Original Article

Impact of body mass index on hepatocellular carcinoma recurrence after liver transplantation through long-term follow-up

Nada El-Domiaty[1,2], Faouzi Saliba[1], Vincent Karam[1], Rodolphe Sobesky[1], Wafaa Ibrahim[3], Eric Vibert[1], Gabriella Pittau[1], Khaled Amer[4], Maysaa A. Saeed[2], Jihan A. Shawky[2], Daniel Cherqui[1], René Adam[1], Didier Samuel[1]

[1]AP-HP Hôpital Paul Brousse, Hepato-Biliary Centre, INSERM UMR 1193, Université Paris Saclay, Villejuif, France; [2]Tropical Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt; [3]Statistics Department, Faculty of Economics and Political Science, Cairo University, Cairo, Egypt; [4]Hepato-Biliary and Liver Transplant Department, International Medical Center, Cairo, Egypt

Contributions: (I) Conception and design: F Saliba, N El-Domiaty; (II) Administrative support: All authors; (III) Provision of study material or patients: All authors; (IV) Collection and assembly of data: N El-Domiaty, F Saliba; (V) Data analysis and interpretation: N El-Domiaty, F Saliba, W Ibrahim; (VI) Manuscript writing: All authors; (VII) Revision and final approval: All authors.

Correspondence to: Prof. Faouzi Saliba. AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, 12 Avenue Paul Vaillant Couturier 94800, Villejuif, France. Email: faouzi.saliba@aphp.fr.

Background: Obesity is associated with increased oncological risk and outcomes but the evidence surrounding the effect of body mass index (BMI) on increased risk of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) is still questionable. The purpose of this retrospective study of a large cohort of adult patients transplanted for HCC was to investigate the effect of BMI on the incidence of HCC recurrence and outcome.

Methods: Data from 427 adult recipients transplanted for HCC between 2000 and 2017 were collected. Patients were classified at time of LT according to the World Health Organization BMI classification into 3 groups; group 1: BMI <25 (n=166), group 2: BMI 25–29.9 (n=150) and group 3: BMI ≥30 (n=111).

Results: There were no significant changes of mean BMI overtime 26.8±5.0 kg/m2 at time of LT and 28.8±23.1 at 5 years. The recurrence rates of HCC after LT in the three groups were 19%, 16% and 17% respectively. The 5, 10 and 15-year recurrence free survival (RFS) rates were respectively 68.6%, 47.3% and 40.8% in group 1, 73.3%, 66.2% and 49.5% in group 2 and 68.8%, 57.5% and 47.7% in group 3 (log rank P=0.47).

Conclusions: Recipient BMI at time of transplant and during follow-up didn't impact the incidence of HCC recurrence nor long-term patient survival, irrespective to the status of the patients and their tumor characteristic at time of LT. The present study clearly confirms that obesity should not be considered, when selecting patients with HCC to LT, as a predictive factor of recurrence.

Keywords: Hepatocellular carcinoma (HCC); obesity; body mass index (BMI); nutrition; liver transplantation (LT); hepatocellular carcinoma recurrence (HCC recurrence)

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Introduction

Hepatocellular carcinoma (HCC) is one of the most lethal human malignant tumor with >600,000 deaths per year worldwide making it the third leading cause of cancer related death (1,2). Over the past quarter century, LT has been established as a durable therapy as it provides complete oncologic resection and correction of the underlying liver disease (3). Major risk factors of HCC are infection with hepatitis B (HBV), hepatitis C (HCV), excess

alcohol intake, obesity, diabetes and metabolic diseases (4). Despite the development of several scores to select patients for LT, the Milan criteria (MC) (single nodule smaller than 5 cm or from two to three nodules of up to 3 cm) are still the most commonly used criteria (5). Tumor recurrence (TR) still occurs in 15% to 20% of cases, being associated with unfavorable prognosis (6,7). Therefore, it is necessary to identify other risk factors for recurrence to refine patient selection and to identify modifiable factors that may reduce the incidence of TR.

Liver transplant recipient BMI has been evaluated as a post-transplant prognostic factor on several occasions, with contradictory results regarding the impact of obesity. Because the burden of disease caused by obesity is largely related to the metabolic syndrome and its cardiovascular consequences, it is questionable whether obesity has a similar impact on thoroughly selected patients such as liver transplant candidates compared with the general population (8-12).

Siegel *et al.* (2012) showed that 25% of patients with HCC who underwent LT were obese and had twice the risk of death, a higher frequency of microvascular invasion, and tendency for a higher rate of TR, suggesting that the increased expression of vascular endothelial growth factor (VEGF) induced by the adipose tissue may stimulate tumor angiogenesis (13). Mathur *et al.* (2013) has confirmed the increased risk of TR, with smaller recurrence free survival (RFS) among overweight patients, suggesting that obesity induces a pro-oncogenic state, via reduction of adiponectin and increase of leptin, which would stimulate HCC proliferation, migration, and invasion (14). While some studies declared that the obesity had no clear impact on post-transplant outcome, and high BMI should not be seen as a formal contra-indication for LT (15) there is a paucity of evidence evaluating the impact of BMI, used as a surrogate measure for obesity, on the occurrence of post-operative complications and oncologic outcomes in patients with HCC undergoing LT. Consequently, the main objective of this study was to evaluate in a large cohort of adult patients transplanted for HCC the relationship between recipient BMI at the time of LT and the incidence and time of HCC recurrence, as well as RFS and survival time after recurrence. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.04.01/rc).

Methods

Data source and patient variables

This is a retrospective cohort study that recruited all patients transplanted for hepatocellular carcinoma at the Hepato-Biliary Center of Paul Brousse Hospital, France, during the period between January 2000 and December 2017. The data were collected from charts and the electronic database system. The study was approved by institutional local ethics board (registration number 16.4.014). Informed consent was waived in relation to the retrospective design of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Of the 567 patients transplanted for liver cancer, 469 patients were transplanted for HCC (82.7%). We excluded those patients who underwent a second transplant for any cause (n=28), combined liver-Kidney transplant (n=8) and those with missing data for BMI (n=6). Patients with incidental HCC were not included in the study. Overall, the total number of patients included in this study was 427 patients. Patients were followed till December 2018.

Data comprised recipient's demographics including age, sex, and preoperative medical history of diabetes mellitus, alcohol intake and etiology of liver disease in addition to the BMI. Recipient factors at time of LT including calculated model for end-stage liver disease (MELD) score (16) and child-Pugh score (17) and biochemical parameters like serum albumin (g/L), estimated glomerular filtration rate (eGFR) (mL/minute/1.73 m^2) and alpha-fetoprotein (AFP) (µg/L) levels were documented. Tumor characteristics at time of transplant and the final pathology of the native liver (size, and number of nodules, tumor differentiation and microvascular invasion) were all considered. Classification according to Milan criteria (5), University of California San Francisco (UCSF) criteria (18) and AFP score (19) were all recorded.

Preoperative tumor assessment while on waiting list and selection for liver transplantation

In our center, the decision to treat and the type of treatment were discussed in a weekly multidisciplinary meeting that involve liver surgeons, hepatologists, radiologists, oncologists and pathologists. While on the waiting list, all patients were re-assessed every 3 months clinically, with

AFP level and imaging using either computed tomography scan (CT) of the chest and abdomen, magnetic resonance imaging (MRI) and Fluorine-18 Fluorodeoxyglucose positron emission tomography (18F-FDG PET) scan and ^{11}C-choline if needed, to rule out tumor progression or need for further treatment. To consider a patient on the waiting list we applied initially the Milan criteria based on the last imaging prior to transplant but since 2014, we applied the AFP score that has to be ≤2 (19). Patients were treated with liver resection, trans-arterial chemoembolization (TACE), radio-frequency ablation (RFA), rarely percutaneous ethanol injection or systemic chemotherapy as bridging or downstaging therapy following the Barcelona Clinic Liver Cancer (BCLC) classification guidelines.

Postoperative surveillance and HCC recurrence diagnosis

Thoraco-abdominal-pelvic CT scan was performed every 4 months for the first 2 years of follow-up, then every 6 months till the end of the fifth year. Thereafter, CT scan was performed annually till ten years or if symptoms occurred. Diagnosis of tumor recurrence was based on imaging. A biopsy was performed if the image was inconclusive.

Detailed follow-up protocols based on the relative risk of HCC recurrence have been published previously, measurement of AFP was routinely performed at outpatient clinic visits and the general principles of treatment for recurrent HCC lesions were applied to LT recipients with HCC recurrence (20). HCC recurrence was defined as direct detection of metastatic lesion(s) by imaging study and pathological confirmation by biopsy.

Study design

Patients were classified into three BMI groups at the time of transplant according to the BMI classification which is established by the WHO (21) into group 1: non-obese (BMI <25 kg/m^2); group 2: overweight (BMI 25–29.9 kg/m^2) and group 3: obese (BMI ≥30 kg/m^2). Time frames at diagnosis of HCC, at listing and at time of transplant were noted. Data were collected after transplant at different time visits at 1, 3, 5, 10 and 15 years after LT.

Outcomes

The primary outcome of the study was to establish the incidence of HCC recurrence according to BMI group. The secondary outcomes were patient and recurrence free survival and the post recurrence survival according to the recipient BMI class through a long-term follow-up.

Statistical analysis

For each variable, we only used data that were >80% completed with no data imputation for statistical analysis. Statistical analysis was performed using SPSS version 18 (SPSS, Inc., Chicago, IL, USA) and R software version 3.4.4. Continuous and categorial variables were analyzed using the F-test and the Pearson's chi-squared test, respectively. Overall survival was assessed according to Kaplan-Meier methods with the log-rank test. Significance was accepted with P value <0.05 and 95% confidence. Quantitative data were expressed by either the mean ± standard deviation (SD) or the median and inter quartile range (Q3–Q1) (IQR). Qualitative variables were expressed as percentages and frequencies.

Results

Patient's characteristics

A total of 427 patients with a mean age of 57.8±8.5 years (83.8% were males) who underwent LT for HCC were recruited. Based on BMI at LT, there were 166 (38.8%) non-obese patients group 1, 150 (35.1%) overweight group 2 and 111 (25.9%) obese group 3. The mean follow-up was 74.6±58.6 months. Patient's demographic data, clinical history and etiology of the underlying liver disease in the 3 groups are summarized in *Table 1*.

Age, history of chronic alcoholism and diabetes mellitus were significantly higher between both the overweight and obese groups. HCV cirrhosis was the common etiology followed by alcoholic cirrhosis. Non-alcoholic steatohepatitis (NASH) and alcoholic cirrhosis were significantly more common among the overweight and obese groups. The mean serum AFP level (µg/L) at time of HCC diagnosis was significantly different respectively in the 3 groups (662±285 *vs.* 166±198 *vs.* 62±195 µg/L; P=0.038). However, there were no anymore differences in the pre transplant serum AFP across the three groups. The mean preoperative MELD score (13.5±7.4 *vs.* 13.1±7.1 *vs.* 14.8±6.7) didn't differ among the three BMI groups. Most of the patients had a preoperative Child-Pugh score B (42.4%, 41.6%, and 37.6%, respectively; P=0.345).

The post-operative immunosuppression regimen was

Table 1 Patient and tumor characteristics according to BMI category

	Group 1, BMI <25 kg/m^2 (n=166)	Group 2, BMI 25–29.9 kg/m^2 (n=150)	Group 3, BMI ≥30 kg/m^2 (n=111)	P
Age, years	56.4±9.9	58.7±7.8	58.9±6.1	0.026*
Sex, male	131 (78.9)	130 (86.7)	97 (87.4)	0.087
History of chronic alcoholism	49 (29.5)	72 (48.0)	68 (61.3)	<0.001*
History of diabetes mellitus	50 (30.1)	62 (41.3)	50 (45.0)	0.024*
Underlying liver disease				<0.001*
Alcohol	30 (18.0)	49 (32.7)	50 (45.0)	
HCV	67 (40.4)	42 (28.0)	24 (21.6)	
HBV	24 (14.5)	26 (17.3)	10 (9.0)	
NASH	6 (3.6)	15 (10.0)	21 (18.9)	
Others	39 (23.5)	18 (12.0)	6 (5.4)	
MELD score at transplant	13.5±7.4	13.1±7.1	14.8±6.7	0.748
Child-Pugh score				0.345
A	41 (24.9)	42 (28.2)	25 (22.9)	
B	70 (42.4)	62 (41.6)	41 (37.6)	
C	54 (32.7)	45 (30.2)	43 (39.5)	
Serum albumin (g/L)	34±8.5	33.4±6.9	32±6.4	0.921
eGFR (mL/min/1.73 m^2)	96.1±31.6	97.7±27.6	95.8±29.2	0.893
AFP at diagnosis of HCC (μg/L), median (IQR)	13 (72.5–9.5)	6.3 (52.8–4.8)	7.1 (29.6–5.6)	0.038*
AFP at transplant (μg/L), median (IQR)	10 (65.4–8.7)	6.7 (29.6–3.9)	7.8 (52.7–4.8)	0.196
Pre-transplant therapy for HCC				
No treatment	29 (17.5)	28 (18.7)	21 (18.9)	0.264
TACE	78 (47.0)	60 (40.0)	54 (48.6)	
Resection	7 (4.2)	7 (4.7)	4 (3.6)	
Locoregional ablation	19 (11.4)	10 (6.7)	7 (6.3)	
TACE + resection	14 (8.4)	22 (14.7)	5 (4.5)	
TACE + locoregional ablation	19 (11.4)	23 (15.3)	20 (18.0)	
Tumor characteristics at pre-transplant imaging				
Maximum diameter (mm), median (IQR)	23 (24.4–11.6)	21 (23.3–9.9)	25 (25.6–11.9)	0.880
Number of nodules, median (IQR)	2 (1.8–0.9)	2 (1.8–0.9)	2 (2.1–0.9)	0.634
Site of lesions				
Uni-lobar	118 (82.5)	95 (79.2)	72 (72.0)	0.295
Bi-lobar	24 (16.8)	22 (18.3)	25 (25.0)	
Undetectable	1 (0.7)	3 (2.5)	3 (3.0)	
Within Milan criteria	125/159 (78.6)	120/144 (83.3)	79/108 (73.1)	0.831

Table 1 (*Continued*)

Table 1 (*Continued*)

	Group 1, BMI <25 kg/m^2 (n=166)	Group 2, BMI 25–29.9 kg/m^2 (n=150)	Group 3, BMI ≥30 kg/m^2 (n=111)	P
Within UCSF criteria	153/159 (96.2)	136/144 (94.4)	98/108 (90.7)	0.186
UCSF (+)/Milan (–) criteria	28/34 (82.4)	16/24 (66.7)	19/29 (65.5)	0.971
AFP score				0.175
≤2	139/160 (86.9)	132/143 (82.3)	93/104 (95.3)	
>2	21/160 (13.1)	11/143 (17.7)	11/104 (4.7)	
Tumor characteristics at the explant				
Maximum diameter (mm), median (IQR)	25 (26.3–12.9)	25 (29.6–15.6)	25 (25.6–13.6)	0.721
Number of nodules, median (IQR)	2 (2.1–0.9)	2 (2.8–0.9)	2 (3.3–1.3)	0.346
Site of lesions				
Uni-lobar	92/149 (61.7)	85/132 (64.4)	53/94 (56.4)	0.545
Bi-lobar	55/149 (36.9)	46/132 (34.9)	38/94 (40.4)	
Undetectable	2/149 (1.3)	1/132 (0.7)	3/94 (3.2)	
Microvascular invasion	54 (32.9)	46 (31.5)	42 (37.8)	0.943
Differentiation				0.296
Well	78/155 (50.3)	82/144 (56.9)	55/107 (51.4)	
Necrotic	40/155 (25.8)	28/144 (19.4)	18/107 (16.8)	
Moderate	28/155 (18.1)	24/144 (16.7)	18/107 (16.8)	
Poor	4/155 (2.6)	7/144 (4.9)	9/107 (8.4)	
Absence of HCC	3/155 (1.9)	1/144 (0.7)	3/107 (2.8)	
Hepato-cholangiocarcinoma	2/155 (1.3)	2/144 (1.4)	4/107 (3.7)	
Within Milan criteria	109/164 (66.5)	88/146 (60.3)	59 (53.2)	0.214
Within UCSF criteria	129/164 (78.7)	120/146 (82.2)	78 (70.3)	0.501
UCSF (+)/Milan (–) criteria	20/50 (40.0)	32/55 (58.2)	19/45 (42.2)	0.434
Immunosuppression at baseline				
Corticosteroids	152/159 (95.6)	140/147 (95.2)	97/103 (94.2)	0.869
MMF	121/159 (76.1)	117/147 (79.6)	87/103 (84.5)	0.261
Calcineurin inhibitors				
Ciclosporine	39/154 (25.3)	31/145 (21.4)	12/99 (12.2)	0.053
Tacrolimus	115/154 (74.7)	114/145 (78.6)	87/99 (87.8)	

Continuous variables are expressed as either mean ± SD or IQR (Q3–Q1). Categorical variables as n (%) and all the percentages are calculated out of available data. *, significant. HCV, hepatitis C; HBV, hepatitis B; NASH, non-alcoholic steatohepatitis; BMI, body mass index; HCC, hepatocellular carcinoma; UCSF, University of California San Francisco.

similar among the three groups; corticosteroids (95.6% *vs.* 95.2% *vs.* 94.2%, respectively, P=0.869), mycophenolic acid (76.1% *vs.* 79.6% *vs.* 84.5%, respectively, P=0.261) and for calcineurin inhibitors: 74.7%, 78.6% and 87.8% of the patients respectively were on tacrolimus while 25.3%, 21.4% and 12.2% respectively were on cyclosporine (*Table 1*).

Tumor characteristics

Tumor characteristics at time of HCC diagnosis

The first evaluation of HCC at time of diagnosis showed no significant differences respectively in the non-obese, overweight and obese groups in tumor size (28.0±17.6 *vs.* 30.2±22.7 *vs.* 27.2±11.4 mm, P=0.548) and tumor burden (1.8±1.4 *vs.* 1.9±4.2 *vs.* 1.7±0.9, respectively, P=0.856). The majority of patients exhibited comparable AFP score of ≤2 in the three groups (83.6%, 83.3% and 90.3%, respectively; P=0.598). The waiting time between the first diagnosis of HCC and liver transplant was not different across the three groups (21.1±21.7 *vs.* 24.8±20.2 *vs.* 21.6±19.9 months respectively, P=0.354). Similar proportion of patients requiring preoperative downstaging/bridging therapy was observed among the three groups (P=0.264); trans-arterial chemoembolization (TACE) was the commonest used procedure (47% *vs.* 40% *vs.* 48.6%) respectively in the three groups (*Table 1*).

Tumor characteristics at time of transplant

There were no significant differences on imaging (CT scan and/or MRI) at time of transplant across the three groups in respect to the largest tumor diameter (P=0.880), number of nodules (P=0.634) and site of the tumor (P=0.295) (*Table 1*). The majority of the patients among the three groups was respectively within the Milan criteria (78.6% *vs.* 83.3% *vs.* 73.1%; P=0.831) and had an AFP score of ≤2 (86.9% *vs.* 82.3% *vs.* 95.3%; P=0.175).

Tumor characteristics at explant pathology

The pathological evaluation of the explant (*Table 1*) revealed no significant differences respectively in the non-obese, overweight and obese groups regarding largest tumor diameter (27.3±19.1 *vs.* 28.6±19.4 *vs.* 27.1±13.8 mm, P=0.721), tumor burden (2.7±3.0 *vs.* 3.1±4.9 *vs.* 3.6±5.3, respectively, P=0.346) and microvascular invasion (MVI) (32.9% *vs.* 31.5% *vs.* 37.8%, respectively, P=0.943). There were fewer patients with unilobar lesions in the three groups (61.7% *vs.* 64.4% *vs.* 56.4%, respectively; P=0.545) as compared to imaging evaluation at time of transplant (82.5% *vs.* 79.2% *vs.* 72%, respectively, P=0.295). Merely half of the patients had a well-differentiated HCC, with comparable values among the three groups (P=0.296). Overall, numerically more patients were beyond Milan criteria in the obese group at pathology, but no significant difference was observed among the three groups (30.5% *vs.* 37.7% *vs.* 40.5%, respectively, P=0.214).

BMI changes after transplantation

In the overall population, there was a significant difference between the mean BMI respectively at time of transplant and that after 1 year of LT [26.8±5.0 kg/m^2; IQR (23.2–30.1)] *vs.* [26.3±4.8 kg/m^2; IQR (22.8–29.4); paired t-test P value <0.0001]. Afterwards, non-significant changes occurred in mean BMI (*Figure 1*). Despite that the mean BMI after 1 year of LT was mildly different from baseline, BMI at 1 year didn't affect long-term HCC recurrence.

HCC recurrence: incidence, patterns and treatments

The incidence of HCC recurrence was not different among the three groups and was respectively in the non-obese, overweight and obese groups 18.7%, 16% and 17.1% (P=0.819). The site of recurrence was predominantly extra-hepatic in 61.3% of the patients and was not different among the three groups (*Table 2*).

The main treatment of HCC recurrence among the three groups was mainly based on chemotherapy using either Gemcitabine plus Oxaliplatin initially then Sorafenib after its licence on the market (51.6%, 85% and 87.4% respectively) with very poor results. Few patients who developed extrahepatic recurrence (lung, bone, lymph nodes and adrenal glands) underwent different combinations of therapies (chemotherapy, loco-regional treatment and radiotherapy) and only 10 patients with either intrahepatic HCC or lung metastasis recurrence underwent surgical resections (*Table 2*).

The overall survival and post-HCC recurrence survival

The 1-year mortality rate that could reflect surgical outcome was respectively 9.5%, 7.4% and 9.2% in the non-obese, overweight and obese groups. Biliary complications occurred respectively in 7.2%, 2.0% and 4.5%. The incidence of hepatic arterial thrombosis was 1.2%, 2.0% and 0.9%.

The 5 and 10-year patient survival rates were not different among the three groups and were respectively (72.9% *vs.* 74.8% *vs.* 75.7% and 51.6% *vs.* 67.9% *vs.* 59.5%; log rank P=0.66) (*Figure 2*). The 5- and 10-year patient

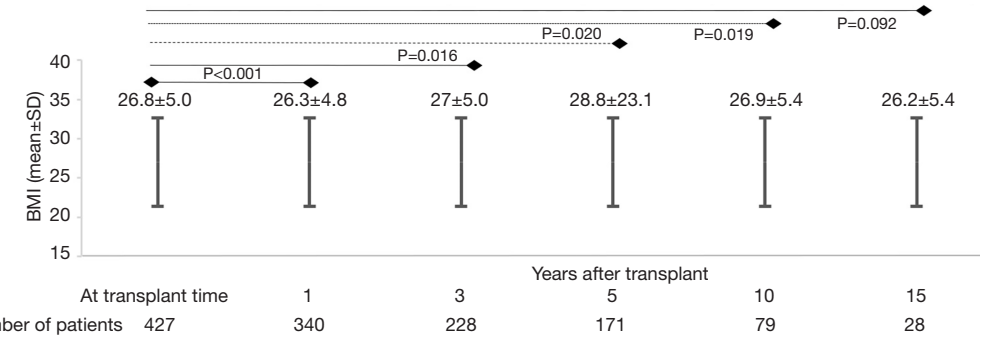

Figure 1 BMI changes over the follow-up years (mean ± SD; paired *t*-tests were performed at each follow up visit and compared to baseline). BMI, body mass index.

Table 2 HCC recurrence: patterns, treatments and outcomes

	Group 1, BMI <25 kg/m^2 (n=166)	Group 2, BMI 25-29.9 kg/m^2 (n=150)	Group 3, BMI ≥30 kg/m^2 (n=111)	P
Incidence of recurrence	31 (18.7)	24 (16.0)	19 (17.1)	0.819
Follow up duration (months)	79.58±60.9	77.1±58.4	68.07±54.5	0.398
Site of recurrence				0.162
Intrahepatic	2/31(6.5)	4/24(16.7)	6/19 (31.6)	
Intra and extra hepatic	9/31 (29.0)	5/24 (20.8)	2/19 (10.5)	
Extrahepatic	20/31 (64.5)	15/24 (62.5)	11/19 (57.9)	
AFP level at recurrence (μg/L), median (IQR)	65 (122.4–43.5)	40 (110.6–29.6)	60 (99.3–30.4)	0.667
Treatment of HCC recurrence				
Chemotherapy	16/31 (51.6)	17/20 (85.0)	14/16 (87.4)	0.043
Chemotherapy + resection	6/31 (19.3)	0	0	
Chemotherapy + radiotherapy	4/31 (12.9)	2/20 (10.0)	1/16 (6.3)	
Radiotherapy	2/31 (6.5)	0	1/16 (6.3)	
Surgical resection	2/31 (6.5)	0	0	
Surgical resection + radiotherapy	1/31 (3.2)	1/20 (5.0)	0	
Patient survival (months)	69±57.3	70.37±57.4	62.08±53.9	0.487
RFS (months)	67.6±58.4	62.6±57.6	62.5±54	0.676
Mortality	54 (33.1)	44 (29.5)	34 (30.9)	0.787

Continuous variables are expressed as either mean ± SD or IQR (Q3–Q1). Categorical variables as n (%) and all the percentages are calculated out of available data. HCC, hepatocellular carcinoma; BMI, body mass index.

RFS rates were comparable among the groups and were respectively (68.6% *vs.* 73.3% *vs.* 68.8% and 47.3% *vs.* 66.2% *vs.* 57.5%; log rank P=0.47) (*Figure 3*).

As it could be expected, the patient survival after diagnosis of HCC recurrence was poor without statistically significant difference among the groups with a median survival respectively of 11, 18 and 15 months. The 3- and 5-year patient survival rates after recurrence were respectively 14.4% *vs.* 18.6% *vs.* 20.5 and 7% *vs.* 9.3% *vs.* 10.2%; P=0.66 (*Figure 4*).

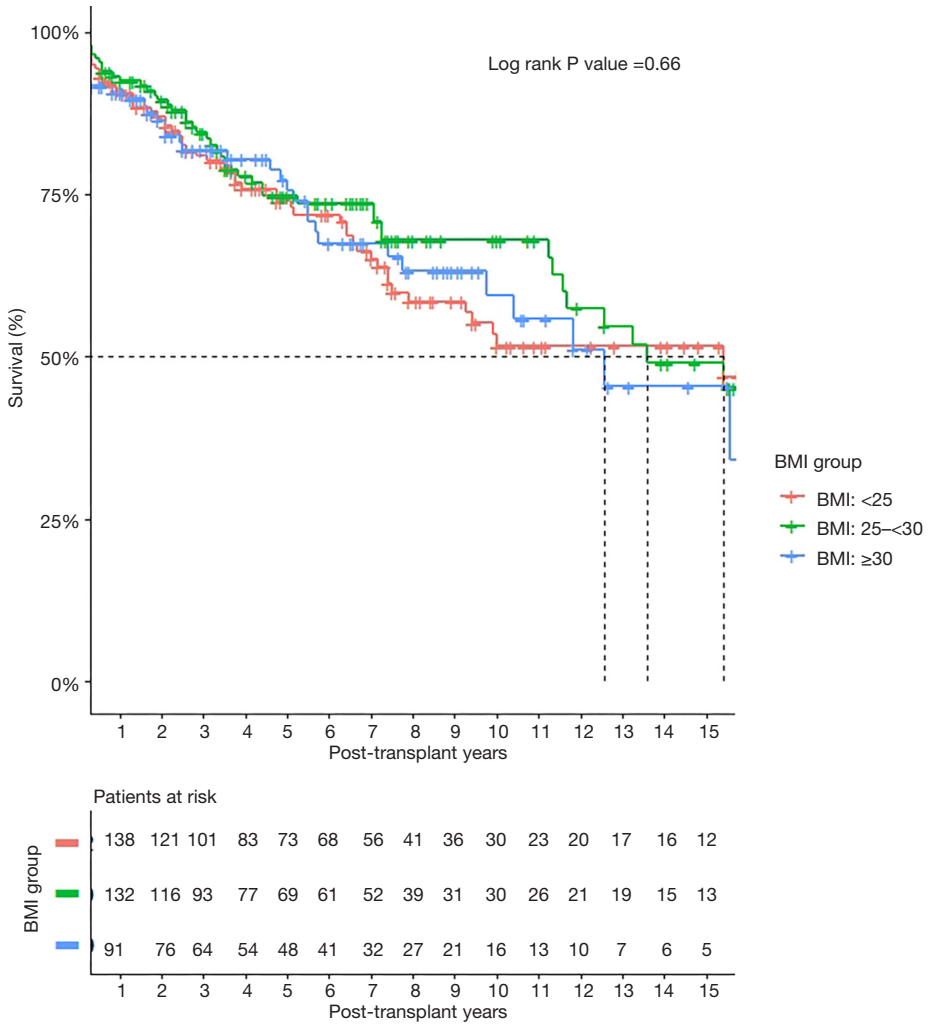

Figure 2 Kaplan-Meier survival curves after liver transplantation for HCC according to BMI groups (10-year survivals were 51.6%, 67.9% and 59.5%). HCC, hepatocellular carcinoma; BMI, body mass index.

Discussion

In view of the controversial and debatable effect of BMI on survival rate and the recurrence of HCC after LT, this retrospective study of a large cohort of patients transplanted for HCC showed the absence of impact of BMI on HCC recurrence after liver transplantation. There was also no difference among the three groups of BMI (normal weight, overweight and obese patients) when analyzing time to recurrence, patient survival from transplant and patient survival after recurrence.

Despite the strict selection criteria, tumor recurrence still occurs in 15–20% of patients transplanted for HCC (6,7). Our data revealed comparable recurrence ranges within the three BMI groups with no statistical difference among BMI groups ranging from 16% to 19%. To our knowledge, few papers reported on the impact of obesity on HCC recurrence. Mathur *et al.* (2013) reported that the incidence of recurrence of HCC was doubled in the presence of overweight and obesity compared to non-obesity, with a significant decrease in the time to recurrence following LT for HCC (14). The decrease in adiponectin coupled with the increase in leptin, in the setting of obesity, synergistically enhances HCC proliferation, migration and invasiveness. This may account for the earlier occurrence and increased incidence of recurrence of HCC in the setting of obesity following LT (14). The mean time of recurrence in our cohort in both overweight and obese groups was 62.5 versus 67.6 months in the non-obese group and this was not

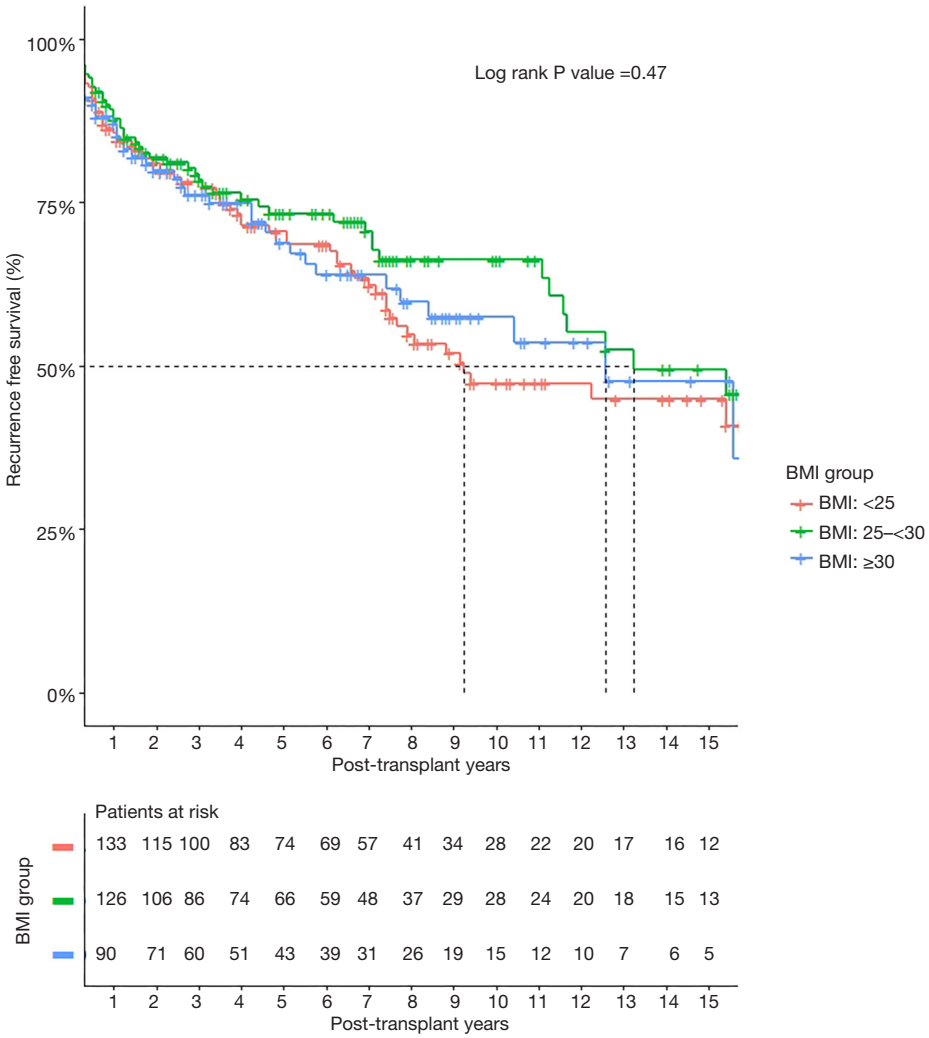

Figure 3 Kaplan-Meier recurrence free survival curves after liver transplantation for HCC according to BMI groups (10-year RFS were 47.3%, 66.2% and 57.5%). HCC, hepatocellular carcinoma; BMI, body mass index.

significant (P=0.67).

The etiology, in transplant recipients of group 2 (BMI 25–29.9 kg/m^2) and group 3 (BMI ≥30 kg/m^2), was mostly due to alcoholic cirrhosis or NASH while in the non-obese patient group 1 (BMI <25 kg/m^2) HCV was more common. This trend is similar to nationwide trends in the etiology of liver disease in obese transplant recipients (9). Data on 18,000 transplant recipients has demonstrated that severe (BMI ≥35 kg/m^2) and morbid (BMI ≥40 kg/m^2) obesity were associated with significant increased incidence of cryptogenic steatohepatitis and NASH (22). The three groups were comparable in terms of their MELD score, tumor characteristics at time of transplant, AFP levels. At explant pathology, the relationship between increased MVI and BMI has previously been considered. Siegel *et al.* (2012) showed that patients with MVI had poor survivals than other patients and those with a BMI >30 were more likely to have MVI than those with lower BMI and hence increased recurrence risk and worsened survival (13). Few studies have shown that vascular invasion in HCC is associated with markers of angiogenesis such as VEGF expression (23,24). A possible explanation for the relationship between increased MVI and BMI is via increased expression of adipokines in patients with higher BMI. Adipose tissue has been shown to induce expression of VEGF and other cytokines in human and animal models (25). In our study we didn't find

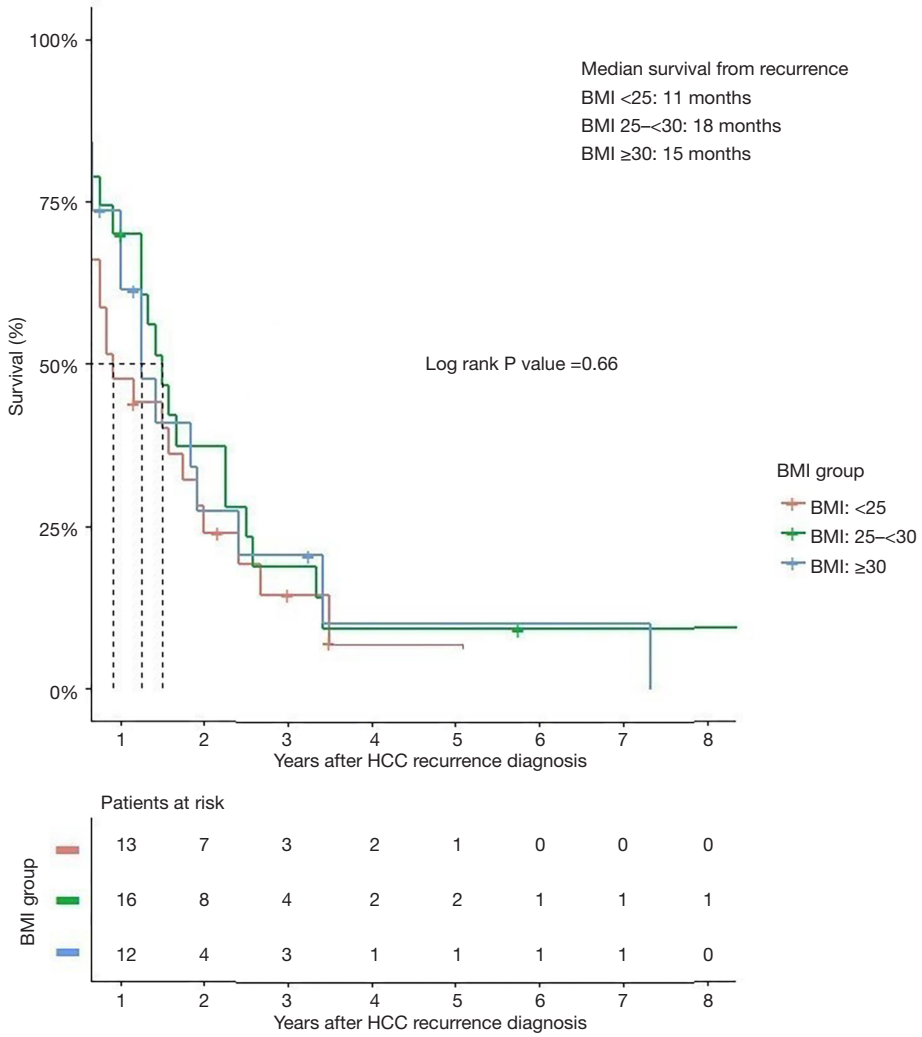

Figure 4 Kaplan-Meier patient survival curves after diagnosis of HCC recurrence according to BMI groups (5-year post recurrence survivals were 7%, 9.3% and 10.2%). HCC, hepatocellular carcinoma; BMI, body mass index.

difference among the three groups on pathology of the explant liver in terms of tumor differentiation, lesion size, number of nodules and MVI.

In this study, 39% of the recurrences occurred in the liver itself following LT. Marsh *et al.* (1997) (26) and Mathur *et al.* (2013) (14) demonstrated comparable percentages with respectively 35% and 42% of recurrences occurring within the transplanted liver itself and this was not influenced by BMI.

Through our long term patients follow-up, we recorded that the 10 years survival rates were comparable among the non-obese (51.6%), overweight (67.9%) and obese (59.5%) groups; these results are aligned with what is reported by several institutions which confirmed that BMI of ≥30 kg/m^2 is not associated with a decrease in survival (27). However, the smaller sample size of patients with BMI ≥35 kg/m^2 (n=28) in our study did not allow elucidation of differences in survival between severely obese patients (BMI ≥35 kg/m^2) and morbid obese (BMI of ≥40 kg/m^2). In the two large UNOS studies, the first demonstrated decreased survival in severely (BMI ≥35 kg/m^2) and morbid obese (BMI of ≥40 kg/m^2) groups (9) and the second indicated that BMI of ≥35 kg/m^2 was a significant predictor of negative outcomes at both the 1-month and 1-year time-points following liver transplantation (28).

The study has some limitations mainly in relation to the

dry body weight and BMI at time of transplant that could be affected by other confounders such as the presence of edema and ascites. Dry weight is somewhat difficult to be assessed in these patients and this had been a limitation in several studies. To note, that the number of patients with Child-Pugh score B and C who most likely could present with ascites were comparable among the three groups (*Table 1*). Ideally, as previously reported, muscle mass (based on pretransplant computed tomography) is a better predictor of post-LT survival as 62% of the patients with a BMI ≥25 kg/m^2 were cachectic, compared with 80% of the patients with a BMI of 18.5 to 24.9 (29).

In conclusion, this study is the first to close examine the relationship between BMI values and the HCC recurrence after LT for HCC through long-term follow-up. The results of the present work in keeping with evidences from literature revealed that: (I) recipient's BMI at time of transplant had no direct impact on the incidence of HCC recurrence after LT through long-term follow up regardless the status of the patients and their tumor characteristic at time of transplant; (II) the overall 5–10 year patient survival and the 5-year patient survival after the diagnosis of the HCC recurrence were comparable among the non-obese, obese and overweight patients. The present study clearly confirms that obesity should not be considered, when selecting patients with HCC to LT, as a predictive factor of recurrence.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2020.04.01/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The data were collected from charts and the electronic database system. The study was approved by institutional local ethics board (registration number 16.4.014). Informed consent was waived in relation to the retrospective design of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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