

Non-B, non-C hepatocellular carcinoma (Review)

HIROKI NISHIKAWA and YUKIO OSAKI

Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Tennoji-ku, Osaka 543-0027, Japan

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Abstract. Although most hepatocellular carcinoma (HCC) is related to viral infection, there is a substantial population of HCC patients (5-20%) who are negative for both markers of hepatitis B virus and hepatitis C virus infection [non-B, non-C (NBNC) hepatitis] in Japan and the incidence of NBNC-HCC has recently tended to increase. The most common cause of liver disease in developed countries is non-alcoholic fatty liver disease (NAFLD), which includes non-alcoholic steatohepatitis (NASH) and its related complications. Increased body mass index and diabetes mellitus are associated with developing NAFLD and NASH, which is a severe form of NAFLD. Furthermore, increasing clinical evidence supports the fact that NAFLD and NASH can progress to liver cirrhosis and even HCC. A detailed understanding of the epidemiology, etiology, molecular mechanism, clinical features and prognosis of NBNC-HCC could improve our screening and therapy of this disease. In this review, we primarily focus on clinical aspects of NBNC-HCC and refer to our current knowledge of this cancer.

Contents

1. Introduction
2. Epidemiological trends, etiology and risk factors of NBNC-HCC
3. Alcohol-related HCC
4. NAFLD and NASH
5. DM
6. Obesity
7. Iron
8. Other causes
9. Mechanism of carcinogenesis in NBNC-HCC
10. Clinicopathological features and prognosis in patients with NBNC-HCC
11. Conclusion

Correspondence to: Dr Hiroki Nishikawa, Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, 5-30 Fudegasaki-cho, Tennoji-ku, Osaka 543-0027, Japan
E-mail: h-nishikawa@osaka-med.jrc.or.jp

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1. Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in Asia and South Africa. HCC usually develops in patients with hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection and alcoholic liver disease (1-3). HCC is diagnosed in more than half a million people worldwide each year, and therefore it is a major global health problem. HCC is the fifth most common cancer in the world and the third most common cause of cancer-related death, behind only lung cancer and gastric cancer (1-5). Japan has one of the highest rates of incidence of HCC among developed countries (4-6).

Although most HCC is related to viral infection, there is a substantial population of HCC patients (5-20%) who are negative for both markers of HBV and HCV infection [non-B, non-C (NBNC) hepatitis] in Japan and the incidence of NBNC-HCC has recently tended to increase (7-12). Furthermore, investigations in the US assessing risk factors for chronic liver disease and HCC have failed to identify HBV, HCV or excessive alcohol intake in a large population (13,14).

The most common cause of liver disease in developed countries is non-alcoholic fatty liver disease (NAFLD), which includes non-alcoholic steatohepatitis (NASH) and its related complications (7,15). The incidence of NASH is reported to be 1-3% among the adult Japanese population, and ~6% in Western countries (7,15). Increased body mass index (BMI) and diabetes mellitus (DM) are associated with developing NAFLD and NASH, which is a severe form of NAFLD (17). Increasing clinical evidence supports the fact that NAFLD and NASH can progress to liver cirrhosis and HCC (7,13-16). The exponentially growing incidence of HCC may be partially attributable to increased numbers of patients with NASH-related cirrhosis, although recent evidence demonstrates that NAFLD or NASH may directly promote liver carcinogenesis independent of the presence of liver cirrhosis (15).

Obesity and the metabolic syndrome are growing epidemics related to an increased risk for several types of cancer including HCC (16). In the liver, inflammatory and angiogenic changes caused by insulin resistance and fatty liver disease are associated with an increased incidence of HCC (17,18). In contrast, regardless of underlying liver disease, liver cirrhosis remains the most important risk factor for the development of HCC, although as mentioned earlier, HCC arising without liver cirrhosis raises the possibility of direct carcinogenesis.

A detailed understanding of the epidemiology, etiology, molecular mechanism, clinical features and prognosis associated with NBNC-HCC could improve our screening and

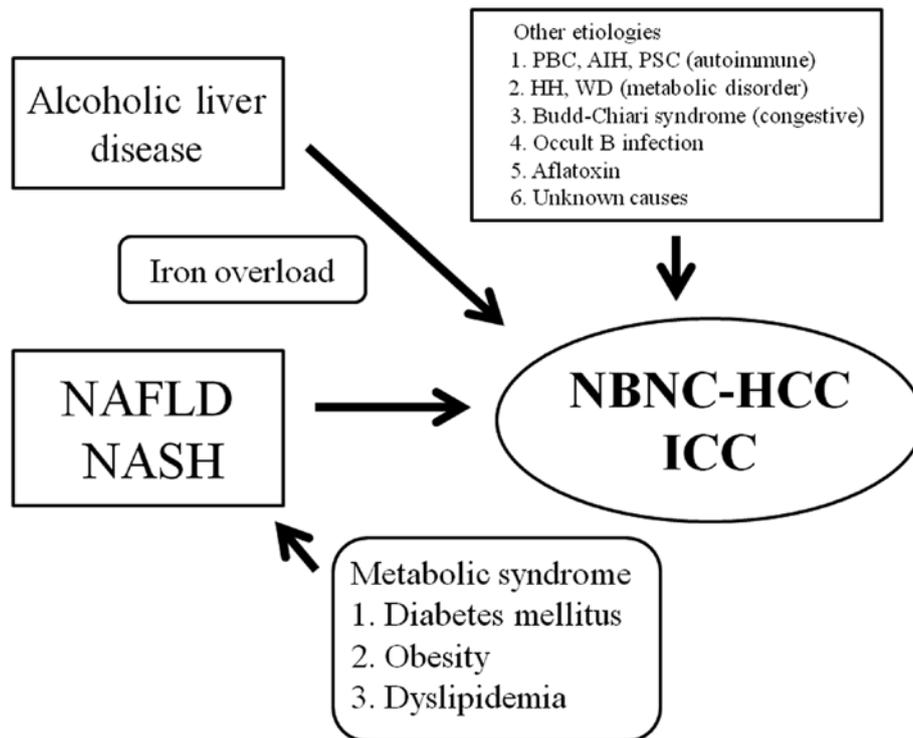


Figure 1. Schematic representation of the etiology of NBNC-HCC. NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ICC, intrahepatic cholangiocarcinoma; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; HH, hereditary hemochromatosis; WD, Wilson disease; OBI, occult hepatitis B infection.

therapy of this disease. In this review, we primarily focus on clinical aspects of NBNC-HCC and refer to our current knowledge of this cancer.

2. Epidemiological trends, etiology, and risk factors of NBNC-HCC

The major causes of cirrhosis in HCC are HBV, HCV and alcohol. The risk of HCC increases sharply in response to chronic liver damage at the fibrosis stage (2). HCV infection is the most prevalent risk factor for HCC in Japan (2,4,5,19). In the US, the leading cause of underlying liver disease among HCC patients is HCV (51%), and the second most common is cryptogenic cirrhosis (CC) (29%) (14).

Although most HCC still occurs in patients with chronic hepatitis C in Japan, the incidence of HCV-related HCC has been decreasing in recent years because of the improvement of therapy for chronic hepatitis C and a decrease in the number of patients newly diagnosed with chronic hepatitis C (6,20-22). In addition, there has been a recent increasing trend in NBNC-HCC in Japan (7). Nagaoki *et al* reported in 1,374 consecutive HCC patients in their institution that 17 and 67% of HCC was related to HBV and HCV, respectively, and 15% was related to NBNC-HCC (10). Tokushige *et al* conducted a nationwide survey of 14,530 Japanese HCC patients. They reported that alcohol-related HCC accounted for 7.2% of all HCC, followed by unknown causes (5.1%) and NAFLD-related HCC (2.0%). The characteristics of these three groups were clearly different (median age, 72 years for NAFLD-related HCC, 68 years for alcohol-related HCC, and 73 years for unknown HCC; female sex, 38, 4 and 37%,

respectively) and obesity and lifestyle-related diseases were significantly more frequent in NAFLD- than alcohol-related HCC and unknown HCC (7). Ertle *et al* reported in 162 HCC patients that HCV-related HCC accounted for 23.3%, HBV-related HCC for 19.9%, alcohol-related HCC for 12.7%, and NAFLD-related HCC for 24.0% (23).

The background liver diseases of NBNC-HCC vary considerably and they include NAFLD, NASH, alcoholic liver disease, autoimmune liver disease such as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), congestive liver disease such as Budd-Chiari syndrome (BCS), congenital metabolic liver disease such as hereditary hemochromatosis and Wilson disease, occult HBV infection (OBI) and aflatoxins, as well as liver disease of unknown etiology. Different etiologies of HCC may cause different clinical characteristics and clinical outcomes. Fig. 1 shows a schematic representation of the different etiologies of NBNC-HCC.

3. Alcohol-related HCC

The alcohol consumption criterion for defining alcoholic liver disease as proposed by the Japanese Study Group on Alcoholic Liver Disease is an ethanol intake of >70 g/day for >5 years. As compared with Western countries, the prevalence of alcohol-related HCC is lower in Japan (19). This is partly because of the high incidence of hepatitis virus-related HCC (19).

The mechanism by which alcohol consumption increases the risk of HCC is primarily due to the development of liver cirrhosis. It has been shown that excessive alcohol consump-

tion of >80 g/day ethanol for >5 years increases the risk of HCC by nearly 5-fold (24). According to a meta-analysis from Italy, hazard ratios (HRs) for HCC development of 1.19 [95% confidence interval (CI)=1.12-1.27], 1.40 (95% CI=1.25-1.56), and 1.81 (95% CI=1.50-2.19) were associated with alcohol consumption of 25, 50 and 100 g/day, respectively. This indicates that the risk of HCC development is proportional to the amount of alcohol consumed, although the risk in those who consume low or moderate levels remains unclear (25).

4. NAFLD and NASH

NAFLD is characterized by liver steatosis without a history of significant alcohol use or liver disease of unknown etiology (26). NAFLD is the most common cause of chronic liver disease worldwide and it is a hepatic manifestation of the metabolic syndrome, which is a constellation of problems that includes hypertension, obesity, insulin resistance and dyslipidemia (26). The prevalence of NAFLD increases with age, however, it has been described in persons of all ages (27). The prevalence of NAFLD and its related complications is expected to increase in the future (28).

The prevalence of NAFLD is reported to range from 10 to 30% in adults and its prevalence is increasing in Japan as well as in Western countries, because of the epidemic rise in DM and obesity (29). NASH is part of the spectrum of NAFLD and it is a severe form of NAFLD. Approximately 10% of patients with NAFLD progress to NASH and 20% of NASH cases can slowly progress to liver cirrhosis and even HCC (13,30). Powell *et al* reported the first case of NASH-related HCC (31). Since then, several case series of NASH-related HCC have been reported and it has attracted the attention of oncologists (32,33). The majority of CC cases are thought to be end-stage NASH because several clinical features such as obesity and DM in patients with CC are associated with NASH. However, histological findings often are not informative when liver cirrhosis is already established because it is hypothesized that CC often represents 'burned out' NASH (34,35). Thus, the impact of NASH on the incidence of liver cirrhosis and HCC may be underestimated. Marrero *et al* reported that 20% of patients in the cryptogenic liver disease group had evidence of NASH on liver biopsies prior to HCC occurrence (14). In addition, half of the patients with CC had prior NASH or suspected NAFLD and they concluded that NAFLD was the underlying liver disease in 13% of patients with HCC.

The natural history and prognosis of NASH remains elusive, because there are few data from prospective cohort studies (36). Ashca *et al* reported that yearly cumulative incidence of HCC was 2.6% in patients with NASH-related cirrhosis (n=195), compared with 4.0% in patients with HCV-related cirrhosis (n=315) (37). Likewise, Yatsuji *et al* conducted a comparative study between 68 patients with NASH-related cirrhosis and 69 with HCV-related cirrhosis, to clarify the incidence of HCC and clinical outcomes (38). They reported that the 5-year rate of HCC development was 11.3% for NASH-related cirrhosis and 30.5% for HCV-related cirrhosis, and the 5-year survival rates were 75.2% for NASH-related cirrhosis and 73.8% for HCV-related cirrhosis. The hepatocarcinogenesis rate in patients with NASH-related cirrhosis is considered to be lower than that in patients with HCV-related cirrhosis.

Metabolic syndrome is reported to be associated with development of HCC and intrahepatic cholangiocarcinoma (ICC). A population-based study from the US comprising 3,649 HCC cases, 743 ICC cases and 195,953 comparative persons demonstrated that metabolic syndrome was significantly more common among persons who developed HCC (37.1%) and ICC (29.7%) than in the comparison group (17.1%). After adjusted multiple logistic regression analyses, metabolic syndrome remained significantly associated with increased risk of HCC (HR=2.13; 95% CI=1.96-2.31) and ICC (HR=1.56; 95% CI=1.32-1.83) (39).

5. DM

El-Serag *et al* conducted a large longitudinal study comprising 173,643 patients with DM and 650,620 without DM (98% male) to elucidate an association between DM and chronic liver disease and/or HCC (41). They demonstrated that DM was associated with an HR of 1.98 (95% CI=1.88-2.09) for chronic non-alcoholic liver disease and an HR of 2.16 (95% CI=1.86-2.52) for HCC development (40). Furthermore, Wang *et al* recently conducted a meta-analysis including a total of 25 cohort studies to examine the relationship between DM and HCC (41). They reported that DM was associated with an increased incidence of HCC (HR=2.01, 95% CI=1.61-2.51), compared with individuals without DM and it was also positively associated with HCC mortality (HR=1.56, 95% CI=1.30-1.87). Thus, DM was demonstrated to be an independent risk factor for progression of chronic liver disease and HCC development.

Up to 70% of patients with type II DM have some degree of fatty liver disease (42). About 10% of patients with liver cirrhosis have overt DM and a larger percentage of patients have impaired glucose tolerance (43). DM may be the result of liver cirrhosis, because in patients with liver cirrhosis, insulin is not cleared properly (44).

El-Serag *et al* conducted a matched case-control study comprising 1,303 cases with DM and 5,212 controls to investigate the effect of statins on HCC development. The adjusted HR for statin reduction of HCC development was 0.74 (95% CI=0.64-0.87) and they concluded that statin use is associated with a significant reduction in the risk of HCC in patients with DM (45).

6. Obesity

Up to 90% of obese individuals have some degree of chronic fatty liver disease and hepatic steatosis correlated significantly with increasing BMI (42,46). Obesity and related metabolic abnormalities, including chronic inflammatory conditions, increase the risk of HCC development. Dysregulation of tumor necrosis factor- α and interleukin-6 expressed in adipose tissue, which are essential cancer promoters in inflammation-related carcinogenesis, is associated with the development of steatosis and liver inflammation. These cytokines are also pivotal in the development of obesity-related HCC (47).

Obesity is reported to be linked to HCC development and HCC patients with obesity may have worsened clinical outcomes (16,48). Based on the prevalence of HCC, it was estimated that 28% of male HCC cases and 27% of female cases were due to overweight or obesity (49). Calle *et al* indicated that

obesity is associated with significantly increased HCC death rates with an HR of 4.52 in patients with BMI >35 kg/m² (16). Another large population-based study from Denmark demonstrated in >40,000 obese patients that the HR of developing liver cancer was increased to 1.9 compared with the general population (50). Likewise, the Korea National Health Insurance Corporation Study reported that there was an HR of 1.53 for development of HCC in men with BMI >30 kg/m² as compared with normal controls, even after controlling for HBV infection, which is the most common cause of HCC in Korea (51).

7. Iron

Liver iron overload is suspected when the levels of serum iron and ferritin are high. In patients with hepatitis virus infection, iron overload, which is distinct from hereditary hemochromatosis, is associated with poor prognosis (52). Furthermore, Sorrentino *et al* measured hepatic iron retrospectively in liver biopsies of 153 patients with NASH-related cirrhosis (51 with HCC and 102 controls without HCC) (53). They reported that iron deposits were more frequent in HCC patients than in controls and the median corrected total iron score was significantly higher in HCC patients. Excessive alcohol consumption and iron overload may act in synergy to promote liver fibrosis and carcinogenesis (54). Ioannou *et al* demonstrated that elevated serum transferrin-iron saturation is associated with an increased incidence of liver cirrhosis or HCC; particularly in patients with heavy alcohol consumption (54). Liver iron overload may be associated with the progression of liver disease and the development of HCC in patients with underlying liver disease of various etiologies. Iron overload is not a benign condition regardless of etiology, and when recognized, surveillance for HCC and adequate therapy for reducing iron overload should be undertaken.

8. Other causes

PBC. There are several reports of NBNC-HCC with other causes than alcohol or NAFLD/NASH. According to the Japanese national data of patients with PBC, the HCC incidence was 2.4% (71/2946) and the HCC incidence according to sex was 5.1% (19/370) in men and 2.0% (52/2576) in women (55). Multivariate analysis of risk factors associated with PBC-related HCC development according to sex revealed histological fibrosis stage at the time of PBC diagnosis as an independent risk factor in women, but not in men (55). The authors concluded that male PBC patients should be particularly carefully screened for HCC from the early stages of PBC.

AIH. Although the clinical outcome in patients with AIH is generally good, there have been several patients with AIH who developed HCC (56). The National Hospital Organization Liver Network Study Group in Japan reported in 193 AIH patients that seven (3.6%) developed HCC during follow-up, and the presence of liver cirrhosis at presentation was an independent risk factor for HCC in patients with AIH.

PSC. PSC is a chronic inflammatory disease involving the biliary tract. PSC can lead to liver cirrhosis due to persistent inflammation in the liver, therefore, it is not surprising that PSC-related cirrhosis can develop into HCC. The risk of HCC

development in PSC patients with liver cirrhosis is estimated to be up to 2% per year (57). However, the incidence of HCC for patients with PSC has not been fully studied (58).

Hereditary hemochromatosis and Wilson disease. Hereditary hemochromatosis is one of the most common autosomal recessive genetic disorders. It is caused by mutations in the HFE gene and/or other mutations in the iron metabolism system and is characterized by excess iron absorption and storage in the liver (59,60). Several population-based and case-control studies have demonstrated that hereditary hemochromatosis markedly elevates the risk of HCC (61-64). A large population-based study from Sweden demonstrated that patients with hereditary hemochromatosis had a 20-fold increased risk of HCC (HR=21, 95% CI=16-22) but an almost unaltered risk of all other cancers (HR=1.2, 95% CI=1.0-1.4) (64).

Wilson disease is an autosomal recessive disorder of copper metabolism (65). A nationwide survey to examine the etiology of liver cirrhosis in Japan found Wilson disease in two (0.01%) of 16,117 patients with liver cirrhosis and HCC (66). Liver cirrhosis is a well-recognized complication of Wilson disease, but HCC is extremely rare (66).

Budd-Chiari syndrome. BCS is a rare hepatic disease caused by occlusion of the hepatic venous outflow. Several reports indicate that hepatic congestion caused by obstruction of hepatic venous outflow can lead to liver cirrhosis and even HCC (67,68). A meta-analysis from China including 16 studies in patients with BCS revealed that the prevalence of HCC in BCS was 2.0-46.2% in 12 Asian studies, 40.0-51.6% in two African studies, 11.3% in one European study and 11.1% in one American study (69). These results suggest that the prevalence of HCC in patients with BCS varies depending on geographical location. However, because a relatively high incidence of HCC in patients with BCS was observed in each study, routine radiological surveillance for HCC is warranted in patients with BCS.

OBI. In a small proportion of individuals, detectable HBV DNA in the serum and/or liver is observed in the absence of circulating hepatitis B surface antigen (HBsAg) (70-72). OBI is defined by the presence of HBV DNA in the liver tissue of individuals who test negative for HBsAg, regardless of the detection of HBV DNA in the serum. The clinical implications of OBI involve causing cryptogenic liver disease and contributing to the progression of liver disease or even HCC (71,73). OBI may maintain direct mechanisms of HBV-related carcinogenesis via the ability to integrate into the host genome, and production of transforming proteins including mainly X and pre-S proteins (73-75). In addition, OBI may exert pro-oncogenic properties through indirect mechanisms (72,74,75). These are associated with its propensity to induce persistent necroinflammation in the liver and to promote the progression of chronic hepatitis to liver cirrhosis. This indicates the step preceding HCC occurrence in the majority of cases.

Aflatoxins. Aflatoxins are naturally occurring mycotoxins produced by *Aspergillus* species. They commonly contaminate foods such as grain, peanuts and corn, and aflatoxin exposure is reported to elevate the risk of HCC (76). Chen *et al* conducted a community-based cohort study combined with

molecular dosimetry of aflatoxin exposure to elucidate the relationship between the risk of HCC development and aflatoxins (77). Elevated aflatoxin exposure measured by detectable aflatoxin B1-albumin adducts was an independent risk factor for HCC development after adjusting for important confounders (HR=5.5, 95% CI=1.2-24.5). However, in Japan, aflatoxin-associated HCC is extremely rare (7).

9. Mechanism of carcinogenesis in NBNC-HCC

Although the detailed mechanism of liver carcinogenesis in patients with NBNC chronic liver disease remains elusive, insulin resistance and oxidative stress may be involved, especially in patients with NASH. NASH is characterized by insulin resistance with hyperinsulinemia, and the insulin resistance is reported to be associated with liver carcinogenesis (26,78). Insulin-like growth factor (IGF)-1 significantly activates mitogen-activated protein kinase, and increases over-expression of the c-Fos and c-Jun proto-oncogenes in cultured hepatoma cells, and IGF-1 is potentially involved in the development of HCC (78-82). c-Jun N-terminal kinase (JNK)1 has also recently attracted attention because it is linked with obesity, insulin resistance, NASH and HCC. Obesity is linked to abnormal elevation of JNK activity (83). In addition, Puri *et al* reported that JNK activation increases hepatic inflammation and apoptosis (84). JNK1 may thus be the most essential kinase that is upregulated in HCC.

Adipose tissue is thought to be an endocrine organ because of its ability to secrete adipokines such as adiponectin and leptin (85). Adiponectin and leptin are related to insulin resistance and obesity (85,86). Adiponectin has emerged as the most abundant circulating adipocytokine and is an anti-inflammatory polypeptide in adipose tissue (85). It is decreased in the presence of insulin resistance and inhibits angiogenesis through modulation of apoptosis in animal models (87). Severe liver steatosis and fibrosis are found in adiponectin knockout mice as compared with wild-type mice (86). In addition, liver adenoma and hyperplastic nodules develop within the liver in adiponectin knockout mice, whereas no tumor formation is found in wild-type mice (86). These observations suggest that adiponectin is inversely associated with liver disease progression. Leptin is the product of the obese gene and is mainly produced by adipose tissue, and promotes angiogenesis and mediates the progression of NASH to HCC in animal models (88,89). Leptin-mediated neovascularization, which coordinates with vascular endothelial growth factor, may accelerate liver fibrosis and cause liver carcinogenesis in patients with NASH, although its role in NAFLD or NASH is still unclear (88,89).

In NAFLD patients, mitochondrial dysfunction also leads to free radical production and oxidative stress, which may provide the 'second hit' that allows progression from steatosis to steatohepatitis, liver cirrhosis and even HCC (90). NASH-related insulin resistance causes inhibition of liver mitochondrial fatty acid oxidation, and increased intracellular fatty acids can lead to oxidative DNA damage via stimulating microsomal peroxidases (91). Oxidative stress may also promote carcinogenesis (92). Insulin resistance, hepatic steatosis, oxidative stress and imbalances in adipokines/cytokines interplay, which are the most essential factors involved in NAFLD pathogenesis and progression, could also have a

pivotal role in liver carcinogenesis, through DNA damage and promoting cellular growth (90,93,94). In HCC patients with obesity, these correlations indicate a possible association between the metabolic syndrome and poor clinical outcomes.

Reactive oxygen species (ROS) can also activate fibrosis (90). Ishii *et al* demonstrated in animal models that eicosapentaenoic acid (EPA) improved steatohepatitis with decreasing serum ROS, which is associated with inhibited development of HCC (95). Treatment with EPA may minimize the risk of HCC development in patients with NASH. However, there are few promising drugs with the potential to reduce the risk of HCC development in patients with NASH.

Overall, obesity and insulin resistance are known to be related significantly to hepatic steatosis (96). Increased levels of hepatic steatosis are linked to more severe necroinflammatory activity and liver fibrosis, and several studies reported that the increase in steatosis may be a predictor for liver fibrosis progression (46,97,98). Subsequently, liver disease occurs more frequently in patients with more severe metabolic disorders, possibly leading to a higher rate of development of HCC.

10. Clinicopathological features and prognosis in patients with NBNC-HCC

Several studies have investigated the clinicopathological features of NBNC-HCC. Takuma *et al* reviewed 11 patients with NASH-associated HCC (6 male, 5 female; mean age, 73.8 years) who received curative treatment (99). They reported that most (91%) patients were diagnosed with obesity, DM, hypertension or dyslipidemia, and 7 patients (64%) also had a non-cirrhotic liver. Duan *et al* reported 169 patients with NAFLD-associated HCC (68 with non-cirrhotic liver and 101 with cirrhosis); 72.8% were male with a median age at abnormal liver function tests and diagnosis of NAFLD and HCC of 60, 64 and 67 years, respectively (100). Most patients had obesity (75%) and DM (59.8%), 32.3% had dyslipidemia, and 53% had hypertension. Nearly all patients were complicated with at least one metabolic disorder. In terms of tumor characteristics, the majority (76%) of the HCC patients had a solitary tumor nodule 0.8-20 cm in diameter (mean 3.4 cm) and most (61.1%) patients had moderately differentiated HCC. Reddy *et al* compared 52 patients with NASH-related HCC and 162 with HCV and/or alcohol-related HCC (101). NASH-related HCC patients were older, more often female, had higher BMI at HCC diagnosis, and more frequently had DM, dyslipidemia and the metabolic syndrome. Liver function at presentation was worse in patients with HCV/alcohol-related HCC.

Whether patients with NBNC-HCC have comparable prognosis to patients with HCC with other causes remains controversial. In a single-center retrospective study of patients with a maximum tumor size <5 cm, who received curative surgery, Kaibori *et al* reported that patients with NBNC-HCC tended to have a higher overall survival rate than those with HCV-related HCC (8). Patients with NBNC-HCC had a significantly higher disease-free survival rate than those with HCV-related HCC, although the difference in overall and disease-free survival between the two groups was not significant.

In a large retrospective comparative study, Li *et al* investigated 675 patients with NBNC-HCC and 3529 with hepatitis B surface antigen-positive/HCV-antibody-negative HCC who

Table I. Reported studies of clinical characteristics and outcomes in non-B and non-C hepatocellular carcinoma.

Authors/ (Refs.)	No. of patients (m/f)	Age	Treatment	LC (yes/no)	Tumor size (cm)	Tumor no. (s/m)	Prevalence of comorbid disease (%)			Survival after therapy
							DM	BMI ≥ 25 kg/m ²	DL	
Kusakabe <i>et al</i> (106)	45 (28/17)	65.8 (mean)	NA	NA	4.4 cm (mean)	30/15	17/45 (38%)	15/45 (33%)	NA	NA
Hatanaka <i>et al</i> (107)	240 (186/54)	67.4 (mean)	NA	NA	5.1 cm (mean)	NA	43/80 (53.8%)	NA	NA	NA
Abe <i>et al</i> (9)	64 (51/13)	69 (median)	NA	53/64 (82.8%)	NA	32/64	29/64 (45.3%)	12/64 (18.8%)	NA	NA
Tokushige <i>et al</i> (105)	34 (21/13)	70 (median)	NA	F3 or F4 (88%)	NA	NA	25/34 (74%)	21/34 (62%)	10/34 (29%)	5-year OS, 69.8% 5-year RFS, 30.2%
Reddy <i>et al</i> (101)	52 (27/25)	65 (median)	TACE, surgery, RFA	38/14	3.0 cm (median)	NA	28/52 (53.8%)	Median, 31.3 kg/m ² Range, 27.6-33.9 kg/m ²	17/52 (32.7%)	3-year OS, 60.9%
Duan <i>et al</i> (100)	169 (123/46)	67 (median)	TACE, surgery, LT, RFA, PEI	101/68	3.4 cm (mean)	128/41	101/169 (59.8%)	127/169 (75%)	32.3%	NA
Kaibori <i>et al</i> (8)	60 (52/8)	66.6 (mean)	Surgery	15/45	5.57 cm (mean)	50/10	25/60 (41.7%)	NA	NA	3-year OS, 75% 3-year RFS, 45%
Li <i>et al</i> (102)	675 (521/154)	181 (≤ 50 years) 494 (> 50 years)	Surgery	367/308	<5 cm, 263 (39%) >5 cm, 412 (61%)	599/76	NA	NA	NA	3-year OS, 57% 5-year OS, 48.8%
Nishikawa <i>et al</i> (108)	260 (199/61)	70 (median)	TACE, surgery, RFA, PEI	NA	3.0 cm (median)	169/91	128/260 (49.2%)	116/260 (44.6%)	NA	3-year OS, 77% 3-year RFS, 36%
Cauchy <i>et al</i> (109)	62 (58/4)	70 (median)	Surgery	F0-2, 24/62 F3-4, 38/62	Range, 2.5-3.5 cm	NA	52/62 (84%)	Median, 30.4 kg/m ² Range, 20.2-42.0 kg/m ²	40/62 (65%)	3-year OS, 75% 3-year RFS, 70%

LC, liver cirrhosis; DM, diabetes mellitus; BMI, body mass index; DL, dyslipidemia; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; LT, liver transplantation; OS, overall survival; RFS, recurrence-free survival; NA, not available; m/f, male/female; s/m, single/multiple.

underwent curative resection (102). There were no significant differences between the two groups regarding overall survival, cumulative incidence of HCC-specific death and recurrence. Furthermore, in their multivariate analysis they found that female sex, serum γ -glutamyl transpeptidase level, tumor size, tumor capsule and tumor differentiation were independent risk factors associated with HCC-specific survival in patients with NBNC-HCC. They also claimed that women with NBNC-HCC should be closely monitored even after curative surgery.

Malik *et al* reported in a single-center prospective study that survival after liver transplantation in patients with HCC and NASH-related liver cirrhosis was 88%, with a mean follow-up of 2.5 years (103). There was no significant difference in 5-year survival between patients transplanted for NASH-related liver cirrhosis with and without HCC. There was no significant difference in 5-year survival after liver transplantation between HCC patients with and without NASH-related cirrhosis. They therefore concluded that patients with NASH and HCC have a favorable clinical outcome after liver transplantation.

Giannini *et al* demonstrated that HCC patients with CC had a significantly greater prevalence of advanced HCC stage, lower amenability to any treatment, and shorter survival compared with HCV-related HCC patients (104). This was because HCC in patients with CC is often diagnosed at an advanced stage owing to the lack of imaging surveillance systems.

Tokushige *et al* conducted prospective studies to clarify the outcomes and recurrence of HCC in NASH, compared with patients with HCV-related HCC (105). The 5-year survival rate was 55.2% and cumulative recurrence of HCC at 5 years was 69.8% in treated NASH-HCC, and both groups showed similar survival and recurrence rates.

Overall, owing to the lack of adequate surveillance of HCC in patients with NBNC liver disease, NBNC-HCC tends to be diagnosed at an advanced stage. However, in NBNC-HCC patients who undergo curative therapy, clinical outcomes after HCC therapy in NBNC-HCC patients are comparable or even better than those in patients with hepatitis-related HCC. Previous reports of clinical characteristics and clinical outcomes in patients with NBNC-HCC are summarized in Table I.

11. Conclusion

Various factors unrelated to hepatitis virus are implicated in the development of HCC. Cumulative evidence suggests that NAFLD and NASH, which are hepatic manifestations of the metabolic syndrome that includes hypertension, obesity, insulin resistance and hyperlipidemia, can progress to cirrhosis and HCC. Obesity or DM itself can be an independent risk factor for the development of HCC. Insulin resistance, oxidative stress and adipokines are closely associated with liver carcinogenesis. Most patients with NBNC-HCC may have at least one metabolic disorder. Owing to the lack of adequate surveillance of NBNC-HCC, HCC tends to be diagnosed at an advanced stage. However, in NBNC-HCC patients who undergo curative therapy, clinical outcomes after HCC therapy in NBNC-HCC patients may be comparable or even better than in patients with hepatitis-related HCC. Furthermore, the ability to decide which patients with liver disease with non-viral causes will develop HCC will have screening implications in the future.

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