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World J Hepatol 2017 April 28; 9(12): 595-602

DOI: 10.4254/wjh.v9.i12.595

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ORIGINAL ARTICLE

Retrospective Study

Diagnosis of morbid obesity may not impact healthcare utilization for orthotopic liver transplantation: A propensity matched study

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Author contributions: Peck JR and Mumtaz K, designed the study; Peck JR, Mumtaz K, Latchana N and Hinton A collected and analyzed the data; Peck JR, Latchana N, Michaels A, Hanje AJ, Hinton A, Elkhammas E, Black SM and Mumtaz K all equally contributed to writing the paper.

Institutional review board statement: This study was IRB exempt.

Informed consent statement: Consent was not obtained but the presented data are anonymized and the risk of identification is low.

Conflict-of-interest statement: None of the authors have any conflicts of interest to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at khalid. mumtaz@osumc.edu.

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Manuscript source: Invited manuscript

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Received: December 4, 2016

Peer-review started: December 5, 2016

First decision: January 21, 2017 Revised: February 15, 2017 Accepted: March 21, 2017 Article in press: March 22, 2017 Published online: April 28, 2017

Abstract

AIM

To study mortality, length of stay, and total charges in morbidly obese adults during index hospitalization for orthotopic liver transplantation.

METHODS

The Nationwide Inpatient Sample was queried to obtain demographics, healthcare utilization, post orthotopic liver transplantation (OLT) complications, and short term outcomes of OLT performed from 2003 to 2011 (n = 46509). We divided patients into those with [body mass index (BMI) \geq 40] and without (BMI < 40) morbid obesity. Multivariable logistic regression analysis was performed



to characterize differences in in-hospital mortality, length of stay (LOS), and charges for OLT between patients with and without morbid obesity after adjusting for significant confounders. Additionally, propensity matching was performed to further validate the results.

RESULTS

Of the 46509 patients who underwent OLT during the study period, 818 (1.8%) were morbidly obese. Morbidly obese recipients were more likely to be female (46.8% vs 33.4%, P = 0.002), Caucasian (75.2% vs 67.8%, P = 0.002), in the low national income quartile (32.3% vs22.5%, P = 0.04), and have ≥ 3 comorbidities (modified Elixhauser index; 83.9% vs 45.0%, P < 0.001). Morbidly obese patient also had an increase in procedure related hemorrhage (P = 0.028) and respiratory complications (P= 0.043). Multivariate and propensity matched analysis showed no difference in mortality (OR: 0.70; 95%CI: 0.27-1.84, P = 0.47), LOS (β : -4.44; 95%CI: -9.93, 1.05, P = 0.11) and charges for transplantation (β : \$15693; 95%CI: -51622-83008, P = 0.64) between the two groups. Morbidly obese patients were more likely to have transplants on weekdays (81.7%) as compared to those without morbid obesity (75.4%, P = 0.029).

CONCLUSION

Morbid obesity may not impact in-hospital mortality and health care utilization in OLT recipients. However, morbidly obese patients may be selected after careful assessment of co-morbidities.

Key words: Deceased donors; Outcome; Complications; Economics; Selection criteria

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Core tip: Morbid obesity is a relative contraindication to orthotopic liver transplantation. Previous studies, mostly in the pre-MELD era, suggested worsened outcomes in these patients. As the prevalence of obesity continues to increase, so will the number of patients who are morbidly obese requiring liver transplantation. Utilizing the Nationwide Inpatient Sample which is the largest publicly available database in the United States, we did not find any difference in mortality, or healthcare utilization when comparing those with and without morbid obesity receiving liver transplantation. Our findings suggest that in highly selected patients, morbid obesity may not be a significant contraindication to transplantation.

Peck JR, Latchana N, Michaels A, Hanje AJ, Hinton A, Elkhammas EA, Black SM, Mumtaz K. Diagnosis of morbid obesity may not impact healthcare utilization for orthotopic liver transplantation: A propensity matched study. *World J Hepatol* 2017; 9(12): 595-602 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i12/595.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i12.595

INTRODUCTION

There has been a great deal of attention given to the outcomes of orthotopic liver transplantation (OLT) in obese patients, with varying reports on morbidity and mortality. A study by Nair et al^[1] investigated graft and patient survival in obese patients receiving OLT in the United States between 1988 through 1996 using the United Network for Organ Sharing database. They found that primary graft non-function and immediate 1-year and 2-year mortality were higher in morbidly obese individuals. They also found increased 5-year mortality in morbidly [body mass index (BMI) of 35.1-40 kg/m²] obese patients. Contrary to that, Pelletier et al^[2], reported no increased risk of post-transplant mortality in obese or morbidly obese patients recruited from 2001 to 2004. The disparities between the aforementioned studies by Nair et al^[1] and Pelletier et al^[2] can likely be attributed to the Nair et al^[1] study occurring in the pre-MELD era as compared to within or just before the application of MELD by Pelletier.

Greater peri-operative morbidity and increased post-operative length of stay appears to be a fairly consistent finding in the morbidly obese patients in various studies^[3-5]. A few studies do report increased wound related and infectious complications in patients with morbid obesity after transplantation^[3,6]. In one study, obese patients surprisingly did not require prolonged ventilation support as compared to non-obese patients^[6].

Studies have also shown socioracial disparities in OLT utilization. In addition to race, women, older patients, individuals with non-commercial insurance, individuals in certain geographic locations (as defined by donor service areas), and those with alcoholic liver disease have been shown to receive lower rates of transplantation^[7].

Large population based studies from United States on health care utilization and short term outcomes of liver transplantation in morbidly obese patients were not found. We hypothesized that provided selected carefully morbidly obese patients undergoing liver transplantation may not have different healthcare utilization and short term outcomes. We studied the health care utilization, inhospital morbidity, mortality and direct charges for care in morbidly obese patients receiving OLT in the United States during 2003-2011.

MATERIALS AND METHODS

Database information

The Nationwide Inpatient Sample (NIS) is the largest publicly available database in the United States. It contains data from over 8 million hospital stays each year, and allows users to track and analyze trends and outcomes of health care. The NIS database is the largest all-payer inpatient care database in the United States, representing an approximately 20% stratified sample of 1044 non-



federal hospitals in 47 states^[8].

The information was collected from the NIS database from years 2003 to 2011 among all adult (age > 18 years) in-patients with a procedure code for liver transplantation as determined by International Classification of Disease-Clinical Modification, Ninth Revision, (ICD-CM) codes. According to weighted estimate, 47185 adult patients were identified who underwent liver transplantation with ICD-CM procedure code 50.59 (other liver transplantation, *i.e.*, non-auxiliary).

The NIS database has limited clinical variables, but it provides a large sample size representative of the United States. Moreover, it is reliable in terms of hard end-points such as inpatient mortality and hospital length of stay. Another unique feature of this database is information on the direct charges for hospital stay, which have not been studied in the past among obese liver transplant recipients. Additional data collected including healthcare utilization were, age, gender, race, income (National Quartile), type of insurance, type of hospital (rural/urban non-teaching vs urban teaching), hospital size, hospital region, and Modified Elixhauser index based on pre-OLT comorbid medical conditions)^[9]. This index counts the number of comorbidities present from a list of 29. We modified it by removing liver failure and morbid obesity.

We divided the patients into those with morbid obesity (BMI \geq 40) and with a BMI < 40. The following ICD-9 codes were used for morbid obesity, 278.01, V85.4, V85.41, V85.42, V85.43, V85.44 and V85.45. Patients without one of the previous codes present were assumed to have a BMI under 40. We chose a BMI cutoff of 40 as previous studies have shown that when compared to lower BMIs, there is a higher sensitivity and specificity when accounting for correct documentation^[10]. Variables studied among two groups were the pre-OLT comorbidities and post-OLT complications. We divided the post OLT complications into two distinct categories, i.e., systemic and technical. Systemic complications included those which were among broader groups of events for which timing was indeterminate (i.e., cardiovascular complications, Post-LT infections, etc.). Technical complications were felt to be related to the actual surgery itself^[11].

Outcomes and predictors

We studied outcomes including mortality during the hospitalization for OLT, length of hospital stay, total direct charges for care (without professional fees) among patients with and without morbid obesity. The NIS quantifies inpatient discharges and does not link patients across hospital discharges. As such, patients with multiple discharges may have been counted multiple times if they had multiple hospitalizations where the procedure code for OLT was documented.

The major pre-, intra, and postoperative complications were identified using ICD-9-CM diagnostic codes (appendix 1). As the ICD-9-CM coding system does not include transplant-specific codes for many of the

postoperative variables that are of particular interest, the best available codes were used.

This study was exempted from review by The Ohio State University Institutional Review Board.

Statistical analysis

SAS 9.3 (SAS Institute, Cary, NC) was used to perform all analyses, employing appropriate survey estimation commands and strata weights. Weighted frequencies and percentages were calculated for all categorical variables; means and 95%CIs were calculated for continuous variables. Differences between patients with and without morbid obesity (BMI \geq 40) were analyzed using χ^2 tests or student's t-tests, as appropriate. Variables significantly associated with morbid obesity on univariate analysis were included in all multivariate models. We performed a multivariate logistic regression for mortality, while multivariate linear regression was used for length of stay and total hospital charges.

Propensity scores were calculated using a multivariate logistic regression model for morbid obesity containing all demographic variables (Age, Gender, Race, Income, Insurance, Hospital Location, Teaching Status, Size, and Region), and comorbid conditions (29 Elixhauser comorbidities excluding obesity and liver failure).

Patients with and without morbid obesity were then matched 1:1 using a greedy matching algorithm with a caliper of 0.2 times the standard deviation of the propensity scores. One hundred and fourty-three pairs were formed. One hundred and fourty-three of the original 145 (unweighted number) patients with morbid obesity were matched with a control. Note that our cohort contains 168 patients with morbid obesity; however, only 145 of the 168 were eligible for matching due to missing data primarily within the race variable.

The gmatch macro written by the Mayo Clinic was used for the matching. The statistical methods of this study were reviewed by Alice Hinton from the Ohio State University (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros).

RESULTS

Demographics

After weighting, the NIS represented 46509 patients who underwent liver transplantation from 2003 through 2011. Of these patients, 818 (1.8%) were morbidly obese. The demographic and hospital characteristic variables are shown in Table 1. The groups were similar with regards to age, type of insurance, type and region of hospital. There were more females among the morbidly obese group (46.8%) as compared to without morbid obesity (33.4%), P = 0.002. There were more transplant recipients belonging to white race (75.2% vs 67.8%, P = 0.002) and low national income quartile (32.3% vs 22.5%, P = 0.04) among morbidly obese patients as



Table 1 Demographic and hospital characteristics in morbidly obese and non-morbidly obese patients who underwent a liver transplant

	No morbid obesity		Moi	<i>P</i> -value	
	n:	= 45691	n	= 818	
Age (mean, CI)	53.23	(52.84, 53.61)	53.33	(52.05, 54.61)	0.87
Gender					0.002
Male	30444	66.64%	435	53.21%	
Female	15242	33.36%	383	46.79%	
Race					0.002
White	25668	67.81%	544	75.15%	
Black	2975	7.86%	32	4.49%	
Hispanic	5638	14.90%	127	17.60%	
Other	3571	9.43%	20	2.75%	
Income (National					0.04
Quartile)					
Low	9947	22.46%	258	32.30%	
Moderate	11190	25.27%	213	26.63%	
High	11816	26.69%	167	20.87%	
Very high	11324	25.58%	161	20.20%	
Type of insurance					0.11
Medicare	11817	25.99%	246	30.10%	
Medicaid	6487	14.27%	74	8.99%	
Private	24983	54.95%	441	53.93%	
Other	2179	4.79%	57	6.97%	
Type of hospital					0.95
Rural/urban	233	0.51%	< 10	0.48%	
non-teaching					
Urban teaching	45069	99.49%	814	99.52%	
Hospital size					0.25
Small/medium	6492	14.33%	88	10.74%	
Large	38809	85.67%	730	89.26%	
Hospital region					0.43
Northeast	7865	17.21%	118	14.42%	
Midwest	9953	21.78%	206	25.24%	
South	15116	33.08%	319	39.02%	
West	12757	27.92%	174	21.32%	
Admission day					0.02
Week day	34444	75.39%	668	81.72%	
Weekend	11247	24.62%	149	18.28%	
Modified					< 0.01
elixhauser index1					
< 3	25123	54.98%	131	16.06%	
≥ 3	20568	45.02%	686	83.94%	

¹After excluding liver failure and obesity.

compared to those without morbid obesity. In addition, morbidly obese transplant recipients had significantly more comorbid conditions with \geq 3 conditions (n=686; 83.9%) on the modified Elixhauser index than those without morbid obesity (n=20568; 45.0%), P<0.001. Lastly, morbidly obese patients were more likely to have transplants on weekdays (81.7%) as compared to those without morbid obesity (75.4%, P=0.028).

Post OLT complications

Table 2 shows the various post OLT complications in patients who underwent liver transplantation. Among systemic post OLT complications, there were significantly more respiratory complications in morbidly obese patients (4.87% vs 1.05%, P = 0.04) after transplant. Contrary to that, hemorrhage complicating a procedure

was significantly higher in non-morbidly obese patients (11.80% vs 7.04%, P=0.03) as compared to morbidly obese patients. However, all other post OLT complications were equally distributed in the two groups. Similarly, hepatic artery thrombosis (P=0.05), anastomotic biliary leaks (P=0.08), and accidental laceration during a procedure (P=0.06) were more frequent in non-morbidly obese, though they did not reach statistical significance. Overall, complication rates were equally distributed in the two groups.

Multivariate analysis

Table 3 shows the adjusted odds ratio (aOR) for mortality and β-coefficients for length of stay and charges for liver transplantation in the non-morbidly obese and morbidly obese groups. Non-morbidly obese patients had a 5.27% mortality whereas the mortality among morbidly obese transplant recipients was 4.83% (aOR: 0.98; 95%CI: 0.50-1.92, P = 0.95). The average length of stay in non-morbidly obese patients was 20.9 d and in morbidly obese patients it was 18.7 d (β: -3.90; 95%CI: -7.94-0.14, P = 0.06). The average total charges for transplantation was \$342324 and \$378452 in non-morbidly obese and morbidly obese patients, respectively (β: \$612; 95%CI: -54780-56004, P = 0.98). Data was adjusted for gender, race, income, modified Elixhauser comorbidity index, weekend admission, and diabetes.

Propensity based analysis

In order to further endorse our findings, a matched cohort on the basis of morbid obesity status was then created using propensity scores. The propensity score analysis was not able to account for the weighting in the dataset. Before weights were taken into account 168 of the OLT patients were morbidly obese. Of the 168 patients 143 (85%) were matched 1:1 with a nonmorbidly obese patient on the basis of propensity scores. Thus, in this cohort, there were a total of 286 patients divided equally into two groups based on morbid obesity status (143 patients each in morbidly obese and nonmorbidly obese groups). After propensity matching, no differences between pre- and post OLT variables in the two groups were statistically significant (appendix 2). This allowed analysis of outcomes based on morbid obesity status alone, thereby reducing selection bias based on various other characteristics. Analysis showed no significant difference in mortality (OR: 0.70; 95%CI: 0.27-1.84, P = 0.47), LOS (β : -4.44; 95%CI: -9.93-1.05, P = 0.11) or charges for transplantation (β : \$15693; 95%CI: -51622-83008, P = 0.64) between two groups (Table 4).

DISCUSSION

In this Nationwide Inpatient Sample database study we found that the diagnosis of morbid obesity may not have a significant impact on the health care utilization in the liver transplant cohort. We found that 1.8% of



Table 2 Complications of patients who underwent a liver transplant

	No morbid obesity		Morbid obesity		<i>P</i> -value
	n = 45691		n = 818		
Systemic complications					
Any	20546	44.97%	394	48.20%	0.5253
Post LT infection	13308	29.13%	297	36.26%	0.2103
Cardiovascular complication	781	1.71%	25	3.05%	0.3858
Infections, surgical wound	2035	4.45%	35	4.29%	0.9301
Cardiac complications	1972	4.32%	49	6.00%	0.2737
Peripheral vascular complications	152	0.33%	0	0.00%	
Respiratory complications	481	1.05%	40	4.87%	0.0433
Digestive system complications	95	0.21%	≤ 10	1.12%	0.2376
Other postoperative infection	2035	4.45%	35	4.29%	0.9301
Pulmonary insufficiency following surgery	269	0.59%	≤ 10	0.57%	0.9654
Unspecified intestinal obstruction	145	0.32%	0	0.00%	
Stroke	149	0.33%	0	0.00%	
Postoperative shock	69	0.15%	≤ 10	0.57%	0.4556
Post LT complication	9927	21.73%	142	17.40%	0.1441
Technical complications					
Any	16044	35.11%	263	32.27%	0.4206
Hepatic artery thrombosis	8940	19.57%	113	13.80%	0.0531
History of exploratory laparotomy exploratory laparotomy	221	0.48%	≤ 10	0.57%	0.8483
Anastomotic leak of biliary tree	1442	3.16%	49	6.00%	0.0837
Perforation of the intestine	148	0.32%	0	0.00%	
Hemorrhage complicating a procedure	5390	11.80%	58	7.04%	0.0278
Accidental laceration during a procedure	965	2.11%	≤ 10	0.67%	0.0611
Iatrogenic pulmonary embolism and infarction	169	0.37%	20	2.49%	0.0862
Iatrogenic pneumothorax	691	1.51%	≤ 10	1.14%	0.6429
Hematoma	3487	7.63%	65	7.94%	0.8931
Seroma complicating a procedure	74	0.16%	≤ 10	1.15%	0.2145
Disruption of wound	25	0.06%	0	0.00%	
Disruption of internal operation wound	179	0.39%	0	0.00%	
Disruption of external operation wound	378	0.83%	20	2.43%	0.1632

Variables are expressed as weighted frequency (percentage) and differences between the groups are analyzed with χ^2 tests. LT: Liver transplantation.

Table 3 Results of multivariate linear/logistic regression for mortality, length of stay and charges for liver transplantation in study cohort

Outcomes	No morbid obesity n = 45691 (%)	Morbid obesity $n = 818 (\%)$	Adjusted OR/β-coefficient (95%CI)	<i>P</i> -value
Mortality	2407 (5.27%)	39 (4.83%)	0.98 (0.50-1.92)	0.95
Length of stay in days, mean (CI)	20.9 (18.7-23.1)	18.7 (15.5-22)	-3.9 ¹ (-7.94-0.14)	0.06
Total charges, mean (CI)	342324 (305778-378870)	378452 (320453-436452)	6121 (-54780-56004)	0.98

¹β-coefficients. Data was adjusted for gender, race, income, modified Elixhauser comorbidity score, weekend admission, and diabetes.

patients who underwent liver transplantation from 2003 to 2011 were morbidly obese, *i.e.*, BMI \geq 40. Moreover, morbidly obese transplant recipients were more likely to be females, Caucasian, low national income quartile, and had OLT surgeries on weekdays; they also had more pretransplant comorbid conditions based on the modified Elixhauser index. The majority of post-OLT complications, except procedure related hemorrhage and respiratory complications were equally distributed in all transplant recipients. Despite these differences, in pre- and post-liver transplant issues, no difference in mortality, LOS or charges for transplantation was observed in the two groups.

In our study the incidence of morbidly obese OLT recipients is equal to previous studies by Nair *et al*⁽¹⁾ but less than Pelletier *et al*⁽²⁾. However, the prevalence

of morbid obesity reported in the general population is approximately 6.4%. This discrepancy is likely due to the plausible super-selective nature of transplantation candidacy. Obese candidates are at a higher risk for mortality may now be more readily identified and carefully selected. Whereas obesity in itself is not an indication for invasive pre-cardiac screening, obesity-related comorbidities such as coronary artery disease, hypertension, and dyslipidemia may warrant cardiac catheterization or additional testing^[12]. This allows for detection of morbidly obese individuals with severe cardiac disease which precludes liver transplantation.

We found no statistically significant difference between healthcare utilization in our cohort of morbidly obese and non-morbidly obese patients. Previous studies have shown that individuals referred for OLT were more likely to have



Table 4 Analysis of outcomes in the propensity matched sample

Outcomes	No morbid obesity $n = 143$	Morbid obesity $n = 143$	Adjusted OR/β-coefficient (95%CI)	<i>P</i> -value
Mortality	10 (7.04%)	< 10 (4.93%)	0.70 (0.27-1.84)	0.47
Length of stay in days, mean (CI)	24.1 (19.5-28.7)	19.6 (16.8-22.5)	-4.44 (-9.93-1.05) ¹	0.11
Total charges, mean (CI)	388530 (344027-33033)	395518 (349932-441105)	15693 (-51622-83008) ¹	0.64

¹β-coefficients.

private insurances^[13]. As would be expected, the majority of individuals who receive liver transplantation also had private insurances (55% and 54% for non-morbidly obese and morbidly obese, respectively); however, there was no overall difference between the two groups among utilization of Medicaid, Medicare, and others (P = 0.11). The vast majority of both groups of liver recipients were transplanted at urban teaching hospitals (> 99%, P = 0.95), similar to trends reported in other studies^[14]. There also was no statistically significant difference between groups for hospital size (P = 0.24) or hospital region (P =0.43). Current guidelines from the American Association for the Study of Liver Disease consider morbid obesity a relative contraindication to liver transplantation^[15]. Previously reported data on outcomes in morbidly obese transplant recipients has been contradictory, with some studies showing equivalent outcomes[16,17] while others showed increased post-operative complications^[18] and decreased survival^[1]. Importantly, we found that there was no statistically significant increase in mortality for morbidly obese liver transplant recipients. This contrasts data from previous studies which suggest higher rates of mortality in morbidly obese patients after transplant. The differences reported in peri-operative mortality and morbidity in studies can potentially be explained by heterogeneity amongst the obese and morbidly obese patients. Also the sample size and effect of era may be responsible for the variability in outcomes.

Obesity has been shown to be protective in patients in many settings, including the intensive care unit and in patients with severe $\mathsf{sepsis}^{[19,20]}.$ There are multiple hypotheses for the improved outcomes seen in obese patients in these settings. It has been demonstrated that obesity leads to loss of tissue homeostasis and development of an inflammatory response characterized by an accumulation of pro-inflammatory type-1 phenotype macrophages^[21,22]. However, critical illness instigates the accumulation of alternatively activated M2 macrophages with a more anti-inflammatory role^[22]. It has also been observed that critically ill obese patients with ARDS have reduced levels of inflammatory cytokines^[23]. The shift to an anti-inflammatory milieu may partially explain a protective role of obesity in LT patients. Another possible explanation relates to the nutritional reserves possessed by obese patients, which may help them tolerate the increased metabolic demands of critical illness^[24].

We also found no statistically significant difference in either length of stay or total hospital charge. We hypothesize that multiple factors may be influencing this outcome. First, selection criteria is more stringent since the development of the MELD system. In addition, as the prevalence of obesity in the United States continues to increase, surgeons and other physicians are more experienced in the nuances of providing care for these patients. Lastly, it is also possible that our short-term outcomes are not reflective of the long-term outcomes in these patients.

Our study did have some important limitations. First, this was a retrospective study based on diagnostic codes and utilizing a database. As we previously mentioned, there were no variable data points, and all our collected information was dependent upon documentation of the presence or absence of pathology.

Another limitation is that we only investigated outcomes during the index hospitalization of transplantation. We did not have data for re-admissions and long term outcomes of transplantation. Though we assume the majority of poor outcomes would happen during or shortly post-operatively, it would be interesting to follow the outcomes over a longer period of time and see if any meaningful differences occur.

An important consideration in the data we used is its dependence upon diagnostic coding and accurate documentation for validity, and was therefore vulnerable to selection bias. Previous papers have theorized that accurate reporting of obesity as comorbidity has historically been inferior to recent reporting. As obesity has been increasingly recognized as a public health epidemic, health care providers would be more likely to accurately document obesity^[25].

Lastly, our method of data collection did not allow for stratifying patients by disease severity, etiology of cirrhosis, or donor factors based on donor risk index. Therefore, survival analyses may be of constrained generalizability due to these limitations.

In conclusion, patients with morbid obesity undergoing OLT have increased respiratory complications and ≥ 3 comorbidities based on modified Elixhauser comorbidity index. Based on NIS database we found that health care utilization during admission for OLT is similar in morbidly obese and non-morbidly obese patients. Keeping in mind the limitations of NIS database, morbidly obese patients may be selected for OLT carefully after assessing their comorbidities. Further studies are needed to evaluate long term outcomes in these patients in era of MELD score based allocation of liver, which may

affect how patients are selected for transplantation in the future.

COMMENTS

Background

There have been varying reports on the morbidity and mortality in obese patients undergoing orthotopic liver transplantation (OLT). Consistently, studies have shown greater peri-operative morbidity as well as increased post-operative length of stay. Studies have also shown socioracial disparities in OLT utilization. Despite this, there have not been any large population based studies from United States on health care utilization and short term outcomes of liver transplantation in morbidly obese patients. The authors hypothesized that provided selected carefully morbidly obese patients undergoing liver transplantation may not have different healthcare utilization and short term outcomes.

Research frontiers

The need for liver transplantation continues to rise, as is the prevalence of obesity. The results of this study contribute to clarifying that carefully selected morbidly obese patients may be acceptable candidates for liver transplantation.

Innovations and breakthroughs

In this study, there was no difference in mortality, length of stay, or charges between morbidly obese and non-morbidly obese individuals receiving liver transplantation. This differs from previous reports.

Applications

This study suggests that morbidly obese patients may be selected for liver transplantation after carefully assessing their comorbidities.

Peer-review

This is a very interesting study performed on a great United States database based on more than 46000 patients undergoing liver transplantation. The retrospective study indicated that morbid obesity might not impact in-hospital mortality and health care utilization in OLT recipients.

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Peck JR et al. Morbid obesity and OLT

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- P- Reviewer: Boin ISFS, Bramhall S, Lai Q, Liang TB, Ohkohchi N,
 Qin JM, Wang GY







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