Review Article

Indian J Med Res 149, January 2019, pp 9-17
DOI: 10.4103/ijmr.IJMR_1456_17

Quick Response Code:

Non-alcoholic fatty liver disease associated with hepatocellular carcinoma: An increasing concern

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Received September 6, 2017

Hepatocellular carcinoma (HCC) is the sixth most common cancer in world and third largest cause of cancer-related deaths. The last few decades have witnessed the emergence of non-viral causes of HCC, the most important being non-alcoholic fatty liver disease (NAFLD). NAFLD ranges from simple steatosis in the absence of excessive alcohol intake to non-alcoholic steatohepatitis (NASH) with or without cirrhosis. About 3-15 per cent of the obese patients with NASH progress to cirrhosis and about 4-27 per cent of NASH with cirrhosis patients transform to HCC. It is also known that HCC can develop *de novo* in patients with NASH without the presence of cirrhosis. Yearly cumulative incidence of NASH-related HCC is low (2.6%) compared to four per cent of viral-HCC. NAFLD has been associated with risk factors such as metabolic syndrome, insulin resistance, altered gut flora and persistent inflammation. Due to alarming rise in metabolic diseases, both in the developing as well as the developed world, it is expected that the incidence of NAFLD/NASH-HCC would rise manifold in future. No definite guidelines have been drawn for surveillance and management of NAFLD/NASH-associated HCC. It is thus important to discuss the entity of HCC in NAFLD at length with special focus on its epidemiology, risk factors, pathophysiology, diagnosis, clinical presentation and prevention.

Key words Hepatocellular carcinoma - metabolic syndrome - non-alcoholic fatty liver disease (NAFLD) - non-alcoholic steatohepatitis - NASH-HCC

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide and accounts for 70-85 per cent of primary liver cancer[1]. HCC mostly (>80%) develops in patients with underlying cirrhosis, frequently of viral aetiology [hepatitis B or C (HBV/HCV)] with an annual incidence of 2-6.6 per cent[2-4]. About 10 per cent cases of the HCC occur in cirrhosis of cryptogenic origin where the aetiology remains unclear[5]. The prevalence of cryptogenic aetiology of HCC is on a rise. This is being attributed to the factors such as reduction in cases of hepatitis-induced HCC due to advancements in the diagnostic and therapeutic options (antiviral therapy) and increased prevalence of non-alcoholic fatty liver disease (NAFLD), resulting in the development of HCC[6].

NAFLD is a benign form of the disease where accumulation of fat occurs (steatosis) in >5 per cent of the hepatocytes histologically. The worldwide incidence

of NAFLD is in the range of 6-35 per cent[7]. NAFLD ranges from simple steatosis in the absence of excessive alcohol intake to non-alcoholic steatohepatitis (NASH) with or without cirrhosis[8], which is a progressive entity affecting about 5-7 per cent of the general population and 30-40 per cent of patients with raised liver enzymes[9]. Histologically, it is akin to alcoholic steatohepatitis with features of necroinflammation, hepatocellular injury, ballooning of hepatocytes, hepatic fibrosis, cirrhosis and HCC[8].

NAFLD has been associated with risk factors such as metabolic syndrome (MS), insulin resistance (IR), altered gut flora and persistent inflammation. About 3-15 per cent cases of the obese NASH progress to cirrhosis and about 4-27 per cent of NASH with cirrhosis cases transform to HCC[9-11]. Yearly cumulative incidence of NASH-related HCC is low (2.6%) compared to four per cent of viral-HCC[11], and it is expected that the incidence would rise manifold in the near future[12]. It is also known that HCC can develop *de novo* in patients with NASH without the presence of cirrhosis[13]. A nationwide survey in Japan reported the incidence of NAFLD-HCC as two per cent, and only about 68 per cent of these patients had underlying cirrhosis[14]. Here we discuss the entity of HCC in NAFLD at length with special focus on its epidemiology, risk factors, diagnosis and clinical features.

Epidemiology of NAFLD/ NASH-associated HCC

The prevalence of NAFLD varies due to the differences in the ethnicity, lifestyle and the diagnostic criteria used. The prevalence of NAFLD and NASH has been reported to be 10-24 and 3-4 per cent, respectively, in the West, while in India, the prevalence of NAFLD ranges from 9 to 32 per cent[15]. The lower end of the spectrum has been reported from a rural community, whereas higher prevalence has been observed in the urban centres, quite similar to that seen in the West[15]. This may be attributed to the lifestyle change and increased incidence of MS in the urban population. Thus, at present, India is facing a double disease burden, infectious diseases on the one side and non-communicable disease on the other side[16]. The prevalence of type 2 diabetes mellitus (T2DM) is around 10 per cent in India and has an association with IR[10,17]. Obesity is also rampant amongst the Indian adolescents and about 90 per cent of the obese have NAFLD. Moreover, NAFLD/NASH is also affecting the non-obese, termed as 'Asian Paradox'[5,13]. In a rural population-based Indian study, eight per cent of the population was diagnosed with NAFLD and more than 50 per cent had a body mass index (BMI) lower than 23 kg/m^2, lower waist-hip ratio and IR[13].

HCC in NAFLD-NASH with cirrhosis

The actual prevalence of NASH-HCC is unknown as the underlying pathology of NAFLD/NASH is not well defined. The features of NASH are more commonly seen in the group of HCC patients who are classified under cryptogenic cirrhosis (CC)[18]. The annual incidence of NAFLD-associated HCC is 2.6 per cent compared to four per cent in hepatitis C-related cirrhosis. The reported overall incidence of HCC in NAFLD-cirrhosis in other studies is 2.4 per cent at seven years and 12.8 per cent over three years[19]. In a meta-analysis, White *et al*[20] showed that 60 per cent of HCC related to NASH had underlying cirrhosis and also documented a lower risk of HCC in NASH compared to those having HCV infection. In India, 72 per cent of non-B non-C HCC has shown the presence of underlying cirrhosis[21]. Cirrhosis of any aetiology (viral hepatitis, alcohol or MS) is considered to be a precursor to HCC[22]. Hence, the increasing incidences of diabetes and obesity raise the concern of increase in NAFLD/NASH-related cirrhosis and HCC in the near future[23].

HCC in NAFLD-NASH without cirrhosis

Although most of studies[5,18,20] have shown significant association between NASH-HCC and cirrhosis, Kawada *et al*[24] demonstrated development of HCC in 75 per cent (6/8) NASH patients with mild-to-moderate hepatic fibrosis but without any evidence of cirrhosis. In a pathological analysis of 128 patients by Paradis *et al*[25], significant number of NASH patients had HCC in the absence of fibrosis compared to HCC occurring due to other causes of chronic liver diseases (F0-F2: 65% in NASH versus 26% in CLD group, $P<0.001$)[25]. Due to many studies[24,25] showing NAFLD/NASH-HCC occurring without cirrhosis, malignant transformation of hepatic adenomas into carcinomas was hypothesized as the underlying probable cause[26,27].

Risk factors of HCC in NAFLD

The risk factors of developing HCC in NASH may be attributed to the excess of following - excessive weight, excess of insulin and excess of hepatic iron load, resulting in advanced fibrosis and cirrhosis. In addition, age and sex are also considered as risk factors for NASH-HCC[28].

Cryptogenic cirrhosis (CC)

NASH is reportedly the most common cause of CC[29]. It may be asymptomatic to begin with and gradually progresses to cirrhosis and HCC. Since the liver fat decreases with progressive fibrosis, diagnosing NASH histologically in such a situation is difficult. Thus, such cases are labelled as cryptogenic[5]. In a large study on patients with multiple large HCCs (predominantly males with mean age of 66±8 yr and BMI of 29.8±4.2 kg/m^2), 8.6 per cent were found to have underlying CC on resection. About 89 per cent of these patients showed steatosis, 50 per cent were obese, 56 per cent had T2DM, 28 per cent had twin ailments of DM and obesity and 50 per cent had aspartate transaminase (AST)/alanine aminotransferase (ALT) ratio less than one[30]. Studies comparing patients of HCC with underlying CC, HCV or HBV cirrhosis have documented significant association of features of MS such as obesity, diabetes, dyslipidaemia and IR with CC[18,31,32]. Similar observations have been depicted in the Indian studies as well[5,33].

Age and gender

Irrespective of aetiology (including NASH), higher HCC rates are encountered in males world over[34,35]. Similarly, age and gender differences are also seen in the prevalence and severity of NAFLD. In the young, NASH is more frequently encountered in males while it is the females who are more commonly affected in the older age (>50 yr). The severity of NASH is also known to be more in females[34,36].

Obesity and diabetes

Obesity is a common risk factor for NAFLD as well as T2DM due to the development of IR[37]. The risk of developing DM even at a lower BMI is peculiar to the Asians where normal weight individuals with a higher prevalence of central obesity (without generalized obesity) have increased predisposition to develop T2DM[38]. Patients with MS are at an increased risk of development of HCC with poor outcomes[39]. About 4-27 per cent of patients with NASH-cirrhosis are known to progress to HCC[40]. Data depicting association of obesity with NAFLD emerges from studies on patients undergoing bariatric or gastric bypass surgery where the prevalence of NAFLD and NASH ranges from 85 to 98 per cent and 24 to 98 per cent, respectively[41-47]. In a study on morbidly obese patients of south India, NAFLD and NASH were diagnosed in 65.7 and 33.6 per cent, respectively and 14.1 per cent of these had advanced fibrosis on histology[48]. On the contrary, in non-obese Asians, NAFLD cases were lower (15-21%)[49].

Excessive deposition of triglycerides in the liver interferes with the metabolism of glucose and fatty acids, leading to adverse effects. A meta-analysis conducted in Europe, United States, and Asia has depicted an increased relative risk [RR, 1.07, 95% confidence interval (CI) 1.01-1.15] of developing HCC in overweight and further higher RR in obese (1.85, 95% CI 1.44-2.37)[50].

Whether NAFLD is a risk factor for DM or a manifestation is debatable. There is a high prevalence of NAFLD (30-70%) in T2DM patients and they are also more prone to malignancies[51]. A 25 per cent increased incidence of cancer with hazard ratio (HR) of 1.27 with even higher HR of 2.24 for liver cancer has been documented followed by cancer of pancreas and kidneys[52,53]. Diabetes and obesity have a positive association with HCC risk with odds ratios of 4.33 (95% CI 1.89-9.86) and 1.97 (95% CI 1.03-3.79), respectively[54].

Iron overload and HCC

Iron overload in the liver may result in hepatic insult and has been identified as a risk factor for HCC in hereditary haemochromatosis (HH), alcoholic liver disease or post-transplant patients and patients with HCC developing in a non-cirrhotic liver[9,10]. NASH-cirrhotics with HCC also have an iron overload[55]. Genetic mutation or oxidative stress causing necro-inflammation and hepatocarcinogenesis has been thought to be the underlying mechanism and these patients have a 200-fold increased risk of HCC development than non-HH patients[56,57]. In a retrospective analysis, David *et al*[21] showed that 85 per cent of the patients with non-B non-C HCC had at least one risk factor for NAFLD.

Pathophysiology of NAFLD/ NASH-HCC

Lipid accumulation in the hepatocytes in the absence of significant alcohol consumption or any other aetiology defines NAFLD. Its progression into necroinflammation, fibrosis and steatohepatitis has been explained by ‘two-hit’ and ‘multi-parallel hit’ theories. After development of hepatic steatosis, other factors such as obesity, IR and genetic mutations act as a ‘second hit’ or ‘multiple parallel hits’ at molecular level, leading to hepatocarcinogenesis[5,21]. In a case series of 11 patients of NASH-HCC, 91 per cent were found to have obesity, diabetes, hypertension

and dyslipidaemia, which contributed to carcinogenic potential in NASH[58]. Obesity and IR incite inflammatory response with increased release of cytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and nuclear factor (NF)-κB and reduce the adiponectin synthesis. TNF-α activates the intracellular molecules which make hepatocytes resistant to insulin and adiponectin antagonizes its action. Thus, increased secretion of TNF-α and reduced levels of adiponectin lead to IR and increased exposure of hepatocytes to free fatty acids[59]. Animal studies performed on rats/ mice have inferred that NASH induced by the high-fat diet was associated with elevated TNF-α, NF-κB and hepatic proliferation[60,61]. Severe hepatic steatosis, fibrosis and hepatocarcinogenesis were associated with hypoadiponectinaemia in adiponectin knock-out mice with NASH as compared to wild-type animal model[62]. IR inhibits oxidation of fatty acids, leading to increase in intracellular fatty acids which cause oxidative damage to DNA by stimulating microsomal peroxidases[58]. IR is also associated with hyperinsulinaemia which induces release of insulin-like growth factor-1 (IGF-1) and insulin receptor substrate-1 (IRS-1) responsible for cell proliferation and inhibition of apoptosis[63].

Oxidative stress and reactive oxygen species (ROS) may induce genetic mutations predisposing to liver cancer. These oxygen radicals induce carcinogenesis by coupling with DNA bases causing mutations[64]. Trans-4-hydroxy-2-nonenal (4-HNE), a mutagen, is considered as an important aetiological agent for human cancers, particularly HCC, that have mutation at codon 249 of the p53 gene[65,66]. Nuclear respiratory factor-1 (Nrf-1) has a protective effect against the oxidative stress by means of various molecular pathways. In animal model, livers of *Nrf1* gene inactivated mice showed steatosis, apoptosis, necrosis, inflammation and fibrosis before developing liver cancer[67].

Even though several causes and pathways have been documented to be involved in the process of hepatocarcinogenesis in NAFLD with cirrhosis, the exact mechanism of HCC developing in non-cirrhotic liver is yet to be unraveled[68].

Diagnosis of NAFLD/ NASH and HCC

The European or American Association of the Study of Liver (EASL/AASLD) laid down the non-invasive criteria for diagnosis of HCC[69]. This consists of either fine needle aspiration cytology (FNAC) or any of two of the following criteria: raised alpha-fetoprotein (AFP) more than 350 ng/ml or arterialization of the liver mass seen on multiphasic computed tomography (CT) or magnetic resonance imaging (MRI). In the absence of raised AFP, arterial enhancement on two imaging modalities could also satisfy the diagnosis.

For differentiating between NAFLD and NASH, liver biopsy is the gold standard technique. However, it is invasive in nature, has sample variability and is not feasible in every patient of MS. Amongst non-invasive investigations, imaging with ultrasound and MRI, and the laboratory tests are used. Ultrasonography (USG) is a readily available modality but is unable to detect fibrosis[70]. USG-based elastography techniques such as transient elastography, acoustic radiation force impulse and shear wave elastography have been used for estimation of fat and fibrosis with promising results but require further validation[71-73]. MR spectroscopy and MR elastography have high diagnostic accuracy in evaluation of steatosis and fibrosis but have limitations in wide usage[74].

Serum markers for detecting steatosis include isolated serum markers and several algorithms incorporating multiple clinical and biochemical parameters. Isolated serum markers include cytokeratin-18 (CK-18) which is the major intermediate filament protein of liver and fibroblast growth factor 21 (FGF21)[75,76]. Algorithm based markers include fatty liver index (FLI), which incorporates BMI, waist circumference and serum levels of triglycerides and gamma glutamyl-transpeptidase (GGTP) to detect hepatic steatosis. Lipid accumulation product (LAP) is another algorithm which includes gender, waist circumference and triglyceride levels[77,78]. In general, population-based study, FLI had an area under the receiver operating characteristic curve (AUROC) of 0.84 and LAP 0.79 for detecting steatosis[77,78]. SteatoTest is another parameter which includes levels of α2-macroglobulin, apolipoprotein A-I, haptoglobin, total bilirubin, GGT, fasting glucose, triglycerides, cholesterol and ALT adjusted for age, gender and BMI[79]. However, it is a complicated parameter and has limited accuracy for detecting steatosis. AST/platelet ratio index, defined as (AST/upper limit of normal AST levels)×100/platelet count, also showed low accuracy in detecting fibrosis (AUROC<0.6)[80]. Numerous other markers are in use of which fibrosis 4 (FIB-4) is the most accurate, has been validated in several studies and consists of readily available and inexpensive variables[81-93].

Clinical features and management of HCC in NAFLD

Several case series and reports describing the clinical manifestations of HCC in NASH are available. In a series of 94 NASH-HCC patients[58], there were predominantly males (64%) with the mean age of 66 yr. Obesity, DM and dyslipidaemia were present in 68, 66 and 24 per cent respectively, and a large proportion of the tumours (69%) were multinodular with a mean tumor size of 3.5 cm. About 26 per cent of the tumours were seen in the non-cirrhotic livers[84-86]. This may be so because, NASH being a histological diagnosis, a marked reduction in the hepatic fat content occurs in advanced fibrosis (end stage liver disease), called 'burned-out NASH', which makes it difficult to diagnose NASH histologically[87].

No specific recommendations exist exclusively for NASH-HCC. Staging and treatment allocation of NASH-HCC is based on the Barcelona Clinic Liver Cancer (BCLC) staging, which is similar to the one used for HCC of other aetiologies[88]. As per this staging system, HCC is staged as very early (BCLC-0), early (BCLC-A), intermediate (BCLC-B), advanced (BCLC-C) and end stage (BCLC-D). Treatment allocation is also recommended by the same classification which remains surgery/transplantation, ablative therapy, intra-arterial therapies and oral multikinase inhibitors for BCLC-0 to BCLC-C respectively, and supportive therapy for the BCLC-D stage patients[88].

Weinmann *et al*[89] described the clinical features and outcome of 1119 HCC patients (all aetiologies including NASH) treated over an 11-yr period and compared the findings of NASH-HCC with others. NASH-HCC patients (n=45) were older (67.6 vs. 65 yr) and had increased frequency of MS. The liver function was preserved to a greater extent and the model for end stage liver disease (MELD) scores were significantly lower in NASH-HCC. Despite better liver function, the overall survival rate was lower in NASH-HCC patients. Independent of the aetiology, BMI showed a positive correlation with overall survival.

NASH-HCC patients differ from the HCV-HCC patients in certain aspects[90]. Quite expectantly, a higher prevalence of obesity, DM and dyslipidaemia is noted, GGTP levels are high and AFP levels are elevated in a little more than one third of the NASH-HCC patients. On the contrary, higher transaminases and elevated AFP have been seen in 69.6 per cent of patients in HCV-HCC group[63]. The five-year survival rate in NASH-HCC was 55.2 per cent while it was 50.6 per cent in HCV-HCC. The five-year recurrence rate after curative therapy in NASH-HCC was lower than HCV-HCC (69.8 vs. 83.1%, respectively)[63]. Wakai *et al*[91] have depicted a better disease free survival but a higher postoperative morbidity and 30-day mortality of NASH-HCC compared to viral-HCC patients. However, further work is needed in this regard.

On studying the differences between patients of NAFLD/NASH with or without cirrhosis, no significant difference has been shown in NAFLD/NASH patients with or without cirrhosis pertaining to the BMI, age, tumour number and differentiation, risk factors or NAFLD grade by Brunt criteria[92].

Prevention of NASH-HCC

Prevention of sedentary life style is mandatory for preventing progression of NAFLD to NASH and further to HCC. An effort to reduce weight proves useful. A weight loss of 3-7 per cent has shown reduction in steatosis proven by histology and imaging[93]. Prevention of obesity, IR and diabetes is vital for reducing HCC risk and the benefits of exercise by burning the extra fat are well known[94]. Use of anti-diabetic drugs such as metformin for the control of DM also prevent development and progression of HCC[95,96].

Surveillance in NASH

All patients with risk factors for developing HCC need surveillance; however, there are no established surveillance protocols for NAFLD/NASH patients. USG is the most easily accessible modality for screening these people but has limited sensitivity and specificity. On the other hand, MRI is not readily available and is expensive. Since there is an alarming prevalence of lifestyle disease such as obesity or diabetes, a cost-effective approach would be desired. No definite guidelines have been proposed and large multicentric studies have been recommended to reach consensus[97-99].

Future perspectives

In-depth understanding of the intricate pathways involved in NAFLD/NASH-associated HCC needs attention and future research needs to be focused on the prevention or progression of NAFLD to NASH, cirrhosis and HCC. Currently, no medical therapy is approved by the Food and Drug Administration (FDA) for NASH. Pharmacotherapeutic targeting is also being examined to prevent hepatic fibrosis. The

use of drugs for dyslipidaemia, IR, oxidative stress, pro-inflammatory cytokines, apoptosis and angiotensin pathway and others is being explored[100]. In addition, HCC in non-cirrhotic NASH is an enigma which needs to be unravelled.

Conclusion

NAFLD/NASH-associated HCC is a huge problem in the present era and has a strong association with MS. Focusing on lifestyle modifications is mandatory for prevention. Clinical presentation, diagnosis and staging of NAFLD/NASH HCC are similar to HCC of other aetiologies. The natural course of NAFLD progresses from steatosis, steatohepatitis, fibrosis, cirrhosis and HCC. Thus, patients of NAFLD/NASH should be considered 'at risk' population and subjected to screening and surveillance. Occurrence of HCC in non-cirrhotic NASH warrants further research.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

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