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HEPATOCELLULAR CARCINOMA IN YEMEN: EPIDEMIOLOGY AND CLINICAL PRESENTATION

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and considered one of the health problems in Yemen due to the increase of the prevalence of hepatitis. This study aimed to determine specific epidemiological andclinical profile of HCC among Yemeni patients. **Methods:** A cross-sectional descriptive study was conducted during the period of 2009 to 2013. Personal, clinical and paraclinical data of a total 120 HCC cases attending or referring to National Oncology Centers in Sana'a, Aden, Hadhramout, and Al-Thawra Modern General Hospital- Sana'a were collected thoroughly by using a structured questionnaire. Statistical Package for Social Sciences (SPSS 20) was used for the analysis of data. **Results:** The mean age of HCC cases was 61.8±12.9 years, aroundtwo thirds (65 %) of the cases were males. More than half of HCC cases (54.2%) were HCV Ab positive, one quarter of them (25.8%) were HBs Ag positive and 1.7% were positive for both viruses.AFP level, a diagnostic level (> 400 ng/ml) was reported in 46.4% of the cases and a level from 20 to 400 ng/ml and < 20 ng/ml were reported in 27.8% and 25.8% of the patients respectively. Tumors in the two lobes, Right lobeand left lobe reported in (58.7%), (23.7%) and (17.6%) of HCC cases respectively, while (59.6%) of the patients hadmultifocal tumors and (58.7%) of them had single tumor. Most of the HCC patients are present at an advanced stage. **Conclusion:** HCC are prevailing among males and the majority of them were HCV Ab and HBs Ag positive and present at an advanced stage. National program for the prevention and treatment of viral hepatitis as well as to improve early HCC diagnosis and interventions is of very important.

KEYWORDS: Hepatocellular carcinoma, HBV, HCV, AFP, Yemen.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant epithelial tumor arising from hepatocytes which is like a liver cell but abnormal cells.[1] Recent study suggested that HCC develops from hepatic stem cells that proliferate in response to chronic regeneration caused by viral injury.[2]

Hepatocellular carcinoma (HCC) is asymptomatic for much of it's natural history. Nonspecific symptoms associated with HCC can include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC can include hepatomegaly and ascites. Paraneoplastic syndromes also can occur include erythrocytosis, hypercalcemia, hypoglycemia and watery diarrhea. The diagnosis of HCC obtains by laboratory findings, radiologic techniques and histopathology.[3]

Liver cancer is largely a problem of the less developed regions where 83% (50% in China alone) of the estimated 782,000 new cancer cases worldwide occurred in 2012. It is the fifth most common cancer in men (554,000 cases, 7.5% of the total) and the ninth in women (228,000 cases, 3.4%). In men, the regions of high incidence are Eastern and South-Eastern Asia (ASRs 31.9 and 22.2 respectively). Intermediate rates occur in Southern Europe (9.5) and Northern America (9.3) and the lowest rates are in Northern Europe (4.6) and South-Central Asia (3.7). In women, the rates are generally much lower, the highest being in Eastern Asia and Western Africa (10.2 and 8.1 respectively), the lowest in Northern Europe (1.9) and Micronesia (1.6). Liver cancer is the second most common cause of death from cancer worldwide, estimated to be nearly 746,000 deaths in 2012 (9.1% of the total). The prognosis for liver cancer is very poor (overall ratio of mortality to incidence of 0.95), and as such the geographical patterns in incidence and mortality are similar.[4]

Almost 80 percent of cases of HCC are due to underlying chronic hepatitis B and C virus infection.[5]

In Middle Eastern countries, liver cancer is a major concern among men, especially in certain countries such as Egypt and Saudi Arabia, and to a lesser extent in other countries of this region. Recent reports demonstrate that the incidence of HCC has increased sharply in the last 5–10 years, with an especially high incidence in Egypt.[6,9]

In Saudi Arabia, and according to the National Cancer Registry, HCC is ranked the sixth most common cancer in males and thirteenth in females with a male to female ratio of 2.6:1.[10] The mean age at diagnosis was 66 years, 74% of patients were males, and hepatitis C was the underlying cause of liver disease in 48%, while hepatitis B in 29%. Most of the patients were diagnosed at advanced stage.[11]

In Yemen, as one of the Middle Eastern countries, HCC is considered as one of the most common health problems. GLOBOCAN estimation of 2008 ranks HCC as the most common cancer in Yemen for all newly diagnosed men with an incidence and mortality of 11.8% and13.9%, respectively, for females corresponding figures are 6.5% and 8.4% respectively making HCC as the fourth most common cancer in females in Yemen (IARC/WHO, 2008).[12] According to National Oncology Center report (2007), HCC is the fourth commonest cancer in Yemen.[13]

MATERIAL AND METHODS

This study was carried out on patients diagnosed as HCC who attended or referred to NationalOncology Centers in Sana'a, Aden, Hadhramout, and Al-Thawra Modern General Hospital, Sana'a in the period between 2009 to 2013. Sample size was calculated by epiInfo program version 1.0 June 14, 2000, after obtaining actual number of population (CLD) from Althawra Modern General Hospital- Sana'a during 2009-2012 which was 1186 divided by 4 which resulted to 296 per year the actual size of population. Expected frequency of the factor under study was (4%) and the worst acceptable result was (7%) at 95 confidence interval sample size 105.

All these cases were diagnosed as HCC cases with focal lesion in the liver on abdominal sonography; enhancement of focal lesion on abdominal triphasic CT, and typical histopathological findings on liver biopsy and FNAC in some cases.

Tumour marker mainly AFP was used in majority of patients and measured by EIA.

Sociodemographic, clinical, biochemical and radiological data were extracted from patient's records including age, gender, address, and occupation, clinical symptoms and signs. Investigations includes T.bilirubin (mg/dl), AST U/L, ALT U/L, Albumin (gm/dl), serum AFP level, Hepatitis Markers **(**HBsAg, anti-HCV Ab) and Schistosoma serology. HBsAg and anti-HCV Ab were tested using ELIZA (standard, commercially available assays) with sensitivity of 100% and specificity of 99.7%. The same method was also used (conventional immunoassay) for measuring AFPwith lower limit of detection of 0.500 I U /ml, some cases with schistosoma serology test by Anti-schistosomal antibodies by indirect haemagglutination test.

Statistical Analysis

The questionnaire was reviewed and all variables were checked for normality. Descriptive statistics were summarized as mean ± SD or median (range) as appropriate. Chi square test were used to assess group differences for categorical variables.

A P value < 0.05 was considered statistically significant. Analyses were done with SPSS version 20.

RESULTS

Therewere78 males (65 %) and 42 females (35 %) with a male to female ratio of 1.9:1 Their age ranged between 20 to 100years with a mean of 61.8 ± 12.9 years. The age group affected above 60 were 66 (55%), most of this group (74.2%) were male, from 41 to 60 were 49 (40.8%) with (51%) male and (49%) female, from 20 to 40 were 5 patients (4.2%) (≤ 60 years 45%).

Table 1: Epidemiological and Laboratory findings of the studied HCC in Yemen.

Variables	HCC	%
Age		
20-40 years	5	4.2
41- 60 years	49	40.8
>60 years	66	55
Sex		
Male	78	65
Female	42	35
M:F	1.9:1	
AFP (97)		
<20	25	25.8
20-400	27	27.8
>400	45	46.4
Etiology (120)		
HCV	65	54.2
HBV	31	25.8
HCV & HBV	2	1.7
Schistosomal	3	2.5
Nonviral	19	15.8

Alpha-fetoprotein levels reached to a diagnostic level (>400 ng/ml) was reported in 45 patients (46.4%). AFP level from 20 to 400 ng/ml and < 20ng/ml occurred in 27 patients (27.8%) and in 25 patients (25.8%) respectively. Out of 120 patients 65 (54.2%) were AntiHCV positive and 31(25.8%) were HBsAg positive, co-infection with HBV and HCV were found in 2 patients (1.7%) and schistosoma serology was positive in 3 patients (2.5%).Etiology of HCC was not identified in 19 patients (15.8%).

The most common presenting symptoms and signs are; abdominal pain (83.4%), sign of CLD (83.4%), ascites (55.8%), splenomegally (55%) and hepatomegally (50%).

Table 2: The most common clinical manifestations.

Symptoms and signs	Number/total	Percentage
Symptoms		
Abdominal pain	100/120	83.4
Jaundice	53/120	44.2
Weight loss	33/120	27.5
Signs		
Sign of CLD	100/120	83.4
Ascites	67/120	55.8
Splenomegally	66/120	55
Hepatomegally	60/120	50

CDC: Chronic liver disease

Table 3: Pathological liver functions of HCC patients (n=120).

Liver function	Result
T.bilirubin (mg/dl)	
Median	1.6
Range	21.8(0.2 – 22)
AST (U/L)	
Median	68
Range	796(8 – 804)
ALT (U/L)	
Median	46
Range	283 (7 – 290)
ALB (gm/dl)	
Mean ± SD	3.0 ± 0.6
<3	67 (55.8)
≥3	53 (44.2%)

AST: Aspartate transaminase
ALT: Alanine transaminase
ALB: Albumin

Table 4: Histopathological findings of the studied HCC cases in Yemen.

Variables	HCC	%
Tumor Focallity (97)		
Single	40	41.2
Multiple	57	58.8
Tumor site (97)		
Right lobe	23	23.7
Left lobe	17	17.6
Both lobes	57	58.7
Tumor size (60)		
< 3cm	8	13.3
3-5 cm	10	16.7
> 5 cm	42	70
Portal Vein thrombosis (95)		
Present	18	18.9
Absent	77	81.1
Distance metastasis (95)		
Present	23	24.2
Absent	72	75.8

The imaging studies were with the following characteristics, 23 of the patients (29.4%) had HCC in right lobe while 17 patients (21.8%) in left lobe and 57 of patients (58.7%) in both lobes. Forty of patients (41.2%) had single tumor and 57 patients (58.8%) had multifocal tumors. The size of the tumor was > 5 cm in 42 patients (70%), from 3 to 5cm in 10 patients (16.7%) and less than 3cm in 8 patients (13.3%). Portal vein thrombosis in 18 patients (18.9%) and 23 patients (24.2%) had metastasis.

Table 5: Correlation between HBsAg/HCVab and AFP of HCC patients.

Item		AFP (ng/ml)				
		<20	20-400	>400	Total	P value
HBsAg +HCV	Positive	(7+13) 20(20.6%)	(4+19) 23(23.7%)	(15+25) 40(41.2%)	83(85.6%)	0.005
	Negative	5(5.2%)	4(4.1%)	5(5.2%)	14(14.4%)	
Total		25(25.8%)	27(27.8%)	45(46.4%)	97 (100)	

The correlation between viral hepatitis positivity showed statistical significant and also there is statistical significant between distant metastasis of the studied patients and their AFP levels (P value 0.05), and there is a statistically significant between tumor number and AFP levels of HCC patients (P value 0.000).

Table 6: Association of morphological characteristics and distant metastasis with AFP of studded patients.

Item		AFP (ng/ml)					
		<20	20-400	>400	Total	χ^2	P value
Tumor size	<3	1(25%)	1(25%)	2(50%)	4	2.19	0.700
	3-5	4(57%)	0(0%)	3(43%)	7		
	>5	13(39%)	6(18%)	14(43%)	33		
Morphology of tumor	Single	14(47%)	11(37%)	5(16%)	30	16.64	0.000
	multifocal	6(13%)	12(25%)	29(62%)	47		
Distant metastasis	Yes	6(32%)	2(10%)	11(58%)	19	4.76	0.05
	No	15(25%)	22(37%)	23(38%)	60		

DISCUSSION

Hepatocellular carcinoma is an important health problem in many parts of the world, especially in areas where high viral hepatitis is prevalent. In Yemen, as one of the Middle Eastern countries, HCC estimated as the most common cancer for all newly diagnosed cases and according to National Oncology Center Sana'a, Yemen report (2007), HCC is the fourth commonest cancer in Yemen.[13]

In present study the mean age 61.8 ± 12.9near to the result of Alswat from Saudi Arabia (2013) which was 66.1 ± 12.1.[11)] And higher than previous study in Yemen which was 53.5 ± 13.9.[14] but agreed with Saeed et al (2012) which was 61.2 ± 12.6. [15]Globally it has been reported that HCC patients are predominantly male and generally older,[16] with a mean age at presentation between 50 and 60 years in most of the studies conducted in both Asia and Western Europe. However, a lower mean age of 33 years at presentation was reported in sub-Saharan Africa.[17,18]

Moreover HCC specific prevalence were highest (55%) in age group> 60 years followed by 41-60 years (40.8%) than 20-40 years (4.2%) agreed with Saeed et al (2012)[15] but different from other two studies in Yemen in which (51.9%) in 40-60 age group.[19,14]

The prevalence of HCC was almost (65%) higher among males patients than females patients, with a male to female ratio of 1.9 to 1. These results were consistent with study in North Africa,[20] but slightly lower than that found in Saudi Arabia 3:1,[11] and higher than study in Yemen 36% male.[15] The reasons for sex difference in this presented study might be due to higher exposure of men to environmental liver carcinogens (such as smoking) and hepatitis virus infections,and testosterone effects could increase androgen receptor signaling in men promoting liver cell proliferation.[21-25]

AFP is the most widely investigated biomarker for HCC diagnosis, and remains the most widely used tumor marker in clinical practice.[26] In patients with liver cirrhosis, fluctuating levels of AFP may reflect flare-ups of viral hepatitis, exacerbation of underlying liver disease, or HCC development,[27] additionally, only 10% to 20% of early-stage HCC patients have abnormal AFP serum levels.[28-31]

Serum levels of AFP is not correlate well with other clinical features of HCC, such as size, stage, or prognosis. Elevated serum AFP occurs in pregnancy, with tumors of gonadal origin (both germ cell and non-germ cell,[32]) and in a variety of other malignancies, of which gastric cancer is the most common.[33]

Elevated serum AFP may also be seen in patients with CLD without HCC such as acute or chronic viral hepatitis.[34-35] AFP may be slightly higher in patients with cirrhosis due to HCV.[36]

A rise in serum AFP in a patient with cirrhosis should raise concern that HCC has developed. It is generally accepted that serum levels greater than 400ng/ml A rise in serum AFP in a patient with cirrhosis should raise concern that HCC has developed. It is generally accepted that serum levels greater than 400ng/ml (normal in most with results of HBV in (26.5%), HCV in (48%), HBV+HCV in (4.1%) and 21 (21.44%) for other etiology.[37] Another previous study in Saudi Arabia the HBV was (28.7%), HCV (48.2%), HBV+HCV (1.8%) and (21.3%) for non-viral etiology.[11]

In present study (25.8%) of patients had HBs Ag positive, (54.2%) of patientshad positive for Anti-HCV, co-infection occurred in (1.7%) of patients, for schistosoma serology (2.5%) of patients were positive, and unknown etiology (15.8%) those results were consistent with studies in Texas, Karachi, and Saudi Arabia but different from previous study in Yemen which may be due to the impact of HBV public education and vaccination program.[13,19,16] This study showedno statistically significant between the HBsAg and HCVAb of the studied patients and their AFP level (P value 0.226, 0.339). The conclusion was that elevated serum AFP was significantly associated with increased risk of HCC in HBV patients or HCV which was similar to previous study.[38-39]

Most common risk factors for the development of HCC viral infections caused by HBV and HCV Chronic HBV infection is the leading cause of HCC in Asia and Africa, while hepatitis C viral infection is the leading cause of HCC in Europe, Japan, and North America.[40,41]

Our study revealed a direct relationship between tumor number and serum AFP level (p value of 0.000), suggesting that, AFT levels increases correlate with increase in number and burden of tumor.[42]

CONCLUSIONS

HCC occurred in age older than 60 years with more prevalent in males than females with male to female ratio 1.9:1, Hepatitis C virus was the main cause for CLD and main risk factor for HCC, with high rate of HCC of unknown etiology. The majority ofHCC patients had tumor size more than 5 cm at the time of presentation.

High rate of complicated HCC (distant metastasis and PV thrombosis) at the time of presentation. There was an association between tumor number, HCV, HBV, AFP and HCC .

The high prevalence of HCV/HBV infection makes screening programmes, and the surveillance of those patients is a very important tool to early detect cases of HCCs.

CONFLICTS OF INTEREST

No conflicts of interest declared.

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