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Original Research Article

The prevalence and associated factors of viral hepatitis and cryptogenic related hepatocellular carcinoma at King Abdulaziz Medical city-Riyadh

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ABSTRACT

Background: Worldwide, viral hepatitis is the major risk factor for HCC with hepatitis B (HBV) being more than hepatitis C (HCV). Saudi Arabia is one of the endemic areas of viral hepatitis. Cryptogenic HCC is thought to arias from unknown causes of liver cancers. Thus, the purpose of this study was to find the prevalence of viral and cryptogenic HCC in King Abdulaziz Medical City-Riyadh (KAMC-R).
Methods: A retrospective chart review was performed for all HCC patients diagnosed between 2010 to 2017 at KAMC-R. Information regarding age, gender, comorbidity, alcohol consumption, serology tests, liver enzymes, body mass index, model for end-stage liver disease score, alpha-fetoprotein and Child-Turcotte-Pugh score were included. The Chi-square test was used to determine the differences between categorical data. A $p<0.05$ was considered statistically significant.
Results: Total of 294 patients with HCC charts were reviewed. HCV and HBV were found in 42.85% and 20.74% of the patients, respectively. Co-infection with HBV and HCV were reported in 1.7% whereas cryptogenic HCC was found in 32.65% of the patients. High BMI and DLP were noticeably higher in cryptogenic group ($p=0.045$ and $p=0.022$ respectively). Multiple lesions were noticed more in HCV group whereas single lesion was more in the cryptogenic group ($p=0.0343$). Also, large lesions (>5 cm) were remarkably found more in cryptogenic HCC whereas small lesions were more in HCV group ($p=0.006$).
Conclusions: Hepatitis C was the major risk factor associated with HCC, followed by Cryptogenic HCC. High BMI and DLP were common features of cryptogenic HCC.

Keywords: Hepatitis C, Hepatitis B, Cryptogenic, Hepatocellular carcinoma, HCC

INTRODUCTION

Liver complications related to end-stage liver disease are still the common causes of morbidity and mortality and leading indication for hospital admission in the most country, especially where viral hepatitis is still an endemic disease. The most dreaded complication is the development of hepatocellular carcinoma (HCC). HCC is the most common type of liver malignancies. Globally, HCC is the sixth most commonly occurring cancer in the world, and the second leading cause of cancer mortality.[1] The incidence worldwide is variable, but it remains huge burden in the developing countries. In Saudi Arabia, liver cancer accounts for 5.2% of all newly diagnosed cancers. HCC was the fourth most common cancer affecting males

and the ninth most common cancer affecting females with an age-standardized incidence rate of 4.8/100000 for males and 2.4/100000 for females.[2] HCC usually arises in the background of cirrhosis from different causes including alcoholism, viral hepatitis B, hepatitis C, hemochromatosis, Wilson disease, type 2 diabetes, and hemophilia. In a small subset of patients, HCC can occur without the background of cirrhosis.[3] Hepatitis C and hepatitis B are still the major risk factors leading to HCC. Hepatitis B infection can cause acute and chronic liver disease, and it is believed that it increases the risk of HCC by 100-fold in chronic inflammation and fibrosis. Thus, haptic cells proliferation and fibrosis altogether may lead to cirrhosis in the top of ccc DNA that get incorporated into the nucleus will lead to gene mutations. On the other hand, hepatitis C causes chronic liver disease and its increased risk of HCC is less compared to hepatitis B with similar mechanism.[4] KSA is one of the endemic areas of both hepatitis B and hepatitis C despite the recent decline.[5]

Cryptogenic hepatocellular carcinoma is thought to arise from non-known causes of HCC like viruses and alcohol. Nonalcoholic fatty liver disease (NAFLD) is one of the known causes of cryptogenic HCC. NAFLD can lead to liver cirrhosis which ultimately progresses to HCC. Some risk factors are associated with cryptogenic HCC like metabolic syndrome and older age.[6] Metabolic syndrome is common in Saudi Arabia with overall prevalence of 28.3% with a dominant male gender.[7] For that reason, we have done a retrospective analysis on patients diagnosed with hepatocellular carcinoma for the period from 2010 to 2017 to find the prevalence of viral and cryptogenic HCC.

METHODS

Participants

This is a retrospective chart review study of medical records of HCC patients diagnosed between the period of 2010 and 2017 at King Abdul-Aziz Medical City (KAMC) in Riyadh. All adult patients with HCC were included. Patients with poor documentations in their medical files or with secondary liver cancer were excluded from the analysis. The study was approved by KAIMRC and KAMC to review the medical records. The patient's privacy was retained, and all patients' identities were not published in the study.

Study tools

After identifying the included patients, we collected the data using a chart containing demographical data such as (age, gender, comorbidities, body mass index (BMI), and alcohol consumption) and clinical data such as (blood workup, Liver Enzymes, Model for End Stage Liver Disease (MELD) score, serum alpha-fetoprotein (AFP), presence of cirrhosis, Child-Turcotte-Pugh (CTP) score system and hepatitis marker.

Identifying HCC

The diagnosis of HCC was based if the dynamic imaging findings (CT with intravenous contrast or MRI only) of a hyper vascular solid liver mass with features characteristic for HCC were present in the setting of underlying risk factors. In the absence of underlying risk factors, the diagnosis of HCC was made with clearly elevated serum alpha-fetoprotein (>400 ng\ml) or with biopsy.

Identifying hepatitis B and C

The presence of hepatitis B surface antigen (HBsAg) and HCV antibody were set as the criterion for hepatitis B and C. Diagnosis of liver cirrhosis was made by ultrasonic liver cirrhosis plus hypersplenism, with biochemical or clinical sign of portal hypertension. Cryptogenic HCC was defined as HCC that is not related to alcohol, viral hepatitis or any other known etiology of liver diseases.

Statistical analysis

Descriptive statistics for categorical data were displayed as numbers and percentages and mean±Standard deviation (SD) or median±inter quartile range (IQR) for continuous data. The groups differences for categorical variables were assessed with Fisher's exact test or the Chi-square test and One-way analysis of variance (ANOVA) was used to compare the dissimilarities between groups for continuous variables. Kruskal-Wallis test was used to assess the difference among subgroups for data violated parametric test assumptions. A p value of <0.05 was considered statistically significant. A statistical analysis system version 9.4 was used for data analysis.

RESULTS

A total of 294 HCC patients who met the inclusion criteria were diagnosed between the period 2010 and 2017 at King Abdul-Aziz Medical City-Riyadh (KAMC-R). Out of 294 patients, there were 61 (20.74%) with HBV-associated HCC, 126 (42.85%) with HCV-associated HCC, 96 (32.65%) with Cryptogenic HCC, 6 (2%) with alcohol related HCC and 5 (1.7%) with hepatitis B/C co-infection related HCC. As shown in Table 1, out of the 294 patients, 73% were male and 28% female, with predominate male gender among the all groups (p=0.0003). The mean age of patients was found to be 67.1 years old, without significant differences among the groups (p=0.2550). According to BMI classification, most of the patients had high BMI 61% which was statistically significant among the Cryptogenic group (p=0.049). There were 48% diabetic and 46% hypertensive patients, without statistical significance among the groups. However, dyslipidemia (DLP) were present in 13% of the patient that was noticeably predominant among the cryptogenic group (p=0.022).

Table 1: Patients demographical and clinical characteristics.

Characteristic	Categories	Statistics	HBV	HCV	HBV+HCV	Cryptogenic	All	P value
Demographic								
Causes		N (%)	61 (20.74)	126 (42.85)	5 (1.7)	96 (32.65)	294	
Gender	Female	N (%)	11 (18)	52 (41.3)	1 (20.0)	17 (17.7)	81 (27.5)	0.0003
	Male		50 (82)	74 (58.7)	4 (80.0)	79 (82.3)	213 (72.5)	
Age (years)		Mean (SD)	65 (9.7)	67.3 (9.8)	64.6 (14.5)	67.3 (11.3)	67.1 (10.4)	0.2550
Body mass index (BMI)	Normal (<25)	N (%)	29 (47.5)	52 (41.3)	3 (60.0)	27 (28.1)	114 (38.8)	0.049
	High (≥25)		32 (52.5)	74 (58.7)	2 (40)	69 (71.9)	180 (61.2)	
Diabetes miletus	No	N (%)	36 (59)	66 (52.4)	4 (80)	43 (44.8)	152 (51.7)	0.1895
	Yes		25 (41)	60 (47.6)	1 (20)	53 (55.2)	142 (48.3)	
Hypertension	No	N (%)	38 (62.3)	67 (53.2)	4 (80.0)	47 (49.0)	158 (53.75)	0.2544
	Yes		23 (37.7)	59 (46.8)	1 (20.0)	49 (51.0	136 (46.25)	
Dyslipidemia	No	N (%)	56 (91.8)	117 (92.9)	5 (100)	77 (80.2)	255 (86.7)	0.022
	Yes		5 (8.2)	9 (7.1)	0 (0.0)	19 (19.8)	39 (13.3)	
Alcohol consumption	No	N (%)	61 (100)	126 (100)	5 (100)	96 (100)	288 (98)	-
	Yes		0 (0)	0 (0)	0 (0)	0 (0)	6 (2)	
Clinical								
MELD score At diagnosis		Median (IQR)	11 (7)	12 (9)	8 (11)	11 (7)	11 (8)	0.7416
ALP (U/L)		Median (IQR)	165.2 (100.4)	161.2 (93.3)	158.2 (40.7)	186.2 (129.8)	170.3 (107.8)	0.3639
ALT (U/L)		Median (IQR)	46.4 (35.3)	58.6 (51.7)	63.8 (27.9)	50.2 (40.8)	53.3 (44.9)	0.2717
AST (U/L)		Median (IQR)	59.6 (42.2)	77.7 (61)	110 (55)	66 (60.6)	70.5 (57.7)	0.0695
Creatinine (mg/L)		Median (IQR)	84.9 (82.1)	95.1 (117)	71.2 (8.7)	98.4 (86)	93.6 (99)	0.8071
GTP (U/L)		Median (IQR)	243 (204.2)	216.7 (193.8)	229 (206.2)	255.8 (257.8)	236 (219)	0.6659
Hbg (g/dl)		Mean (SD)	131.5 (24.4)	125.3 (27.7)	125.4 (30.7)	127 (23.6)	127 (25.7)	0.4901
INR		Mean (SD)	1.2 (0.3)	1.2 (0.5)	1.2 (0.3)	1.16 (0.2)	1.2 (0.4)	0.5938
Sodium (mEq/L)		Mean (SD)	136 (3.5)	135 (4.8)	135 (3.9)	134.9 (4.9)	135.3 (4.6)	0.4621
Platelets ($\times10^9$/L)		Median (IQR)	194.4 (113.5)	181.2 (154.4)	201 (125.7)	226.7 (135.7)	199.5 (140.7)	0.1220
WBC ($\times10^9$/L)		Mean (SD)	6.1 (2.4)	5.9 (2.6)	6.2 (1.6)	6.7 (2.2)	6.2 (2.4)	0.1004
AFP level (ng/mL)	<10	N (%)	32 (52.5)	44 (34.9)	0 (0.0)	55 (57.3)	133 (45.3)	0.0007
	10-399		19 (31.1)	58 (46.0)	4 (80.0)	18 (18.8)	99 (33.7)	
	400-1000		0 (0.0)	7 (5.6)	0 (0.0)	4 (4.2)	12 (4)	
	>1000		10 (16.4)	17 (13.5)	1 (20.0)	19 (19.8)	50 (17)	
Number of lesions	Single	N (%)	31 (50.8)	67 (53.1)	3 (60.0)	67 (69.8)	171 (58.1)	0.03438
	Two		25 (41)	37 (29.4)	2 (40.0)	17 (17.7)	83 (28.3)	
	Multiple		5 (8.2)	22 (17.5)	0 (0.0)	12 (12.5)	40 (13.6)	
Tumor size (cm)	<2	N (%)	9 (14.8)	50 (39.7)	1 (20)	22 (23)	82 (27.9)	0.0006
	2-5		29 (47.5)	54 (42.9)	3 (60)	35 (36.5)	124 (42.2)	
	>5		23 (37.7)	22 (17.5)	1 (20)	39 (40.5)	88 (29.9)	
Extrahepatic metastasis	No	N (%)	48 (78.7)	102 (81)	2 (40)	84 (87.5)	240 (81.65)	0.15902
	Yes		13 (21.3)	24 (19)	3 (60)	12 (12.5)	54 (18.35)	

Denominator of the percentage was the total number of subjects. IQR : Inter quartile Range, SD: Standard deviation; MELD: Model for End Stage Liver Disease, ALP: Alkaline Phosphatase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GTP: Guanosine triphosphate, Hbg: Hemoglobin, WBC: white blood cells.

The median MELD score at time of diagnosis was 11 but without statistical significance among the groups (p=0.7416). Biochemical markers were similar in all groups. Alpha-fetoprotein (AFP) level was normal in 45% whereas high AFP level (1000 ng/mL) were found in 17% of the patients. The distribution of AFP level was significantly different among the groups (p=0.0007). The tumor characteristics were remarkably different in the

numbers and sizes of the lesions between the groups. Regarding the lesion numbers, most of the patient had a single lesion accounting for 58%. Single lesions were significantly more with cryptogenic group while multiple lesions were more in HCV-associated HCC (p=0.0343). In addition, most of the patients had a tumor size between 2 to 5 cm. large lesions (>5 cm) were significantly more with cryptogenic group while small lesions (<2 cm) were more in HCV-associated HCC (p=0.0006).

Table 2: Comparison of liver cirrhosis presence between all groups.

Liver cirrhosis	Total	No N (%)	Yes N (%)	P value
All	294	25 (8.5)	269 (91.5)	0.0386
HBV	61	6 (9.84)	55 (90.16)	
HCV	126	5 (4)	121 (96)	
HBV+HCV	5	0 (0)	5 (100)	
Cryptogenic	96	14 (14.58)	82 (85.42)	

Table 3: Child-Turcotte-Pugh (CTP) score comparison between all groups.

Child-Turcotte-Pugh (CTP) score	Total N	Grade A N (%)	Grade B N (%)	Grade C N (%)	P value
All	294	115 (39.1)	104 (35.3)	75 (25.5)	0.00001
HBV	61	36 (59)	16 (26.2)	9 (14.7)	
HCV	126	55 (43.6)	48 (38)	23 (18.2)	
HBC+HCV	5	1 (20)	2 (40)	2 (40)	
Cryptogenic	96	21 (21.8)	35 (36.4)	40 (41.6)	

As shown in Table 2, liver cirrhosis was found in 91.5 of the patients and it was significantly common in HCV-associated HCC (96%) (p=0.0386). According to Child-Turcotte-Pugh (CTP) score, most of the patients had grade A (39.1%) followed by grade B (35.3%) then grade A (25.5%), with statistical significance among the groups as shown in Table 3 (p=0.00001).

DISCUSSION

Our research was conducted at King Abdulaziz Medical City-Riyadh (KAMC-R), and it involved 294 patients diagnosed with HCC between the period of 2010 to 2017. Male gender represented more than two third of the patients, similar to other local studies.[8-10] Physiological differences between males and females can play a role in the pathogenesis of HCC. For instance, estrogen seems to prevent HCC development by inhibiting the production of Interleukin 6 (IL-6) and ultimately protecting the liver cells injury and proliferation.[11]

Older age is a well-known risk factor for the development of HCC. In our finding, most of the patients were older with a median age of 67 years, similarly with most of the previous local studies.[9,10,12]

This might be related to delayed development of HCC among viral hepatitis, especially in HCV.[13] In our study, the most important risk factor for HCC was HCV, which is consistent with most of the previous studies.[8-10] However, cryptogenic HCC was the second common after hepatitis C, which is in contrast to a previously reported local study conducted in the same institute where it found that HBV was the second common after HCV.[10] This decrease in HBV-related HCC could be linked to the increased awareness of both social and clinical practice, better living condition and implantation of vaccination program by Saudi Ministry of Health thirty years ago.[14]

Alcohol consumption is a well known cause of chronic liver disease, including HCC. Alcohol involves in the pathogenesis of HCC directly by the genotoxic effects, and indirectly by liver cirrhosis.[15] Alcohol related HCC represented only 2% in our finding, and this is because alcohol is strictly prohibited in Saudi Arabia as per the guidelines of Islam. Obesity is well established risk in liver cancer.[16] In our patients, more than half had high BMI and, it was noticeably more associated in cryptogenic HCC than viral HCC. This is in keeping with other reports which found that high BMI is related with HCC development, particularly in cryptogenic HCC, which could be related to the generation of hepatic oxidative stress with high BMI.[16-18]

Diabetes Mellitus (DM), hypertension (HTN), and dyslipidemia (DLP) are common risks for HCC development and they are considered as independent risk factors in the absence of liver cirrhosis.[19,20] Almost half of our patient had DM and HTN but without significant differences between the groups. However, DLP was significantly higher in cryptogenic HCC, which is also in agreement with other reports that found high risk of HCC in metabolic syndrome, particularly in cryptogenic HCC.[21]

The morphology of HCC lesions at diagnosis was also described in our study. Most of the patients had a single lesion with 2-5 cm, which in constant with the previous study.[10] Single and large HCC lesions (>5 cm) were significantly more with cryptogenic HCC, which is in keeping with other studies.[22-24] However, multiple and small lesions (<2 cm) were noticeably found more in patients with HCV-related HCC. Cryptogenic HCC lacks the surveillance and diagnostic markers which possibly can explain the advance tumor size at diagnosis.

Alpha-feta protein (AFP) is an important serum marker for the HCC which has a high specificity and low sensitivity. It is considered as an independent risk factor associated with the progression and survival of patients. AFP can be elevated in the setting of liver cirrhosis or hepatitis, even if there is no liver tumor.[25] In our study, more than half of the patient had elevated AFP. High AFP levels (>1000) are significantly more associated with hepatitis B/C co-infection, whereas normal AFP levels are more in cryptogenic HCC. High AFP in viral HCC may be related to the liver inflammation and viral replication but not due to the presence of liver tumor.[26,27] Extra-hepatic metastasis was found only in 18% of the patients, similarly to the previous report.[10]

Liver cirrhosis is the most common condition associated with HCC and it was found in 92% of our patients, similarly to other studies.[28,29] Despite the recent decline, HCV is still the leading cause of chronic liver disease.[30] In our finding, liver cirrhosis was significantly more in HCV related HCC and less in cryptogenic HCC. This is also in keeping with another study found that cryptogenic HCC had the lowest prevalence of cirrhosis.[15] According to Child-Turcotte-Pugh grading, most of the patients had grade A followed by grade B. Notably, Cryptogenic HCC had significantly advanced liver stage, similarly to another study showed that cryptogenic HCC was commonly diagnosed in late stage with poor liver condition.[31]

Although our research reached its aim, we had some limitations. Since we used a retrospective study design, it is possible that we missed or excluded some patients due to insufficient data in their medical files. In addition, we conducted the study in one center which could limit the generalizability. In Summary, HCV was the major risk factor of HCC followed by Cryptogenic HCC. Old age, male gender, DM, DLP, HTN, and high BMI were common features associated with HCC. High BMI, DLP, single and large HCC lesions were more noticed in cryptogenic HCC whereas multiple and small lesions were more with HCV. Liver cirrhosis was very common, especially with HCV. We recommend early screening and treatment of chronic viral hepatitis, especially in hepatitis C. Increasing numbers of cryptogenic HCC indicate the importance of conducting further investigations to know the possible risks and pathogenesis related to its development.

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