Hepatitis B Virus Infection can Cause Hepatocellular Carcinoma in Less Advanced Liver Cirrhosis: A Comparative Study of 142 Patients from North India

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Background and aims: **The clinical profile of patients with hepatocellular carcinoma (HCC) may differ depending on the etiology of HCC. There is no study from India comparing the clinical profile of patients of HCC due to hepatitis B virus (HBV) infection with other etiologies.** ***Methods:*** **We retrospectively reviewed the records of patients clinically diagnosed as HCC between Nov 2000 and Dec 2012 admitted under a single unit of Department of Gastroenterology at our hospital. We compared the clinical presentation of patients of Hepatitis B virus etiology (HBV group) with other etiologies (Non-HBV group).** ***Results:*** **One hundred and forty-two patients were included (median age 60 years [range 30–83], 92% males). The etiology was HBV in 56 (39%) and among the non-HBV group (*n* = 86, 61%) the etiological spectrum was following: alcohol 31 (22%), cryptogenic 26 (18%), HCV 27 (19%), and miscellaneous 2 (1%). The median age of presentation was significantly less for HBV group than in non-HBV (56 [30–77] vs. 62 [42–83] years, *P* < 0.01). Clinical evidence of cirrhosis was significantly less common in the HBV group than non-HBV group (74% vs 98%, *P* < 0.01). HBV group had lower CTP score than non-HBV (median CTP score 7 vs 8,*P* < 0.05). Ascites was more common in non-HBV group than HBV group (65% vs 43%, *P* = 0.018). The BCLC staging was: A 13%, B 23%, C 35%, and D 29%, and there was no difference in tumor characteristics or BCLC staging between HBV or the non-HBV group.** ***Conclusions:*** **HBV is a common cause of HCC in India, accounting for 39% of cases. The tumor characteristics of HCC due to HBV is similar to other etiologies, however, HBV causes HCC at an earlier age, and in less advanced or even absence of cirrhosis, thus further consolidating the directly carcinogenic potential of HBV. (J Clin Exp Hepatol 2013;3:288–295)**

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most frequent cause of cancer death.[1,2] Each year, HCC is diagnosed in more than half a million people worldwide.[3] There is a striking parallel between the geographical distribution of the rates of chronic Hepatitis B virus (HBV) infection and that of HCC.[4] Most of the burden of disease (85%) is borne in developing countries, with the highest incidence rates reported in regions where infection with HBV is endemic: Southeast Asia and sub-Saharan Africa.[2] India lies in the intermediate endemic zone of HBV infection with hepatitis B surface antigen (HBsAg) carrier frequency of 2–4% in the community.[5] In India, as per the National Cancer Registries maintained by the Indian Council of Medical Research, HCC forms 1.6% of all cancers in the country.[6]

Major risk factors for hepatocellular carcinoma include infection with HBV or HCV, alcoholic liver disease, and nonalcoholic fatty liver disease.[3] In most cases, hepatocellular carcinoma develops within an established background of cirrhosis (70–90% of all patients).[7] However, because HBV is an oncogenic virus, it can cause HCC in the absence of cirrhosis. Factors associated with increased risk of HBV associated HCC include demographic characteristics (male sex and older age), lifestyles (heavy alcohol consumption and smoking), viral factors (genotype C, D F, high level of HBV DNA, core/precore mutation) and clinical factors (cirrhosis, elevated alpha-fetoprotein (AFP) and alanine aminotransferase (ALT)). HBV-related HCC has extremely poor prognosis with median survival less than 16 months. Survival rates of HBV-related HCC ranged from 36% to 67% after 1 year and from 15% to 26% after 5 year of diagnosis.[8]

The clinical profile of patients with HBV-related HCC may differ from those of HCC due to other etiologies. Since India lies in the intermediate endemic zone of HBV

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Abbreviations: HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; AFP: alpha-fetoprotein; ALT: alanine aminotransferase; HIS: hospital information system; FNAC: fine needle aspiration cytology; BCLC: Barcelona Clinic Liver Cancer
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infection[5] and more than 50% cases of HCC in India are due to HBV infection,[9] it is pertinent that the profile of HBV-related HCC in India be adequately studied. The present study was designed to investigate the characteristics of HBV-related HCC as compared to HCC due to other etiologies, presenting to a tertiary care center in north India.

PATIENTS AND METHODS

Patients

From June 2000 to December 2012, all consecutive patients of HCC who were examined as inpatients at one of the two units of the Department of Gastroenterology and Hepatology, Sir Ganga Ram Hospital, New Delhi, a private tertiary referral center in North India, were considered for this retrospective study. Their records were retrieved and analyzed. The records of patients admitted prior to 2010 were hand-written in specified proforma, while patients admitted from 2010 onwards had electronic records available on the hospital information system (HIS).

The diagnosis of HCC was based on clinical, histologic, serologic or imaging findings. Only those patients were included in the study whose records had a clear description of the presentation and etiology of HCC. We excluded patients who had incomplete records of clinical presentation, laboratory investigations or imaging findings. The included patients were divided into two groups: 'HBV group' included those cases of HCC whose etiology was HBV (either alone or in combination with other factors). 'non-HBV group' included cases of HCC due to other etiologies.

Patient Evaluation

Clinical evaluation included detailed history and physical examination. Investigations included complete blood count, liver function tests and viral markers for HBV and HCV. Upper gastrointestinal endoscopy was done in most patients to detect the presence of esophageal varices. Serum alfa-fetoprotein (AFP) levels were also recorded if available. The reports of chronic hepatitis viral markers: HBsAg and anti-HCV were recorded for etiologic work-up. Radiological work-up comprised of an abdominal ultrasonography and triple-phase contrast-enhanced CT abdomen. Diagnosis of cirrhosis was made on the basis of clinical, biochemical, radiologic or endoscopic findings. HBV cirrhosis was diagnosed when detectable HBsAg in serum was present. HCV cirrhosis was diagnosed when detectable anti-HCV, HCV RNA or both was present in serum. Alcoholic cirrhosis was labeled when the patient had a history of alcohol consumption of ≥80 g/day for more than 5 years. Severity of cirrhosis was graded based on the Child-Pugh classification.[10] The diagnostic criteria for HCC were any of the following: hypervascular liver mass on triple-phase contrast-enhanced CT abdomen (with or without raised AFP) or fine needle aspiration cytology (FNAC). Staging of HCC was done according to the Barcelona Clinic Liver Cancer (BCLC) staging classification.[11]

Statistical Methods

The study was designed to compare the clinical presentation of patients of HBV etiology (HBV group) with other etiologies (non-HBV group). Continuous data was expressed as median (range) and compared using Mann–Whitney U test. Categorical data was expressed as number (percent) and compared using Fisher Exact test. Statistical analysis was performed using SPSS 17 (Chicago, Illinois).

RESULTS

Patients

A total of 156 patients were admitted from June 2000 to December 2012 in a single unit of the department of Gastroenterology and Hepatology of Sir Ganga Ram Hospital, New Delhi, India with the diagnosis of HCC. One hundred and forty-two patients were included in the study, and rest 14 patients were excluded as their records were incomplete. Eighty-six of these 142 patients were admitted from 2010 onwards when HIS became functional and rest of the 56 included patients were admitted from 2000 to 2009 when only hand-written proforma-based records were available and hence these 56 patients were not consecutive. Ten of the excluded patients belonged to the period from 2000 to 2009 and rest 4 belonged to the later period.

Etiology of Hepatocellular Carcinoma

The etiology of HCC, based on the clinical and laboratory parameters in these 142 patients, is given in Table 1. The most common etiologic group was viral (HBV or HCV), either alone or in combination, which was present in 58.5% (83/142) patients. Within the viral etiology group the most common virus responsible was HBV as single agent, which was present in 34.5% patients (49/142). HCV as single agent was responsible in 15.5% patients (22/142). Combination of HBV with HCV, or either virus with alcohol, was responsible in 8.4% patients (12/142).

After viral etiology, the next most common etiology was alcoholic liver disease, present in 21.8% patients (31/142), followed by cryptogenic liver disease, present in 18.3% patients (26/142). Budd-Chiari syndrome was responsible for HCC in one patient and autoimmune liver disease in another patient (both clubbed together under the category of miscellaneous etiology) (Table 1).

Demographic Characteristics

The median age of included patients was 60 years (range 30–83 years) (Table 2). Majority of the patients (75% [106/142]) belonged to the age group of 50–70 years. Only 14% belonged to the age group of <50 years and rest 11%

Table 1 Etiology of HCC.

Etiology groups	Frequency (n = 142)	Etiological Sub-groups	Frequency (n = 142)
Viral etiology (either alone or in combination)	83 (58.5%)	HBV	49 (34.5%)
		HCV	22 (15.5%)
		HCV + HBV	4 (2.8%)
		HCV + ALD	5 (3.5%)
		HBV + ALD	3 (2.1%)
Alcohol etiology	31 (21.8%)		
Cryptogenic etiology	26 (18.3%)		
Miscellaneous etiology	2 (1.4%)	BCS	1 (0.7%)
		Autoimmune	1 (0.7%)

Abbreviations: ALD, alcoholic liver disease; BCS, Budd-Chiari syndrome; HBV, hepatitis B virus; HCV hepatitis C virus.

belonged to the age group of >70 years. The median age of the patients of viral etiology (57 [30–77] years) was significantly less than the alcohol (61 [46–76] years) and cryptogenic etiology (66 [54–83] years). Relatively younger patients (<50 years old) were more common in the viral etiologic group (21%) than the other etiologic groups.

Ninety-two percent patients (130/142) were males and rest 8% (12/142) were females. All patients with alcohol etiology were males.

Presence of Diabetes Mellitus

The prevalence of diabetes mellitus was found to be 25% in HCC patients (35/142) (Table 2). This prevalence is much higher than the prevalence of diabetes mellitus in general population of India (7.8%).[12] When frequency of diabetes mellitus was analyzed for different etiology groups it was found that the prevalence of diabetes was higher ($P < 0.05$) when the etiology was cryptogenic (58% [15/26]) compared to other etiologies. There was no significant difference in the prevalence of diabetes in alcohol group (19% [6/31]) compared to viral group (17% [14/83]; $P > 0.05$).

Presence of Cirrhosis

Clinical or imaging evidence of cirrhosis was found in 89% patients (126/142) and in rest 11% patients HCC developed in presumably non-cirrhotic livers (Table 2). Cirrhosis was present in all patients of alcohol etiology, while cirrhosis was present in 83% in viral etiology ($P < 0.05$ compared to alcohol) and 92% in cryptogenic etiology (P = NS compared to alcohol). The two patients (8%) in the cryptogenic etiology who did not have cirrhosis had fibrolamellar variant of HCC.

Severity of Underlying Liver Disease

The median Child-Turcotte-Pugh (CTP) score was 8 (range 5–14) and the median MELD score was 14 (range 6–36). The CTP score in patients of alcohol etiology (10 [range 6–14]) was significantly higher than the CTP score in viral etiology (7 [range 5–13];$P < 0.05$) or in cryptogenic etiology (8 [range 5–11];$P < 0.05$). Similarly the MELD score in patients of alcohol etiology (18 [range 8–36]) was significantly higher than in viral etiology (13 [range 6–35];$P < 0.05$) and cryptogenic etiology (12 [range 7–30];$P < 0.05$). Overall, 30% (43/142) patients belonged to CTP class A, 45% (63/142) patients belonged to CTP class B, and 25% (36/142) patients belonged to CTP class C. In the alcohol etiology group, patients with CTP class C were more common (52%) than in viral etiology (20%) or cryptogenic etiology (12%) ($P < 0.05$, for both).

Ascites was present in 58% patients (83/142) and hepatic encephalopathy at admission was present in 10% patients (14/142). Both these complications were equally distributed in all the etiologic groups.

Upper GI endoscopy was done in 79 patients and esophageal varices were present in 76% patients (60/79). Sixteen percent patients (23/142) had history of variceal bleeding in past (bleeders). Frequency of variceal bleeding was significantly higher in alcohol etiologic group (29%) than the viral group (12%).

The median serum bilirubin level was 2.0 (range 0.3–31.6) mg/dL, INR level was 1.4 (range 0.9–4.6) and albumin 3.0 (range 1.3–4.9) g/dL. Serum bilirubin was significantly higher in the alcohol group (3.3 [0.6–20.0] mg/dL) than the viral group (1.9 [0.3–31.6] mg/dL). Both, INR and serum albumin values were worse in the alcohol group than the viral and cryptogenic groups. Hemoglobin, WBC, and platelet counts were similar in all the etiologic groups, while median serum creatinine was higher in the alcohol group than the viral group.

Tumor Characteristics

The tumor characteristics of the patients are given in Table 3. Single tumor was found in only 45% of patients while in majority (55%) the tumor were two or more in

Table 2 Demographic, clinical and laboratory parameters in all HCC patients and in patients of different etiologic groups.

Parameters	All patients (*n* = 142)	Viral etiology (*n* = 83)	Alcohol etiology (*n* = 31)	Cryptogenic etiology (*n* = 26)	Miscellaneous etiology (*n* = 2)
Age, years[a,b]	60 (30–83)	57 (30–77)	61 (46–76)	66 (54–83)	56 (50–61)
Age group[b]					
<50 years	20 (14%)	17 (21%)	3 (10%)	0 (0%)	0 (0%)
50–70 years	106 (75%)	60 (72%)	24 (77%)	20 (77%)	2 (100%)
>70 years	16 (11%)	6 (7%)	4 (13%)	6 (23%)	0 (0%)
Gender					
Males	130 (92%)	73 (88%)	31 (100%)	25 (96%)	1 (50%)
Females	12 (8%)	10 (12%)	0 (0%)	1 (4%)	1 (50%)
Diabetes mellitus[b,c]	35 (25%)	14 (17%)	6 (19%)	15 (58%)	0 (0%)
Cirrhosis[a]	126 (89%)	69 (83%)	31 (100%)	24 (92%)	2 (100%)
CTP score[a,c]	8 (5–14)	7 (5–13)	10 (6–14)	8 (5–11)	6 (6–7)
MELD score[a,c]	14 (6–36)	13 (6–35)	18 (8–36)	12 (7–30)	10 (10–11)
CTP class[a,c]					
A	43 (30%)	27 (33%)	5 (16%)	10 (38%)	1 (50%)
B	63 (45%)	39 (47%)	10 (32%)	13 (50%)	1 (50%)
C	36 (25%)	17 (20%)	16 (52%)	3 (12%)	0 (0%)
Ascites	83 (58%)	48 (58%)	21 (68%)	14 (54%)	0 (0%)
HE	14 (10%)	5 (6%)	5 (16%)	4 (15%)	0 (0%)
Varices present	60/79 (76%)	34/45 (76%)	14/16 (88%)	11/17 (65%)	1/1 (100%)
Bleeders[a]	23 (16%)	10 (12%)	9 (29%)	4 (15%)	0 (0%)
Serum bilirubin, mg/dL[a]	2.0 (0.3–31.6)	1.9 (0.3–31.6)	3.3 (0.6–20.0)	1.7 (0.4–23.2)	1.8 (0.7–3.0)
INR[a]	1.4 (0.9–4.6)	1.4 (0.9–4.6)	1.6 (1.0–3.2)	1.3 (0.9–3.3)	1.0 (1.0–1.1)
Serum albumin, g/dL[a,c]	3.0 (1.3–4.9)	3.1 (1.4–4.9)	2.8 (1.3–4.0)	3.2 (1.4–3.8)	3.4 (2.9–3.8)
Hb, g/dL	11.1 (5.4–16.7)	11.2 (5.4–16.7)	10.9 (6.5–16.2)	10.4 (7.4–14.6)	11.4 (11.0–11.8)
WBC, n/mm^3	6.4 (1.0–27.5)	6.3 (1.0–22.4)	6.5 (2.7–27.5)	6.7 (2.8–15.2)	5.2 (4.3–6.0)
Platelets, n×10^3/mm^3	109 (15–740)	109 (20–680)	109 (15–740)	114 (35–411)	162 (88–235)
Serum creatinine, mg/dL[a]	1.0 (0.4–5.0)	1.0 (0.4–5.0)	1.2 (0.5–2.6)	1.0 (0.5–2.8)	1.1 (1.0–1.3)

Abbreviations: CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy.
Notes: All values are expressed in median (range) or number (%).
[a]$P < 0.05$ for viral vs alcohol etiology.
[b]$P < 0.05$ for viral vs cryptogenic etiology.
[c]$P < 0.05$ for alcohol vs cryptogenic etiology.

number (multicentric) and more commonly involving both the liver lobes (in 50% patients). The median size of the largest lesion was 6.8 cm (range 1.0–16.2 cm). If both lobes were not involved, then right lobe of the liver was the predominant site of the tumor. Portal vein thrombosis was present in 55 (39%) patients. Distant metastases were present in 18% patients (25/142). Reports of alfa-fetoprotein were available in 69 patients and the median value was 458 IU/mL. The median AFP in the cryptogenic etiology was significantly lower than the viral etiology. Rest all parameters of tumor characteristics were similar in all the broad etiologic groups.

Barcelona Clinic Liver Cancer Staging

BCLC staging was available for 126 patients. Most patients belonged to BCLC class C (35%, 44/126) followed by BCLC class D (29%, 36/126). The distribution of BCLC classes in all the etiologic groups were similar, except, in the alcoholic group BCLC-D stage

Table 3 Tumor characteristics in different etiologies.

Parameters	All patients (*n* = 142)	Viral etiology (*n* = 83)	Alcohol etiology (*n* = 31)	Cryptogenic etiology (*n* = 26)	Miscellaneous etiology (*n* = 2)
Lesions					
Single	51/114 (45%)	26/66 (39%)	15/23 (65%)	10/24 (42%)	–
Multi	63/114 (55%)	40/66 (61%)	8/23 (35%)	14/24 (58%)	1/1 (100%)
Median size of largest lesion, cm	6.8 (1.0–16.2)	6.0 (1.0–14.7)	8.0 (1.5–14.2)	5.8 (1.5–16.2)	8.6 (8.6–8.6)
Lobes					
Both	53/106 (50%)	36/63 (57%)	4/19 (21%)	12/23 (52%)	1/1 (100%)
Right	38/106 (36%)	20/63 (32%)	9/19 (47%)	9/23 (39%)	0/1 (0%)
Left	15/106 (14%)	7/63 (11%)	6/19 (32%)	2/23 (9%)	0/1 (0%)
PVT	55 (39%)	32 (39%)	14 (45%)	8 (31%)	1 (50%)
Median AFP, IU/mL (*n* = 69)[b]	458 (1–73072)	758 (1–73072)	235 (3–2708)	49 (2–13320)	29635 -
Distant metastasis	25 (18%)	16 (19%)	4 (13%)	4 (15%)	1 (50%)
BCLC stage[a]					
A	17/126 (13%)	12/73 (16%)	3/28 (11%)	2/24 (8%)	0/1 (0%)
B	29/126 (23%)	16/73 (22%)	2/28 (7%)	11/24 (46%)	0/1 (0%)
C	44/126 (35%)	28/73 (38%)	7/28 (25%)	8/24 (33%)	1/1 (100%)
D	36/126 (29%)	17/73 (23%)	16/28 (57%)	3/24 (13%)	0/1 (0%)

Abbreviations: PVT, portal vein thrombosis; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.
Notes: All values are expressed in median (range) or number (%).
[a]$P < 0.05$ for viral vs alcohol etiology.
[b]$P < 0.05$ for viral vs cryptogenic etiology.

was significantly more common than the viral etiology (Table 3).

Hepatitis B Virus Etiology Versus Non-hepatitis B Virus Etiology

Patients with HBV as etiology alone (*n* = 49) were compared with patients with non-HBV etiologies (*n* = 86) for patient characteristics (Table 4) and tumor characteristics (Table 5). The age of the patient in the HBV group was 56 years (range 30–77 years) which was significantly lower than the age of patients of non-HBV etiology group (62 [range 42–83] years; $P < 0.01$). In the HBV group 22% of patients (11/49) were less than 50 years of age and only 4% (2/49) were above 70 years; while in the non-HBV group only 8% patients (7/86) were less than 50 years of age and 16% (14/86) were above 70 years of age (Table 4).

HCC was present in the non-cirrhotic livers more commonly in the HBV group than other group (26% versus 2%, $P < 0.01$). The two patients in the non-HBV group who developed HCC in absence of cirrhosis had the fibrolamellar variant of HCC. In addition, the liver disease was of less severity in the HBV group with median CTP score of 7 in the HBV group than non-HBV etiology group (median CTP score 8). The high CTP score in the non-HBV group was mainly due to higher number of patients with hepatic encephalopathy (14% vs 4%, $P = 0.084$) and ascites (65% vs 43%, $P = 0.018$). In addition, serum albumin was significantly lower in the non-HBV group than in the HBV group (Table 4).

The tumor characteristics and the BCLC staging was similar between the HBV and the non-HBV etiology groups (Table 5).

DISCUSSION

The results of our study suggest that HBV is a common cause of HCC presenting to our tertiary care hospital in north India, accounting for 39% of cases, either alone or in combination with other etiologic agents. The tumor characteristics of HCC due to HBV is similar to other etiologies, however, HBV caused HCC at an earlier age, and in less advanced or even absence of cirrhosis, thus confirming the directly carcinogenic potential of HBV.

There have been only few studies from India on etiological and clinical profile of patients of HCC from India. The largest study is by Paul et al[9] from north India where the author analyzed the clinical profile, etiology and therapeutic outcome in 324 hepatocellular carcinoma patients presenting to their center. In their series, HBV alone was found

Table 4 Demographic, clinical and laboratory parameters in HCC patients of HBV etiology (alone) compared with non-HBV etiologies.

Parameters	HBV etiology (*n* = 49)	Non-HBV etiology (*n* = 86)	*P* value
Age, years	56 (30–77)	62 (42–83)	<0.01
Age group			0.013
<50 years	11 (22%)	7 (8%)	
50–70 years	36 (74%)	65 (76%)	
>70 years	2 (4%)	14 (16%)	
Gender			0.352
Males	43 (88%)	80 (93%)	
Females	6 (12%)	6 (7%)	
Diabetes mellitus	8 (16%)	26 (30%)	0.099
Cirrhosis	36 (74%)	84 (98%)	<0.01
CTP score	7 (5–13)	8 (5–14)	0.010
MELD score	13 (7–35)	15 (6–36)	0.193
CTP class			0.029
A	22 (45%)	20 (23%)	
B	18 (37%)	40 (47%)	
C	9 (18%)	26 (30%)	
Ascites	21 (43%)	56 (65%)	0.018
HE	2 (4%)	12 (14%)	0.084
Varices present	17/25 (68%)	39/50 (78%)	0.475
Bleeders	4 (8%)	18 (21%)	0.057
Serum bilirubin, mg/dL	1.8 (0.3–31.6)	2.2 (0.4–23.2)	0.118
INR	1.4 (0.9–3.2)	1.4 (0.9–4.6)	0.403
Serum albumin, g/dL	3.3 (1.4–4.9)	2.9 (1.3–4.3)	0.017
Hb, g/dL	10.7 (6.7–16.7)	11.2 (6.5–16.2)	0.849
WBC, n/mm^3	6.3 (1.0–22.4)	6.4 (1.1–27.5)	0.738
Platelets, n × 10^3/mm^3	110 (20–347)	105 (15–740)	0.891
Serum creatinine, mg/dL	0.9 (0.4–5.0)	1.1 (0.5–2.8)	0.099

Abbreviations: CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy.
Notes: All values are expressed in median (range) or number (%). Seven patients with mixed etiology involving HBV (i.e. HBV + HCV and HCV + ALD) were excluded from analysis.
Notes: All values are expressed in median (range) or number (%). Seven patients with mixed etiology involving HBV (i.e. HBV + HCV and HCV + ALD) were excluded from analysis.

to be etiologic agent in 51% of cases, and in another 8% of cases HBV was the etiologic agent in combination with other etiologic factors like alcohol and / or HCV. In another large series of HCC from India by Kumar et al,[13] out of 191 patients of HCC, the etiologic work-up was available in 147 patients. HBV was the most common viral etiologic agent associated with HCC, observed in 107 of 147 (73%) patients either alone or as cofactor with alcohol or HCV. In another series of 266 HCC patients, Asim et al[14] from north India found that 58% of HCC patients were hepatitis B positive. In our study HBV accounted for 39% of HCC patients. Thus all the studies from India suggest that HBV infection is the most important risk factor of HCC in India. The slightly lower percentage of HBV in our study than the above three studies[9,13,14] maybe due to referral bias. Since HBV is commoner in the lower socio-economic strata, most patients of HBV get referred to government hospitals from where these three studies have been reported; while ours is a private hospital.

The current global estimate of the number of HBV-infected individuals is 350 million.[15,16] Chronic HBV infection accounts for about 60% of the total liver cancer in developing countries and for about 23% of the cancer in developed countries, while hepatitis C virus (HCV) infection accounts for about 33% of the total liver cancer in developing countries and for about 20% in developed countries.[17,18] Chronic carriers of HBV have up to a 30-fold increased risk of HCC[19] and approximately 25% of

Table 5 Tumor characteristics in HCC patients of HBV etiology (alone) compared with non-HBV etiologies.

Parameters	HBV etiology (*n* = 49)	Other etiology (*n* = 86)	*P* value
Lesions			0.275
Single	14/36 (39%)	36/72 (50%)	
Multi	22/36 (61%)	36/72 (50%)	
Size of largest lesion, cm	8.0 (1.2–14.0)	5.6 (1.0–16.2)	0.272
Lobes			0.487
Both	20/36 (56%)	28/64 (44%)	
Right	12/36 (33%)	25/64 (39%)	
Left	4/36 (11%)	11/64 (17%)	
PVT	19 (39%)	34 (40%)	1.000
AFP, IU/mL (*n* = 64)	1079 (1–73072)	227 (2–41797)	0.255
Distant metastasis	9 (18%)	15 (17%)	1.000
BCLC stage			0.321
A	5/42 (12%)	12/78 (15%)	
B	9/42 (21%)	17/78 (22%)	
C	19/42 (45%)	23/78 (29%)	
D	9/42 (21%)	26/78 (33%)	

Abbreviations: PVT, portal vein thrombosis; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.
Notes: All values are expressed in median (range) or number (%). Seven patients with mixed etiology involving HBV (i.e. HBV + HCV and HCV + ALD) were excluded from analysis.

these individuals will develop HCC.[20] India lies in the intermediate endemicity zone of HBV infection[21] and the overall HBV positivity rate in India had often been quoted as being 4.7 %.[22] A recent meta-analysis quoted a rate of 2.4%.[23] Taking a conservative estimate of 2% and India's current population as 1.2 billion,[24] more than 6 million people are likely to develop HCC.

The prevalence of cirrhosis in persons with HCC is about 80%–90% in autopsied series worldwide, and, therefore, approximately 10%–20% of cases of HCC develop in persons without cirrhosis.[25,26] The annual risk of HBV-induced HCC varies according to the presence or absence of concomitant cirrhosis. It is estimated that in areas of high HBV endemicity, persons with cirrhosis have an approximately 16-fold higher risk of HCC than the inactive carriers, and a 3-fold higher risk for HCC than those with chronic hepatitis but without cirrhosis.[25] In HBV carriers without cirrhosis, the risk is 0.02–0.3% in Caucasians and 0.4–0.6% per year in Asians. In those with cirrhosis, the risk is 2.2% and 3.7% respectively in Caucasians and Asians.[4] We in our study found that in up to 25% patients of HCC due to HBV, there was no cirrhosis. In addition, we found that the liver disease was less advanced in HBV group than non-HBV group. Both these observations from our study point towards direct oncologic potential of HBV.

It has become evident now that HBV viral load >2000 IU/mL is associated with a high risk of malignant transformation.[4] Although the mechanisms of oncogenesis of HBV remain obscure, several factors have been identified to be associated with a high risk of developing HCC among chronic hepatitis B (CHB) patients. HBV exerts its oncogenic potential through a multi-factorial process, which includes both indirect (necro-inflammation and regeneration injury) and direct (by integration of its DNA in the host genome) mechanisms that likely act synergistically.[15,27] That HCC can develop in non-cirrhotic HBV-infected patients, favors a direct carcinogenic effect of HBV primarily attributed to its ability to integrate into the human genome.[28] Integrated HBV sequences have been found in the host chromosome of 80%–90% of HBV-related HCC.[29] This integration can cause rearrangement of host genomic DNA, which might confer a selective growth advantage on target cells, leading to the development of preneoplastic nodules, or provide an additional step in tumor progression.[30] HBV integrations appear to be partially preferential to particular genomic regions that encode cellular regulatory genes of importance in cell proliferation, differentiation, and viability.[28]

We staged the patients as per the BCLC classification[11] and found that up to two third of patients belonged to BCLC-C or -D, when only palliative treatment can be offered. Only 13% patients present in early stage (BCLC-A) who are candidates for curative treatment options. We did not find any difference in BCLC staging of HBV and non-HBV HCC. The tumor characteristics were also similar in the HBV and non-HBV groups. Thus our study shows

that HBV, even though causes HCC in less advanced cirrhosis, nevertheless, the tumor properties are similar to non-HBV etiologies.

There are a few limitations in our study. First, this being a retrospective study, the completeness of the parameters depends on the availability of data. Hence, all patients did not undergo, the entire set of investigations, and we had to be content with limited data (e.g. AFP level was available in only 69 patients). Secondly, a few patients with cryptogenic etiology of HCC may have been occult-HBV-HCC cases. Since, IgG-HBc was not done in most patients we do not know how many such cases may have been present.

In conclusion, HBV is a common cause of HCC in India, accounting for more than one third of cases. The tumor characteristics of HCC due to HBV is similar to other etiologies, however, HBV causes HCC at an earlier age, and in less advanced or even absence of cirrhosis, thus confirming the directly carcinogenic potential of HBV. Since, India has a large HBV-infected population, large scale measures to prevent HBV-related are HCC are urgently needed.

CONFLICTS OF INTEREST

All authors have none to declare.

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