methods

Between 1990 and 2005, we performed 1150 LT at our center. Of those, 700 adult LT patients (≥ 18 years of age) with complete data were included in this study. Recipient and donor demographic data and clinical and financial outcome variables were obtained through a standardized review of three data sources: (1) the Transplant Center Clinical Database, (2) a separate Institutional Review Board-approved complication database, and (3) Hospital provided expenditure information for all patient encounters (in-patient, outpatient, and emergency room) for each patient, including three months prior to the first liver transplant, during each transplant event, and three months after the last liver transplant. BMI was used to define the degree of obesity. Patients were divided into four groups for analysis: group 1, BMI < 25 (normal); group 2, BMI ≥ 25 and < 30 (overweight); group 3, BMI ≥ 30 and < 35 (obese); and group 4, BMI ≥ 35 (morbidly obese). Model for End-stage Liver Disease (MELD) score was used in the model as a surrogate to control for degree of illness at the time of transplantation. The calculated MELD score at time of transplantation, not an exception MELD score, was used. MELD was calculated from available preoperative laboratory data for patients prior to the inception of MELD in February, 2002. Data was retrospectively analyzed with respect to post-transplantation complications and graft and patient survival. Hepatic graft failure was defined as retransplantation or death with a functioning graft.

We calculated descriptive statistics for our four patient groups. The categorized data in each group were compared by chi-square or Fisher's exact probability test. Continuous variables in the characteristics were expressed as mean \pm standard deviation and compared by one-way ANOVA or Kruskal-Wallis test. Non-parametric variables were also compared using Kruskal-Wallis test with Scheffé's F test. Actuarial patient and graft survival rates were determined beginning at the time of first

transplantation. Actuarial survival estimates were calculated by the method of Kaplan-Meier and compared by log-rank test in univariate analysis. A multivariate analysis was performed using Cox proportional hazards regression to control for confounding variables and collinearity.

A General Linear Model (GLM) with a log link function was used to examine the impact of obesity on costs. Costs were transformed into the natural log of the total dollar cost to address the fact that health care expenditure data are known to be highly skewed, even within high cost categories such as LT. In addition, because the patients' cost data span a number of years, the consumer price index for medical care was used to inflate prior year costs to 2005. In addition to patient age and patient gender, the following variables were included as covariates in our cost model: MELD score, re-transplantation, return to the operating room (OR) for any complication, and the presence of a fungal infection. These variables were selected as covariates because of their known or presumed association with the costs of LT. Statistical significance was set a priori at $p < 0.05$. Data were analyzed using the Statistical Analysis System (SAS) software.

This study was approved by our Institutional Review Board.

Results

In our cohort, BMI ranged from 15 to 42 (mean; 26.7 ± 4.96). As shown in Figure 1, distribution into the groups was as follows; group 1; $n = 288$ (41.1%), group 2; $n = 246$ (35.1%), group 3; $n = 129$ (18.4%), and group 4; $n = 37$ (5.3%).

Table 1 shows the recipient and donor characteristics for each group. There were no significant differences between the groups except for indication for LT ($p < 0.01$), prevalence of recipient pre-transplant diabetes ($p < 0.01$), and donor age ($p < 0.05$) (Table 1). Distribution of MELD score (18.6 ± 3.2 , 18.4 ± 3.6 , 18.8 ± 3.1 and 18.3 ± 2.5), cold ischemic time (8.0 ± 3.3 , 8.3 ± 3.4 , 8.5 ± 2.9 and 8.9 ± 2.8), and use of immunosuppression (tacrolimus; 53%, 54%, 55% and 54%) were also similar between groups.

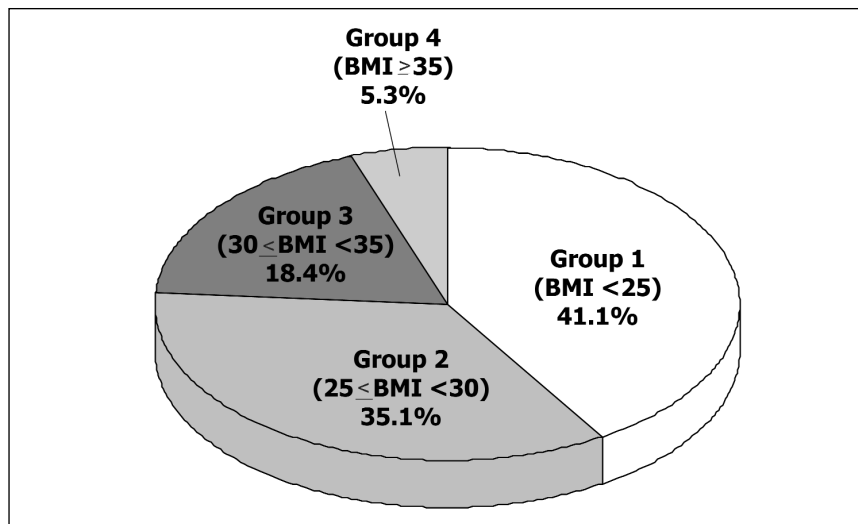


Fig. 1: Patient distribution according to BMI in our study cohort. Distribution into the groups were as follows; group 1; $n = 288$ (41%), group 2; $n = 246$ (35%), group 3; $n = 129$ (19%), and group 4; $n = 37$ (5%). Only a small subset of group 4 was severely obese (BMI ≥ 40 , $n = 4$, 0.6% of total population).

Graft Survival

There were no differences in graft survival rates among the four groups (Log-rank test; $p=0.25$) (Figure 2A, Table 2). Overall 1-year, 3-year, and 5-year graft survival rates in each group were as follows; group 1, 76%, 64%, 60%; group 2, 84%, 77%, 70%; group 3, 79%, 66%, 67%; group 4, 88%, 77%, and 70%. In analyzing causes of graft loss, death with function was the most common cause of graft loss (32%). There were no differences in the cause of graft loss among the four groups (Table 2). In multivariate Cox proportional hazard analysis, only advanced donor age (60 years or more) independently affected graft survival ($p < 0.0001$, Hazard Ratio (HR) = 1.95, 95% confidential interval (CI); 1.45-2.62). Recipient BMI ($p=0.21$) was not associated with graft survival.

Patient Survival

There were also no significant differences in patient survival rates among groups ($p=0.61$) (Figure 2B, Table 2). Overall 1-year, 3-year, and 5-year patient survival rates in each group were as follows; group 1, 82%, 71%, 67%; group 2, 87%, 79%, 73%; group 3, 84%, 73%, 70%; group 4, 89%, 79%, and 73%. The most common causes of death were infection (5.9%), graft failure (4.3%), multiple organ failure (3.6%), malignancy (3.4%), and cardio-

vascular disease (3.4%). There were no differences in the causes of death among the four groups, including cardiovascular complications (3.1%, 3.3%, 4.7% and 2.7%, respectively). In a multivariate analysis, advanced donor age (60 years or more) was the only independent prognostic factor for patient survival ($p=0.0004$, HR=1.81, 95% CI; 1.31-2.52).

Postoperative Complications

Several surgical and medical complications were investigated after LT in relation to BMI values (Table 3). There was no significant difference in occurrence of acute graft rejection (46%, 41%, 40%, and 35%, respectively, $p=0.442$), vascular complications (19%, 13%, 17%, and 21%, $p=0.235$), biliary complications (23%, 25%, 22%, and 27%, $p=0.867$), wound dehiscence (1.0%, 2.4%, 3.9%, and 2.7%, $p = 0.299$), late incisional hernia (1.7%, 4.5%, 6.9%, 2.7%, $p=0.058$), or post-transplant glucose intolerance (12%, 15%, 19%, and 21%, $p=0.397$) between the groups.

Overall Costs

Figure 3 shows length of hospital stay (LOS) after LT and overall hospital costs in each group. BMI was not related to hospital LOS (20.8 ± 21.5 , 20.0 ± 25.9 , 20.9 ± 25.1 , and 20.6 ± 26.2 days,

Tab. 1: Recipient and donor characteristics based on recipient body mass index

| | Group 1 (BMI < 25) (n=288) | Group 2 (BMI ≥ 25 & < 30) (n=246) | Group 3 (BMI ≥ 30 & < 35) (n=129) | Group 4 (BMI ≥ 35) (n=37) | p |
|------------------------------|----------------------------------|---|---|---------------------------------|-------|
| Recipient age (yrs) | 49±12 | 51±10 | 52±9 | 51±7 | NS |
| Recipient sex (male/female) | 173 (60%) / 115 | 166 (67%) / 80 | 83 (64%) / 46 | 19 (51%) / 18 | NS |
| Recipient race | | | | | NS |
| White | 250 (87%) | 220 (89%) | 121 (94%) | 35 (94%) | |
| African American | 21 (7.3%) | 14 (5.7%) | 7 (5.4%) | 2 (5.4%) | |
| Other | 17 (5.9%) | 11 (4.5%) | 1 (0.8%) | 0 | |
| Etiology | | | | | |
| HCV | 119 (41%) | 122 (50%) | 72 (56%) | 25 (68%) | <0.01 |
| HCC | 22 (7.6%) | 21 (8.5%) | 11 (8.5%) | 2 (5.4%) | NS |
| FHF | 20 (6.9%) | 8 (3.3%) | 5 (3.9%) | 2 (5.4%) | NS |
| Recipient pre-transplant DM | 33 (11%) | 43 (17%) | 30 (23%) | 8 (22%) | <0.01 |
| MELD score | 18.6±3.2 | 18.4±3.6 | 18.8±3.1 | 18.3±2.5 | NS |
| Donor age (years) (range) | 38±19 | 38±18 | 42±18 | 43±19 | <0.05 |
| Donor sex (male/female) | 160 (56%) / 128 | 151 (62%) / 95 | 83 (64%) / 46 | 22 (59%) / 15 | NS |
| Donor race | | | | | NS |
| White | 223 (77%) | 206 (84%) | 103 (80%) | 30 (82%) | |
| African American | 38 (13%) | 26 (11%) | 11 (8.5%) | 5 (14%) | |
| Other | 28 (9.7%) | 13 (5.3%) | 14 (11%) | 2 (5.3%) | |
| Donor source | | | | | NS |
| Cadaveric | 285 (99%) | 243 (99%) | 127 (98%) | 37 (100%) | |
| Living | 3 (1.2%) | 3 (1.2%) | 2 (1.5%) | 0 | |
| Donor cause of death | | | | | NS |
| Cardiovascular | 136 (47%) | 105 (43%) | 65 (50%) | 19 (51%) | |
| Others | 153 (53%) | 141 (57%) | 64 (50%) | 18 (49%) | |
| Cold Ischemic Time (hrs) | 8.0±3.3 | 8.3±3.4 | 8.5±2.9 | 8.9±2.8 | NS |
| Immunosuppression agent used | | | | | |
| cyclosporin | 114 (40%) | 91 (37%) | 49 (38%) | 13 (36%) | NS |
| tacrolimus | 152 (53%) | 132 (54%) | 71 (55%) | 20 (54%) | NS |

abbreviations: BMI: body mass index, HCV: hepatitis C, HCC: hepatocellular carcinoma, FHF: fulminant hepatic failure, DM: diabetes mellitus, MELD: Model for End-stage Liver Disease, NS: not significant

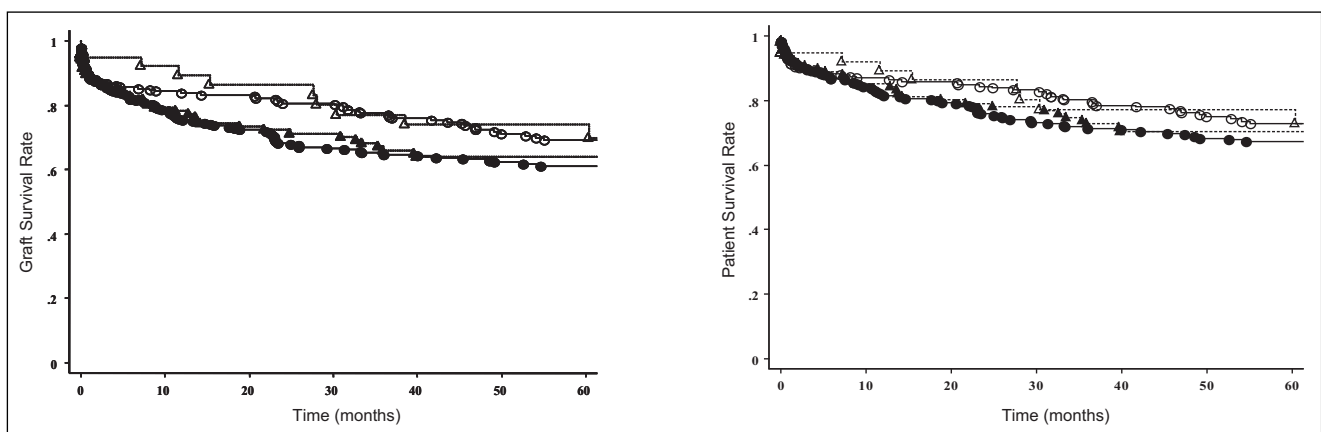


Fig. 2: (A) Kaplan-Meier graft survival in each patient group based on BMI. There was no significant difference between the four groups. (B) Overall patient survival in each group. There was also no significant difference between the groups. Legends: solid line with closed circle; Group 1 (non-obese), solid line with open circle; Group 2 (overweight), dotted line with closed triangle; Group 3 (obese), and dotted line with open triangle; Group 4 (morbidly obese).

Tab. 2: Graft and patient survival in each group

| | Group 1 (BMI < 25) (n=288) | Group 2 (BMI ≥ 25 & < 30) (n=246) | Group 3 (BMI ≥ 30 & < 35) (n=129) | Group 4 (BMI ≥ 35) (n=37) | p |
|------------------------|--|---|---|--|----------|
| Graft survival rate | | | | | |
| 1-year | 76% | 84% | 79% | 88% | NS |
| 3-year | 64% | 77% | 66% | 77% | NS |
| 5-year | 60% | 70% | 67% | 70% | NS |
| Cause of graft loss | | | | | |
| Death with function | 84 (29%) | 63 (26%) | 43 (33%) | 13 (35%) | NS |
| Vascular complications | 12 (4.2%) | 3 (1.2%) | 3 (2.3%) | 1 (2.7%) | NS |
| Primary nonfunction | 7 (2.4%) | 9 (3.7%) | 3 (2.3%) | 1 (2.7%) | NS |
| Rejection | 7 (2.4%) | 1 (0.4%) | 1 (0.8%) | 0 | NS |
| Others | 5 (1.7%) | 6 (2.4%) | 2 (1.6%) | 1 (2.7%) | NS |
| Patient survival rate | | | | | |
| 1-year | 82% | 87% | 84% | 89% | NS |
| 3-year | 71% | 79% | 73% | 79% | NS |
| 5-year | 67% | 73% | 70% | 73% | NS |
| Cause of patient death | | | | | |
| Infection | 18 (6.3%) | 15 (6.1%) | 7 (5.4%) | 1 (2.7%) | NS |
| Graft failure | 17 (5.9%) | 5 (2.0%) | 7 (5.4%) | 1 (2.7%) | NS |
| Malignancy | 12 (4.2%) | 5 (2.0%) | 6 (4.7%) | 1 (2.7%) | NS |
| Multiple organ failure | 8 (2.8%) | 9 (3.7%) | 6 (4.7%) | 2 (5.4%) | NS |
| Cardiovascular | 9 (3.1%) | 8 (3.3%) | 6 (4.7%) | 1 (2.7%) | NS |
| Cerebrovascular | 6 (2.1%) | 4 (1.6%) | 0 | 0 | NS |

abbreviations: BMI: body mass index, NS: not significant

Tab. 3: Postoperative complications in each group

| | Group 1 (BMI<25) (n=288) | Group 2 (BMI≥25 & <30) (n=246) | Group 3 (BMI≥30 & <35) (n=129) | Group 4 (BMI≥35) (n=37) | p |
|-------------------------------------|--|--|--|--|----------|
| Acute graft rejection | 132 (46%) | 102 (41%) | 51 (40%) | 13 (35%) | NS |
| Vascular complications | 55 (19%) | 32 (13%) | 22 (17%) | 8 (21%) | NS |
| postoperative bleeding | 29 | 22 | 12 | 4 | |
| hepatic artery thrombosis | 16 | 4 | 7 | 4 | |
| portal vein thrombosis | 4 | 5 | 2 | 0 | |
| Biliary complications | 66 (23%) | 62 (25%) | 29 (22%) | 10 (27%) | NS |
| Bile leak | 38 | 37 | 14 | 6 | |
| Biliary tract stenosis | 35 | 26 | 15 | 4 | |
| Wound dehiscence | 3 (1.0%) | 6 (2.4%) | 5 (3.9%) | 1 (2.7%) | NS |
| Late incisional hernia | 5 (1.7%) | 11 (4.5%) | 9 (6.9%) | 1 (2.7%) | NS |
| Posttransplant glucose intolerance* | 27/218 (12%) | 26/173 (15%) | 16/86 (19%) | 6/28 (21%) | NS |

abbreviations: BMI: body mass index, NS: not significant

* In posttransplant impaired glucose tolerance, patients with history of diabetes preoperatively were excluded from denominators

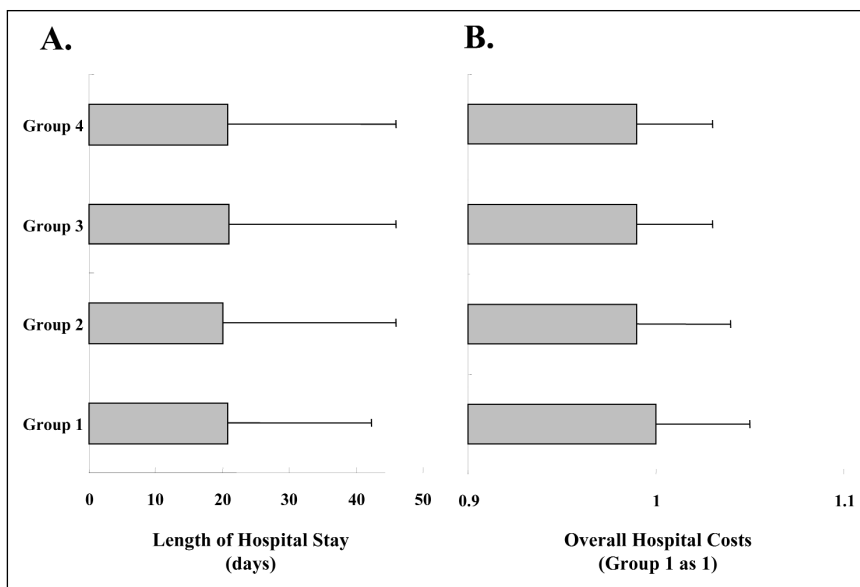


Fig. 3: Comparison of length of hospital stay and overall hospital costs among four groups based on BMI. (A) There were no significant differences between the four groups in length of hospital stay (group 1; 20.8 days, group 2; 20.0 days, group 3; 20.9 days, and group 4; 20.6 days). (B) There were also no significant differences between the groups with respect to overall hospital costs (Group 1 as 1, Group 2; 0.99, Group 3; 0.99, and Group 4; 0.99), which were corrected for age, gender, calculated MELD score, re-transplant status, and return to the operating room.

$p=0.748$) (Fig 3A). There were no differences between the four groups with respect to overall hospital costs (Group 1 as 1, Group 2; 0.99, Group 3; 0.99, Group 4; 0.99), corrected for age, gender, calculated MELD score, re-transplant status, and return to the operating room.

Discussion

We failed to detect any impact of obesity on clinical or financial outcome after LT in our patient population. There were no significant differences in graft or patient survival rates among the four groups. Also, there were no differences between the groups in cause of death including cardiovascular events. In addition, obesity did not affect posttransplant complications, LOS, nor overall hospital costs.

The severe shortage of organs necessitates a careful assessment of potential recipients with respect to their operative risks and likelihood of prolonged survival to maximize the life-years of the allograft. Due to a possible adverse effect of obesity on outcome after organ transplantation, many transplant centers have placed an upper limit on the level of BMI at which obese patients were

excluded from transplantation candidate. Two recent studies using a large cohort of patients from the UNOS database reported that mild obesity (BMI ranging from 30 to 35) did not significantly affect either short-term or long-term outcome after LT, and morbidly obese patients (BMI ≥ 35) are associated with an increased prevalence of adverse cardiovascular events leading to a significantly lower 5-year patient survival (8, 13).

We failed to detect any impact of morbid obesity on clinical outcome in our patient population. The lower rates of morbidly obese patients in our study (5.3 %) compared with other reported national rates (11.3 %) may contribute to our result (8, 13). We generally do not list patients with BMI ≥ 35 unless there are extenuating circumstances. It is a retrospective analysis and there remains the possibility for other factors to influence outcome that we have not controlled for. Those conditions may have led to a decrease in our ability to detect differences in this group.

LT is a complex, interdisciplinary, and expensive form of therapy, and periodically there have been some reports analyzing LT in light of financial outcome (7, 14-19). Financial outcome during LT, especially hospital costs, are gener-

ally influenced by two major preoperative factors; (1) the overall patient health status (with or without significant comorbidities), and (2) the degree of pretransplant liver function abnormality (15, 19). Otherwise, the preoperative factors that affect financial outcome of LT are still largely unknown. Obesity is considered to be a potential factor that causes high hospital costs and healthcare expenditures (20-22). Some reports showed higher peritransplant costs or charges in obese patients undergoing liver or kidney transplantation (7, 14). Due to limited data so far published in the setting of organ transplantation, however, the impact of obesity on peritransplant financial outcome and resource utilization is still not well understood. In the current study using a relatively large cohort, the results showed no significant differences between the BMI-classified groups in overall hospital costs, as well as clinical outcome. The limitation of our study is lower population of morbidly obese patients (5.3 %). In conclusion, obesity did not influence either the clinical or financial outcome following LT in our patient population. Further analysis in a larger population is warranted to determine if patients with morbid obesity have a significant impact on resource utilization and hospital costs.

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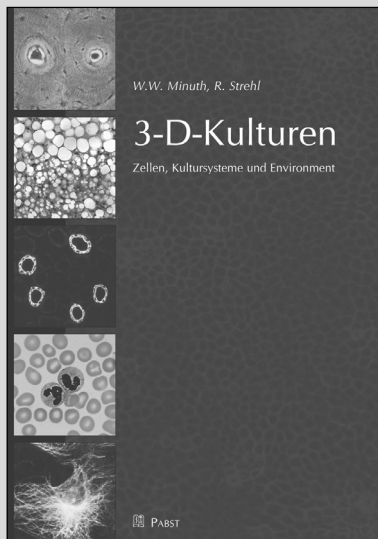
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Shiro Fujita, M.D., Ph.D.
Division of Transplantation and
Hepatobiliary Surgery
Department of Surgery
PO Box 100286
Gainesville FL 32610-0286
USA
fujita@surgery.ufl.edu

W.W. Minuth, R. Strehl

3-D-Kulturen Zellen, Kultursysteme und Environment



Es gibt viele Bücher, in denen beschreiben wird, wie Zellen kultiviert werden. Das vorliegende Buch jedoch zeigt, wie aus zweidimensionalen Zellkulturen dreidimensionale (3-D) Gewebestrukturen entstehen können. Es bietet eine Einführung in die Welt von innovativen 3-D-Kulturen, die in der Tumorbiologie, der pharmazeutischen Forschung, in den verschiedenen Feldern der experimentellen Biomedizin, im Bereich der zukünftigen Stammzelltherapie und beim Tissue engineering Verwendung finden. Das Buch ist leicht verständlich geschrieben und somit besonders geeignet für die im Labor

arbeitenden technischen Mitarbeiter, für Studierende und junge Wissenschaftler/innen der Medizin, Biologie, Pharmazie, Biomaterialforschung und Biotechnologie.

Anschaulich wird zuerst der Übergang von der klassischen Zellkultur zur 3-D-Kultur beschrieben. Informiert wird über die unterschiedlichen Arten der Zell- und Gewebekulturen, über die Auswahl der Medien und über die verschiedenen Arbeitstechniken. In Verbindung mit vielen Abbildungen werden möglichst anschaulich die technischen Voraussetzungen, aktuelle Entwicklungen und die biomedizinischen Perspektiven mit 3-D-Kulturen behandelt.

Besondere Bedeutung hat die kritische Bewertung der entstehenden 3-D-Kulturen. Ziel der Experimente ist, dass histiotypische Eigenschaften in den 3-D-Kulturen entstehen und die Ausbildung von atypischen Eigenschaften vermieden wird. Deshalb wird intensiv über die Bewertung der Differenzierung in den entstehenden Geweben informiert. Besondere Bedeutung hat diese Frage beim Arbeiten mit Stammzellen. Es reicht nicht aus, die Stammzellen zu isolieren und zu vermehren, vielmehr sollen daraus funktionelle Gewebe entstehen, die sicher und damit risikolos angewendet werden können.

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