ORIGINAL ARTICLE

Epidemiology and clinical features of patients with hepatocellular carcinoma at a tertiary hospital in Jeddah

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Abstract

Background: This study describes the epidemiology and clinical features of hepatocellular carcinoma (HCC), and it investigates any association between Child-Pugh's classification and HCC.

Materials and Methods: A retrospective chart review was performed for HCC cases diagnosed between 2008 and 2014 at King Abdulaziz University Hospital. We documented the age at cancer diagnosis, gender, occupation, ethnic origin, HCC etiology, Child-Pugh scores, tumor characteristics, alpha-fetoprotein (AFP), and alkaline phosphatase (ALP) levels at diagnosis, and treatment administered. The Chi-square test was used to determine differences between categorical variables.

Results: We included 128 patients. Hepatitis B and C viral infections were documented in 24.2% and 33.6% of the patients, respectively. Patients with tumors >5 cm were more likely to have Child's Class C disease, whereas those with tumors ≤2 cm were more likely to have Child's Class A ($P < 0.001$). Similarly, patients with bilobular or metastatic tumors were more likely to have Child's Class C disease ($P = 0.001$ and 0.002, respectively). No difference in Child-Pugh score was found between patients with single or multiple tumors ($P = 0.480$). Furthermore, patients who were both hepatitis B and C positive were more likely to have Child's Class C disease ($P = 0.018$). Likewise, those who had abnormal AFP and ALP levels ≥1000 ng/mL were more likely to have Child-Pugh's Class C liver disease ($P = 0.021$ in both cases).

Conclusion: Hepatitis C and B infections were the main risk factors associated with HCC.

Key words: Child-Pugh criteria, cirrhosis, epidemiology, hepatitis, hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, is the third highest cause of cancer deaths worldwide.[1] It is the fifth most common type of cancer in men and the seventh in women.[2] A recent report indicates a sharp increase in the incidence of HCC over the last decade in Gulf countries.[3] The sudden increase in HCC is attributed to a rise in the incidence of infection from the hepatitis C virus (HCV), escalating obesity, and an increase of diabetes mellitus cases.[3]

In Saudi Arabia (SA), liver cancer is unevenly distributed among gender and age. The uneven distribution is evidenced by the fact that men have approximately 3 times the risk of developing liver cancer compared to women. The risk of a patient developing HCC also increases with age. According to a previous hospital-based study,[4] approximately 80% of primary liver cancer cases seen in SA are the result of underlying chronic

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hepatitis B and C viral infections.[5] Recent findings have demonstrated a decrease in the overall prevalence of viral hepatitis; however, the substantial population of infected patients is at high risk of developing HCC.[6] Furthermore, another study reported that the incidence of HCC is expected to rise dramatically in SA in the next three decades.[7]

A small number of hospital-based studies conducted in SA have assessed the clinical and epidemiologic characteristics of patients with HCC.[5,8,9] According to multiple sources, HCC has a higher incidence in men.[2,5] Most patients present to the hospital with comorbid diagnoses of advanced cancer and chronic liver disease.[5] This study describes the epidemiologic and clinical features of HCC as well as investigates any association between Child-Pugh's classification and HCC.

Materials and Methods

This was a retrospective chart review of the electronic medical records of cancer cases diagnosed between 2008 and 2014 at King Abdulaziz University Hospital (KAUH), a tertiary hospital in Jeddah, Western Province, with a bed capacity of 845 beds and serves the main population of Jeddah.

Adult patients were included by utilizing criteria for HCC from the International Classification for Disease, 10th edition.[10] All types of secondary liver cancer were excluded from analysis. The procedures followed were in accordance with the ethical standards of the Biomedical Ethics Committee of KAUH and the Helsinki Declaration of 1975. Permission to conduct this study was granted by the Biomedical Ethics Committee of KAUH (reference number, 57–15 year, 2015).

After identifying the cases that fulfilled the inclusion criteria, we then collected demographic and clinical data such as the patient's age at the time of HCC diagnosis, gender, occupation, ethnic origin, history of alcohol consumption, etiology of liver disease, and the Child-Pugh score. Other pertinent information gathered involved data on tumor characteristics (distribution, size, stage, and the presence of cirrhosis), alpha-fetoprotein (AFP), and alkaline phosphatase (ALP) levels at diagnosis, as well as treatment administered.

Statistical analysis

The data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 16. Descriptive statistics were performed for all variables. The Chi-square test was used to determine differences between categorical variables. Differences were considered statistically significant at the 0.05 level. Results are expressed as frequency (percent).

Results

We included 128 patients. Men comprised approximately three-quarters of the sample [Table 1]. Most patients were

Table 1: Demographic characteristics of the patients

Variables	Frequency (%)
Gender	
Male	99 (77.3)
Age (years)	
≥40	121 (94.5)
Social class	
High social class	2 (1.6)
Average social class	12 (9.4)
Low social class	73 (57.0)
Unknown	41 (32.0)
Nationality	
Saudi	49 (38.3)
Egyptian	4 (3.1)
Sudanese	8 (6.3)
Yemeni	41 (32.0)
Others	26 (20.3)
Alcohol consumption	
No	122 (95.3)

Table 2: Clinical and paraclinical characteristics of the patients

Variables	Frequency (%)
Symptoms	
Abdominal pain	24 (18.8)
Abdominal distension	1 (0.8)
Jaundice	1 (0.8)
Weight loss	6 (4.7)
Fever	1 (0.8)
Multiple	87 (68.0)
None	2 (1.6)
Signs	
Abdominal mass	1 (0.8)
Hepatomegaly	14 (10.9)
Ascites	8 (6.3)
Jaundice	4 (3.1)
Multiple	92 (71.9)
None	9 (7.0)
Bilirubin (μmol/L)	
<34	67 (52.3)
35-50	14 (10.9)
>50	47 (36.7)
ALP (μmol/L)	
Abnormal	101 (78.9)
Liver enzymes	
Abnormal	111 (86.7)
Albumin (g/L)	
>35	22 (17.2)
28-35	48 (37.5)
<28	58 (45.3)

Contd...

Table 2: Contd...

Variables	Frequency (%)
AFP level (ng/mL)	
<5	32 (25.0)
5-400	38 (29.7)
400-999	6 (4.7)
≥1000	52 (40.6)
Disease duration	
≤3 months	38 (29.7)
3-6 months	2 (1.6)
6 months-1 year	4 (3.1)
1-2 years	7 (5.5)
2-5 years	4 (3.1)
>5 years	2 (1.6)
Unknown	71 (55.5)
Child-Pugh class	
A	29 (22.7)
B	51 (39.8)
C	45 (35.2)
Treatment	
Surgical resection/transplant	2 (1.6)
Percutaneous ethanol injection	1 (0.8)
Radiofrequency ablation	3 (2.3)
Chemoembolization	9 (7.0)
Palliation	87 (68.0)
Multiple	18 (14.1)
No identified cause	8 (6.3)
Survival status	
Alive	2 (1.6)
Dead	63 (49.2)
Unknown	63 (49.2)

Reference values: AFP (<10 ng/mL), albumin (35-50 g/L), ALP (30-100 μmol), bilirubin (3-17 μmol/L). AFP=Alpha-fetoprotein; ALP=Alkaline phosphatase

Table 3: Etiology of liver cancer and tumor characteristics among the patients

Variables	Frequency (%)
Cause	
HBV	31 (24.2)
HCV	43 (33.6)
HCV + HBC	4 (3.1)
Others	49 (38.3)
No identified cause	1 (0.8)
Cirrhosis	
Yes	80 (62.5)
No	51 (39.8)
Tumor number	
Single	51 (39.8)
Multiple	77 (60.2)
Tumor distribution	
Unilobular	49 (38.3)
Bilobular	79 (61.7)
Tumor size (cm)	
≤2	63 (49.2)
>5	65 (50.8)
Tumor stage	
Localized	36 (28.1)
Loco-regional	35 (27.3)
Metastatic	57 (44.6)

HBV=Hepatitis B virus; HCV=Hepatitis C virus

Table 4: Tumor characteristics by Child-Pugh class*

Variables	Child-Pugh class			*P*
	A	B	C	
Tumor number				
Single	13 (25.5)	27 (52.9)	11 (21.6)	0.480
Multiple	19 (24.7)	26 (33.8)	32 (41.5)	
Tumor distribution				
Unilobular	13 (26.5)	15 (30.6)	21 (42.9)	0.001
Bilobular	17 (21.5)	24 (30.4)	38 (48.1)	
Tumor size (cm)				
≤2	22 (34.9)	19 (30.2)	22 (34.9)	<0.001
>5	9 (13.8)	31 (47.7)	25 (38.5)	
Tumor stage				
Localized	17 (47.2)	15 (41.7)	4 (11.1)	0.002
Locoregional	17 (48.6)	18 (51.4)	0 (0.0)	
Metastatic	17 (29.8)	22 (38.6)	18 (31.6)	

*Data are presented as frequency (%) unless otherwise specified

of a low socioeconomic status; nonsaudis accounted for two-thirds of the sample. Less than 5% of the sample had a documented history of alcohol consumption. Abdominal pain was the chief complaint in 18.8% of the patients. In 68.0% of the cases, patients presented with multiple complaints.

AFP levels were normal in 25.0% of the sample, whereas 40.6% had AFP levels ≥1000 ng/mL. Cirrhosis was diagnosed in 60.2% of the patients, and approximately two-fifths had Child's Class B disease [Table 2]; a smaller proportion had Child's Class A (22.7%) or Class C cirrhosis (35.2%). Palliation was offered to 68.0% of the patients while 14.1% underwent multiple therapies. Less than 2% of the patients survived to 5 years. Disease duration ranged from ≤3 months to >5 years, with 29.7% of the patients having a duration of ≤3 months.

The most common risk factors included HBV and HCV infections, documented in 24.2% and 33.6% of the patients, respectively. More than half of the patients (60.2%) had multiple liver tumors, and approximately 50.8% of the cases had tumors >5 cm in diameter. Patients with unilobular lesions comprised about two-fifths of the sample [Table 3]. Metastatic disease was documented in 44.6% of the patients; 28.1% and 27.3% had localized and locoregional disease, respectively.

Patients with tumors >5 cm were more likely to have Child's Class C disease, whereas those with tumors ≤2 cm were more likely to have Child's Class A [$P < 0.001$; Table 4]. Similarly, patients with bilobular or metastatic tumors were

Table 5: Etiology and laboratory findings categorized by child's class*

Variables	Child class			P
	A	B	C	
Cause				
HBV	10 (31.0)	10 (31.0)	11 (35.5)	0.018
HCV	6 (14.0)	24 (55.8)	13 (30.2)	
HBV + HCV	1 (25.0)	0 (0.0)	3 (75.0)	
Others	13 (26.5)	18 (36.7)	18 (36.7)	
No identified cause	0 (0.0)	0 (0.0)	1 (100.0)	
ALP (μmol/L)				
Normal	12 (44.4)	9 (33.3)	6 (22.2)	0.021
Abnormal	17 (16.8)	42 (41.6)	39 (38.6)	
AFP level (ng/mL)				
<5	13 (40.6)	11 (34.4)	8 (25.0)	0.021
5-400	5 (13.2)	17 (44.7)	16 (42.1)	
400-999	2 (33.3)	4 (66.7)	0 (0.0)	
≥1000	9 (17.3)	19 (36.5)	24 (46.2)	

*Data are presented as frequency (%) unless otherwise specified. Reference values: AFP (<10 ng/mL), ALP (30-100 μmol). AFP=Alpha-fetoprotein; ALP=Alkaline phosphatase; HBV=Hepatitis B virus; HCV=Hepatitis C virus

more likely to have Child's Class C disease ($P = 0.001$ and 0.002, respectively). No difference in Child-Pugh score was found between patients with single or multiple tumors ($P = 0.480$).

Table 5 shows that patients who were both HBV and HCV positive were more likely to have Child's Class C disease ($P = 0.018$). Likewise, those who had abnormal ALP levels, and AFP levels ≥ 1000 ng/mL were more likely to have Child-Pugh's Class C liver disease ($P = 0.021$ in both cases).

Discussion

The present work is a 7-year analysis of HCC cases at KAUH. Our analysis revealed that HCV and HBV infection were the most common risk factors, similar to another report that investigated the presentation of HCC at our institution.[9] In patients with HCC, it is thought that carcinogenesis results from chronic hepatitis and cirrhosis caused by HBV and HCV.[11] Unlike HBV, HCV is a single-stranded RNA virus that does not integrate into the genome of the host. There is currently no evidence to substantiate that HCV has oncogenic properties; however, HCC has been reported in rare cases of noncirrhotic HCV infection, implying that a direct oncogenic effect cannot be totally excluded.[12] Interestingly, about one-third of the patients in our study developed HCC in the absence of any clinical evidence of cirrhosis. While other etiologic factors may be responsible for HCC in our patients, we believe that further investigations may be necessary to explain the occurrence of HCC among noncirrhotic patients.

According to a previous study conducted at KAUH,[9] HCV-associated cirrhosis was the most frequent cause of HCC, followed by HBV-associated cirrhosis. Similar findings have been reported in other hospital-based studies conducted in SA,[5,8] contrary to the fact that HBV-associated disease was previously reported as the predominant cause of HCC in SA.[13] The decrease in HBV-associated HCC has been linked to the Saudi Ministry of Health's implementation of HBV vaccination programs approximately three decades ago.[14]

As previously stated, men comprised nearly three-quarters of our sample. This finding coincides with the report of other authors[9,11] who found that HCC showed a strong affinity for male gender, being 4 times more common in men as compared to women. While this finding may, in part, be due to the cumulative result of other associated factors (the higher incidence of cirrhosis and higher frequency of smoking and alcohol intake in men), experimental models[15,16] suggested that sex hormones and/or hormone receptors may be responsible.

Less than 5% of our patients reported a history of alcohol consumption. Other studies conducted among HCC patients in SA[5,8,9] did not mention the role of alcohol as a potential risk factor for liver disease. Relevant to the fact that importation and distribution of alcohol are banned in SA, alcohol consumption is not currently deemed a public health problem. Chronic alcohol abuse often complicates HCC, and there is evidence that alcohol may have a cocarcinogenic role in the presence of other agents such as tobacco, HBV, HCV, and hepatotoxins.[11]

Cirrhosis, the most common condition associated with HCC, was diagnosed in over half of the patients in the current study. Approximately two-fifths had Child's Class B disease, a smaller proportion had Child's Class A (22.7%) or Class C disease (35.2%). Furthermore, patients with tumors >5 cm were more likely to have Child's Class C disease, whereas those with tumors ≤2 cm were more likely to have Child's Class A. Previous reports[17,18] state that the relationship between tumor size and Child-Pugh classification varies, and staging systems incorporate tumor size and Child-Pugh classification to link stage with prognosis or a treatment algorithm. The Cancer of the Liver Italian Program Criteria, for example, incorporate the Child-Pugh criteria with tumor characteristics: The features of the tumor, whether unifocal, multifocal, or diffuse, whether there is vascular involvement or elevated AFP levels.[19]

In the current report, HBV and HCV positive patients were more likely to have Child's Class C disease, a finding that we believe is related to the natural history and cytopathogenic effect of the hepatitis viruses on hepatocytes.[20] We also cannot exclude the fact that patients with viral hepatitis typically present to our institution late in the disease process. Most are asymptomatic, and sometimes the infection is detected incidentally during screening or

blood donation.[21] We also determined that patients with abnormal ALP and AFP levels ≥1000 ng/mL were more likely to have Child-Pugh's Class C liver disease. Previous investigations[22-24] of patients with HCC demonstrated that preoperative serum ALP and AFP levels predicted their outcome. While the role of AFP as a diagnostic and prognostic factor is controversial,[25] some researchers reported that it can be nonspecifically high in patients with cirrhosis and viral hepatitis.[26] As a result, AFP levels can vary in patients with HCC based on the etiology of underlying hepatic disease.

This retrospective analysis has all the limitations inherent in retrospective studies. We did not control for confounding factors such as age, family history, alcohol consumption, smoking, and exposure to hepatotoxins, which have been reported as risk factors for HCC. Due to insufficient data regarding risk factors and lifestyle, it may be beneficial to conduct a cross-sectional study to explore clinical and epidemiological features of HCC at our institution.

Conclusion

Hepatitis C and B viral infections are the main risk factors associated with HCC among our patients. A large amount of information has been accumulated on the clinical and epidemiological aspects of HBV and HCV infections in our context, but more research should be conducted to explore risk and prognostic factors among patients with HCC. Our finding of a relevant association between Child-Pugh score and HCC further supports the fact that a system incorporating the Child-Pugh's criteria can be useful in staging HCC.

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Conflicts of interest
There are no conflicts of interest.

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