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Diabetes, body mass index and outcomes in hepatocellular carcinoma patients undergoing liver transplantation

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Abstract

Introduction—For many cancers, features of the metabolic syndrome, such as diabetes and obesity, have been associated with both increased risk of cancer development and poor outcomes.

Materials and Methods—We examined a large retrospective cohort of 342 consecutive patients who underwent liver transplantation for hepatocellular carcinoma between January, 1999 and July, 2010 at our institution. We evaluated the relationship between diabetes, obesity, HCC recurrence, and overall survival.

Results—We found that a body mass index (BMI) >30 was an independent predictor of poor overall survival in a multivariable Cox model, approximately doubling the risk of death after transplant. BMI >30 was also a predictor of recurrent HCC, although this was of borderline statistical significance (HR for recurrence 1.9, 95% CI 0.9–4.1). We also found increased BMI to be an independent predictor of microvascular invasion (MVI) within HCC tumors, lending a possible explanation to these results. Those with diabetes had worsened overall survival compared to those without diabetes in univariate, but not multivariable analysis, possibly related to longer wait times.

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Conclusions—Our findings suggest a relationship between higher BMI, tumor vascular invasion, increased recurrence, and worsened overall survival. These findings may help explain why those with high BMI have worse outcomes from their cancers. A better understanding of the role of obesity and diabetes in patients with cancer should help develop better predictors of outcome and improved treatment options for patients with HCC.

Keywords

Liver transplantation; hepatocellular carcinoma; diabetes; obesity; outcomes

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, with over 500,000 new cases per year.[1] Its age-adjusted incidence rates in the United States have doubled over the last 20 years, with a substantial proportion of this increase attributed to the chronic hepatitis C, and the increasing incidence of metabolic syndrome in the United States.[2, 3] The overall prognosis of patients with HCC in the U.S. is poor, especially for HCC patients who do not receive curative therapy.[4, 5]

The purpose of our study was to evaluate the relationship between obesity and diabetes, and HCC recurrence and survival in a large cohort of patients undergoing liver transplantation at our institution. We previously performed a pilot study of 138 patients who underwent liver resection or liver transplant for hepatocellular carcinoma, and found that those with a high body mass index were significantly more likely to have microvascular invasion on their pathology specimens. However, BMI was not an independent predictor of worsened overall survival, perhaps because of small sample sizes. [6] In patients with HCC who have undergone resection, some studies have found that prior diabetes does not impact survival, but does lead to increased cancer recurrence;[7] others found worsened overall survival but no increased risk of recurrence, [8] and still others have found no effect of diabetes on perioperative outcome, long-term survival, or disease-free survival. [9]

In this manuscript, we assess the relationship between BMI, tumor vascular invasion, and survival in a larger and more homogeneous cohort of patients undergoing liver transplantation. We also examine the relationship between BMI and tumor recurrence, which we had not looked at previously. Finally, we evaluate whether a history of diabetes pre-transplant yield similar associations with vascular invasion, increased risk of recurrence, and worsened overall survival.

Results

We analyzed 342 consecutive patients; the median age was 58, and 78% were men. Underlying HCV was noted in 70% of patients, and 16% had underlying HBV. About a third were diabetic (10 were type 1, and the remainder type 2), and 25% had a BMI>30. Other characteristics of our patients are shown in Table 1. Median 1, 3 and 5 year overall survivals were 85%, 68%, and 58% respectively. Recurrence-free survivals were 92%, 86%, and 82% respectively. Diabetics were more likely to be obese than non diabetics, although this relationship just missed statistical significance ($p=0.07$). We did not define a “NASH” etiology separately because of the difficulties defining NASH pathologically in HCC patients, the majority of whom have developed cirrhosis, which obscures the underlying pathology.

We next evaluated univariate predictors of overall survival. Favorable prognostic features included absence of vascular invasion on tumor explant, absence of a high-grade tumor, having a lower than median AFP, and having a shorter than median wait list time. Having

alcohol-related and HBV-related liver disease were of borderline significance predicting better survival ($p=0.06$, data not shown).

Similar to other groups, we found that being diabetic was a significant univariate predictor of worsened overall survival using Kaplan-Meier analysis ($p=0.003$). [10, 11] We attempted to determine why this was the case, and assessed the relationship between being diabetic and having a high grade tumor, having vascular invasion, being outside Milan criteria, or having an AFP greater than the median, but none was significantly associated with being diabetic. We did find that those with diabetes waited on average 3 months longer on the wait list than those without diabetes. Those with diabetes did not have worsened overall survival on multivariable analysis, and did not have a significantly higher risk of tumor recurrence.

In a multivariable Cox model for overall survival, we included median AFP, median age, diabetes history, BMI>30, HBV, HCV, ETOH use, high grade disease, being outside Milan criteria, having vascular invasion on explant, and wait list time (Table 2). We found that high AFP, any vascular invasion, and BMI>30 all approximately doubled the risk of death. Those with HBV lived about 4 times as long as those without HBV.

As in our previous pilot study of 138 HCC patients undergoing surgery and resection, here again we found a significant relationship between increased BMI and microvascular invasion seen on explant ($p=0.04$). Those with a BMI>30 were significantly more likely to have microvascular invasion than those with a lower BMI (31% vs 20%).

We then evaluated univariate predictors of recurrent hepatocellular carcinoma, using Kaplan-Meier curves. Vascular invasion was strongly related to recurrence as expected ($p<0.001$), as was being outside Milan ($p<0.001$), having high grade disease ($p<0.001$), and having a high AFP ($p<0.001$). In a multivariable model of recurrence which included AFP, age, HBV, HCV, ETOH-related disease, BMI>30, diabetes history, vascular invasion, grade, Milan criteria and length of time on the wait list, only high median AFP, high grade disease, and vascular invasion were independent predictors of recurrence; BMI>30 approximately doubled risk of recurrence but was of marginal statistical significance. (Table 3)

Discussion

For many common cancers, features of the metabolic syndrome such as diabetes and obesity have been associated with both increased risk of cancer development and poor outcomes. [12] In our large cohort of patients with HCC undergoing liver transplantation for HCC, we found body mass index (BMI) to be an independent predictor of worsened survival on multivariable analysis. BMI also independently predicted an approximate doubling in risk of recurrence, although the 95% confidence interval spanned 1 (0.9–4.1). As expected, patients with microvascular invasion had poorer survivals than other patients, and we show that those with a BMI>30 were more likely to have microvascular invasion in their tumors. We hypothesize that this worsened survival and increased recurrence risk may be related to increased microvascular invasion (MVI) within HCC tumors in those patients with a higher BMI.

One possible explanation for the relationship between increased microvascular invasion and body mass index is via increased expression of adipokines in patients with higher BMI. Adipose tissue has been shown to induce expression of vascular endothelial growth factor (VEGF) and other cytokines in human and animal models. [13] Vascular invasion in HCC and other cancers is associated with markers of angiogenesis, such as (VEGF) expression. [14, 15] [16, 17] These data support the hypothesis that HCC, in the setting of increased BMI, may be associated with increased angiogenesis, and thus have higher rates of recurrence and worsened overall survival.

It is possible that those who were obese had more post-operative complications than those who were not. We did not have access to post-operative complication rate, but we did examine length of stay in those who were obese versus those who were not obese, and found no significant difference between them ($p=0.56$). High BMI is also associated with HCV recurrence, but unfortunately we did not have data on HCV recurrence after transplant. It is possible that this may have also contributed to the worse survival outcomes seen.[18]

One of our hypotheses was that diabetes might also affect tumor aggressiveness via increased angiogenesis, but diabetes was not found to be related to vascular invasion in our dataset. It was also not a significant independent prognostic feature for recurrence or survival in our multivariable analyses. Prospective studies with plasma markers related to insulin resistance and better evaluation of performance status and comorbidities may help to clarify this question in the future.

One limitation to our work is its retrospective nature. A related limitation is that we were unable to obtain data on other variables which play a role in predicting outcome, such as performance status. Further, we could not adjust for the presence of ascites, which could confound BMI measurements. We also did not have etiology of death (cancer vs non cancer). However, we were able to validate and expand our pilot data using a much larger sample size.

In summary, we found a significant relationship between increased BMI and the presence of microvascular invasion in 342 patients who underwent liver transplant for HCC. A BMI >30 was an independent predictor of worse overall survival on multivariable analysis, and also was associated an increased risk of HCC recurrence. In addition, those who were diabetic had worsened overall survival in univariate analyses, but not in multivariable analyses. This may be related to increased wait times for diabetic patients.

Materials and Methods

We reviewed 342 patients who underwent liver transplant for hepatocellular carcinoma between January, 1999 and July, 2010 at our institution. Data were collected from available paper charts and an electronic database using an IRB-approved protocol. We assessed age at transplant, gender, self-reported race/ethnicity, health history (ie hepatitis, diabetes, body mass index (BMI) (defined as weight in kilograms divided by height in meters squared), alcohol use (defined as drinking $>$ than 2 drinks/day over a year or more at any time, or having a primary or secondary diagnosis of alcohol-related liver disease). When more than one BMI was available, we used the one closest to transplant. We defined tumors using AASLD criteria, and recorded tumor characteristics (including being within Milan by imaging, above or below median AFP (using the highest value before transplant), grade, and vascular invasion on explant pathology. We also evaluated time on the wait list, defined as time from listing until transplantation.

Pathologic examination

Microvascular invasion (MVI) was defined as identification of hepatocellular carcinoma tumor cells within endothelial-lined spaces on standard hematoxylin and eosin-stained slides. Grade was evaluated according to Edmondson and Steiner. [19] None of the pathologists was aware of the study hypotheses. A subset of about 10% of slides were centrally reviewed by one pathologist (HR).

Statistical analysis

Chi-square or Fisher exact tests were used to evaluate differences between patients with respect to the above variables. We used Kaplan–Meier curves, multivariable regression

models, and Cox proportional hazard models to determine risk factors for recurrence and mortality. Survival was determined from the date of HCC diagnosis defined based on patient history, to the date of death. All statistical analyses were performed with SAS software (Cary, NC).

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Table 1

Subject and tumor characteristics

<u>Characteristic</u>	<u>Median</u>	<u>Min</u>	<u>Max</u>	<u>N</u>	<u>%</u>
Age	57.6	27.2	74.8		
Lab MELD	11.8	3.1	38.8		
MAX AFP	22.5	1.7	24564.0		
Days on wait list	147	0	3832		
Gender					
Male				268	78
Female				74	22
Race/ethnicity					
White				191	56
Hispanic				74	22
Black				31	9
Asian				42	12
Other				4	1
DM					
Yes				106	31
No				233	69
BMI>30					
Yes				77	25
No				237	75
Ethanol use					
Yes				73	25
No				224	75
Hepatitis C					
Yes				239	70
No				101	30
Hepatitis B					
Yes				54	16
No				285	84
Within Milan					

<u>Characteristic</u>	<u>Median</u>	<u>Min</u>	<u>Max</u>	<u>N</u>	<u>%</u>
Yes				225	73
No				82	27
Vascular invasion					
Yes				86	25
No				256	75
Grade 4					
Yes				45	14
No				269	86
TNM stage					
I				30	9
II				141	41
III				131	38
IV				40	12
Child-Pugh score					
A				141	46
B				89	29
C				74	24
Chemoembolization					
Yes				242	71
No				99	29
Radiofrequency ablation					
Yes				51	17
No				246	83
Resection					
Yes				17	5
No				325	95

Table 2

Cox proportional hazards model of predictors of all-cause mortality

Variable	OR	95% CI
AFP		
<22.5	1	Referent
22.5	2.1	1.2–3.7
Age		
<57.6	1	Referent
57.6	1.3	0.8–2.2
DM		
No	1	Referent
Yes	1.2	0.7–2.0
BMI		
<30	1	Referent
30	1.8	1.1–3.0
Hepatitis B		
No	1	Referent
Yes	0.2	0.1–0.9
Hepatitis C		
No	1	Referent
Yes	0.7	0.3–1.4
Ethanol Use		
No	1	Referent
Yes	0.8	0.4–1.6
Grade 4		
No	1	Referent
Yes	1.1	0.6–2.1
Within Milan		
No	1	Referent
Yes	0.7	0.5–1.2
Vascular invasion		
No	1	Referent
Yes	1.8	1.1–2.9

All variables adjusted for each other

Table 3

Cox proportional hazards model of time to recurrence

Variable	OR	95% CI
AFP		
<22.5	1	Referent
22.5	4.4	1.6–12.1
Age		
<57.6	1	Referent
57.6	1.1	0.5–2.3
DM		
No	1	Referent
Yes	0.8	0.3–1.8
BMI		
<30	1	Referent
30	1.9	0.9–4.1
Hepatitis B		
No	1	Referent
Yes	0.3	<0.1–1.6
Hepatitis C		
No	1	Referent
Yes	0.4	0.1–1.3
Ethanol Use		
No	1	Referent
Yes	1.8	0.6–5.0
Grade 4		
No	1	Referent
	3.8	1.8–8.2
Within Milan		
No	1	Referent
Yes	0.5	0.3–1.1
Vascular invasion		
No	1	Referent
Yes	4.5	1.9–10.6

All variables adjusted for each other