ISSN : 2309-3234

TMSS MEDICAL COLLEGE JOURNAL

Volume 04, No. 01, January 2015

An Official Publication of TMSS Medical College, Bogra

TMSS Medical College Journal

January 2015

An Offical Publication
of
TMSS Medical College, Bogra

TMSS Medical College Journal

Vol.3, No. 1, January 2015

An Offical Publication of TMSS Medical College, Bogra, Bangladesh

Published by

Dr. Md. Abdul Mazid
on behalf of the TMSS Medical College

Graphic Designer

Md. Sirajul Islam
TMSS, Bogra

Printed by

TMSS Printing Press
Bogra, Bangladesh

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Cirrhosis is not Imperative for The Development of Hepatitis B Related Hepatocellular Carcinoma

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Abstract

Background: The etiological agent of HCC is known in more than 90% of cases, in South East Asia, hepatitis B is the most common cause. In Bangladesh, HBsAg positivity in the healthy population is 5.4%. The relative risk (RR) of HCC is 100 in HBV carriers versus non - carriers. In HBV carriers with cirrhosis, the RR is 961 compared to uninfected controls. Cirrhosis is an almost invariable precursor to HCC, except in chronic hepatitis B. **Objectives:** To find out the relationship of cirrhosis with the development of hepatitis B-related hepatocellular carcinoma. **Methods:** This observational study was carried out in the Department of Hepatology, BSMMU from January 2012 to December 2013. The study was approved by the Ethical Institutional Review Board (IRB) of BSMMU, Dhaka. The diagnosis of HCC was confirmed by pathological examination or AFP elevation (400ng/ml) combined imaging (CT/MRI) and diagnosis of cirrhosis was made clinically on the basis history, clinical examination and laboratory investigations including imaging or pathological examination after exclusion of hepatitis C virus infection (Anti HCV+ve) and significant alcohol intake (>20 gm. /day). All patients were HBsAg positive done by ELISA test. **Results:** A total 44 patients were included in this study. Among them, 91% were male (n=40) and 09 % were female (n=4).The mean age was 48.2 (±12.9) years. Maximum (50%) patient's ages were belonged to 35-54 years. Cirrhosis was 79.5% (n=35) and no cirrhosis was found 20.5% (n=9). The difference was statistically significant (P = 0.001) among the two groups.Imaging finding of liver size showed hepatomegaly (74%), normal size (19%) and small liver (7%). **Conclusions:** From our observation we can conclude that cirrhosis is an independent risk factor for hepatitis B virus related HCC and also shows that inactive carriers are still at risk of HCC.

Keywords: Hepatitis B; Hepatocellular carcinoma; Cirrhosis

Introduction

HCC is the sixth most common malignant tumor and the third most common cause of cancer deaths worldwide[1]. The etiological agent of HCC is known in more than 90% of cases. In South East 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].

HBV infection is a serious global health problem. About 378 million people throughout the world are chronically infected with this virus[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]. Beasley *et al.*[6], in a seminal prospective study, showed the relative risk (RR) of HCC to be about 100 in HBV carriers versus non- carriers. The yearly incidence of HCC in the HBV surface antigen (HBsAg) positive group was 0.5%, increasing to 1% by age 70. In HBV carriers with cirrhosis, the

RR was 961 compared to uninfected controls, with an incidence of HCC of 2.5% per year.

Cirrhosis is an almost invariable precursor to HCC, except in chronic hepatitis B. This has led to the concept that cirrhosis is a preneoplastic lesion or that cirrhosis is a common pathway by which different liver diseases result in HCC. The common factor linking all liver diseases with HCC would be the presence of repeated or persistent low - grade necrosis or cell injury, followed by regeneration, predisposing to an increased possibility of oncogenic mutations developing in actively dividing cells in damaged liver tissue[7].

Based on this hypothesis, we find out the relationship of cirrhosis and non-cirrhosis with the development of hepatitis B-related hepatocellular carcinoma

Materials 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, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2012 to December 2013. Aims and objectives of the study along with its procedure, risks and benefits of this study was explained to the patients and attendants in easily understandable local language (Bangla) and then informed written consent was taken from each participant. Prior to the commencement of the study, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU.

Patients were divided into two groups. Group A (Cirrhosis-related HCC) and Group B (non-Cirrhosis with HCC). The inclusion criteria were: HCC patients were recruited prospectively. The diagnosis of HCC was confirmed by á-fetoprotein elevation (>400 ng/ml) combined with computed tomography (CT) and/or magnetic resonance imaging (MRI) or Pathological examination (Biopsy/FNAC) [Figure 1] and diagnosis of cirrhosis was made by – History, examination and investigations including imaging or Pathological examination (Biopsy). 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 taking 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, BSMMU. 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 and laboratory characteristics

Table I includes the demographic and laboratory parameters of the subjects in the study within two groups, including gender, age, haemoglobin (Hb), platelet count (PLT), prothombin time (PT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, serum albumin and á-fetoprotein (AFP).The Cirrhosis related group and the other group without Cirrhosis had statistically different laboratory results for PLT, PT, INR, ALT, AST, serum bilirubin, serum albumin and á-fetoprotein ($p<0.05$).

Table I: Demographic and laboratory parameters of the subjects in the study (n=44)

Groups	Cirrhosis (n=35)	No Cirrhosis (n=9)	P value
Demographic parameters			
Gender (M/F)	32/3	8/1	.614[ns]
Age (Y) (± SD)	48.2 ± 12.8	48 ± 14.1	.206[ns]
Laboratory parameters (± SD)			
Hb (g/dl)	11.37 ± 1.8	11.7 ± 1.51	.208[ns]
PLT (10^9/L)	217.2 ± 97.6	266.6 ± 118.1	.039[s]
PT (sec)	15.37 ± 2.2	14.18 ± 2.3	.048[s]
INR	1.29 ± .19	1.19 ± .18	.045[s]
ALT (U/l)	81.5 ± 53.8	53.11 ± 33.7	.038[s]
AST (U/l)	174.9 ±166.9	37.5 ± 23.9	.012[s]
T-Bil (mol/l)	112.57 ± 122.98	26.56 ± 16.37	.041[s]
ALB (g/dl)	2.9 ± 0.6	3.5 ± 0.4	.003[s]
AFP (ng/ml)	17241.63 ± 18479	7469.5. ± 14186	.049[s]

ns= not significant, s= significant

Distribution of the study population by age range

Table II shows distribution of the study population by age range. Maximum (50%) patients' ages were belonged to 35-55 years. The mean age was found 48.20 ±12.92 years with range from 18 to 80 years. The mean age difference was not statistically significant (P=0.206) between two groups.

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

Age range	Frequency	Percent	Cumulative Percent
< 20	01	02.3	02.3
21 -30	05	11.4	13.7
31- 40	11	25.0	38.7
41- 50	11	25.0	63.7
51- 60	10	22.7	86.4
> 60	06	13.6	100.0
Total	44	100.0	100.0

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. Male was also predominant in both groups, which were 91% (32) in cirrhosis - related HCC group and 89% (08) in non-cirrhosis with HCC group. The difference was not statistically significant (P=0.614) between the two groups.

Distribution of the study population according to cirrhosis status

Figure 3 shows the cirrhosis status in the study population. Cirrhosis was 79.5% (35) and no cirrhosis was found 20.5% (9). Among cirrhosis group, Child –Pugh A, B and C was 6.8% (3), 31.8% (14) and 40.9% (18) respectively. The difference was statistically significant (P=0.001) among the two groups.

Distribution of tumor nodule in the study population

Table III shows tumor nodule in the study population by imaging methods (USG and CT/MRI). Among 44 patients 19(43%) was multiple nodules, 18(41%) was single nodule and 7(16%) was diffuse HCC. Multiple nodules 51.4% (18) was predominant among the cirrhosis group whereas single nodules 88.9% (08) was predominant among the non-cirrhosis group. The difference was statistically significant (P=0.004) among the two groups.

Table III: Distribution of tumor nodule in the study population (n = 44).

Nodule status	Groups				P value*
	Cirrhosis (n = 35)		Non-cirrhosis (n=09)		
	n	%	n	%	
Single	10	28.6	8	88.9	0.004s
ultiple	18	51.4	1	11.1	
Diffuse	07	20.9	0	0	
Total	35	100	9	100	

s=significant

*Chi square test was done to measure the level of significant

Distribution of liver size by ultrasonography (USG) in the study population

Figure 4 shows distribution of liver size by USG in the study population. Among 44 patients, hepatomegaly, normal size liver and small size liver was 74% (33), 19% (8) and 7% (3) respectively.

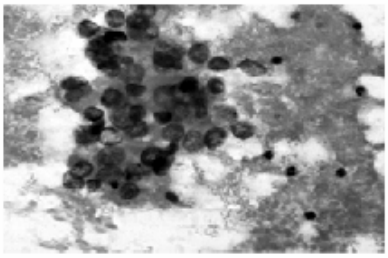

Figure 1. Cytopathic feature of Hepatocellular carcinoma (Haematoxylin and eosin stain , Courtesy: Department of Pathology, Bangabandhu Sheikh Mujib Medical University). ID no:18

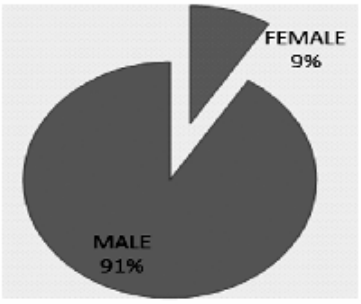

Figure 2. Gender distribution of the study population (n= 44).

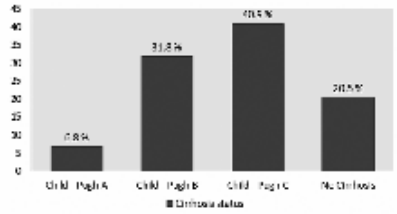

Figure 3: Distribution of the study patients according to cirrhosis status (n=44)

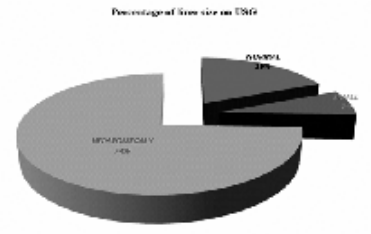

Figure 4. Distribution of Liver size by imaging (n=44)

Discussion

This is the first study from Bangladesh in which the characteristics of HBV related HCC have been studied. HBV infection accounts for most primary HCC and treating HBV infection 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

etiologic factors[8]. The age distribution of patients with HCC in the present study was similar to 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[9-13]. The male preponderance is similar to our previous Bangladeshi study and other studies from India, Pakistan and France[9-11,13,14]. 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.

Underlying cirrhosis was observed in almost 79.5% of our cases. HCC is accompanied by liver cirrhosis in 70–90%[15]. The cirrhosis along with HCC is reported in 70–86% of Indian autopsy studies. The clinical studies have shown 30–80% incidence of associated cirrhosis in HCC[15-16]. The present study is in conformity with the previous studies from Bangladesh[10] and India[11]. The strong association between cirrhosis and HCC is supported by the evidence of its intermediating role in the pathogenesis of HCC because of chronic viral hepatitis[20]. The number of patients without cirrhosis (20.5%) in the present study is similar to those in Indian clinical and autopsy studies[11, 18, 21] and in a study of Kumar et al.[22]. 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[23]. Like previous studies most of the lesions were multiple in cirrhotic group and single in non-cirrhotic group. However, three fourth of the patients had hepatomegaly, one-fourth having normal size and small size liver.

From our observation we can conclude that cirrhosis is an independent risk factor for hepatitis B virus related HCC and also shows that inactive carriers are still at risk of HCC. Limitation of this study is its small sample size and single center.

Conclusion

HBV is the major risk factors for HCC in Bangladesh and significant risk increase was evident in the absence of cirrhosis. Hepatocellular carcinoma in the early 21st century can be considered a potentially curable disease. Early detection of HCC leads to treatment responses are more durable and cure is more frequently possible. Surveillance is effective for enhancing survival. Therefore surveillance for HCC should be standard care for all patients with cirrhosis and also in hepatitis B patients without cirrhosis.

Conflict of Interest Statement

No potential conflicts of interest are disclosed.

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