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ORIGINAL ARTICLE

Risk factors for non-alcoholic fatty liver disease are common in patients with non-B non-C hepatocellular carcinoma in India

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Abstract

Aim of the study The aim of the study was to analyze the prevalence of risk factors for non-alcoholic fatty liver disease (NAFLD) in patients with non-B non-C hepatocellular carcinoma (HCC).

Methods Between June 2012 and November 2014, patients with HCC, negative for hepatitis B surface antigen and hepatitis C virus antibody, were included in this study. All patients were assessed for risk factors for NAFLD such as diabetes mellitus (DM), hypertension, dyslipidemia, metabolic syndrome, and obesity.

Results Forty-seven patients with non-B non-C HCC (males, 37; age, 60±10 years; mean±SD) were studied. Model for end-stage liver disease score was 11±4. Twenty-five patients were in Child's class A. History of significant alcohol intake was noted in 11 (23%) patients. Prevalence of risk factors for NAFLD were obesity 24 (51%), DM 22 (47%), metabolic syndrome 21 (45%), hypertension 16 (34%), and dyslipidemia 13 (28%). Forty (85%) patients had at least one risk factor for NAFLD. The mean duration of at least one NAFLD risk factor was 7.5 years, prior to diagnosis of HCC. Thirteen (28%) patients were positive for anti-HBc; however, none of the study patients had detectable HBV DNA in blood.

Conclusions Eighty-five percent of the patients with non-B non-C HCC had at least one risk factor for NAFLD. None of the study patients had occult hepatitis B infection. NAFLD is emerging as the major etiological contributing factor for non-B non-C HCC in India.

Keywords Hepatocellular carcinoma · NAFLD · Non-B non-C HCC · Occult hepatitis B

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Introduction

Hepatocellular carcinoma (HCC) contributes to 20% of cancers across the globe and is the third commonest cause of cancer-related mortality worldwide [1]. Nearly 75% of HCC are linked to hepatitis B and C viruses [2]. However, there is still sizeable number of patients with HCC who have absence of viral markers in their blood and are termed to have non-B non-C HCC [3]. Non-B non-C HCC can be due to a variety of etiological causes including non-alcoholic fatty liver disease (NAFLD), alcohol, and cryptogenic causes. NAFLD is part of the liver pathophysiology in metabolic syndrome [4].

Occult hepatitis B infection is also recognized as a risk factor for HCC [5]. The prevalence of occult hepatitis B infection in HBsAg-negative HCC patients in USA (where the prevalence of chronic hepatitis B is low) is 16%, while in China (where hepatitis B is endemic), it may be as high as 70% [1, 6].

Studies of non-B non-C HCC from different countries in Asia suggest different causative factors. In Japan, risk factors of NAFLD are among the main causes for developing non-B non-C HCC [7], while in Korea, occult hepatitis B infection is

more common [8]. Although multiple studies on the cause of HCC have been done in developed countries, data from developing countries is still scarce, especially in non-B non-C sub-group. In India, there has been a recent trend of increasing diabetes and metabolic syndrome [9, 10], and the prevalence of these conditions is not clearly known in HCC patients in India. According to WHO, the prevalence of diabetes mellitus in India in 2015 was 8.7% [11], and currently, India is considered as one of the countries with the highest number of diabetics in the world. Various studies from India have estimated the prevalence of NAFLD, metabolic syndrome, hypertension, and obesity in general population to be 5% to 28% [12], 16% to 31% [13], 17% to 29% [14], and 24% to 31% [15], respectively. In this study, we studied the prevalence of risk factors for NAFLD and of occult hepatitis B infection in patients with non-B non-C HCC.

Methods

Study design and eligibility criteria

This prospective, cross-sectional study was done between June 2012 and November 2014 in the Departments of Gastroenterology and Hepatology, Christian Medical College Hospital, Vellore, a tertiary care hospital in southern India. All adult patients (>18 years) with a diagnosis of non-B non-C HCC presenting to the outpatient department were enrolled in the study after informed consent. The diagnosis of HCC was based on imaging techniques, as per the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines [16, 17], which is either a dynamic CT or MR scan of the liver showing intense arterial uptake of the focal lesion followed by "washout" of contrast in the venous-delayed phases. Non-B non-C HCC patients were defined as those who satisfied the criteria for the diagnosis of HCC, who tested negative for HBsAg and HCV antibody. Any patient unwilling to participate in the trial or with uncertain diagnosis of HCC was excluded from the study.

Etiological analysis of non-B non-C HCC

The various etiologies for HCC analyzed in patients with non-B non-C HCC were as follows:

Risk factors for NAFLD: The following five risk factors were screened in all patients: hypertension, diabetes, dyslipidemia, obesity, and metabolic syndrome [18, 19]. To classify the severity of obesity, we used the suggested cut-offs of body mass index for Asian Indians [19] according to which the normal BMI was within 18.0–22.9 kg/m^2, overweight between 23.0 and 24.9 kg/m^2, and obesity if more than 25 kg/m^2. Weight prior to the HCC diagnosis was taken for calculating BMI, to overcome the possible effect of cancer-associated cachexia. Lifetime body weight was defined as the number of years of being overweight or obese [20].

Occult hepatitis B infection was defined as the presence of HBV DNA in the serum of individuals who were HBsAg-negative [21]. Detailed histories of risk factors for NAFLD and of alcohol intake were obtained by direct interviews with patients. History of ingestion of >60 g/day of alcohol for >10 years in men and >20 g/day for >10 years in women was considered as significant alcohol intake [22].

Patients with shrunken coarse liver on imaging or cirrhosis on liver histopathology were considered to have cirrhosis. We considered presence of NAFLD risk factor in patients with non-B non-C HCC as HCC attributable to NAFLD. Patients who had HCC without any evident risk factor for causation were termed cryptogenic HCC.

Evidence of NAFLD on liver histology

When deemed necessary by the clinician, on a case by case basis, ultrasound-guided liver biopsies were taken from the focal liver lesion to confirm/better characterize the malignant lesion. In these patients, separate biopsies were not taken from normal liver tissue adjacent to tumor. Six patients underwent liver transplantation and one underwent surgical resection. For the purpose of this study, we looked for evidence of NAFLD on histology, both in the liver tissue adjacent to the tumor and within the tumor.

Statistical methods

Data was analyzed using SPSS version 15. Continuous variables were depicted as mean±SD and categorical variables as numbers (percentage). Chi-square test was the test used to assess the significant differences in categorical variables between two groups. Odds ratio and 95% confidence intervals were calculated and a 'p'-value less than 0.05 was considered statistically significant. All reported p-values were two-sided.

The study was approved by the research and ethics committees of our institution.

Results

One hundred and thirty-eight consecutive patients with HCC were screened during the study period, of which 60 patients had non-B non-C HCC. From the latter, 13 patients were excluded and 47 patients were finally included into the study (Fig. 1). The baseline demographics of the study patients are

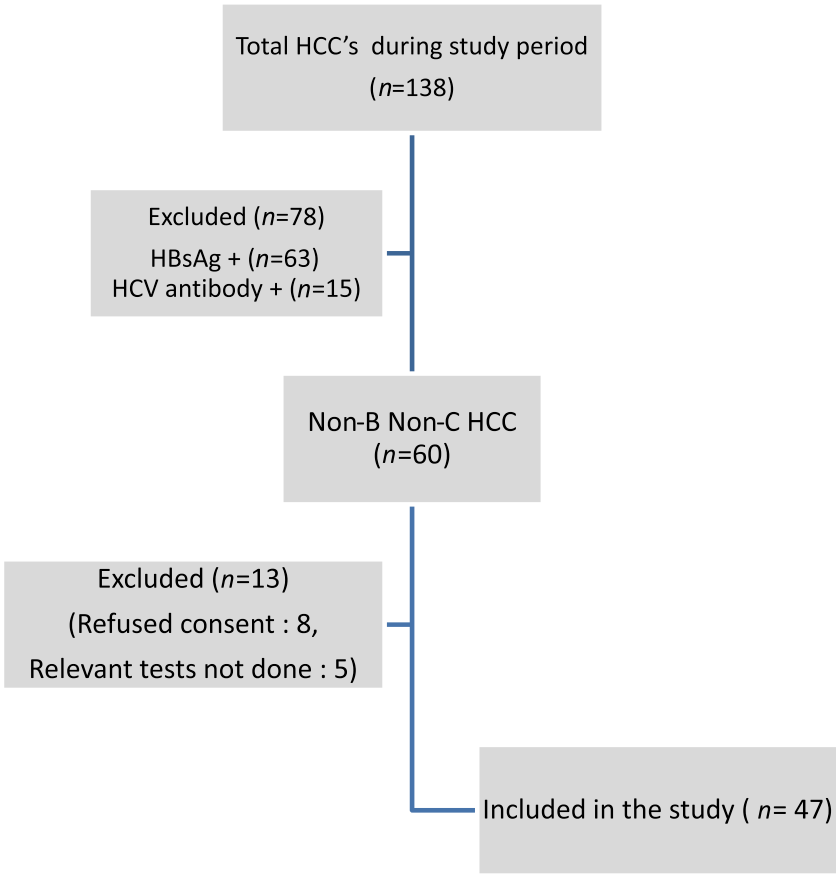

Fig. 1 Patient flow chart

given in Table 1. None of the patients had family history of HCC.

Thirty-four (72%) patients had cirrhosis. Mean tumor size (on imaging) was 7.1±4.7 cm. The mean tumor sizes in patients with and without cirrhosis were 6.7 and 8.3 cm, respectively, which were not statistically significant. Eight patients had normal serum alpha-fetoprotein levels. Thirteen (28%) patients had portal vein thrombosis.

Curative treatments for HCC were performed in nine patients—liver transplant (6 patients), radiofrequency ablation (2), and resection (1).

Etiological factors for non-B non-C HCC

Risk factors for NAFLD The prevalence of risk factors for NAFLD in non-B non-C HCC patients is shown in Table 2. Forty (85%) patients had at least one risk factor for NAFLD. In these patients, the mean duration of at least one NAFLD risk factor was 7.5 years (Table 3).

Sixteen (34%) non-B non-C HCC patients had normal BMI while seven (15%) patients were overweight. Twenty-four (51%) patients were obese and their lifetime body weight as obese was 8.9 years (Table 3). Of the 24 obese patients, 18 (75%) patients had at least one risk factor for NAFLD.

Of 34 non-B non-C HCC patients with cirrhosis, 31 (92%) patients had at least one NAFLD risk factor. The commonest risk factors were diabetes, obesity, and metabolic syndrome. There was no significant difference in proportion of NAFLD risk factors in patients with cirrhosis compared to that in patients with no cirrhosis.

Significant alcohol consumption Eleven (23%) patients had history of significant alcohol consumption. Of the 11 patients with alcohol-related HCC, 5 patients had one, 1 patient had two, 4 patients had three, and one patient had four risk factors for NAFLD. All the patients were males and were in the 50–70-year age group.

Out of the 47 non-B non-C HCC patients, 29 (62%) patients had HCC attributable to NAFLD. Eleven (23%) patients had both significant alcohol consumption and ≥ 1 risk factors for NAFLD as co-factors.

Occult hepatitis B infection None of the patients had occult hepatitis infection (i.e. HBV DNA was negative in all the patients). However 13 (28%) patients were positive for anti-HBc. Out of the 13 patients, 12 (92%) patients had underlying cirrhosis.

Table 1 Baseline characteristics of 47 study participants with non-B non-C hepatocellular carcinoma

Baseline characteristics	Total number of patients=47
Demographic data	
Age, years (mean±SD)	60±10
Sex (male/female)	37/10
Region, *n* (%)	
Southern India	24 (51)
Eastern India	18 (38)
From outside India	3 (7)
Northeast India	2 (4)
BMI (in patients without ascites, *n*=33) (kg/m^2)	24±4
Underlying cirrhosis, *n* (%)	34 (72)
Severity of liver disease	
MELD score (mean±SD)	11±4
Child class (A/B/C)	25/17/5
Baseline HCC status	
AFP—median (range) (IU/mL)	287 (0.7–334,000)
Multifocal/single lesion	10/37
Average tumor size[a] (in cm)	7.16±4.7
BCLC classification—A/B/C/D	11/10/21/5

BMI body mass index, *MELD* model for end-stage liver disease, *AFP* alpha-fetoprotein, *BCLC* Barcelona clinic liver cancer

[a] For multifocal lesions, the largest lesion size was taken

Cryptogenic HCC Seven (15%) patients had cryptogenic HCC (no risk factors for HCC detected). Of 34 patients with cirrhosis, cryptogenic HCC was noted in three (9%) patients.

Histological findings

Histological findings in the tumor and in the adjacent liver tissue and the clinical details of these patients are given in Table 4. The liver tissue adjacent to the tumor showed steatosis (6 patients), steatohepatitis (1 patient), and cirrhosis (mixed macro- and micronodular (4 patients) and micronodular (3 patients). One patient had moderate periportal bridging fibrosis and another one had mild portal fibrosis. In two patients, the biopsy sample did not contain any non-malignant liver tissue and had only the tumor. The patient with steatohepatitis was not an alcohol consumer and had two risk factors for NAFLD present.

Two patients with mild hepatic steatosis had ≥ 2 risk factors for NAFLD while two patients with moderate steatosis did not have any risk factor for NAFLD. In three patients, the tumor tissue per se showed steatosis changes (Table 4 and Fig. 2).

Discussion

This prospective study showed that in the 47 patients with non-B non-C HCC, 85% had at least one risk factor for NAFLD, while no patients had occult hepatitis B infection.

In our study, of the 138 HCC patients at the study entry, hepatitis B was the commonest etiology found (46%). The prevalence of non-B non-C HCC was 43%. An earlier study from our center reported hepatitis B- and hepatitis C-related HCC to be 45% [23] while studies from other parts of India have reported it to be around 24% to 31% [24–26]. In other

Table 2 Prevalence of risk factors for non-alcoholic fatty liver disease and of significant alcohol intake in 47 non-B non-C hepatocellular carcinoma patients

	All non-B non-C HCC (*n*=47)	HCC with cirrhosis (*n*=34)	HCC, no cirrhosis (*n*=13)	*p*-value
NAFLD, *n* (%)				
Prevalence of NAFLD risk factors				
Diabetes mellitus	24 (51)	20 (59)	4 (31)	0.085
Hypertension	16 (34)	15 (44)	1 (8)	0.018
Dyslipidemia	13 (28)	9 (26)	4 (31)	0.768
Obesity	24 (51)	19 (55)	5 (38)	0.196
Metabolic syndrome	21 (45)	17 (50)	4 (31)	0.236
Prevalence of combination of NAFLD risk factors				0.064*
Nil	7 (15)	3 (8)	4 (31)	
One	11 (23)	9 (26)	2 (15)	
Two	13 (28)	9 (26)	4 (31)	
Three	5 (11)	2 (6)	3 (23)	
Four	9 (19)	9 (26)	0	
Five	2 (4)	2 (6)	0	
Alcohol, *n* (%)	11 (23)	9 (26)	2 (15)	0.701
Alcohol+NAFLD risk, *n* (%)	9 (19)	7 (21)	2 (15)	0.685

NAFLD non-alcoholic fatty liver disease, *HCC* hepatocellular carcinoma

*p-value comparing prevalence of combination of NAFLD risk factors between the cirrhotic and non-cirrhotic patients

Table 3 Duration of risk factors for non-alcoholic fatty liver disease in 47 patients with non-B non-C hepatocellular carcinoma

Risk factor	Number (%)	Duration: number of years (mean±SD)
Diabetes mellitus	24 (51)	7.7 (± 5.6)
Dyslipidemia	16 (34)	5.0 (± 4.4)
Hypertension	13 (28)	8.5 (± 5.1)
Obesity	24 (51)	8.9 (± 3.4)

Asian countries, the reported prevalence of non-B non-C HCC ranges from 12% to 20% [7, 27, 28] while western literature reports 20% to 42% [29, 30].

As histological features of NAFLD may disappear once cirrhosis or HCC develops, it may be difficult to identify NAFLD as an etiology in patients with HCC [31]. In view of this, we looked for the risk factors for NAFLD in HCC patients and considered the HCC to be attributable to NAFLD in these patients. In our study of non-B non-C HCC patients, the commonest risk factors for NAFLD were obesity, diabetes mellitus, and metabolic syndrome, and at least one risk factor for NAFLD was present for 7.5 years prior to diagnosis of HCC. Hypertension, dyslipidemia, diabetes mellitus, obesity, and alcohol abuse have been found to be much more prevalent in patients with non-B non-C HCC than others [32]. Another study from India in which 216 biopsy-proven NAFLD patients were analyzed, the authors found a prevalence of dyslipidemia in 93%, diabetes mellitus in 23%, and hypertension in 20% [33].

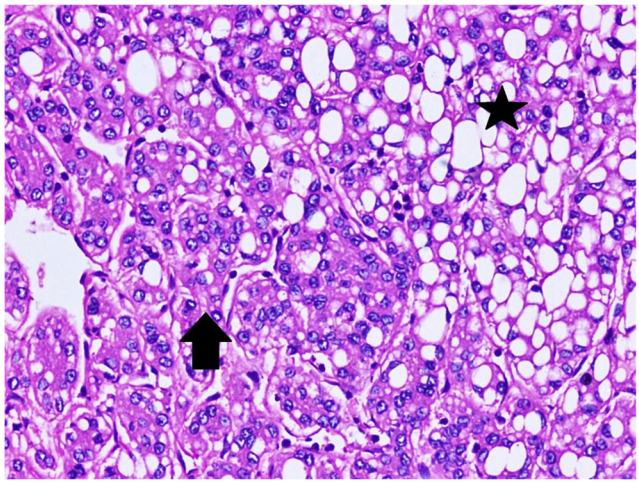

Fig. 2 Hepatocellular carcinoma (arrow) with steatosis (star)—(200× H&E)

Jain et al. examined 101 HCC explant livers and steatohepatitis pattern was found in 50% of the cases of NAFLD-associated HCC [34]. Sixty-two percent of the patients with steatohepatitic HCC had risk factors for NAFLD. However, in our study, only three patients had steatosis in the tumor tissue, and one of these patients also had steatohepatitis in the adjacent liver. Twenty-three percent of the patients had history of significant alcohol consumption, 82% of whom had

Table 4 Details of patients who underwent histopathological examination of hepatocellular carcinoma

	Anti-HBc	Significant alcohol intake	Number of NAFLD risk factors	Histopathology				
				Tumor tissue			Liver tissue adjacent to tumor	
				Histologic grade (differentiation)	Micro vascular invasion	Steatosis	Steatosis (S)/steato-hepatitis (SH)	Fibrosis (F)/ cirrhosis (C)
1	−	−	3	Moderate	+	−	Moderate macrovesicular S	Mild portal fibrosis
2	−	+	1	Moderate	+	−	−	Mixed C
3	−	−	0	Well	−	+	Moderate microvesicular S	Mixed C
4	+	+	1	Well	−	+	Mild mixed S	Mixed C
5	−	−	0	Well	−	−	Mild mixed S	Mixed C
6	+	−	1	Well	−	−	Mild mixed S	Micro C
7	−	−	2	Well	+	+	Moderate mixed SH	Micro C
8	−	−	1	Moderate to poor	+	−	−	Moderate portal and periportal bridging fibrosis
9	−	−	0	Moderate	−	−	No normal liver tissue	
10	−	−	0	Moderate	−	−	No normal liver tissue	
11	−	−	3	Well	+	−	Mild mixed S	Micro C

Nature of specimens: liver resection (patient no. 1), explants (patient nos. 2–7), ultrasound-guided liver biopsies (patient nos. 8–10), and slide and block review of liver biopsy (patient no. 11)

NAFLD non-alcoholic fatty liver disease

cirrhosis at presentation. Other studies from India have shown prevalence of significant alcohol consumption to be 21% to 59% in patients with HCC [25, 26]. We found that 11 (23%) patients had alcohol-related HCC. Out of the 11 patients with significant alcohol consumption, all 11 had at least one risk factor for NAFLD present. Seven (15%) patients did not have any other risk factors for HCC. Another study from Delhi showed alcoholism (50%) and cryptogenic cirrhosis (50%) as the underlying causes of non-B non-C HCC in 134 patients [25].

The mean age at diagnosis of HCC in our study was 60±10 years and 79% were males. While other studies from India report maximum incidence of HCC in the fifth to sixth decades [35, 36], studies from around the world show the mean age at diagnosis to be 65–70 years [23, 26].

Underlying cirrhosis was present in 72% of our patients. Majority of the patients (83%) with diabetes mellitus had cirrhosis at presentation. Similarly, in anti-HBc-positive patients, 92% had cirrhosis. Other Indian studies have shown a 60% to 90% incidence of cirrhosis in patients with underlying HCC [23, 26, 35]. Studies in patients with non-B non-C HCC have shown increased incidence of earlier stage of cirrhosis (by Child score) compared to patients with viral HCC [27].

Majority of the patients in our study were in Child class A with mean model for end-stage liver disease (MELD) score of 11±4. Since most of our patients presented with advanced HCC with underlying mild liver disease, there was no obvious co-relation between severity of the underlying liver disease and the development of HCC. The same has been previously shown in other studies [26].

Twenty-three percent patients had multifocal HCC at presentation which is lower than what is reported in other studies (34% to 70%) [25, 35]. As in other studies from India, our study also documented a very high proportion of advanced HCC lesions. Only 9 (19%) of the 47 patients underwent curative treatment for HCC. Hence, HCC surveillance in patients with cirrhosis and early referral to higher centers if there is any suspicion of hepatocellular carcinoma are needed.

In our study, we looked at the serum HBV DNA positivity. Multiple studies from Asian countries have found higher incidence of occult hepatitis B infection ranging from 47% to 70% [1, 37] (by estimating serum HBV DNA) in patients with HCC, while Indian studies show a lower incidence (6%) [38]. Prevalence of occult hepatitis B infection in healthy anti-HBc seropositive blood donors in an earlier study from our institution was 0.07% [39]. Another study from our institution showed the prevalence of occult hepatitis B infection in 62 patients with chronic liver disease to be 3% [40].

The limitations of our study include the relatively small sample size, recall bias of the patients in assessing the exact duration of risk factors of NAFLD, and the fact that assessment of NAFLD risk factors in patients with advanced liver disease and HCC may not be fully representative.

In conclusion, this study suggests that NAFLD is an important emerging cause of HCC in India. Occult hepatitis B was not noted in any patient with non-B non-C HCC. Therapeutic interventions to prevent NAFLD progression to HCC are urgently needed in India.

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Compliance with ethical standards

Conflict of interest DD, AR, AG, CBK, TAK, DB, PA, BR, PJ, JR, and CEE declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

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