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ORIGINAL ARTICLE

Attribute Features of Hepatitis B Related Hepatocellular Carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the third most common cause of cancer death in 46 countries. The highest incidence of HCC is in Asia accounting 76% of all cases and caused by Hepatitis B. Evolution to HCC may be the direct effect of the virus itself, or it may be an indirect effect through the process of the inflammation, regeneration, and fibrosis associated with cirrhosis**.**
Objective: We find out the characteristics of hepatitis B related HCC.
Methods: This observational study was carried out in the Department of Hepatology, BMU (Bangladesh Medical University); sample of this study was collected from January 2017 to December 2018. The diagnosis of HCC was confirmed by pathological examination or AFP elevation (400ng/ml) combined imaging (CT/MRI) after exclusion of hepatitis C virus infection and significant alcohol intake. All patients were HBsAg positive.
Results: A total of 44 patients were included in this study. Among them, 91% were male (n=40) and mean age was 48.2 (±12.9) years with range from 23 to 80. Only 11.4% know about their liver disease. Abdominal pain (95.5%), weight loss (86.4%) & anorexia (97.7) were the cardinal presentations. Cirrhosis and PVTT were 79.5% and 41%. AFP level > 400ng/ml was 64 % and IL28B Genotype (rs12979860) showed Genotype (CC)& Allele (C) frequency of were 45.5% & 64.8% respectively**.**
Conclusions: Population-based vaccination programs against HBV and universal infant vaccination have the potential to reduce the incidence of HCC in the future. Suppression of HBV replication with antiviral may reduce the risk of HCC. Early detection and treatment are warranted.

Keywords: IL28B Genotype; Hepatocellular carcinoma.

INTRODUCTION

Globally impact in 2020 showed 905,700 people were diagnosed with and 830,200 people died from liver cancer. Liver cancer ranks among the top three causes of cancer deaths in 46 countries. The number of new cases and deaths from liver cancer could rise by >55% by 2040 [1]. The etiological agent of HCC is known in more than 90% of cases. In Southeast Asia, hepatitis B is the most common underlying cause. The highest incidence of HCC is in Asia, accounting for about 76% of all cases worldwide [2]. Hepatitis B is a liver-infecting virus that can lead to cirrhosis and liver cancer. WHO estimates that 240 million people were living with chronic hepatitis B infection in 2024, with 0.9 million new infections each year [3]. Approximately 15-40% of CHB patients will develop cirrhosis, liver failure and HCC [4]. Bangladesh is within the intermediate zone of prevalence of HBV infection. HBsAg positivity in healthy population is 5.4% [5]. Evolution to HCC may be the direct effect of the virus itself, or it may be an indirect effect through the process of the inflammation, regeneration, and fibrosis associated with cirrhosis due to the HBV infection. HBV DNA has been shown to become integrated within the chromosomes of infected hepatocytes, the integration of viral genetic material occurring in a critical location within the cellular genome.

The hepatitis Bx (HBx) gene product has been implicated in causing HCC because it is a transcriptional activator of various cellular genes associated with growth control. The HBx gene expression is also associated with activation of the Ras–Raf–mitogen-activated protein kinase pathway, an important cellular

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pathway that has been implicated in hepatocarcinogenesis. In addition, HBx has been found to interact with p53, interfering with its function as a tumor suppressor. Another viral gene product that has been implicated in causing HCC is the truncated HBsAg gene product [6]. Based on this hypothesis, we find out the characteristics of hepatocellular carcinoma in hepatitis B infected individuals.

MATERIAL AND METHODS

Study Population

This is a hospital based observational study of 44 HCC patients. Patients with HBsAg positive done by ELISA test and features suggestive of HCC attending at outpatient & inpatient department of Hepatology, Bangladesh Medical University (BMU), Dhaka, Bangladesh was enrolled in this study; samples of the study were collected from January 2017 to December 2018. Aims and objectives along with its procedure, risks and benefits of this study were explained to the patients and attendants in easily understandable local language (Bangla) and then informed written consent was taken from each participant. The inclusion criteria where HCC patients were recruited prospectively. The diagnosis of HCC was confirmed by α-fetoprotein elevation (≥400 ng/ml) combined with computed tomography (CT) and/or magnetic resonance imaging (MRI) or Pathological examination (Biopsy/FNAC) [Figure 1] and exclusion criteria were alcohol abuse (>20g/day) and infection with HCV (anti-HCV positivity).

Procedure for fine needle aspiration (FNA) from liver space occupying lesions SOL(s)

After receiving informed written consent, patients laid with empty bladder. The site was painted with iodine solution and draped. Skin and deeper tissue was infiltrated with local anesthesia (2% xylocaine) at the proposed puncture site using a 23 G needle.

Under real-time USG guidance and using 22 G disposable spinal needles the cavity was entered and aspirated material was collected. The prepared glass slides ware fixed with 95% ethanol and kept in Kaplan's jar after labeling. Samples were sent for cytopathological examination to the Department of Pathology, BMU. Dressings were applied at the needle puncture sites and patients were followed up for next 6 hours.

Statistical Analysis

All data was recorded systematically in a preformed data collection sheet and quantitative data expressed as mean ± SD. Qualitative data analyzed by chi square test and quantitative data by student's T test or Mann Whitney's U test. Differences in laboratory parameters compared using one-way ANOVA.P value of ≤0.05 was considered to be statistically significant. All statistical computations were performed by using SPSS version 20 (Statistical Package for Social Science).

RESULTS

Demographic characteristics

Table I demonstrated the demographic parameters of the subjects in the study, including age, gender, history of smoking, marital status, occupation, educational status, monthly income, family history of liver disease, history of known liver disease, known diabetes mellitus & history of blood transfusion.

Presenting Clinical features

Table II included abdominal pain, weight loss, anorexia, abdominal and/or legs swelling, bleeding per mouth, mass in the abdomen, itching, pallor, fever & stigmata of chronic liver disease including jaundice, leukonychia, palmer erythema, gynecomastia, spider telangiectasia, edema, ascites, palpable spleen, testicular atrophy.

Laboratory characteristics

Table III includes the laboratory parameters including hemoglobin (Hb), platelet count (PLT), prothrombin time (PT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, serum albumin, α-fetoprotein (AFP), imaging study, endoscopy of upper GI study & IL 28B Genotype (rs12979860).

Table I: Demographic characteristics of the subjects in the study (n=44)

Age	
Mean ± SD	48.20±12.91 years
Range	23 to 80 years
Gender (%)	
Female	09
Male	91
History of smoking (Yes) (%)	40.1
Marital Status (Yes)	93
Occupation (%)	
Housewife	09.1
Service	38.6
Farmer	27.3
Business	11.4
Others	13.6
Educational status (%)	
Illiterate	29.5
< SSC	27.3
< HSC	11.4
HSC & above	31.8
Monthly income (%)	
< 10,000 TK	34.0
10,000 – 20,000 TK	45.5
>20,000 TK	20.5
Family history of live disease (Y) (%)	27.3
History of known liver disease (Y) (%)	11.4
Known diabetes mellitus (Y) (%)	29.5
History of Blood transfusion(Y) (%)	09.1

Table II: Presenting Clinical features of the subjects in the study (n=44)

Upper abdominal pain (%)	95.5
Weight loss (%)	86.4
Anorexia (%)	97.7
Abdominal and/or legs swelling (%)	43.2
Bleeding per mouth (%)	04.5
Mass in the abdomen (%)	04.5
Itching (%)	04.5
Pallor (%)	34.1
Fever (%)	04.5
Stigmata of chronic liver disease (%)	
No stigmata	20.5
< 3 Signs	06.8
3 Signs	09.1
4 Signs	09.1
>4 Signs	54.5
Some patients had multiple symptoms at presentation	

Table III: Laboratory characteristics of the subjects in the study (n=44)

Parameter (Mean ± SD)	
Haemoglobin (g/dl)	11.43 ± 1.72
Platelet count (10^9/L)	227.2 ± 102.71
Prothombin time (Sec)	15.12 ± 2.20
INR	1.28 ± .19
Alanine aminotransferase (U/L)	76.52 ± 51
Aspartate aminotransferase (U/L)	82.52 ± 41
Serum bilirubin (µmol/L)	94.98 ± 115.06
Serum albumin (g/dl)	3.02 ± 0.55
Imaging study	
Multiple nodules (%)	43
Single nodule (%)	41
Diffuse HCC	16
Portal vein thrombus (PVT) (%)	41
Endoscopy of upper GIT	
Varices	46.5
Portal hypertensive gastropathy	02.3
Both	27.9
Normal	23.3
IL 28B Genotype (rs12979860) (%)	
Genotype CC	45.5
Genotype CT	38.6
Genotype TT	15.9
Allele T	35.2
Allele C	64.8

Distribution of the study population by age range

Table IV shows distribution of the study population by age range. Maximum (50%) patients' ages had belonged to 35-55 years. The mean age was to be found 48.20 ±12.92 years with range from 18 to 80 years.

Gender distribution of the study population

Figure 2 shows male gender was predominant 91% (40) of the study population. Male female ratio was 10:01.

Distribution of the study population according to serum AFP

Figure 3 shows the serum AFP level > 400ng/ml, 15-400 ng/ml and < 15 ng/ml was 64 % (28), 18 % (8) and 18 % (8) respectively.

Table IV: Distribution of the study population by age range (n = 44)

Age range	Frequency N & (9%)	Cumulative Percentage(%)
<20	01 (02.3)	02.3
21-30	05 (11.4)	13.7
31-40	11 (25)	38.7
41-50	11 (25)	63.7
51-60	10 (22.7)	86.4
>60	06 (13.6)	100

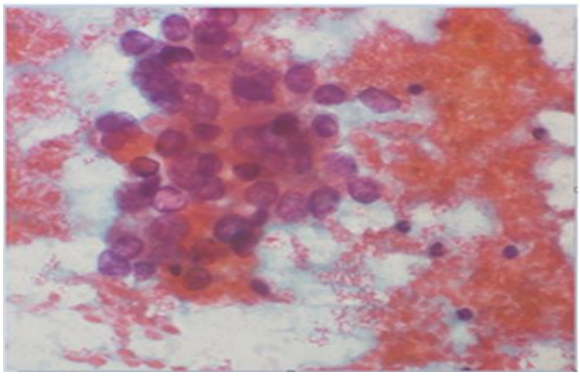

Figure 1: Cytopathic features of HCC. H&E stain, (Courtesy: Department of Pathology, BMU). ID no:18.

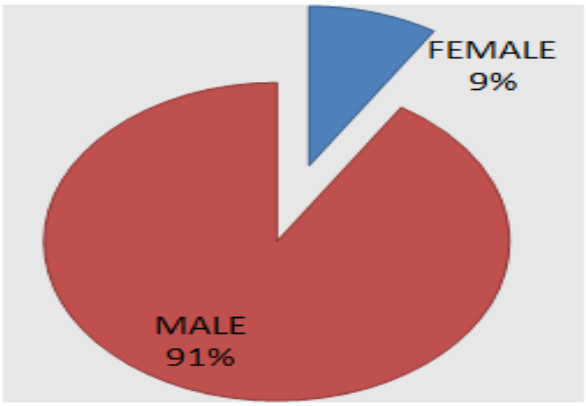

Figure 2. Gender distribution of the study population (n= 44).

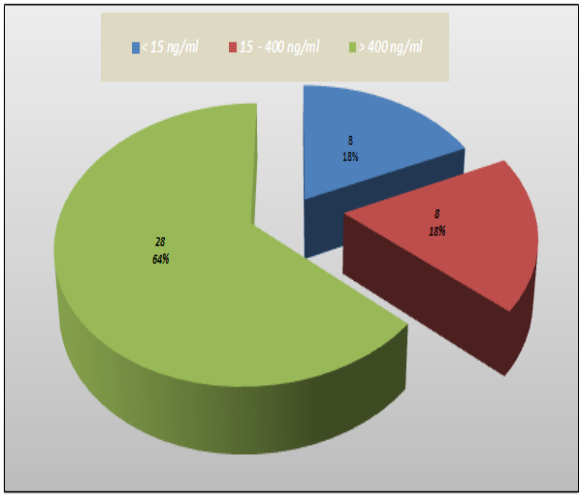

Figure 3. Distribution of the study patients according to serum AFP (n=44).

DISCUSSION

This is the study from Bangladesh in which the characteristics of HBV related HCC have been studied. HBV infection accounts for most primary HCC and treating HBV substantially reduces the risk of HCC development. Chronic HBV infection is recognized as the most important causal factor for HCC in humans.

The incidence of HCC increases with age. The development of HCC is uncommon before 40 years of age in western world. However, the pattern of HCC incidence by age is sometimes dependent on the geographic pattern or on etiological factors. The age distribution of patients with HCC in the present study was like other studies in past. Studies from Bangladesh (M Khan *et al* & Gani ABMS *et al*), India (Sarma MP *et al*), China (Shan R *et al*) and Pakistan (Abbas Z *et al*) have shown the maximum incidence of HCC in the fifth to sixth decade [7-11]. The male preponderance is like our previous Bangladeshi study and other studies from India and Pakistan [7-9&11]. The population-based data show a male to female ratio of 3:1–2:1.1.22 However, high preponderance of HCC in males reported in hospital-based data could suggest a gender bias in seeking medical treatment.

This study revealed that proper screening of chronic hepatitis B infected individual is absent in Bangladesh. Most of the patients were unaware of their chronic infection before attending the tertiary hospital. All patients presented with complaints like abdominal pain, weight loss, anorexia, abdominal and/or legs swelling, bleeding per mouth, itching, pallor, fever and palpable mass in the abdomen. Only 11.4% of patients know their liver disease previously and family history of live disease is known only 27.3%. The extent of liver cirrhosis was also in progressive state. Unfortunately, most of the patients attended the physician after development of HCC. American Association for the Study of Liver Diseases (AASLD) recommendations for HCC Surveillance.

Among HBsAg carriers [12] includes- Asian males over the age of 40 years, Asian females over the age of 50 years, all patients with cirrhosis who are seropositive for HBsAg, those with a family history of HCC, those who were born in Africa and are over the age of 20 years & Patients with high serum levels of HBV DNA and ongoing hepatic injury.

Underlying cirrhosis was observed in almost 79.5% of our cases. HCC is accompanied by liver cirrhosis in 70–90% [13]. The cirrhosis along with HCC is reported in 70–86% of Indian autopsy studies. The present study is in conformity with the previous studies from Bangladesh [8] and India [9]. The strong association between cirrhosis and HCC is supported by evidence of its intermediating role in the pathogenesis of HCC because of chronic viral hepatitis. The number of patients without cirrhosis (20.5%) in the present study and an increased risk was observed for HBV marker irrespective of the cirrhosis status of the HCC patients. This result confirms that HBV is the major etiological factor associated with HCC development. These findings are in agreement with biological data. HBV plays a direct role in liver cell transformation; thus, it can lead to HCC without the development of cirrhosis [6].

Alpha-fetoprotein (AFP) is a glycoprotein, belonging to the intriguing class of onco-development protein and generally designated as tumor marker such as HCC. Our study revealed 64 % positivity and similar with is 62.9% in Murugave KG et al. [14], 58.1% in Tangkijvanich P et al. [15], 54.6% Sarma MP et al. [9], 52% in Abbasi A et al [11]. These data suggest that in patients thought to have HCC on clinical grounds, AFP levels about 400 ng/ml should strongly confirm the presence of HCC by a tissue diagnosis. However, clinicians should remember that some patients with primary hepatic cancer will have normal AFP levels, and normal or moderately elevated levels should not be used to exclude the diagnosis of HCC.

Portal vein tumor thrombus (PVTT) is a crucial factor that can worsen the prognosis of HCC because it can lead to the wide dissemination of tumors throughout the liver and cause a marked deterioration of hepatic function. Despite this marked progress in medical science, the prognosis of advanced HCC remains poor, particularly in patients with tumor thrombus in the portal vein (PV). HCC has a high frequency of PV invasion, which is reportedly observed in 11% to 42% of patients with HCC [16 - 17]. PVTT was observed in

almost 41 % of our cases. The present study is in similarity with the previous studies.

Several genome-wide association studies (GWAS) have identified a strong association between single nucleotide polymorphisms (SNPs) in and near IL28B (which encodes IFN- λ) and response to therapy [18]. As a therapeutic agent, IFN- λ might have longer and more potent effects than IFN-α. IFN- λ interacts with a trans membrane receptor to induce potent antiviral responses that are mediated through the activation of the JAK-STAT and MAPK pathways [19]. In vitro and in vivo models have shown the importance of IFN- λ in the immune response to several viral pathogens, including hepatitis C virus (HCV) and HBV [20]. To our knowledge, this was the first time in Bangladesh to analyze the genetic polymorphism in IL28B rs12979860 in the hepatitis B related hepatocellular carcinoma and showed that the frequency of CC, CT, TT was 45.5%, 38.6%,15.9% respectively and Allele of C & T frequency were 64.85% & 35.2%. Shan R et al. (2012) pointed out that the IL28B rs12979860 C/T polymorphism might affect susceptibility to the chronic HBV infection and progression of HCC. Of note, the T allele and non-CC genotypes have strong predictive effect of increasing susceptibility of chronic HBV infection and HCC [10].

HBV-related HCC is most common in developing countries like ours. Population-based vaccination programs against HBV and universal infant vaccination will have the potential to dramatically reduce the incidence of HCC in the future. Prolonged suppression of HBV replication with nucleoside or nucleotide analogs may reduce the risk of HCC in patients with chronic hepatitis B. The most important challenges are early detection and treatment. Currently, HBV related HCC is often detected late at a time when surgical interventions and liver transplantation are no longer feasible. Inexpensive, easily applied, and noninvasive biomarkers for HCC in high-risk patients would be helpful to identify patients that can be resected or more successfully treated.

CONCLUSION

Upper abdominal pain, weight loss and anorexia are significant signs that liver cirrhosis in patient is progressing to cancer. For patients with chronic Hepatitis B, the IL28 B rs 12979860 genotype test is crucial for detecting the future risk of liver cirrhosis and liver cancer.

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