JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2023.69885
J Inonu Liver Transpl Inst 2023;1(3):94–99

Original Research

Is Obesity a Risk Factor for Recurrence in HCC Patients Who Undergo Liver Transplantation?

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Abstract

Objectives: It is known that obesity is associated with increased complications and early recurrence after cancer surgery. This may also be the case in patients with hepatocellular carcinoma (HCC) who treated with liver transplantation (LT).

Methods: This retrospective observational study aimed to investigate the potential impact of pre-transplant body mass index (BMI) on tumor recurrence and disease-free survival (DFS) in patients who underwent LT for HCC. The study analyzed data from 423 HCC patients who underwent LT at the Inonu University Liver Transplant Institute between 2006 and 2023.

Results: The median age of the 423 patients included in the study was 56 years (range: 18-72), with 367 (86.8%) of them being male. The median BMI was 26 kg/m^2 (range: 16.4-46.9). The recurrence rates were 24.3% in the non-obese group, 18.3% in the overweight group, and 16.7% in the obese group (p=0.239). The mean DFS durations were 8.4 years ± 0.6 in the non-obese group, 8.7 years ± 0.5 in the overweight group, and 9.7 years ± 0.9 in the obese group (p>0.05).

Conclusion: This study suggests that obesity should not be considered a predictive factor for HCC recurrence when selecting candidates for liver transplantation.

Keywords: Body mass index, Hepatic malignancy, Hepatectomy, Recurrence, Survival

Please cite this article as "Angin YS, Usta S, Ceylan C, Ince V, Isik B, Carr BI, Yilmaz S. Is Obesity a Risk Factor for Recurrence in HCC Patients Who Undergo Liver Transplantation? J Inonu Liver Transpl Inst 2023;1(3):94–99".

Liver cancers are the sixth most common cancer worldwide, with approximately 1,000,000 annually new cases, and it ranks as the third most common cause of cancer-related deaths, accounting for 856,000 deaths.[1] Factors that increase the likelihood of developing hepatocellular carcinoma (HCC) comprise infections like hepatitis B virus (HBV) and hepatitis C virus (HCV), excessive alcohol consumption, obesity, and exposure to environmental toxins.[2] A common feature among these risk factors is their potential to cause liver injury and cirrhosis.

While treatment options for HCC vary depending on tumor progression and the functional status of the liver, LT has emerged as a curative treatment option as it can eliminate both malignancy and cirrhosis. Despite the development of criteria for transplant candidates, such as the Milan and Expanded Malatya criteria, tumor recurrence still occurs at rates of 15% to 20%.[3,4] Therefore, it is essential to identify risk factors for recurrence. Age, male gender, high alpha-fetoprotein levels, elevated gamma-glutamyl transferase (GGT) levels, portal vein invasion, and high-grade atypia

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Submitted Date: 17.10.2023 **Revised Date:** 07.12.2023 **Accepted Date:** 07.12.2023 **Available Online Date:** 23.01.2024

in tumor cells have been identified as risk factors that increase the likelihood of recurrence following curative treatments.[5-9]

Obesity is known to be associated with various malignancies, including HCC.[10] Additionally, the accumulation of visceral fat tissue has been identified as a risk factor for both the development and recurrence of HCC.[11] However, the pathophysiology of the relationship between obesity and HCC recurrence remains unclear. It has been suggested that conditions associated with obesity, such as chronic inflammation and insulin resistance, may contribute to tumor growth. Elevated levels of vascular endothelial growth factor (VEGF) linked to obesity can enhance tumor angiogenesis and, consequently, increase recurrence. Moreover, obesity-related adiponectin and leptin have been reported to stimulate HCC proliferation, migration, and invasion.[12] The impact of obesity on post-LT outcomes for HCC is still a subject of debate.

The primary objective of this study was to examine the impacts of pre-transplant body mass index (BMI), a crucial determinant of obesity, on tumor recurrence and survival of individuals who underwent LT for HCC.

Methods

Patient Selection and Study Design

In this observational study, data from 517 patients those who have received living donor liver transplantation (LT) due to HCC between March 2006 and May 2023 at the Inonu University Liver Transplant Institute were retrospectively analyzed. The inclusion criterion for the study was the presence of HCC confirmed by explant pathology. After excluding 10 patients under 18 years of age and 84 patients with a follow-up duration of less than 90 days, data from the remaining 423 patients were analyzed. The treatment decisions for the patients were made during multidisciplinary meetings involving transplant surgeons, gastroenterologists, interventional radiologists, medical oncologists, nuclear medicine specialists, and radiation oncologists. Compliance with in Milan, Malatya, and Expanded Malatya criteria was primarily considered when deciding on transplantation. Post-transplant follow-up and immunosuppressive treatments were administered as previously described in another study.[13-18] Demographic information such as age, gender, and BMI was collected for the patients. Preoperative etiology, Child-Pugh groups, Model for End-Stage Liver Disease (MELD) scores (pre-transplant last labMELD, not exceptional MELD for HCC), bilirubin, creatinine, alpha-fetoprotein levels, recurrence status, and survival times were recorded. Tumor characteristics based on explant pathology, including tumor size, number of nodules, vascular invasion, and differentiation levels, were also noted. The patients were divided into three groups according to their BMI: <25 kg/m^2 (Group A), 25-30 kg/m^2 (Group B), and >30 kg/m^2 (Group C), based on the World Health Organization (WHO) classification.[13]

Statistical Analysis

The study assessed the normal distribution of numerical data using the Kolmogorov-Smirnov test. Continuous numerical variables were then subjected to analysis through the Mann Whitney U test, and the resulting data included median, minimum, and maximum values. Categorical variables underwent Chi-square analysis, with frequency and percentage values provided. Univariate logistic regression analysis was conducted for each variable, specifically those exhibiting statistically significant p-values within similar variables. To examine disease-free survival across different BMI groups (group A < 25 kg/m^2, 25 kg/m^2 ≤ group B < 30 kg/m^2, and group C ≥ 30 kg/m^2), the Kaplan-Meier method and log-rank test were utilized. Statistically significant results were defined as p-values less than 0.05. These analyses were carried out using SPSS version 23.

Results

The median age of the 423 patients included in the study was 56 years (range: 18-72), with 367 (86.8%) of them being male. The median BMI was 26 kg/m^2 (range: 16.4-46.9). The most common etiology of HCC was viral (80.4%) (Table 1).

The distribution of data among the three groups is presented in Table 2. Of the 423 patients, 169 were non-obese (BMI < 25 kg/m^2), 186 were overweight (30 kg/m^2 > BMI ≥ 25 kg/m^2), and 78 were obese (BMI ≥ 30 kg/m^2). The obese group tended to have a higher proportion of female patients.

Data on age, gender, Child-Pugh and MELD scores, albumin, bilirubin, serum creatinine, and alpha-fetoprotein levels can be found in Table 2. No notable distinctions were observed with in three groups regarding Child and MELD scores, albumin, bilirubin, serum creatinine, and alpha-fetoprotein values (p>0.05).

The data obtained from explant pathology, including the largest tumor diameter, vascular invasion, and tumor differentiation parameters, showed no significant differences among the groups (p>0.05). However, A disparity existed in the quantity of nodules among the groups (p=0.036). Additionally, while the largest tumor diameter was not statistically significant, it tended to be lower in the group with BMI >30 kg/m^2. Additionally, the likelihood of vascular inva-

Table 1. Demographic data and preoperative classification of HCC

Variables	Median (min-max)	n (%)
Age, years	56 (18-72)	
Gender		
Female		56 (13.2)
Male		367 (86.8)
Child		
A		147 (34.8)
B		185 (43.7)
C		91 (21.5)
MELD	13 (5-41)	
Etiology		
Viral		340 (80.4)
Cryptogenic		57 (13.5)
Ethanol		7 (1.7)
Budd Chiari		10 (2.4)
Metabolic		1 (0.2)
Another		8 (1.9)
Milan Cr.		
In		211 (49.9)
Out		212 (50.1)
Malatya Cr.		
In		263 (62.2)
Out		160 (37.8)
Exp. Malatya Cr.		
In		285 (67.4)
Out		138 (32.6)
BMI, kg/m^2	26 (16.4-46.9)	

HCC: Hepatocelluler Cancer; MELD: Model for End Stage Liver Disease; Child: Child-Pugh Classification; BMI: Body Mass Index.

sion was observed to be greater in patients with lower BMI. The recurrence rates were 24.3% in the non-obese group, 18.3% in the overweight group, and 16.7% in the obese group (p=0.239).

The mean DFS durations were 8.4 years ± 0.6 (95% CI: 7.2-9.5) in the non-obese group, 8.7 years ± 0.5 (95% CI: 7.6-9.8) in the overweight group, and 9.7 years ± 0.9 (95% CI: 7.8-11.5) in the obese group (Table 3, Fig. 1) (p>0.05).

Discussion

The impact of preoperative BMI on post-LT HCC recurrence remains a subject of debate. The primary objective of this study was to examine the relationship between preoperative BMI and post-LT HCC recurrence and DFS in individuals who received LT for HCC. The study ultimately found that preoperative BMI did not significantly affect post-LT HCC recurrence and DFS.

While many criteria have been established for LT in HCC patients, recurrence still occurs in 15-25% of patients. In our study, the recurrence rates ranged from 16.7% to 24.3% among the BMI groups, with no significant differences. Siegel et al. reported that 25% of HCC patients who underwent LT were obese, and these patients had a higher rate of tumor recurrence and increased risk of death. They attributed this to higher vascular endothelial growth factor (VEGF) levels induced by adipose tissue.[19] Mathur et al. supported Siegel's findings with their results, suggesting that obesity increased the risk of tumor recurrence. They proposed that obesity promoted a pro-oncogenic state by reducing adiponectin and increasing leptin levels, thereby stimulating HCC proliferation and migration.[11] However, some studies argue that obesity does not have a significant effect on post-transplant outcomes, and high BMI should not be considered a contraindication for LT.[20] In our study, while there was no statistical significance, the group with a BMI >30 kg/m^2 had a lower recurrence rate compared to the other two groups.

We observed that 10-year DFS rates were similar within the categories of individuals who are not obese, those who are overweight, and those who are classified as obese. This finding aligns with studies suggesting that survival in patients with a BMI >30 kg/m^2 is comparable to non-obese groups.[21,22]

In our study, the three groups had comparable tumor characteristics based on explant pathology. While Siegel and colleagues argued that patients with microvascular invasion had a worse prognosis, and BMI >30 kg/m^2 was linked to greater frequency of vascular invasion, our study found no significant differences in tumor size, differentiation, and vascular invasion among the groups. Moreover, although not statistically significant, the obese group had lower rates of poor differentiation, vascular invasion, and low recurrence rate. On the other hand, the most common symptom of patients with HCC is weight loose which is one of a finding of advanced stage tumors, so, we believe that, in low BMI group had more aggressive behavior as in the explant pathology revealed. These findings emphasize the complex and multifaceted nature of the relationship between obesity and HCC recurrence.

Strengths of our study include a large sample size and even distribution of variables among the groups. However, its retrospective nature and the lack of knowledge about the patients' BMI during follow-up can be considered limitations. Overall, our study suggests that further research is needed to demonstrate the effectiveness of obesity on tumor recurrence, especially in patients with HCC.

Table 2. Outcomes of clinicopathological data between groups

Variables	BMI<25kg/m²		25kg/m²≤BMI<30kg/m²		BMI≥30kg/m²		p
	Median (min-max)	n (%)	Median (min-max)	n (%)	Median (min-max)	n (%)	
Age, years	55 (18-71)		56 (23-72)		57.5 (38-72)		0.014
Gender							
Female		15 (9.4)		21 (11.3)		20 (25.6)	0.001
Male		144 (90.6)		165 (88.7)		58 (74.4)	
Child							
A		62 (39)		61 (32.8)		24 (30.8)	0.699
B		65 (40.9)		83 (44.6)		37 (47.4)	
C		32 (20.1)		42 (22.6)		17 (21.8)	
AFP	14.8 (0.2-20179)		11.5 (0.4-10424)		14.6 (1.1-2324)		0.675
MELD	12 (6-41)		12.25 (5-34)		14 (6-26)		0.094
MTD	3.5 (0.1-24)		3 (0.1-24)		2.55 (0-20)		0.061
NOD	2 (1-36)		1 (1-20)		2 (1-21)		0.036
Differentiation							
WELL		62 (39)		79 (42.5)		32 (41)	0.735
INT		66 (41.5)		81 (43.5)		34 (43.6)	
POOR		31 (19.5)		26 (14)		12 (15.4)	
Venous Invasion							
ABSENCE		81 (50.9)		100 (53.8)		46 (59)	0.430
MIKRO		54 (34)		68 (36.6)		22 (28.2)	
MAKRO		24 (15.1)		18 (9.7)		10 (12.8)	
Milan Cr.							
IN		68 (42.8)		101 (54.3)		42 (53.8)	0.076
OUT		91 (57.2)		85 (45.7)		36 (46.2)	
Malatya Cr.							
IN		88 (55.3)		124 (66.7)		51 (65.4)	0.078
OUT		71 (44.7)		62 (33.3)		27 (34.6)	
Eks. Malatya Cr.							
IN		98 (61.6.)		133 (671.5)		54 (69.2)	0.139
OUT		61 (38.4)		53 (28.5)		24 (30.8)	
Etiology							
Viral		129 (81.1)		152 (81.7)		59 (75.6)	0.525
Cyriptogenic		19 (11.9)		24 (12.9)		14 (17.9)	
Ethanol		1 (0.6)		3 (1.6)		3 (3.8)	
Budd Chiari		6 (3.8)		3 (1.6)		1 (1.3)	
Metabolic		1 (0.6)		0 (0)		0 (0)	
Another		3 (1.9)		4 (2.2)		1 (1.3)	
Albumin, g/dL	2.9 (1.5-5.2)		2.95 (1.6-5.2)		2.8 (1.2-4.2)		0.358
Bilirubin, mg/dL	1.73 (0.23-20.7)		1.82 (0.3-44.7)		1.96 (0.32-17.3)		0.648
Creatinine, mg/dL	0.78 (0.5-13.8)		0.8 (0.4-2.8)		0.8 (0.47-1.8)		0.777
Recurrence		39 (24.3)		34 (18.3)		13 (16.7)	0.239
DFS, years	3.34 (0.08-15.08)		2.84 (0.08-14.86)		3.68 (0.33-15.78)		0.323

AFP: Alpha-feto protein; MELD: Model for end stage liver disease; MTD: Maximum tumor diameter; NOD: Number of nodules; DFS: Disease free survival.

Conclusion

The findings of this study align with existing evidence from the literature, indicating that the recipient's BMI at the time of liver transplant does not have a direct influence on the occurrence of HCC recurrence during long-term follow-up, regardless of the patients' condition and the characteristics of their tumors at the time of transplantation. In essence, this study strongly affirms that when choosing candidates

Table 3. Disease free survival of groups

	Mean (SD) DFS (years)	95%CI	p
BMI Status			
Group A	8.382(0.584)	7.237-9.527	0.287
Group B	8.719(0.542)	7.657-9.781	
Group C	9.702(0.943)	7.853-11.551	
Total	9.095(0.39)	8.33-9.86	

DFS: Disease Free Survival; SD: standart deviation; CI: Confidence Interval, p<0.05 was considered statistically significant.

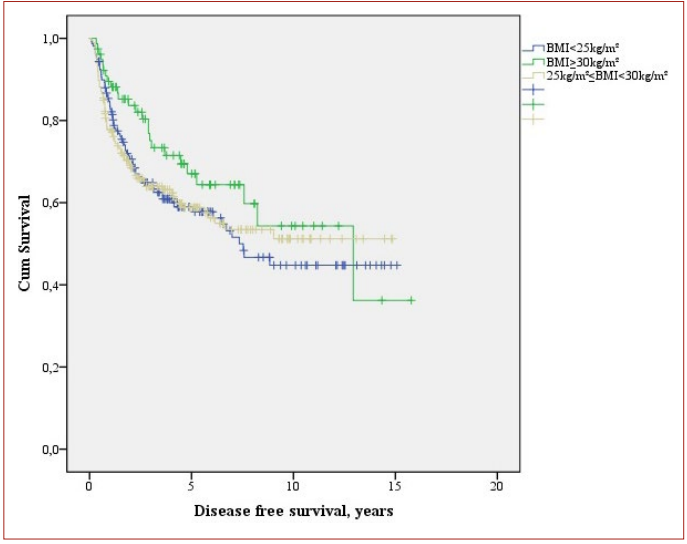

Figure 1. Kaplan-Meier DFS curves after liver transplantation for HCC according to BMI groups. BMI: body mass index.

with HCC for liver transplantation, obesity should not be regarded as a predictive factor for recurrence.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – V.I.; Design – Y.S.A.; Supervision – S.Y.; Materials – C.C.; Data collection &/or processing – S.U.; Analysis and/or interpretation – CC; Literature search – B.I.; Writing – Y.S.A.; Critical review – B.I.C.

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