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A Clinicopathological Study of Hepatocellular Carcinoma: A Cross Sectional Study

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Abstract **Original Research Article**

The purpose of the present study was to find out the clinicopathological characteristics of Hepatocellular Carcinoma (HCC) patients**.** All the clinically suspected patients were recruited as per inclusion and exclusion criteria. The relevant socio-demographic characteristics, clinical findings as well as the physical examination were performed after talking written consent from all the study subjects. The ultrasonography was performed to all the patients. After that, the patients were sent to the department of pathology for histopathological examination. The descriptive cross-sectional study was carried out in the Department of Oncology of National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh from July 2014 to June 2015 for a period of 12 months. Total sample size was 52 in this study and age distribution of HCC was found from 25 years to 97 years to with the mean age 50.57 ± 12.09 years. Males were predominant (78.0%), male and female ratio was 3.72:1. The common presenting features of HCC were abdominal pain and swelling, fever and jaundice; viral marker was positive in 86.5% of patients (HBsAg-67.3%, Anti HCV-19.2%) with normal tumor marker alpha-fetoprotein (AFP) in 69% of the patients. Okuda staging shows 82.7% patients within stage I and Stage II and performance status, 38.5% patients were unable to carry out normal activity. Sonological findings revealed 69.2% patients had ≤2 cm tumor size, 88.4% had ascites lastly splenomegaly was present among 86.5% respondents.

Keywords: Hepatocellular Carcinoma (HCC), α-fetoprotein (AFP), Cirrhosis, Hepatitis.

INTRODUCTION

Cancer of the liver is the sixth most frequently diagnosed cancer worldwide, with approximately 905677 new cases and the third leading cause of cancer related death with approximately 830180 for both sexes worldwide, after lung and colorectal cancer reported in 2010 [1]. Liver cancer is a common tumor where mortality rate is so high, however most cases are detected in last stage. Primary liver cancer is called one of the most frequent and dangerous malignant tumors worldwide [2]. Hepatocellular carcinoma (HCC) forms approximately 80% of all primary tumors of liver. This malignancy occurs more often among men than women, with the highest incidence rates reported in East Asia [3]. The incidence rates of HCC in the United States have historically been lower than in many countries. However, in present years, Incidence of HCC age-adjusted rates have doubled and the mortality rate of primary liver cancer have raised quicker than mortality rates for any other leading cause of cancer [4-5].

Approximately 90% of primary liver cancers in the United States are HCCs, while most of the remaining 10% are intrahepatic cholangiocarcinomas [6]. Overall, 75–80% of global HCC cases are attributable to persistent viral infections with either hepatitis B virus (50–55%) or hepatitis C virus (25–30%) [7]. The geographical variability in the incidence of HCC has been assigned to the exchanging placement and the natural history of HBV and HCV infections. The most high-risk areas are Asian and African countries, the primary cause of HCC is HBV except

Japan where HCV is the most focusing cause. While on the contrary, in developed countries for example, United States and European countries HCV are playing an important role. Half of HCC cases were both HBsAg along with anti-HCV in areas with decreased incidence as well as United States and some North European countries, where heavy alcohol consumption, obesity and diabetes mellitus may be of greater importance [8]. Patients with small localized tumor usually have HCC related symptoms.

A particular manifestation of HCC can be bleeding from esophageal varies. This presentation is not frequent, occurring as first clinical sign only in 1%-8% of cases of HCC. In advanced terminal stage, hepatomegaly, upper abdominal mass, abdominal pain, general malaise, anorexia, abdominal fullness, weight loss, jaundice are frequent signs of presentation of HCC. Some studies indicated that it is present at the diagnosis of HCC in 28% of African patients, but less frequent in Chinese, Japanese or European countries, edema and gastrointestinal bleeding are commonly present. Intraperitoneal bleeding is one of the most serious complications of advance tumors [9-10].

MATERIALS AND METHODS

This descriptive cross-sectional study was carried out in the Department of Medical Oncology of National Institute of Cancer Research & Hospital (NICRH), Bangladesh from July 2014 to June 2015. All the clinically suspected HCC patients at any age with both sexes admitted at the Department of Oncology of NICRH were selected as study population. The sample was collected by purposive sampling technique after fulfilling inclusion and exclusion criteria and taking informed consent during the study period. For confirmation of diagnosis, if α-fetoprotein was found raised, CT scan was performed; and when α-fetoprotein was found lower than normal, core biopsy or FNAC was done.

Patients were included as per inclusion criteria all the HCC diagnosed clinically, biochemically, ultrasonography of both sexes of any age group patients and in exclusion criteria, HCC with secondary carcinoma, already treated, unconscious patients. A total 52 patients were enrolled in this study. To demonstrate patient condition in terms of performance, 2 types of classification may be used; Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group (ECOG). In this study, KPS was used. The demographic information, relevant history, examination findings and investigation reports of all the study subjects were recorded in the questionnaire. Data were collected by face-to-face interview, physical examination, laboratory examination (biochemical and histopathology) and ultrasound. Any complication during the procedure and hospital admission, if required, were also recorded. Computer based statistical analysis were executed along with definite techniques and systems. Quantitative data were expressed in the form of mean (± Standard Deviation) and qualitative data were put up as frequency and percentage.

Okuda staging

The Okuda Staging System classifies patients into three stages based on the following variables [11]

Criterion	Cut-Off
Tumor size*	> 50% = "+", < 50% = "-"
Ascites	Clinically detectable = "+"; undetectable = "-"
Serum albumin	< 3 g/dl = "+"; > = 3 g/dl "-"
Serum bilirubin	>3 mg/dl = "+"; < 3 mg/dl = "-"
Stage	Number of Criterion
I	No positives
II	One or two positives
III	Three or four positives

RESULTS AND OBSERVATION

All the clinically suspected HCC patients admitted at Department of Medical Oncology of NICRH were selected as per inclusion and exclusion criteria. Results are as follows:

Figure 1 below shows a histogram regarding age distribution of the respondents. It was found that, majority of the patients, that is 40.40% were aged 51 years or above, followed by 40-50 years of age which were 36.10% of the patients.

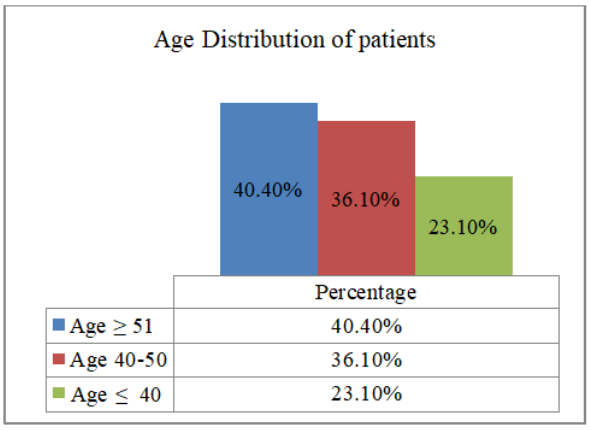

Figure 1: Histogram showing distribution of patients according to age (n=52)

Figure 2 below containing a bar diagram represents certain socio-demographic characteristics of the respondents. It can be seen that, maximum patients, which is 78.80% were males in gender. With regards to educational status, it was found that, most of the patients (61.50%) were illiterate.

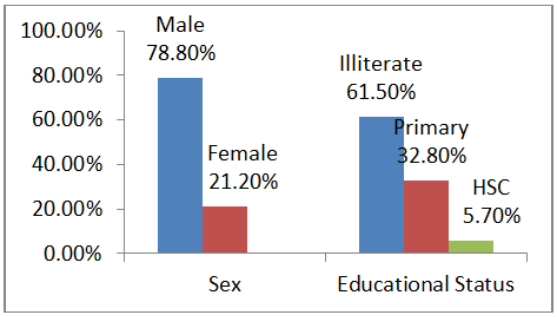

Figure 2: Bar diagram showing demographic presentation of the patients (n=52)

Table 1: Distribution of patients according to sign and symptoms (n=52)

Signs and Symptoms	n (%)	Duration (months) (Mean ±SD)
Right hypochondrial pain	42 (80.8)	4.91 ± 4.01
Right hypochondrial swelling	28 (53.8)	4.01 ± 2.06
Fever	26 (50.0)	3.22 ± 1.58
Weight Loss	11 (21.2)	5.00 ± 1.84
Jaundice	8 (15.4)	3.62 ± 1.76
Melaena	6 (11.5)	5.50 ± 6.36
Hepatic Encephalopathy	3 (5.8)	1.25 ± 0.35

Table 1 shows sign and symptoms of the patients. Right hypochondrial pain was found to be the most frequently occurring symptom, which was present among 80.8% of the patients. 28 patients presented with right hypochondrial swelling. Fever, jaundice, hepatic encephalopathy and weight loss were also presented. With regards to duration of symptoms, melaena and weight loss persisted for longest duration, which is 5.50 ± 6.36 and 5.00 ± 1.84 months respectively.

Table 2: Distribution of the patients according to risk factors (n=52)

Risk factor	Frequency (n)	Percentage (%)
Chronic Liver Disease	38	73.1
History of sharing razor/toothbrush	31	59.6
History of unscreened blood transfusion	25	48.0
History of alcohol consumption	23	44.2
History of needle stick injury	7	13.5
History of I/V drug misuse	6	11.5
History of exposure	3	5.8
HBV, HCV positive mother	1	1.9

Table 2 above shows risk factors of the patients. History of chronic liver disease was present among maximum patients, that is 38 (59.6%). Razors/toothbrushes were shared by 31 (59.6%) patients. Unscreened blood was transfused among 25 (48.1%) patients. History of alcohol intake was found in 23 (44.2%) participants. Intravenous (I/V) drug was misused by 6 (11.5%) patients and 7 (13.5%) patients were injured by needle stick. One patient had HBV/HCV positive mother.

Table 3: Distribution of patients according to personal history (n=52)

Factors	Frequency (n)	Percentage (%)
Smoking	25	48.38
No personal history	22	42.12
Alcohol abuse	2	3.8
Past history of major illness (such as ischemic heart disease, cerebrovascular disease)	2	3.8
Family history of cancer	1	1.9

Table 3 demonstrates personal history of patients. Smoking habit was present among majority of the patients, that is 25 (48.38%) patients. In addition to smoking, alcohol consumption, past history of major illness and family history of cancer were present. 22 (42.12%) patients did not have any personal history.

Table 4: Distribution of patients according to general examination (n=52)

	Frequency (n)	Percentage (%)
Appearance		
Ill looking	50	96.2
Depressed	2	3.8
Body Built		
Below average	43	82.7
Normal	6	11.5
Emaciated	3	5.8
Posture		
On choice	47	90.4
Propped up	5	9.6
Nutritional status in BMI (kg/m^2)		
Underweight (BMI:<18.5)	27	51.9
Normal (BMI: 18.5-24.9)	20	38.5
Overweight (BMI: 25.0-29.9)	5	9.6
Anemia		
Mild	45	86.5
Moderate	4	7.7
Absent	3	5.8
Others		
Jaundice	19	36.5
Cyanosis	1	1.9
Dehydration		
Mild	49	94.2
Moderate	3	5.7
Performance status according to Karnofsky Performance Scale [KPS]		
Minor sign or symptoms	7	13.5
Normal activity with effort	9	17.3
Unable to carry out normal activity	20	38.5
Requires occasional assistance	16	30.8
Vital signs		
Pulse [Mean ± SD]	77.54±5.57	
Systolic BP [Mean ± SD]	132.60±6.9	
Diastolic BP [Mean ± SD]	78.43±7.72	
Respiratory rate [Mean ± SD]	14.68±1.07	
Temperature [Mean ± SD]	98.33±4.31	

*BMI=Body Mass Index; BP=Blood pressure; SD=Standard Deviation.

Table 4 illustrates general examination of the patients. Almost 96.2% patients appeared to look ill; body built was below average for 82.7% patients. Nutrition was poor among 19.2% patients. Mild anemia was diagnosed among 86.5% patients. Jaundice was seen among 36.5% patients. Highest 38.5% patients were unable to carry any normal activity, occasional assistance was required by 30.8% patients.

Table 5: Distribution of the patients according to abdominal examination (n=52)

Trait	Frequency (n)	Percentage (%)
Shape of the abdomen		
Normal	38	73.1
Distended	13	25.0
Scaphoid	1	1.9
Ascites		
Present	46	88.4
Absent	6	11.6
Umbilicus		
Inverted	36	69.2
Normal	13	25.0
Visible vein	6	11.5
Visible peristalsis	1	1.9
Any striae/ scar mark	1	1.9

Table 5 shows abdominal examination findings of the patients. It was evident that, maximum patients had normal shape of abdomen, that is 38 (73.1%), followed by distended abdomen which was found in 13 (25%) patients. Regarding the umbilicus, most of the patients presented with inverted umbilicus, which is 36 (69.2%). It was also seen that, one patient each had visible peristalsis and any striae or scar mark respectively.

Figure 3 below is a histogram demonstrating the distribution of the patients according to Okuda staging. It is clearly evident that, 42.30% of the patients belonged to Okuda stage I. The next prominent percentage of patients, that is 40.40% were a part of Okuda stage II. The remaining patients belonged to Okuda Stage III.

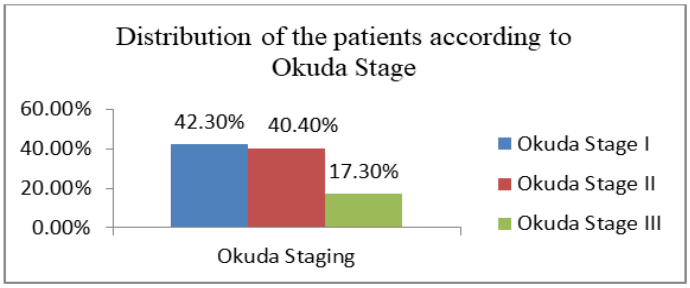

Figure 3: Distribution of patients according to Okuda stage

Table 6: Hematological parameter of the patients (n=52)

Blood parameters	Mean ± SD	Range
Haemoglobin (g/dL)	10.90 ± 1.63	7.90 - 15.10
WBC (cells/µL)	8718 ± 7850	500 - 60000
Platelet(cells/µL)	327972 ± 452421	4000 - 3300000
ESR (mm/hour)	61.58 ± 35.50	3.20 - 140.00
Serum Albumin (g/dL)	3.52 ± 0.79	2.20 - 5.90
Serum Total Protein (g/dL)	6.84 ± 1.06	3.90 - 9.80
Serum Bilirubin(mg/dL)	2.36 ± 1.95	0.34 - 10.79
ALT (u/L)	75.62 ± 45.70	25.00 - 273.00
ALP (u/L)	309.91 ± 187.12	104.00 - 999.00
Prothrombin Time (seconds)	13.91 ± 1.38	11.40 – 17.60
Blood Urea (mmol/L)	37.48 ± 11.27	19.00-78.00
Serum Creatinine (mg/dL)	0.97 ± 0.29	0.59 – 2.10
Serum α- fetoprotein (ng/mL)	6999 ± 25218	0.20 – 125740

*WBC=White blood cell; ESR=Erythrocyte Sedimentation Rate; ALT=Alanine Transaminase; ALP=Alkaline Phosphatase.

Table 6 above shows different types of blood parameters of the patients. It was found that, mean ± SD of Haemoglobin was 10.90 ± 1.63 g/dL; WBC was 8718 ± 7850cells/µL; platelet was 327972 ± 452421cells/µL; S. Bilirubin was 2.36 ± 1.95 mg/dL; Alkaline Phosphate was 309.91 ± 187.12 (u/L) and Serum α- fetoprotein was found to be 6999 ± 25218 ng/mL.

Table 7: Sonological findings among the respondents (n=52)

Findings	Frequency (n)	Percentage (%)
Size of the tumor		
≤2 cm	36	69.2
>2 cm	16	30.8
Ascites		
Present	46	88.4
Absent	6	11.6
Splenomegaly		
Present	45	86.5
Absent	7	13.5

Table 7 above demonstrates the sonological findings found in the patients. With regards to tumor size, majority of the patients, 36 (69.2%) had ≤2 cm. Ascites and splenomegaly was found in maximum patients, 46 (88.4%) and 45 (86.5%) respectively.

Figure 4 below is a pie chart illustrating serum α-fetoprotein levels. Regarding that, 69% patients had normal levels of serum α-fetoprotein. On the other hand, serum α-fetoprotein level was raised in 31% patients.

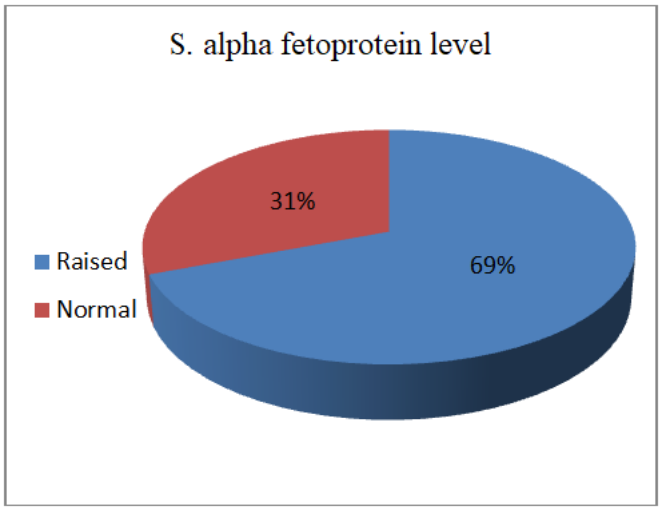

Figure 4: Pie chart showing distribution of patients according to serum α-fetoprotein level

Table 8: Distribution of the patients according to risk factors of Hepatocellular carcinoma (n=45).

Risk Factors	Frequency (n)	Percentage (%)
HBs Ag	35	67.3
Ab to HCV	10	19.2

*HBsAg=Hepatitis B Surface Antigen; Ab to HCV= Antibody to Hepatitis C

Table 8 above shows risk factors of Hepatocellular carcinoma. HBs Ag was present in 35 (67.3%) and Antibody to HCV was found in 10 (19.2%) patients.

DISCUSSION

The most common form of primary liver cancer is hepatocellular carcinoma and is histologically and etiologically distinct from other forms of primary liver cancer. Approximately 70%–90% of patients with HCC have an established background of chronic liver disease and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic steatohepatitis· HCC is a heterogeneous incidence in worldwide by cause of the variable prevalence of related risk factors. It is estimated that 72% of cases occur in Asia (more than 50% in China), 10% in Europe, 7.8% in Africa, 5.1% in North America, 4.6% Latin America and 0.5% in Oceania [13].

In this study, 40.4% patients were ≥ 51 years, 36.5% were 41-50 years and 23.1% were ≤ 40 years old. Therefore, this indicates that the middle age people are more commonly affected by HCC. Krasner (1978) have reported that in Britain, HCC is common among the over 50 years of age people [14]. In Japan, mean age of HCC patients was 55.5 years [15]. Age of the HCC patients in this study is consistent with the above studies.

In this study, male and female ratio was 3.72:1. A similar study reported that, in eastern Asia, age adjusted incidence rates for liver cancer in men range from 29.21 (in Japan) to 48.77 (in Korea) per 100,000 [16]. In another study, it was reported that males were more prone to be affected from HCC than female and the ratio is five times greater15. In Philippines, the male and female ratio of HCC was found to be 5.4:1 [17]. Comparing our study and other studies males were predominant than females.

In this study, maximum patients were either illiterate (61.5%) or primarily educated (32.8%). The literacy rate of our nation at 2015 was 65.14%, hence our study findings were not consistent with it [18]. However, the sample we took reflected these findings. Illiteracy may be one of the reasons of HCC because they are not aware regarding the transmission of Hepatitis B virus and Hepatitis C virus.

Most commonly reported clinical features were hypochondrial pain (80.8%), hypochondrial swelling (53.8%) and fever (50.0%) as found in this study. Jaundice is a common feature of presentation of HCC. Some studies proved that, 28% cases of African patients had jaundice at the time of diagnosis of HCC (28.0%), but less common symptom of onset of HCC is abdominal pain. Prior reports suggested that, in black South African patients, abdominal pain was frequent in 95% of cases while it was referred by 46%, 51% and 38% of Japanese, Chinese and Italian patients respectively. Fever occurred more frequently in patients with massive HCC and in no cirrhotic individuals. Fever was found in 35.0%, 17.0%, 2.0% and 12.0% of HCC patients in Africa, Japan, China and Italy respectively [19].

Unscreened blood was transfused among 48.1% patients, IV drug was misused by 11.5% patients, 13.5% patients were injured by needle stick and razors/toothbrushes were shared by 59.6% patients in this study. The most alarming risk factor for the occurrence of HCC was recorded to be cirrhosis of the liver [20]. However, about one quarter of HCC cases diagnosed in the United States did not have any known predisposing risk factors. It is known that, chronic liver disease [CLD] is one of the causative factors of HCC. Hence the initial presenting symptoms appear to be similar. The major known risk factors for HCC are viral like chronic hepatitis B and hepatitis C, toxic materials like alcohol and aflatoxins, metabolic cause like diabetes and non-alcoholic fatty liver disease, hereditary haemochromatosis and immune related conditions like primary biliary cirrhosis and autoimmune hepatitis [21]. Regarding personal history of the patients, 48.1% were smokers and 3.8% were alcohol abusers. Two patients had past history of major illnesses namely ischemic heart disease or cerebrovascular disease. One patient had family history of carcinoma.

With context to appearance, almost (96.2%) patients looked ill; body building was below average among 82.7% patients. Nutrition was poor among 19.2% patients. Mild anemia was seen in 86.5% patients; moderate in 7.7% patients. Jaundice was found among 36.5% patients; oedema in 13.5% patients. Most of the patients had dehydration. Maximum (38.5%) patients were unable to carry out any normal activity, 16 (30.8%) patients required occasional assistance, 9 (17.3%) had normal activity with effort and 7 (13.5%) had minor signs or symptoms. Maximum patients (51.9%) were found to be underweight and only 5 (9.6%) were overweight.

Ascites was present in 46 patients. Inverted umbilicus was found in 69.2% patients; visible vein in 11.5% patients; scar mark was in one patient; swelling or mass was present in 9.6% patients. Ultrasound revealed 69.2% had tumor size ≤2 cm, 88.4% had ascites and 86.5% developed splenomegaly. Maximum patients, that is 69% had normal levels of serum alfa-fetoprotein. Albumin was more than 3 mg/dl in 57.7% of patients; bilirubin was more than 3 mg/dl in 38.5% patients.

AUTHOR'S CONTRIBUTION

Dr. Fatima Sarker was the principal investigator who prepared, organized, wrote, and approved the final version of the manuscript. All the remaining authors read and approved the final manuscript.

CONCLUSION

Hepatocellular carcinoma is a multifactorial disease. Therefore, the approach of the disease should be multidisciplinary. The present study gives an idea that there may be some correlation between HCC and clinicopathological profile.

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