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ORIGINAL ARTICLE

Diabetes Mellitus and Prediabetes in Patients with Hepatocellular Carcinoma in a Tertiary Philippine Hospital

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Abstract

Background. Diabetes mellitus (DM) has been shown to be associated with an increased risk for hepatocellular carcinoma (HCC). DM and obesity are coexisting conditions that can increase the risk and severity of nonalcoholic fatty liver disease (NAFLD), leading to HCC even in the absence of cirrhosis. With the rising incidence of HCC and DM worldwide, it is important to identify the clinical characteristics of individuals with DM among those with HCC in our local setting.

Objectives. To determine the prevalence of DM among Filipino patients with HCC at our institution, determine their demographic and clinical profile, and compare the characteristics of HCC patients with and without DM.

Methodology. This is a retrospective, analytical, cross-sectional study involving patients with HCC seen at The Medical City's Center for Liver Disease Management and Transplantation from January 2010 to December 2014. A chart review was conducted and patients were grouped according to the presence or absence of DM. Data on demographics, body mass index (BMI), comorbidities, social and family history, risk factors for liver disease, and laboratory test results were gathered. STATA 12.0 was used for data analysis.

Results. We included 180 patients with HCC in the analysis. The prevalence of type 2 DM and prediabetes was 52.78%. The median age of patients with DM and prediabetes was 65 years, and 58 years for patients without DM (p=0.002). The average BMI was 27.35 $\pm$ 4.68 for patients with DM, and 25.04 $\pm$ 5.11 for those without DM (p=0.002). Among the patients without DM, 50.59% had hepatitis B virus (HBV) infection compared to 24.21% of patients with DM (p=0.000). Twenty one percent of patients with DM had cryptogenic cirrhosis compared to 8.24% of patients without DM (p=0.016). Patients with DM had a higher proportion of hypertension (66.32% vs. 42.35%, p=0.001) and dyslipidemia (48.42% vs. 10.59%, p=0.000).

Conclusion. The prevalence of DM and prediabetes among HCC patients is higher in our institution compared to findings from previous studies. HCC patients with DM were older, and had increased BMI, higher proportion of hypertension and dyslipidemia, lower incidence of HBV infection, and higher incidence of cryptogenic cirrhosis.

Key words: hepatocellular carcinoma, diabetes mellitus

INTRODUCTION

In 2012, liver cancer was reported to be the fifth most common cancer in men, the ninth in women, and the second most common cause of cancer death worldwide.[1] In the Philippines, it is the fourth most common cancer, with incidence rates of 14 per 100,000 persons for males, and 4.8 per 100,000 persons for females.[2] Major risk factors for hepatocellular carcinoma (HCC) include infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD).[3] In some studies, however, none of these major etiologies were identified in cases of HCC, suggesting that there might be other less commonly known risk factors associated with HCC such as diabetes mellitus (DM).[4]

DM is now the most common cause of liver disease in the United States with the entire spectrum of liver findings being seen in these patients including abnormal liver enzymes, NAFLD, cirrhosis, and HCC.[5] NAFLD affects 10-24% of the general population and can potentially progress to cirrhosis and liver failure.[6] DM and obesity are coexisting conditions that can increase the risk and severity of NAFLD, leading to HCC even in the absence of cirrhosis.[7,8] Among Filipino patients, one study found a 12.2% prevalence of NAFLD in a single hospital.[9] They were younger in age compared to previous studies, and female sex, obesity, elevated liver enzymes, and the presence of DM were characteristic features of these patients. Other studies have likewise shown a significant association of NAFLD with DM, obesity and metabolic syndrome.[10,11]

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Several epidemiologic studies done in different geographic regions have shown an association between DM and HCC. A systematic review of 13 case-control studies and 13 cohort studies indicated that DM is associated with a 2.5-fold increase in the risk for HCC.[12] One of the studies in this review suggested a temporal relationship by showing that DM preceded the development of liver disease, and it also found that a longer history of DM significantly strengthened the association.[4] The positive association between DM and HCC may be confounded by the presence of other risk factors. While those studies that adjusted for viral hepatitis and alcohol use found no change or minimal change in the risk estimate, other potential confounders such as obesity, diet and physical activity were not addressed.[12]

In the Philippines, two studies conducted at the Philippine General Hospital have shown similar clinical characteristics of patients diagnosed with HCC. The mean age of diagnosis is 54 years, the male-to-female ratio is 3.5:1 to 4:1, and the most common risk factors are chronic hepatitis B and alcohol use.[13,14] Hepatitis B remains hyperendemic in the Philippines with an HBsAg seroprevalence of 16.7%.[15] In addition, Lucas et al., reported a 13.5% prevalence of DM among HCC patients, which was three times the national prevalence of DM at that time.[13]

With the rising incidence of HCC and DM worldwide, it is important to identify the clinical characteristics of individuals with DM among those with HCC in our local setting. At our institution, internal reports suggest a much higher prevalence of DM among patients with HCC, hence the need to confirm existing local data. The Medical City is a private tertiary hospital and while it caters mainly to residents of Metro Manila, it also receives referrals from rural areas. The Medical City's Center for Liver Disease Management and Transplantation (CLDMT) opened in 2008 and is a valuable repository of information on Filipino patients with HCC.

OBJECTIVES

1. To determine the prevalence of DM among Filipino patients with HCC at The Medical City's CLDMT
2. To determine the demographic and clinical profile of patients with HCC
3. To compare the characteristics of HCC patients with and without DM

METHODOLOGY

Study design

This is a retrospective, analytical, cross-sectional study.

Study population

This study included all Filipino adult patients aged 19 years and above seen at The Medical City's CLDMT from January 2010 to December 2014 with a diagnosis of HCC. Patients with other non-HCC liver tumor/s (e.g. metastatic liver cancer, cholangiocarcinoma) were excluded.

Sample size

The sample size was calculated[16] based on a desired width of the 95% confidence interval of 0.10, or an accuracy of $\pm$ 0.05, and an estimated prevalence of 13.5% as noted from the reference article by Lucas et al. A minimum of 180 subjects with HCC were required for this study.

Methods

Data was retrieved mainly by reviewing outpatient medical records from the CLDMT. Inpatient medical records were reviewed when available to supply missing outpatient chart data. A census of all liver cancer patients was generated from January 2010 to December 2014, and the diagnosis of HCC for each patient was verified. The diagnosis of HCC was based on histopathology or through the demonstration of typical dynamic radiologic findings on computerized tomography or magnetic resonance imaging. The hallmark of HCC is the presence of arterial enhancement, followed by washout of the tumor in the portal-venous and/or delayed phases. The diagnosis of type 2 DM was based on physician notes, use of relevant medications, and/or an HBA1c $\geq$6.5% prior to or at the time of diagnosis with HCC. Patients not known to have diabetes but who had an HBA1c of 5.7% to 6.4% prior to or at the time of diagnosis with HCC were labeled as having prediabetes.

For all subjects, demographic data included age, sex, and nationality. Body mass index (BMI) was calculated and cut-offs for Asians was used to classify subjects into the following categories: underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), and obese ($\geq$25 kg/m^2).

Information on the presence of co-morbidities (hypertension, dyslipidemia, obesity, CKD and others), alcohol and smoking history, and family history was collected. The month and/or year of diagnosis of HCC was based on physician notes, histopathology reports, and imaging tests. The risk factors for underlying liver disease were classified into hepatitis B, hepatitis C, NAFLD, alcoholic and cryptogenic cirrhosis.

Data on the duration of DM prior to diagnosis of HCC, the presence of diabetes-related complications, the use of relevant medications (oral drugs and insulin), and the level of control based on HBA1c results was collected.

Results of laboratory tests done such as liver function tests (ALT, AST, alkaline phosphatase, bilirubins, GGT, albumin, platelet count, INR), hepatitis profile and lipid profile were tabulated.

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Statistical analysis

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Independent sample T-test, Mann-Whitney U test and Chi-squared/Fisher's Exact test were used to determine the difference of mean, median and frequency between groups, respectively. Missing data was neither replaced nor estimated, as these are count variables which cannot be imputed. Patients with incomplete charts were included only in the analysis of variables for which data was available. If data on a specific variable was missing for a particular patient, the patient was not included for that variable only. STATA 12.0 was used for data analysis.

Ethical consideration

The protocol was submitted to the Institutional Review Board for approval. All patient information was kept strictly confidential. All data gathered was kept solely in the possession of the primary investigator.

RESULTS

Of the 233 patient charts retrieved with a possible diagnosis of HCC, 53 patients were excluded due to misdiagnosis. A total of 180 patients with a confirmed diagnosis of HCC were included in this study. Among these patients, 91 were found to have type 2 DM, and 4 patients were diagnosed with prediabetes. There were no cases of type 1 DM identified. The prevalence of type 2 DM and prediabetes was 52.78% among patients with HCC in our institution.

Table 1 compares the demographic and clinical profile of HCC patients with and without DM. Patients with DM were significantly older with a median age of 65 years; the median age for patients without DM was 58 years. In both groups, patients with HCC were predominantly male. The male-to-female ratio was 5.33:1 for patients with DM, and 4.4:1 for patients without DM. For the 170 patients with documented weight and height measurements, average BMI was significantly increased in the diabetic group, with 67% falling into the obese category. Information on alcohol and smoking history was inadequate. Quantity of alcohol intake and cigarette pack years were often lacking. There was a stronger family history of DM among those diagnosed with this condition that those without it.

For both groups, hepatitis B infection was the leading risk factor for underlying liver disease, but the number of cases was significantly increased in the non-diabetic group (50.59% vs. 24.21%, p=0.000). Of the 27 patients with cryptogenic cirrhosis as their underlying risk factor for liver disease, a significant number had DM (21.05% vs. 8.24%, p=0.016).

Among patients with DM who had available data on the duration of their disease, the average duration of DM prior to the diagnosis of HCC was 7 years. Majority had been diagnosed with DM at least 5 years prior to being diagnosed with HCC. 71% were on oral hypoglycemic agents only (Table 2).

Patients with DM had a higher proportion of hypertension (66.32% vs. 42.35%, p=0.001) and dyslipidemia compared to non-diabetics (48.42% vs. 10.59%, p=0.001) (Table 3).

Table 1. Demographic and clinical profile of HCC patients with and without DM

	Diabetic (n=95)	Non-diabetic (n=85)	P-Value
	Frequency (%); Mean ± SD; Median (Range)		
Age (years), median (range)	65 (42 to 90)	58 (21 to 82)	*0.002*§
Sex, frequency (%)			0.590ǂ
Male	80 (84.21)	70 (81.18)	
Female	15 (15.79)	16 (18.82)	
Weight (kg), mean ± SD	73.89 ± 14.82	68.15 ± 17.32	*0.021**
Height (cm), mean ± SD	164.09 ± 7.41	164.56 ± 9.42	0.724*
BMI (kg/m^2), mean ± SD	27.35 ± 4.68	25.04 ± 5.11	*0.002**
BMI categories, frequency (%)			
Underweight	0	5 (6.10)	*0.001*ǂ
Normal	13 (14.77)	22 (26.83)	
Overweight	16 (18.18)	22 (26.83)	
Obese	59 (67.05)	33 (40.24)	
Alcohol history, frequency (%)			0.066ǂ
Never	39 (45.35)	26 (34.67)	
Previous	31 (36.05)	26 (34.67)	
Current	16 (18.60)	23 (30.67)	
Smoking history, frequency (%)			0.727ǂ
Never	44 (52.38)	37 (50.68)	
Previous	28 (33.33)	28 (38.36)	
Current	12 (14.29)	8 (10.96)	
Family history, frequency (%)			
HCC	14 (14.74)	6 (7.06)	0.102ǂ
DM	49 (51.58)	21 (24.71)	*0.000*ǂ
Risk factors for underlying liver disease, frequency (%)			
HBV	23 (24.21)	43 (50.59)	*0.000*ǂ
HCV	2 (2.11)	6 (7.06)	0.151ǂ
NAFLD/NASH	16 (16.84)	8 (9.41)	0.188ǂ
Alcohol	8 (8.42)	4 (4.71)	0.318ǂ
Cryptogenic	20 (21.05)	7 (8.24)	*0.016*ǂ
Unknown	29 (30.53)	21 (24.71)	0.384ǂ
With Cirrhosis, frequency (%)	45 (47.37)	37 (43.53)	0.606ǂ

Statistical tests used: * - Independent Sample T-test; ǂ - Chi-squared test; § - Mann-Whitney U test; ǂ - Fisher's Exact test

Table 2. Duration of diabetes and medications used by HCC patients with diabetes (n=95)

	Frequency (%)
Diabetes duration (years)	
Less than 5 years	19 (32.20)
5 years to 10 years	14 (23.73)
More than 10 years	26 (44.07)
Undocumented	36 (37.89)
Diabetes medication	
OHAs only	59 (71.08)
Insulin only	21 (25.30)
OHA and Insulin	3 (3.61)
Undocumented	12 (12.63)

Table 3. Co-morbidities of HCC patients with and without DM

	Diabetic (n=95)	Non-diabetic (n=85)	P-Value
Hypertension	63 (66.32)	36 (42.35)	***0.001***
Dyslipidemia	46 (48.42)	9 (10.59)	***0.000***
CKD	7 (7.37)	4 (4.71)	0.457
Others	33 (34.74)	17 (20.00)	***0.028***

Statistical tests used: Chi-squared test
Data are presented as frequency (%)

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Table 4 provides a summary of the clinical chemistries done in all patients with HCC. There is insufficient evidence to demonstrate a difference in blood test results between patients with and without DM.

Table 4. Clinical chemistries of HCC patients with and without DM

	Diabetic	Non-diabetic	P-Value
Platelet count (n=155)			0.701
Decreased	17 (20.73)	17 (23.29)	
Normal	65 (79.27)	56 (76.71)	
INR (n=149)			0.404ǂ
Increased	2 (2.38)	4 (6.15)	
Normal	82 (97.62)	61 (93.85)	
FBS (n=100)			***0.000***
Increased	50 (89.29)	10 (22.73)	
Normal	6 (10.71)	34 (77.27)	
HbA1c (n=61)			***0.042***ǂ
Increased	22 (40.74)	0	
Normal	32 (59.26)	7 (100)	
ALT (n=155)			0.915
Increased	27 (32.53)	24 (33.33)	
Normal	56 (67.47)	48 (66.67)	
AST (n=147)			0.916
Increased	61 (77.72)	53 (77.94)	
Normal	18 (22.78)	15 (22.06)	
Alkaline phosphate (n=130)			0.357
Increased	34 (50.00)	26 (41.94)	
Normal	34 (50.00)	36 (58.06)	
GGT (n=55)			0.660
Increased	21 (80.77)	22 (75.86)	
Normal	5 (19.23)	7 (24.14)	
Undocumented	69 (72.63)	56 (65.88)	
Albumin (n=149)			0.541
Decreased	41 (50.62)	31 (45.59)	
Normal	40 (49.38)	37 (54.41)	
AFP (n=151)			0.093
Increased	55 (67.90)	56 (80.00)	
Normal	26 (32.1)	14 (20.00)	

Statistical tests used: Chi-squared test; ǂ - Fisher's Exact test
Data are presented as frequency (%)

DISCUSSION

The prevalence of DM among patients with HCC varies from region to region. In the United States, Hassan et al., reported a prevalence of 33.3%,[17] while Taura et al., reported 25% among Japanese patients.[18] In the Philippines, Lucas et al., reported a 13.5% prevalence of DM among HCC patients at one hospital.[13] In our study, the prevalence of type 2 DM and prediabetes was 52.78%, which is much higher compared to the findings of the previously mentioned international and local studies.

The study by Lucas et al., was conducted at a government hospital in Manila that caters mostly to indigent patients, and included only those patients that had been hospitalized, thus it is possible that the diagnosis of DM was underestimated in its study population. The higher prevalence of DM among HCC patients at our center may also be reflective of an increasing prevalence of DM in our country's general population. From 2003 to 2008, the estimated national prevalence of DM increased from 4.6% to 7.2%.[19] The subjects in our study also came from a single center, therefore, we cannot claim that they are representative of the entire population. Nonetheless, it is important to note that our institution is a referral center for patients coming from all over the Philippines, both urban and rural areas, and with diverse socioeconomic backgrounds.

In our study, we found that, regardless of the presence or absence of DM, patients at our center were diagnosed with HCC at a later age compared to patients in two other local studies done at the Philippine General Hospital. Lucas et al., reported a mean age of 54 years at the time of diagnosis with HCC, and Daez et al., had a similar mean age of 54.42 years. Furthermore, HCC patients with DM were significantly older compared to those without DM. Although not statistically significant, there was a greater proportion of male patients among those with DM (5.3:1 vs. 4.3:1). The higher median age and higher male-to-female ratio of patients without DM in our study is in agreement with previous findings that patients who develop HCC in the background of metabolic syndrome are more predominantly males, and are older at the time of diagnosis as compared to patients with HCC due to other causes.[20]

The older age at diagnosis of HCC among patients without DM may also be linked to their underlying risk factors for liver disease. While we found that HBV infection remains to be the leading cause of HCC, there is a significantly lower incidence of HBV among those patients with DM. This has also been previously observed among Japanese and Chinese patients.[18,21] Compared to other countries in the Asia Pacific region where the prevalence of HBV infection has already fallen, the Philippines remains hyperendemic for HBV perhaps because the universal HBV vaccination program, although first introduced in 1992, was only fully implemented in 2007.[15]

It is estimated that 5-30% of HCC cases do not have readily identifiable risk factors for HCC such as viral hepatitis and alcohol.[20] Many cases of cryptogenic cirrhosis are now being attributed to NAFLD, and its more severe stage, non-alcoholic steatohepatitis (NASH). Diabetes-associated NASH leading to HCC has been described.[12] In our study, we found that there were significantly more patients with DM among those with cryptogenic cirrhosis. This is similar to previous studies showing that DM is indeed prevalent in patients with HCC and cryptogenic cirrhosis.[12]

For both groups, a large proportion of HCC patients were overweight or obese, with those patients with DM having significantly increased BMI compared to those without DM. Obesity is associated with a higher incidence of many types of cancers including HCC.[22] A BMI greater than 30 kg/m^2 is an independent predictor of poor overall survival.[23] The main mechanism involved appears to be hyperinsulinemia, a positive energy balance and other hormonal abnormalities.[22] Since both obesity and DM are characterized by hyperinsulinemia and increased cancer incidence, it is difficult to identify the contribution of each individual risk factor.[22] There was a higher proportion of hypertension and dyslipidemia among patients with HCC and concurrent DM. There are few studies that examine the individual association of these conditions with HCC,

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but taken together as components of the metabolic syndrome, it is well established that this syndrome contributes to the development of HCC.[20]

For most of our patients with DM, the diagnosis of DM preceded the diagnosis of HCC by at least 5 years. Unfortunately, data on glycemic control in terms of HBA1c levels was lacking in many patients. Most charts also failed to mention if there were any diabetes-related complications present, and many did not indicate the specific type of anti-diabetic medications that patients were taking and their compliance with treatment.

In the study by Hassan et al., the adjusted odds ratio was higher with increasing duration of DM.[17] Furthermore, it was found that certain medications were implicated in the development of HCC. The risk for HCC was greater for patients on sulfonylureas and insulin, while biguanides and thiazolidinediones were associated with lower HCC risk.[17] The degree of glycemic control is another factor that can determine who among patients with DM are at higher risk of being diagnosed with HCC. Donadon et al., reported that among patients with HCC, HBA1c levels were significantly higher in those with DM compared to patients with cirrhosis and control groups of patients with DM. There was a 26-50% increase in the HCC risk for each 1% increase in HBA1c level.[24]

The Philippines has recently been recognized as a newly industrialized country, one whose economy is somewhere in between those of developing and developed nations. While infectious diseases remain to be a problem, noncommunicable diseases such as DM have become a growing concern in developing and newly industrialized countries. This shift is believed to have been brought about by lifestyle related risk factors associated with social and economic changes.[25] There is a need therefore for public health programs to widen their focus from eradication of infectious diseases and to address lifestyle related diseases that were previously thought to be just a concern of the developed world. Until then, it is likely that diseases like HCC that are multifactorial in etiology will continue to be a significant cause of morbidity and mortality. There are currently no guidelines for HCC screening aimed specifically at patients with DM. However, given that there is such a high prevalence of DM among Filipino HCC patients at our institution, it is important to raise the awareness of physicians regarding the association of these two conditions. Diabetes prevention and control should be emphasized, and liver-related symptoms in patients with DM should prompt appropriate investigations.

This study has several limitations. The retrospective nature affected the completeness of the data and we were unable to gather enough information on certain variables that we had intended to collect. There were many charts that had missing laboratory results and many physician notes were incomplete. In the future, a prospective design is recommended to improve on the quality of data collected. A multi-center recruitment of subjects would be ideal in order to have a sample population that is more representative of HCC patients in the Philippines. While our study was not designed to determine whether DM is a risk factor for the development of HCC, our preliminary findings showing a high prevalence of DM among HCC patients could generate more interest in related research areas. It would be worthwhile to investigate how DM affects HCC prognosis and if control of DM will lead to better outcomes for patients with HCC.

CONCLUSION

The prevalence of DM among patients with HCC is higher in our institution compared to findings from previous international and local studies. HCC patients with DM were older, had increased BMI, and had a higher proportion of hypertension and dyslipidemia. They also had a lower incidence of HBV infection and a higher incidence of cryptogenic cirrhosis.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors have declared no conflict of interest.

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