

## THE CLINICAL PROFILE OF HEPATOCELLULAR CARCINOMA PATIENTS AT THE PHILIPPINE GENERAL HOSPITAL

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### ABSTRACT

**Objective:** To describe the clinical characteristics of patients diagnosed with hepatocellular cancer admitted at the Philippine General Hospital from January 2001 to December 2006

**Background:** Hepatocellular carcinoma (HCC) is the third leading site of cancer in the Philippines. Although risk factors for HCC are already established, significance of risk factors may vary among regions. Diabetes has also not been examined as a risk factor among Filipinos.

**Methodology:** This is a descriptive study with data collection done through chart review. All charts with the diagnosis of hepatocellular carcinoma admitted from 2001 to 2006 were retrieved from the Medical Records Section. Participants included all adult hepatocellular carcinoma patients, diagnosed with HCC either by: (1) biopsy or (2) mass > 2cm and elevated  $\alpha$ -fetoprotein >200. Demographic data, risk factors, and laboratory exams were collated. Descriptive statistics were generated using SPSS 15.0.

**Results:** Two hundred twenty two patients were included in the study. Males outnumbered females (3.5:1). Majority were older than 50 years old. The most common symptom is abdominal pain. Two thirds had a history of drinking alcohol. Almost half were smokers. Thirty eight patients (40.0%) had previous hepatitis B and 66 patients (52.3%) had chronic Hepatitis B. Only 3 (6.2%) patients had hepatitis C infection. Two thirds had no evidence of cirrhosis. Thirteen percent of the population had diabetes mellitus while 20% of the HBsAg-negative patients had diabetes mellitus. Eighty seven percent were in the advanced stage and 11.7% were terminal stage.

**Conclusion:** The most common risk factors for HCC are still hepatitis B infection and alcohol drinking. Diabetes mellitus deserves to be investigated as an important contributing factor to the development of HCC, especially in HBsAg-negative patients. Most patients belonged to late stages of the disease but a selection bias is recognized. Our study indicates the need for screening patients at risk so early-stage disease can be detected.

**Keywords:** Hepatocellular carcinoma,  $\alpha$ -fetoprotein, risk factors, hepatitis, cirrhosis

**Conflicts of Interest:** None

### INTRODUCTION

Hepatocellular cancer (HCC) is the fifth most common tumor in the world. It is an important cause of cancer mortality, with approximately one million deaths annually.<sup>1</sup> In the Philippines, HCC is the third leading site of cancer for both sexes.<sup>2</sup> It ranks second among males and 9th among females. In 1998, there were estimated 5,249 new HCC cases (3906 males and 1343 females) and 4,403 deaths.<sup>3</sup>

The most common risk factors for HCC include chronic hepatitis B infection, hepatitis C infection, cirrhosis of any etiology, heavy alcohol use and aflatoxin intake. Other authors have implicated smoking as a risk factor<sup>4</sup> while others have argued against this.<sup>5</sup>

Hepatocellular carcinoma is more prevalent in the Philippines and Asia because of the increased incidence of Hepatitis B. This also accounts for the younger age of onset of the disease (one to two decades earlier) in these populations.<sup>6</sup> The Philippines is considered a hyperendemic region for Hepatitis B with a 55-68% exposure rate based on serological detection of at least one HBV marker.<sup>3</sup> It is, therefore, expected that Filipino HCC patients will be younger than their Western counterparts.

Characteristics of HCC patients have been described in the literature. However, only a few studies focused on the Filipino population. In 1979, Lacuesta described 30 biopsy-proven hepatoma cases in a tertiary center in Davao according to age

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and liver function tests.<sup>7</sup> In 1981, Domingo, *et al* described the typical Filipino HCC patient as male, under 50 years old, and has no recollection of liver disease or exposure to drugs or chemical carcinogens and has no family history of cancer.<sup>8</sup> In 2000, Sollano studied 126 cases in a tertiary hospital. Eighty-seven percent were positive for HBsAg and none tested positive for Hepatitis C.<sup>9</sup>

There is no recent study describing the demographics, risk factors and clinical status of patients diagnosed with HCC in the Philippines. Although risk factors for HCC are already established, significance of risk factors may vary among regions, as depicted for example, by the high prevalence of Hepatitis B and HCC in the Philippines compared to other countries. These risk factors may influence the age of onset of the disease, prognosis of patients and screening recommendations for a population. With the recognition of diabetes mellitus as a risk factor for chronic liver disease and hepatocellular carcinoma, it is worthwhile to explore this as another risk factor for HCC among Filipinos. This has not been done in previous studies.

As there are currently no general recommendations to screen for HCC among Filipinos, data on the clinical profile of Filipino HCC patients may lead to new recommendations for screening for HCC and its risk factors among Filipinos.

### *Research Question*

What are the clinical characteristics of hepatocellular cancer patients admitted at the Philippine General Hospital from January 2001 to December 2006?

### *General Objective*

To describe the clinical characteristics of patients diagnosed with hepatocellular cancer admitted at the Philippine General Hospital from January 2001 to December 2006

### *Specific Objectives*

- To characterize the clinical and laboratory features of HCC patients at presentation
- To describe the hepatitis profile of the HCC patients
- To determine the proportion of HCC patients with Diabetes Mellitus

## **MATERIALS AND METHODS**

### *General Study Design*

This is a descriptive study, with data collection done through chart review. All charts with the diagnosis of “hepatocellular carcinoma”, “hepatoma” or “liver cancer” admitted within the time period were retrieved from the Medical Records Section of the Philippine General Hospital. In order to increase the yield of cases, we also cross-referenced the Pathology Department database.

### *Participants*

The study included hepatocellular patients admitted from January 2001 to December 2006 diagnosed with HCC either by (1) biopsy or (2) liver mass >2 cm by ultrasound or computed tomographic scan and elevated  $\alpha$ -fetoprotein >200.<sup>10</sup> Patients from both charity and pay wards were included. HCC patients from the Out-Patient Department of the institution were not included in the study because charts are not classified according to diagnoses in the Out-Patient Records Section.

### *Outcome Measures*

Demographic data, presenting symptoms and laboratory exams were collated. (See Appendix 1).

### *Definition of Terms*

- Cirrhosis- biopsy-proven or nodular liver on imaging (ultrasound or computed tomographic scanning)
- Ascites- based on physical examination or documented by imaging

### *Statistical Analysis*

Data collected were encoded in Microsoft Excel. Descriptive statistics (frequencies and percentages) were generated using SPSS 15.0 for Windows.

## **RESULTS**

### *Demographics*

A total of 301 charts were retrieved but only two hundred twenty two patients were included in the study based on our definition of hepatocellular carcinoma. The patients were aged 29 to 86 years old. Mean age was 54 years old. Sixty-five percent

were older than 50 years old. Table I compares the young (less than 50 years) and old (greater than or equal to 50 years) subgroups.

**Table I. Comparison Between the Young and Old Subpopulations**

Characteristics	Young (n=68)	Old (n=154)
M:F	7.5:1	2.7:1
HBsAg-positive	28 (n=36)	38 (n=90)
anti-HBc-positive	22 (n=24)	62 (n=74)
HBeAg-positive	2 (n=17)	3 (n=47)
HBsAg-negative/anti-HBc-positive	4 (n=23)	34 (n=71)
anti-HCV-positive	0 (n=15)	3 (n=33)
Alcoholic-beverage drinking	53 (n=68)	95 (n=154)
Smoking	28 (n=68)	72 (n=154)
Cirrhosis	23 (n=68)	53 (n=154)

Comparison of the patients according to age showed that the younger patients had a higher male-female ratio of 7.5:1 than the older patients (M:F::2.7:1). A greater proportion of the young patients had chronic hepatitis B (78% vs 42%) while more patients in the old group had past hepatitis B (48% vs 17%). The three patients who had anti-HCV were all older than 50 years. More alcoholic beverage drinkers were found in the young group (30% vs 24%) while the number of smokers was slightly higher in the old group (46% vs 41%). The presence of cirrhosis was equal between the two groups.

**Table II. Comparison Between the Male and Female Subpopulations**

Characteristics	Male (n=172)	Female (n=50)
Age range in years (mean age)	29-86 (53.75)	32-83 (59.22)
HBsAg-positive	55 (n=103)	11 (n=23)
anti-HBc-positive	71 (n=81)	13 (n=17)
HBeAg-positive	5 (n=53)	2 (n=11)
HBsAg-negative/anti-HBc-positive	32 (n=78)	6 (n=16)
anti-HCV-positive	3 (n=38)	0 (n=10)
Alcoholic-beverage drinking	140 (n=172)	8 (n=50)
Smoking	91 (n=172)	9 (n=50)
Cirrhosis	65 (n=172)	12 (n=50)

Males outnumbered females with a sex ratio of 3.5:1. Table II shows the differences between the male and female patients in our population. The female patients were older than the males with mean age of 59 years versus 54 years, respectively. The male patients had a greater proportion with positive HBsAg (53% vs 48%), positive anti-HBc (88% vs 76%), past hepatitis B (41% vs 38%), positive anti-HCV (7.8% vs 0%), alcoholic beverage drinkers (81% vs 16%) and smokers (53% vs 22%). The presence of cirrhosis was also more prevalent among males (38% vs 22%).

### Chief Complaint

Chief complaints of the patients on admission are presented in Table III. The most common presenting complaint was abdominal pain, which was the reason for consultation of 57.7%. The second most frequent complaint is a palpable abdominal mass (17.6%). Patients rarely presented with ascites (1.4%) or encephalopathy (1%). Only 1 patient was asymptomatic on admission (0.5%).

**Table III. Distribution of Patients According to Chief Complaint**

Chief Complaint	Frequency	Percentage (%)
abdominal enlargement	12	5.4
abdominal mass	39	17.6
abdominal pain	128	57.7
ascites	3	1.4
asymptomatic	1	.5
cough	2	.9
decreased sensorium	2	1
diarrhea	1	.5
dysphagia	1	.5
dyspnea	2	.9
gen body weakness	11	5.0
generalized edema	1	.5
hematemesis	4	1.8
jaundice	13	5.9
vomiting	2	.9
Total	222	100.0

### Hepatitis Profile

The availability of a complete hepatitis profile for the patients was variable. Hepatitis B surface antigen (HBsAg) status was only available for 126 patients. Sixty six patients (52.3%) were HBsAg-positive while 60 patients (47.6%) were HBsAg-negative patients. HBeAg, a measure of viral replication and high infectivity, was only positive in seven out of 64 patients (10.9%) with available data. Among the HBsAg-reactive patients, only five patients were HBeAg-positive (12%). However, we should note that 34 patients had no available data on HBeAg status. Overall, there were 66 patients (52.3%) with chronic hepatitis B and 38 patients (40%) with past hepatitis B among those with available test results.

**Table IV. Comparison Between the HBsAg-Positive and HBsAg-Negative Subpopulations**

Characteristics	HBsAg-positive (n=60)	HBsAg-negative (n=60)
Age range in years (mean age)	29-74 (50.65)	32-83 (59.28)
anti-HBc-positive	44 (n=44)	38 (n=50)
HBeAg-positive	5 (n=32)	2 (n=32)
anti-HCV-reactive	1 (n=24)	2 (n=22)
Alcoholic-beverage drinking	46 (n=66)	47 (n=60)
Smoking	25 (n=66)	42 (n=60)
Cirrhosis	31 (n=66)	26 (n=60)
Diabetes Mellitus	8 (n=66)	12 (n=60)

Table IV shows the features of HBsAg-positive and HBsAg-negative patients. The HBsAg-negative patients were older (mean 59 years, range 32-83 years) than the HBsAg-positive patients (mean 50 years, range 29-74 years). Majority (63%) of the HBsAg-negative patients were anti-HBc-positive. Another dissimilarity of HBsAg-positive and HBsAg-negative patients was the higher proportion of alcoholic-beverage drinkers (78% vs 69.6%) and smokers (70% vs 38%) in the HBsAg-negative group. Both HBsAg-positive patients (47%) and HBsAg-negative patients (43%) had cirrhosis in less than half of patients. More diabetics were seen in the HBsAg-negative group (20%) than in the HBsAg-positive group (12%).

On the other hand, Hepatitis C infection was examined less frequently. Only 48 patients (21%) were examined for hepatitis C infection. Of these patients, only three (6.2%) were anti-HCV-positive. These three patients were older than 50 years. One of these anti-HCV-positive patients had concomitant chronic hepatitis B infection while another patient had cirrhosis. This cirrhotic patient was a medical doctor, diabetic, heavy alcoholic drinker and smoker.

#### Alcohol and Smoking

Two-thirds of the population had a history of alcoholic ingestion. Moreover, non-alcoholic beverage drinkers, occasional and heavy alcoholic beverage drinkers were almost equal in number. Most alcoholic beverage-drinkers were also smokers (61.5%). However, smokers comprised less than half of the population (45.5%).

#### Cirrhosis

**Table V. Comparison Between the Cirrhotic and Noncirrhotic Subpopulations**

Characteristics	Cirrhotic (n=76)	Noncirrhotic (n=146)
Age range in years (mean age)	29-86 (54.26)	29-83 (55.36)
HBsAg-reactive	31 (n=57)	35 (n=69)
anti-HBc-reactive	40 (n=48)	44 (n=50)
HBeAg-positive	2 (n=34)	5 (n=30)
HBsAg-negative/anti-HBc-positive	17 (n=44)	21 (n=50)
anti-HCV-reactive	1 (n=22)	2 (n=26)
Alcoholic-beverage drinking	57 (n=76)	91 (n=146)
Smoking	39 (n=76)	61 (n=146)
Diabetes Mellitus	14 (n=76)	16 (n=146)
Ascites	22 (n=68)	47 (n=154)
Encephalopathy	5 (n=76)	7 (n=146)
Total bilirubin >3mg/dL	16 (n=40)	21 (n=64)
Albumin <3g/dL	36 (n=53)	45 (n=80)
Platelet count <150,000	8 (n=52)	8 (n=93)
INR>1.6	6 (n=64)	14 (n=121)
AST >37 U/L	45 (n=48)	75 (n=84)
ALT >65 U/L	33 (n=60)	54 (n=96)
BCLC A/B/C/D	0/0/70/6	0/1/125/20

Approximately one-third had cirrhosis in the patient population (Table V). Majority of the patients with cirrhosis (69.7%) and without cirrhosis (69.2%) were older than 50 years. The mean age in the cirrhotic and noncirrhotic group was almost the same (54 and 55 years, respectively). The proportion of HBsAg-positive patients was the slightly higher in the cirrhotic (54%) than the noncirrhotic subset (50%). In contrast, more noncirrhotic patients (16.6%) had positive HBeAg status than cirrhotics (5.8%). The number of patients with past hepatitis B was slightly greater in the noncirrhotic group (42% vs 35%). Fewer patients had a history of alcoholic beverage drinking in the noncirrhotic group (62% vs 75%). More smokers were found among patients with cirrhosis (51%) than in those without cirrhosis (42%). Diabetes mellitus was observed in 18% of patients with cirrhosis and 11% of patients without cirrhosis. Notable differences in the laboratory exams included greater prevalence of elevated aspartate aminotransferase (94% vs 89%) and hyperbilirubinemia (40% vs 33%) among the cirrhotic patients.

#### Comorbidities

Most patients (68%) had no confounding illness. The most common comorbidity was hypertension, occurring in 14% of the study population. This was followed by diabetes mellitus with 13.5% prevalence in our study population. Other comorbidities noted were pulmonary tuberculosis (2.3%), bronchial asthma (2.3%), breast cancer (0.9%) and chronic kidney disease.

#### Laboratory Exams

Of 105 patients with available data bilirubin levels, thirty three (31.4%) had elevated levels. Eighty one of 131 patients with available results had hypoalbuminemia. Majority had normal protime (77%) and platelet count (58%) results. Measures of liver damage were increased in our patients. One hundred twenty of 132 (91%) had elevated aspartate aminotransferase and 88 of 156 (56.4%) had elevated alanine aminotransferase values.

#### Staging and Treatment

On staging by Barcelona Clinic Liver Cancer Classification, 87.8% were in the advanced stage and 11.7% were terminal stage.

Eighty percent of patients did not undergo any intervention for their condition. The most common modalities employed were resection of the hepatic mass (done in 17 patients) and

transarterial chemoembolization (done in 16 patients). Other treatments implemented were chemotherapy, tamoxifen and alcohol injection. Different combinations of these were also applied in other patients.

## DISCUSSION

Majority of our patients were older than 50 years old. This is in contrast to the findings of the two Filipino studies by Domingo (1981) and Lacuesta (1979) where most patients were younger than 50. The age distribution is more similar to recent studies abroad. Motola-Kuba<sup>11</sup> and Kim *et al*<sup>1</sup> reported a peak incidence among the 65-69 years of age and 6th decade of life, respectively. Wong and Tsai<sup>12</sup> described the mean age at 60 among Filipinos in their United States Study. This shift in the maximum age of occurrence from the young to the old may reflect differences in risk factors and utility of preventive measures such as the Hepatitis B vaccine which was initially implemented in 1980 in the Philippines. However, data on the use of Hepatitis B vaccine by patients in our study could not be obtained through our methodology. Important differences noted between the young and older patients in our study were the presence of chronic hepatitis B and past hepatitis B. The older patients had a greater proportion of past hepatitis B (HBsAg-negative/anti-HBc-positive) while the younger patients had chronic hepatitis B. This is similar to other report.<sup>1,13</sup> No patient in the young group had hepatitis C, but this can be because Hepatitis C was quite infrequent in our study population.

The male predominance of the population in this study is consistent with previous literature. The sex ratio of 3.5:1 is lower than the previously reported ratio of 5:1 to 6:1 by Domingo.<sup>8</sup> It is again more comparable to recent reports. A male-female ratio of 2-4:1 is described by Bosch, *et al*<sup>14</sup> in Mexico and a ratio of 1.6:1 by Chen, *et al*<sup>15</sup> in Taiwan. The reasons for the disparity between men and women are obscure, but they may include environmental factors such as a higher prevalence of persistent HBV or HCV infection, alcohol abuse and smoking in men than in women<sup>16</sup> as seen in our study population. Genetic and hormonal factors may also be important, as has been underscored in a recent study by Naugler, *et al*.<sup>17</sup> Men have an increased risk for HCC even when young while the risk increases with age in women. However, our study has a selection bias because only admitted patients were included in the study. Women generally seek consult more and HCC cases in women may have been diagnosed in the earlier stages and thus, may not necessitate admission.

Chronic hepatitis B is the strongest risk factor for HCC in Asians and Filipinos. Sixty six patients in our study had chronic hepatitis B. This may be an underestimate because of the unavailability of data for 96 patients. An important mode of transmission of chronic hepatitis B in the Philippines is through vertical transmission. In 1984, Tiangco-Torres *et al*. examined 533 pregnant and puerperal women and found that HBV exposure rate was 59.7% and HBsAg-positivity rate was 9.2%. Of the HBsAg positive women, 20.7% also had HBeAg and 62.1% had anti-HBe. Based on these data, it is estimated that 27,600 neonates from 1.5 million live births per year in this country will get maternally transmitted HBV infection.<sup>18</sup>

Hepatitis C infection is another well recognized risk factor for HCC. It is the most common chronic blood-borne infection and is endemic worldwide. Local data, however, showed varying rates of 17%, 36%, 12.9%, 35% and 11% among pediatric patients with chronic liver disease, hemodialysis, homosexuals, parenteral drug users and blood donors, respectively.<sup>3</sup> Mappala reported a prevalence rate of 8.8% among cirrhotics and 94.4% among cirrhotics with HCC.<sup>19</sup> HCV infection was detected uncommonly in our study population, appearing in only three patients. Mechanism of carcinogenesis of HCV remains unclear because HCV does not incorporate its genome into the host genetic material. Repeated cycles of regeneration and repair in cirrhosis may lead to mutant strains of the virus.<sup>6</sup> Only one of three anti-HCV-positive patients had cirrhosis in our population. But due to the small number of anti-HCV positives, it will be inaccurate to generalize that HCV does not lead commonly to cirrhosis in HCC patients.

Cirrhosis is a strong risk factor for HCC, irrespective of the etiology. The annual risk of developing HCC among patients with cirrhosis is 1-6%.<sup>20</sup> However, almost two-thirds of our patients had no cirrhosis. In addition, the difference between the cirrhotics and noncirrhotics based on HBsAg-positivity was not large (54% vs 50%). This is probably because the pathogenesis of HBV infection leading to HCC does not require the development of cirrhosis. Chiesa found an odds ratio of 17.6 and 20.3 for HBsAg-carriers in the presence and absence of cirrhosis, respectively.<sup>21</sup> It has been well established that integrated HBV DNA may account for the hepatocarcinogenesis in chronic HBV carriers and in the presence of HBeAg, the surrogate marker for the presence of HBV DNA, HCC is seen more frequently among HBsAg-carriers. In a study by Yang, the relative risk of hepatocellular carcinoma was 9.6

(95% confidence interval, 6.0 to 15.2) among men who were positive for HBsAg alone and 60.2 (95% confidence interval, 5.5 to 102.1) among those who were positive for both HBsAg and HBeAg, as compared with men who were negative for both.<sup>22</sup> We regret that HBV DNA levels were not documented in our patients but fortunately, HBeAg was tested. A higher proportion of patients were positive for HBeAg in the noncirrhotic group compared to the cirrhotic group, accounting for some of the HCC cases.

However, HBeAg was still quite uncommon in our patients, occurring in only 12% of those tested. This is comparable to Chen, *et al's* study in 2006.<sup>15</sup> They found that there was a dose-response relationship between cumulative hepatocellular carcinoma incidence and serum HBV DNA level for a subcohort who were seronegative for HBeAg, had a normal ALT level, and did not have liver cirrhosis, which included most participants (80%). Most participants seronegative for HBeAg (72.0%) still had a detectable serum HBV DNA. This suggests that HBV DNA levels should be determined in patients with HBsAg regardless of HBeAg status and presence or absence of cirrhosis because they may be at risk for HCC depending on HBV DNA levels.

A notable variation between the cirrhotic and noncirrhotic group is the presence of antibody against the hepatitis B core antigen in HBsAg-negative patients. More patients with noncirrhotic livers had positive anti-HBc in the subset of HBsAg-negative patients (previous hepatitis B infection). Previous hepatitis B infection is a less well known risk factor for HCC. When Uetake studied 91 patients with HBsAg-negative and anti-HCV-negative alcoholic cirrhosis, he found that the occurrence rate of HCC in patients with anti-HBc and without anti-HBc were 15.6% and 2.9%, respectively, at the 5th year of observation.<sup>23</sup> In 2002, Yano compared HCC patients with past hepatitis B to HCC patients with chronic hepatitis B. A significant difference between the two groups was that patients with past hepatitis B were older (72.1 years old) at diagnosis than patients with chronic hepatitis B (56.2 years old).<sup>24</sup> This is parallel to our findings. These HBsAg-negative/anti-HBc-positive patients either had acute hepatitis B or had delayed natural clearance of HBsAg among chronic HBV carriers. It is also possible that deletion, mutation, or rearrangement in the HBV surface gene may cause the serum HBsAg to become seronegative. However, it has been generally accepted that chronic HBV carriers are usually infected in infancy or early childhood as a result of vertical or horizontal spread, and HBsAg persists in carriers for a long time. Conversely, those infected with HBV during adulthood

usually clear HBsAg from their sera. This explains the older age of development of HCC in patients who clear the HBsAg from their sera. Thus, the risk of HCC persists in long-term HBV carriers from Asia who lose HBsAg, and these patients should continue to undergo surveillance.<sup>25</sup>

Among our patients with and without cirrhosis, an increased prevalence of diabetes mellitus (DM) was noted. It was observed in 13.5% of the HCC patients: in 18% of the patients with cirrhosis and in 11% of the patients without cirrhosis. Furthermore, DM was observed in 20% of HBsAg-negative patients and in 12% of HBsAg-positive patients. These rates are more than double the national prevalence of DM of 4.0%.<sup>26</sup> Diabetes Mellitus is an implicated risk factor in HCC recently. Subjects with a history of diabetes had an OR of 2.7 (95% CI, 1.6–4.3) for HCC compared with nondiabetic subjects in a United States study. In this study, a synergistic interaction on HCC risk was observed between heavy alcohol consumption and diabetes (OR =4.2; 95% CI, 2.6–5.8), and between diabetes and viral hepatitis (OR =4.8; 95% CI, 2.7–6.9).<sup>27</sup> A number of possible mechanisms might explain this association. First, since most case subjects with diabetes are non-insulin dependent and are characterized by hyperinsulinemia, insulin or its precursors may interact with liver cells to stimulate mitogenesis or carcinogenesis. The substantial reduction in IGF-I and IGFBP-3 levels among diabetic, as compared with nondiabetic, HCC case subjects in a study by Lagiou, *et al* may reflect an intimate link between pancreatic and hepatocellular processes, the nature of which are poorly understood.<sup>28</sup> Alternatively, the metabolic effects of diabetes may increase the risk of HCC through nonalcoholic steatohepatitis and cryptogenic cirrhosis.

Nonalcoholic steatohepatitis may also be a risk factor for HCC. Marrero suggested that the underlying liver disease in 13% of their patients with HCC may be due to nonalcoholic steatohepatitis.<sup>29</sup> Hypertension, a component of Metabolic Syndrome linked to nonalcoholic steatohepatitis, was fairly common among our HCC patients. But this may be reflective of the prevalence of hypertension in the Philippines which is around 17%.<sup>26</sup> Other components of the metabolic syndrome such as body mass index, waist to hip ratio and dyslipidemia should be explored if related to hepatocellular carcinoma among Filipinos.

Most patients were symptomatic on admission. Thus, by the Barcelona Clinic Liver Cancer (BCLC)

Classification, patients fell under the stages advanced (Stage C) and terminal (Stage D). Only one patient was classified as intermediate stage, because he was the only patient who was asymptomatic and was diagnosed by screening. There is no universally accepted staging system for HCC but recently, Marrero, *et al.*<sup>30</sup> and Grieco, *et al* have compared all systems available and validated the BCLC system in the United States and in Italy, respectively.<sup>31</sup> The Barcelona-Clinic- Liver-Cancer (BCLC) staging system was developed based on the combination of data from several independent studies representing different disease stages and/or treatment modalities. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms. The main advantage of the BCLC staging system is that it links staging with treatment modalities and with an estimation of life expectancy that is based on published response rates to the various treatments.<sup>10</sup> Based on this, available modalities for advanced stage patients are chemoembolization and new therapies in the setting of randomized controlled trials. Prognoses of these patients are already known. Patients at intermediate stages (asymptomatic patients, no invasive pattern; BCLC stage B) showed a 1-, 2-, and 3-year survival rate of 80%, 65%, and 50%, respectively, while those with advanced stages (either symptomatic or invasive pattern, or both; BCLC stage C) demonstrated survival rates of 29%, 16%, and 8%, respectively. Patients at terminal stages bear a poor prognosis, with less than a 6-month life expectancy and no survival benefit from treatment. They deserve only symptomatic treatment.<sup>31</sup> But then again, we recognize that our study population is skewed because of an admission rate bias inherent in our inclusion criteria.

### Limitations

Our study's limitations stem primarily from our methodology. Since the data collection was done through chart review, completeness of data was not controlled by the investigators. Thus, pertinent data such as occupation, exposures to the blood-borne viruses Hepatitis B and C, immunization history, family history, full hepatitis panel, height, weight and lipid profile were not obtained. It would have been more comprehensive to incorporate data of patients seen in the clinics. We could have seen patients that belonged to earlier stages of the disease unlike our inpatients.

## CONCLUSION

The hepatocellular carcinoma patients admitted in the Philippine General Hospital from January 2001 to December 2006 were mostly males and older than 50 years. Patients frequently had chronic hepatitis B infection or previous hepatitis B infection and a history of alcohol drinking but their livers were noncirrhotic. The positivity rate of HBeAg is low. Diabetes mellitus was increased among the HCC patients, especially in patients with negative HBsAg. Most patients belonged to the late stages of the disease, limiting treatment options. This study adds supporting evidence on the importance of vaccination against hepatitis B and avoidance of alcohol abuse. More importantly, it implies that diabetes should be explored as a significant risk factor for HCC among Filipinos. It suggests screening patients at risk so early stage disease can be detected.

A prospective study is recommended to include complete data on symptoms, length of survival and risk factors, especially risk factors that are already established such as hepatitis B and alcohol abuse, and risk factors that are not as well known like diabetes.

## APPENDIX 1

### DATA COLLECTION TOOL

1. Age/Sex
2. Date of Hospital Confinement/Consult
3. Occupation
4. Chief Complaint
5. Presence/Absence of the following:
  - a. HBsAg
  - b. HBeAg
  - c. Anti-HBc
  - d. Anti-HCV
  - e. alcoholic history
  - f. smoking history
  - g. cirrhosis of any cause
7. AST
8. ALT
9. albumin
10. PT
11. platelet count
12. bilirubin
13. hepatic encephalopathy
14. ascites
15.  $\alpha$ -etoprotein
16. comorbidities (DM, HPN, Dyslipidemia)
17. Child-Pugh Score
18. Barcelona Clinic Liver Cancer (BCLC) Stage
19. Treatment

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**MEDICAL AUDIT**

*1<sup>st</sup>, 2<sup>nd</sup> & 4<sup>th</sup> Thursdays, 9 am,  
PGH Guazon Hall, where specific issues about mortalities are addressed;*

**MULTI-DISCIPLINARY CONFERENCE**

*3<sup>rd</sup> Thursdays, 9 am,  
PGH Guazon Hall, where interesting cases and management dilemmas are presented;*

**MEDICAL GRAND ROUNDS**

*4<sup>th</sup> Thursdays, 10 am,  
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