MEDICAL SCIENCE MONITOR

REVIEW ARTICLES

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 6615-6623
DOI: 10.12659/MSM.915722

Received: 2019.02.16
Accepted: 2019.04.19
Published: 2019.09.03

Non-Cirrhotic Liver is Associated with Poor Prognosis of Hepatocellular Carcinoma: A Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Yan Liu*
BCDEF 2 Hao Li*
EF 3 Nan Ye
EF 4 Cheng-Jun Luo
B 5 Ye-Yu Hu
ABCDEF 6 Hao Wu
AF 7 Jian-Ping Gong

1 Department of Gastroenterology, Chengdu Fifth People's Hospital, Chengdu, Sichuan, P.R. China
2 Department of Gastroenterology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, P.R. China
3 Department of Hepatobiliary Surgery, Dongyang People's Hospital, Jinhua, Zhejiang, P.R. China
4 Department of Gastroenterology, Chengdu Fifth People's Hospital, Chengdu, Sichuan, P.R. China
5 Department of Clinical Medicine, Southwest Medical University, Luzhou, Sichuan, P.R. China
6 Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China
7 Chongqing Key Laboratory of Hepatobiliary Surgery and Department of Hepatobiliary Surgery, Second Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China

* Yan Liu and Hao Li contributed equally to this work

Corresponding Authors: Hao Wu, e-mail: whwh1hero@163.com, Jian-Ping Gong, e-mail: gongjianping11@126.com

Source of support: Key Foundation of Sichuan Municipal Commission of Health and Family Planning (No. 17ZD008). Foundation of Scientific Research of Sichuan Medical Association (No. S16007). The Sichuan Applied Basic Research Project of Sichuan Science and Technology Department (2018JY0276). Chengdu Science and Technology Innovation Research and Development Project (2018-YF05-01228-SN)

Primary hepatocellular carcinoma (HCC) is the fifth most frequently reported malignancy, and it is also the second most common cause of cancer-related deaths worldwide. Although most HCC cases have been reported to develop from cirrhosis, accumulating data suggest that HCC is also closely related to non-cirrhotic chronic liver disease. Traditionally, HCC was thought to develop mostly from cirrhosis; however, an increasing number of reports have found that HCC can develop directly from inflammation without cirrhosis. The incidence of HCC in non-cirrhotic liver (HCC-NCL) is high, especially in developed countries. Studies have found that the most common cause of HCC-NCL is neglected fatty liver disease. This type of HCC has unique clinical characteristics and is closely related to metabolic disorders. Unfortunately, the prevention of HCC-NCL has not received enough attention worldwide, and there is also a lack of specific screening methods and clinical guidelines. This article mainly reviews the etiology, incidence, clinical characteristics, and screening markers of HCC-NCL to improve the understanding and prevention of this disease.

MeSH Keywords: Carcinoma, Hepatocellular • Epidemiologic Factors • Liver Cirrhosis • Prognosis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915722

3017 1 — 99

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Hepatocellular carcinoma (HCC) is the fifth most frequently reported malignancy, with more than 500 000 new cases diagnosed each year [1,2]. In the last decade, the incidence of HCC was approximately 0.4 per 1000 persons in the United States. HCC has become the third most common cause of cancer [3]. Two-thirds of HCC patients are male, and the mean age of presentation is 63.7 years [4]. China, Senegal, Gambia, and South Korea are high-incidence areas of HCC [2]. HCC is most commonly associated with viral infection, including hepatitis B virus (HBV) (19.3%) and hepatitis C virus (HCV) (23.3%) infection. The second leading cause of HCC is nonalcoholic fatty liver disease (NAFLD), which accounts for approximately 24% of cases. In contrast, alcoholic steatohepatitis and cryptogenic hepatitis are less common causes of HCC, accounting for 12.7% and 15.3% of cases, respectively [5]. Characteristics associated with metabolic syndrome, including obesity, type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidemia, are also important pathogenic factors related to HCC [4]. In addition, cirrhosis may be a critical risk factor for the development of liver cancer; however, research has shown that HCC can also occur in fatty liver disease, and this type of liver cancer is not associated with cirrhosis [6–10]. Notably, this type of HCC has not attracted enough attention and is often discovered at a late stage. In this study, we review the etiology, incidence, and clinical characteristics of HCC without cirrhosis, compare the treatment and prognosis of HCC in non-cirrhotic liver (HCC-NCL) and HCC in cirrhotic liver (HCC-CL), and discuss some screening markers and preventive measures to improve the knowledge and prevention of non-cirrhotic liver cancer.

Cause of HCC-NCL

HCC development may or may not go through the stage of cirrhosis. HCC-NCL is associated with chronic HBV or HCV infection, NAFLD/nonalcoholic steatohepatitis (NASH), dietary exposure to aflatoxins, hepatic adenoma, and fibrolamellar variations [11–16]. A small number of patients with HCC-NCL are infected with HBV. A study revealed that these patients are usually hepatitis B e antigen (HBeAg)-positive and have a low hepatitis B viral load [17]. Some retrospective studies have shown that the most common cause of HCC-NCL is NAFLD [18–20]. In another study, 3 of 9 patients with HCC-NCL had NAFLD/NASH; the remaining patients had no potential chronic liver disease, but both groups of patients had more than 2 characteristics of metabolic syndrome [5,11]. Some clinical studies and reviews also support the perspective that NAFLD/NASH and HCV infection primarily develop into HCC-NCL [21–25]. However, it takes a long time for only NASH and simple steatosis to develop into HCC [26,27]. HCC-NCL induced by aflatoxins is more likely to be related to NAFLD/NASH [11–15]. In addition, a study investigating 193 patients with HCC found adeno-associated virus type 2 (AAV2) in 11 patients, which can lead to the development of HCC-NCL [28]. Kyoung-Jin found that this viral fragment consists of 5' inverted terminal repeat (ITR), replication protein (Rep), and capsid protein (VP1) in Korean patients [29].

Incidence of HCC-NCL

The incidence of HCC-NCL is differs across different countries and regions around the world [30]. In European countries such as Italy, only 1.7% (52/3027) of HCC cases develop from non-cirrhotic liver disease. Based on a clinico-histopathological assessment of North American patients, 42.6% of 804 cases were HCC-NCL [31]. Brancatelli [32] also reported that 54% of 39 HCC patients in the United States had HCC-NCL. A systematic review of 19 randomized controlled trials concluded that 6.7% to 50.1% of HCC cases had no cirrhosis [26]. Globally, the incidence of HCC caused by NAFLD is similar to that of HCC-NCL. A study in the United States showed that 27.6% (31/112) of patients with NAFLD-related HCC only had F0 to F2 stage disease (F0–F2 stages for non-cirrhotic disease and F3–F4 stages for cirrhotic disease). Another American study [10] including 169 NAFLD patients from 25 small cohorts found that 40% of the patients had HCC-NCL. A study found non-cirrhotic liver in 40.2% (68/169) of patients with NAFLD-related HCC, and a retrospective study showed that 43% (36/83) of patients with NAFLD-related HCC had no evidence of cirrhosis [33]. Furthermore, Japanese scholars have indicated that 38% of NAFLD-related HCC cases were non-cirrhotic [34]. Finally, 2 studies from Germany showed lack of cirrhosis in 47.2% (17/36) and 22.2% (10/45) of NASH patients with liver cancer [5,35].

Characteristics of HCC-NCL

Many studies have shown that the majority of patients with HCC-NCL are male. A German study with 93 patients with HCC-NCL reported a male-to-female ratio of 2.7: 1 [36]. Typically, patients with HCC-NCL are older than patients with HCC-LC. A study in the United States found that patients with HCC-NCL had a mean age of 67.5 years old, while patients with HCC-LC had a mean age of 62.7 years old. A German study showed similar results, with mean ages of 69 and 66 years, respectively [33,36]. The median age of male patients is 71 years, and that of female patients is 66 years [36]. An Australian study showed that the average age of NAFLD patients with HCC-LC was 69 years and that NAFLD patients with NCL-HCC were generally older [35]. Moreover, scholars in France found that a lower degree of fibrosis in the paracancerous tissues of HCC was associated with a larger tumor diameter (F0–F2 stage tumors were 10.1±6.7 cm and F3–F4 stage tumors were

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

6.6±3.5 cm in diameter) [9]. We examined several cases without obvious fibrosis and found that the median size of HCC lesions was 5.33±4.58 cm [6,11,23,37–45]. HCC-NCL tumors are also more likely to be highly differentiated. Studies have found that 75% (15/20) of highly differentiated tumors are in F0–F2 stage, while only 45% (5/11) of highly differentiated tumors are in F3–F4 stage [9,35]. Another clinicopathological study came to a similar conclusion, showing that in HCC-NCL, 83% (5/6) of the tumors had moderate differentiation and 16% (1/6) had high differentiation, with a small number of tumors with low differentiation [23]. Furthermore, HCC lesions can be single or multiple. HCC-NCL more often presents as single tumors than does HCC-CL [46]. One study including 31 cases of HCC without significant fibrosis showed that in 23 of the cases, the lesion was surrounded by an envelope, while 8 were lacked an envelope. In contrast, all examined HCC-CL lesions were enveloped. Additionally, in contrast with HCC-CL, HCC-NCL has satellite nodules and vascular invasion, but the difference is not statistically significant [9]. The incidence of portal vein thrombosis is almost equal in HCC patients with and without cirrhosis. Patients with HCC-NCL display no clinical symptoms at the early stage and can have asymptomatic masses, and their liver function, especially in the case of NASH patients with HCC, is not significantly abnormal [17,23,47,48]. Furthermore, compared with HCC-CL, HCC-NCL is usually accompanied by normal alpha-fetoprotein (AFP) levels [48].

Therefore, although HCC-NCL is often discovered during physical examination, unfortunately, it is usually found at a late stage. Lobular inflammation occurs in 63.6% of patients with HCC-NCL. Additionally, patients with HCC-NCL have relatively fewer Mallory bodies in biopsy specimens [33]. Furthermore, for young women on oral contraceptives, hepatocellular adenoma (HCA) has a higher risk of progressing to HCC [49], but HCC evolving from HCA can occur without significant fibrosis [9].

Relationship between HCC-NCL and Metabolic Disorders

HCC-NCL is closely related to metabolic disorders. Some studies have found that HCC patients with metabolic disorders do not have significant fibrosis (65.5% [20/31] of cases have F0–F2 disease) [9]. Some clinical researchers have found that most patients with HCC-NCL are diagnosed with metabolic disorders. Approximately 33.3% of patients with HCC-NCL have a body mass index (BMI) of more than 25 kg/m^2, 45.16% are diagnosed with diabetes, and 40% (22/55) have a history of nicotine abuse [36].

The main cause of HCC-NCL is NAFLD/NASH, and NASH is closely related to metabolic disorders. Metabolic disorders are also closely related to HCC. One study showed that 98.6% (71/72) of patients with NAFLD-related HCC had at least 1 type of metabolic disorder, and 76.4% (55/72) had 2 or more types [5].

Independent risk factors for HCC associated with NASH include obesity (BMI >25 kg/m^2, present in approximately 95% of NASH patients), T2DM (in approximately 64% of NASH patients compared with other liver diseases), hypertension (in more than 70% of NASH patients), hyperlipidemia (in approximately 50% of NASH patients), coronary artery disease (in approximately 30.6% of NASH patients), and heart failure (in approximately 17.5% of NASH patients) [5,11,23,50].

Treatment of HCC-NCL

Treatments for HCC include oral or intravenous chemotherapy, surgery, liver transplantation, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), alcohol ablation, preoperative portal vein embolization, and sorafenib therapy (multitarget tyrosine kinase inhibitors extend the survival of HCC patients who cannot undergo resection or transplantation) [4,51,52]. In the absence of obvious fibrosis, the main treatment methods for HCC are hepatectomy, liver transplantation, and local ablation [36,53,54]. The indications for surgery are isolated tumors without liver cirrhosis or portal hypertension. Since the livers of patients with HCC-NCL are healthier than those of HCC-CL patients, hepatectomy is more feasible in patients with HCC-NCL [48,55–57]. The proportions of patients with HCC-NCL and HCC-CL receiving hepatectomy, palliative treatment, TACE/RFA, and liver transplantation are 66.7%, 13.9%, 22.3% and 0% and 17%, 0%, 61.7%, and 72.3%, respectively [33,44]. Some studies claim that patients with HCC-NCL are not good candidates for liver transplantation [35,48,58,59]. In 2 recent studies from the United States, no patients with HCC-NCL underwent liver transplantation [11,33]. HCV infection is also an important cause of HCC-NCL. Notably, HCV-infected patients with NAFLD-related HCC are more likely to undergo transplantation than patients with NAFLD/NASH alone [4].

Prognosis of HCC-NCL

The mortality rate of patients with HCC-NCL is similar to that of patients with HCC-CL, even though HCC-CL can be found early, while HCC-NCL is usually found at a late stage. Late diagnosis is an important reason for the poor prognosis of patients with HCC-NCL. A study in the United States showed that the 1-year disease-free survival rate of patients with HCC-NCL was 63%, and the 3-year and 5-year survival rates were 39% and 31%, respectively [60]. Another American study showed similar results: the 1-year and 5-year overall survival rates of patients with HCC-NCL were 84.6%, and 38.4%, respectively [51].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Additionally, in Italy, the median overall survival time was 26 months, and the 5-year survival rate was 23.7%, close to that in the United States [61], but the 5-year survival rates were not significantly different. There was no significant difference in 5-year survival between patients with HCC-NCL and those with HCC-CL [33]. A recent cohort study confirmed that the median survival rates of patients with HCC-NCL diagnosed with Barcelona Clinic Liver Cancer (BCLC) stage A, B, and C disease were 945, 925, and 229 days, respectively [36].

Older age is closely related to increased mortality of all patients with HCC-NCL. Mortality can increase by 10% with each year increase in age [33]. Patients with HCC-NCL also have a high recurrence rate (86% in the United States and 39% in the Netherlands) [33,44], especially intrahepatic recurrence [48]. According to TNM stages, the cumulative probability of stratified recurrence is 33.7% at 1 year and 57.5% at 5 years[51]. Additionally, patients with HCC-NCL who are infected with HBV have a longer survival time than patients with HCC-CL (21 *vs.* 11 months) [17]. Furthermore, patients with HCC-NCL undergoing hepatectomy have a significantly better prognosis than patients receiving nonsurgical treatment [60]. After curative hepatectomy, no significant difference is observed in the survival rate between patients with HCC-NCL with and without HBV infection. The overall survival rates of patients with HCC-NCL with and without NASH were 43.4 months and 25 months, respectively, but without a significant difference [62].

Researchers have identified various prognostic factors influencing the recurrence and overall survival of patients with HCC-NCL, including perioperative blood transfusion, portal vein thrombosis, vascular invasion, lymph node positivity, tumor size, nodular state, presence of satellite nodule, marginal state, and tumor grade [63–69] Recent retrospective studies have shown that increased preoperative gamma glutamyl transferase (GGT) and AFP levels may be a new adverse prognostic factor for primary HCC-NCL [70,71]. Patients with the best prognosis had small HCC lesions without vascular invasion or satellite nodules and had undergone R0 resection without intraoperative blood transfusion[48]. We summarize the incidence, age, tumor size and status, treatment, recurrence, and mortality of HCC-NCL in the Table 1.

Prevention of HCC-NCL

HCC has no special manifestations in the early stage. Similar to other tumors, it is usually diagnosed when symptoms begin to emerge. NAFLD is a common cause of HCC-NCL, and NAFLD is easily overlooked because it is considered a benign condition. With improvements in living standards and changes in dietary habits, T2DM, obesity, NAFLD, and metabolic disorders are becoming increasingly common worldwide. NAFLD is becoming more common in developing countries, and it affects more than 30% of the population in industrialized countries [11,72,73]. Due to increased incidence of NAFLD, the incidence of NAFLD-related HCC has also increased annually in recent years. Therefore, early detection of NAFLD is important for the prevention of HCC-NCL.

Generally, doctors only screen or monitor patients with cirrhosis for preventing HCC [11]. HCC-NCL developed in NAFLD is easily overlooked in clinical practice, and there are no screening guidelines for it. Therefore, the disease becomes severe before diagnosis, resulting in a poor prognosis [33,74].

Currently, we lack screening guidelines for NAFLD-related HCC-NCL, which could otherwise reduce the severe morbidity. Moreover, healthcare providers may not realize the importance of screening for HCC-NCL [4]. According to the 2012 American Association for the Study of Liver Diseases (AASLD) guidelines, "the risk of NAFLD-HCC may be limited to patients with advanced fibrosis and cirrhosis" [75], but there are no specific recommendations for diagnosis and treatment.

The European Association for the Study of the Liver (EASL) states that it is impractical to systematically monitor and screen for the presence of HCC risk in patients with NAFLD and to stratify the risk of liver cancer in the NAFLD population through the study of genetic polymorphisms, as it is costly [76]. In addition, abdominal ultrasound monitoring is less likely to detect tumors when screening patients with NAFLD, due to attenuations of ultrasound beams; the liver appears bright on ultrasound images, with uneven echo features and focal fat infiltration, leading to a low recognition rate or high misreading rate for small nodules [77,78]. Thus far, there is still no clear guidance on how to prevent HCC through intervention of NAFLD.

Mechanisms and Markers of HCC-NCL

Only a handful of studies on the mechanism of HCC-NCL exist, and the available studies mainly involve basic research on NAFLD/NASH-related HCC. For example, hepatic 8-hydroxy-2'-deoxyguanosine (8-OHdG) content may serve as a marker of oxidative stress and could be a particularly useful predictor of NASH-related HCC [79]. In human NAFLD-related HCC, squalene epoxidase (SQLE) is overexpressed, and its expression is associated with poor patient outcomes [80]. Activation of apoptosis inhibitor of macrophage (AIM), which usually is associated with IgM pentamers in blood, is a sensitive diagnostic marker for NASH-related HCC [81]. Mutations in the telomerase reverse transcriptase (TERT) promoter and chromosome 8p loss are characteristics of NAFLD-related HCC [82]. Apoptosis antagonizing transcription factor (AATF) also offers a potential target for therapeutic intervention of NAFLD-related HCC [83].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Epidemiology and characteristics of NAFLD/NASH-HCC.

Year	Authors	PMID	Country	Statistics time (years)	Patient source	Race	Total people	Male	NAFLD/ NASH-HCC ratio	NAFLD/NASH-HCC-NCL ratio
2008	Grace G et al.	18976012	USA	2004–2007	The University of Illinois at Chicago Medical Center	N	50	66.7% (2/3)	N	6% (3/50)
2009	Chagas AL et al.	19787150	Brasil	1998–2006	Department of Gastroenterology of Clinic Hospital of University of São Paulo School of Medicine	N	394	57% (4/7)	1.7% (7/394)	14.2% (1/7)
2009	Paradis V et al.	19115377	France	1995–2007	Beaujon Hospital	N	128	96% (30/31)	24% (31/128)	35% (11/31)
2009	Kawada N et al.	19672551	Japan	1990–2006	Osaka Medical Center for Cancer and Cardiovascular Diseases	N	807	50% (3/6)	1% (8/807)	75% (6/8)
2011	Ertle J et al.	21128245	Germany	2007–2008	Department of Gastroenterology and Hepatology at University Hospital Essen	Central Europe: 125, Southern Europe: 14, Eastern Europe: 4, Asia: 7	162	83.3% (125/162)	24% (36/162)	11% (4/36)
2012	Duan XY et al.	22251466	China	1990–2010	Pubmed database	Australia: 1, Brazil: 1, Japan: 80, France: 23, UK: 2, Spain: 2, USA: 24, Germany: 36	169	72.8% (123/169)	100% (169/169)	40% (68/169)
2013	Alexander J et al.	23302015	USA	1990–2010	Three tertiary care centers in the United States	N	157	64% (101/157)	15.3% (24/157)	N
2014	Schütte K et al.	24990270	Germany	1994–2013	The University Hospital of Magdeburg	N	664	73% (68/93)	N	14% (93/664)
2015	Perumpail RB et al.	26250831	USA	2010–2012	Brooke Army Medical Center (BAMC)	N	44	83.3% (5/6)	N	13.6% (6/44)
2015	Mohamad B et al.	26558795	USA	2003–2012	Cleveland Clinic Foundation	White: 77,African American: 4,other: 2	83	65% (54/83)	N	43% (36/83)
2015	Leung C et al.	25632192	Australia	2000–2012	The Victorian Liver Transplant Unit	N	54	87% (47/54)	13% (39/54)	20.5% (8/39)
2015	Weinmann A et al.	25884354	Germany	2000–2010	University Medical Centre of the JohannesGutenberg University Mainz	Caucasian origin: 1100 (98.3%)	1119	77.8% (35/45)	4.0% (45/1119)	N
2015	Younossi ZM et al.	26274335	USA	2004–2009	Surveillance, Epidemiology and End Results (SEER)-Medicare linked database	White: 3031 (60.9%) Other: 1348 (39.1%)	4 979	61.3% (430/401)	14.1% (701/4979)	N

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1 continued. Epidemiology and characteristics of NAFLD/NASH-HCC.

Year	HCC-NCL tumor diameter (cm)	HCC-NCL tumor status	HCC-NCL age (years)	HCC-NCL influencing factor	HCC-NCL treatment	Mortality rate	Recurrence rate	Reference
2008	0.5–10	N	57±13	Obesity, diabetes, hypertension, dyslipidemia	N	N	N	77
2009	1.0–5.2	A single nodule: 57%	63±13	Obesity, hypertension, dyslipidemia, hyperuricemia	N	N	N	6
2009	N	A single nodule: 78%	67±7	Obesity, diabetes, hypertension, dyslipidemia	N	N	N	9
2009	N	N	N	Obesity, diabetes, hypertension, dyslipidemia	Hepatic resection: 100%	N	N	23
2011	N	N	68.6±8.4	Obesity, diabetes, hypertension, dyslipidemia	N	N	N	5
2012	0.8–20	A single nodule: 76%	67	Obesity, diabetes, hypertension, dyslipidemia	Tumor resection: 57.7%, liver transplantation: 14.6%, percutaneous ethanol injection: 3.1%, radiofrequency ablation: 8.5%, transarterial embolization: 19.2%, transarterial infusion chemotherapy: 1.5%,microwave coagulation therapy: 0.8%	32,40%	18,80%	10
2013	N	N	63.8±12.5	Diabetes, hypertension, dyslipidemia	Hepatic resection: 100%	N	N	90
2014	N	N	69 (32–85)	Obesity, hypertension	Resection: 23.66%,RFA/ thermoablation: 5.38%, liver transplantation: 1.08%	N	N	35
2015	N	N	72±8	Obesity, diabetes, hypertension, dyslipidemia	Right hepatectomies: 33%, core liver biopsies: 50%	N	N	11
2015	N	A single nodule: 80.6%	67.5±12.3	Obesity, positive family history of cancer, diabetes, metabolic syndrome, hypertension, smoking, alcohol consumption	Hepatic resection: 66.7%, loco-regional therapy: 22.3%	47%	86%	32
2015	4,7	N	65	Obesity, diabetes, hypertension, dyslipidaemia	Liver transplantation: 12.5%	N	N	34
2015	1.5–16.5	N	67.6	Obesity, diabetes, hypertension, cardiovascular complications, dyslipidemia, myocardial infarction, apoplectic stroke, thrombocytopenia	Resection or orthotopic liver transplantation: 4.4%	N	N	46
2015	N	N	73±8	Male, race, any type of chronic liver diseases	Liver transplantion: 5.7%	61.20%	N	84

N – not repotred.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Furthermore, the PNPLA3 rs738409 C>G polymorphism is associated with a high risk of advanced NAFLD-related HCC [84]. Caveolin (CAV)-1 is also overexpressed in clinical specimens from patients with NAFLD-related HCC and is a potential therapeutic target in these patients [85]. MicroRNA (miR)-21 plays a causative role in NAFLD and HCC via modulation of the HBP1-p53-Srebp1c pathway *in vivo* and *in vitro* [86]. Histone deacetylase (HDAC)-8 promotes insulin resistance and β-catenin activation in NAFLD-related HCC and offers a novel epigenetic target to prevent or treat HCC in obese patients [87]. p62 potentially represents a critical pathophysiological factor in NAFLD-related HCC [88]. Cisd2 interacts with Serca2b to regulate Ca2+ homeostasis in hepatocytes, and Cisd2 haploinsufficiency induces NAFLD/NASH and promotes HCC development [89].

Nevertheless, it is crucial to find a specific marker to detect HCC-NCL in patients. Certain noninvasive tests and biomarkers may help screen and monitor HCC-NCL. For example, immunohistochemical markers such as CD34, cytokeratin (CK)-7, CK19, phosphatidylinositol proteoglycan 3 (GPC-3), glutamine synthase, and β-catenin may help in the diagnosis and prediction of HCC-NCL [90–92]. In recent years, some studies have found that the level of activity regulator of SIRT1 (AROS) is significantly correlated with tumor size, tumor diversity, vascular invasion, and tumor differentiation, as well as disease-free survival rate, and can be used as a marker for the detection of HCC-NCL [93]. MiRs are 18–25 nucleotide noncoding RNAs that can regulate gene expression [94]. For example, the levels of miR-24 and miR-27a in HCC-CL are significantly reduced, while miR-21 levels are generally increased in HCC-NCL [95]. A Chinese study noted that increased hsa-miR-1296 and hsa-miR-149 expression, as well as TNM stages, were risk factors of HCC-NCL, whereas increased hsa-miR-23c expression was associated with improved survival in patients with HCC-NCL. High expression of hsa-mir-149 was found to be an independent risk factor for prognosis in HCC-NCL [94]. Relative telomere length (RTL) in circulating cell-free serum DNA is significantly correlated with HCC risk and may be a new noninvasive biomarker of HCC-NCL in the presence of HBV infection [96]. Italian researchers have found that the T allele of membrane-bound O-acyl transferase (MBOAT)-7 at rs641738 can reduce the expression of MBOAT 7, resulting in an increased prevalence of HCC-NCL. These authors used this noninvasive biomarker to detect NAFLD-related HCC-NCL [97]. Furthermore, contrast-enhanced magnetic resonance imaging (MRI) monitoring is also applicable for patients with vascular liver disease associated with HCC-NCL [98,99].

Conclusions

The number of patients with NAFLD has dramatically increased, and the prevalence of NAFLD-related HCC has also increased. HCC-NCL is becoming a major public health challenge due to the lack of specific monitoring tools, which limits the possibility of treatment due to delayed diagnosis. At present, there is no relevant guideline for its diagnosis and treatment. Thus, for the general population, the best and only possible effective strategy is prevention. Therefore, public awareness of this disease should be advocated to achieve effective prevention.

Conflicts of interest

None.

References:

1. Ferrin G, Aguilar-Melero P, Rodriguez-Peralvarez M et al: Biomarkers for hepatocellular carcinoma: Diagnostic and therapeutic utility. Hepat Med, 2015; 7: 1–10
2. El-Serag HB, Rudolph KL: Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology, 2007; 132(7): 2557–76
3. Hong YP, Li ZD, Prasoon P et al: Immunotherapy for hepatocellular carcinoma: From basic research to clinical use. World J Hepatol, 2015; 7(7): 980–92
4. Sanyal A, Poklepovic A, Moyneur E et al: Population-based risk factors and resource utilization for HCC: US perspective. Curr Med Res Opin, 2010; 26(9): 2183–91
5. Ertle J, Dechene A, Sowa JP et al: Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer, 2011; 128(10): 2436–43
6. Chagas AL, Kikuchi LO, Oliveira CP et al: Does hepatocellular carcinoma in non-alcoholic steatohepatitis exist in cirrhotic and non-cirrhotic patients? Braz J Med Biol Res, 2009; 42(10): 958–62
7. Tokushige K, Hashimoto E, Horie Y et al: Hepatocellular carcinoma in Japanese patients with nonalcoholic fatty liver disease, alcoholic liver disease, and chronic liver disease of unknown etiology: Report of the nationwide survey. J Gastroenterol, 2011; 46(10): 1230–37
8. Yasui K, Hashimoto E, Komorizono Y et al: Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. Clin Gastroenterol Hepatol, 2011; 9(5): 428–33; quiz e50
9. Paradis V, Zalinski S, Chelbi E et al: Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: A pathological analysis. Hepatology, 2009; 49(3): 851–59
10. Duan XY, Qiao L, Fan JG: Clinical features of nonalcoholic fatty liver disease-associated hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int, 2012; 11(1): 18–27
11. Perumpail RB, Wong RJ, Ahmed A et al: Hepatocellular carcinoma in the setting of non-cirrhotic nonalcoholic fatty liver disease and the metabolic syndrome: US Eexperience. Dig Dis Sci, 2015; 60(10): 3142–48
12. Kew MC: Synergistic interaction between aflatoxin B1 and hepatitis B virus in hepatocarcinogenesis. Liver Int, 2003; 23(6): 405–9
13. Rooks JB, Ory HW, Ishak KG et al: Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. JAMA, 1979; 242(7): 644–48
14. Stoot JH, Coelen RJ, De Jong MC et al: Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: A systematic review including more than 1600 adenoma cases. HPB (Oxford), 2010; 12(8): 509–22
15. Hussain S P, Schwank J, Staib F et al: TP53 mutations and hepatocellular carcinoma: Insights into the etiology and pathogenesis of liver cancer. Oncogene, 2007; 26(15): 2166–76
16. Kabbage L, El Kouhen M, Taghy A et al: A rare presentation of hepatocellular carcinoma in non-cirrhotic liver. Pan Afr Med J, 2017; 28: 69

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

17. Techathuvanan K, Srisajjakul S, Pongpaibul A et al: Comparison between disease free survival of hepatocellular carcinoma after hepatic resection in chronic hepatitis B patients with or without cirrhosis. J Med Assoc Thai, 2015; 98(4): 334–42
18. Schulz PO, Ferreira FG, Nascimento Mde F et al: Association of nonalcoholic fatty liver disease and liver cancer. World J Gastroenterol, 2015; 21(3): 913–18
19. Wong SW, Ting YW, Chan WK: Epidemiology of non-alcoholic fatty liver disease-related hepatocellular carcinoma and its implications. JGH Open, 2018; 2(5): 235–41
20. Liu K, McCaughan GW: Epidemiology and etiologic associations of non-alcoholic fatty liver disease and associated HCC. Adv Exp Med Biol, 2018; 1061: 3–18
21. Karagozian R, Derdak Z, Baffy G: Obesity-associated mechanisms of hepatocarcinogenesis. Metabolism, 2014; 63(5): 607–17
22. Starley BQ, Calcagno CJ, Harrison SA: Nonalcoholic fatty liver disease and hepatocellular carcinoma: A weighty connection. Hepatology, 2010; 51(5): 1820–32
23. Kawada N, Imanaka K, Kawaguchi T et al: Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. J Gastroenterol, 2009; 44(12): 1190–94
24. Albeldawi M, Soliman M, Lopez R et al: Hepatitis C virus-associated primary hepatocellular carcinoma in non-cirrhotic patients. Dig Dis Sci, 2012; 57(12): 3265–70
25. Fischer MA, Raptis DA, Donati OF et al: MR imaging features for improved diagnosis of hepatocellular carcinoma in the non-cirrhotic liver: Multi-center evaluation. Eur J Radiol, 2015; 84(10): 1879–87
26. Madhoun MF, Fazili J, Bright BC et al: Hepatitis C prevalence in patients with hepatocellular carcinoma without cirrhosis. Am J Med Sci, 2010; 339(2): 169–73
27. Younossi ZM, Otgonsuren M, Henry L et al: Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology, 2015; 62(6): 1723–30
28. Nault JC, Datta S, Imbeaud S et al: Recurrent AAV2-related insertional mutagenesis in human hepatocellular carcinomas. Nat Genet, 2015; 47(10): 1187–93
29. Park KJ, Lee J, Park JH et al: Adeno-associated virus 2-mediated hepatocellular carcinoma is very rare in Korean patients. Ann Lab Med, 2016; 36(5): 469–74
30. Simonetti RG, Camma C, Fiorello F et al: Hepatocellular carcinoma. A worldwide problem and the major risk factors. Dig Dis Sci, 1991; 36(7): 962–72
31. Nzeako UC, Goodman ZD, Ishak KG: Hepatocellular carcinoma in cirrhotic and noncirrhotic livers. A clinico-histopathologic study of 804 North American patients. Am J Clin Pathol, 1996; 105(1): 65–75
32. Brancatelli G, Federle MP, Grazioli L et al: Hepatocellular carcinoma in noncirrhotic liver: CT, clinical, and pathologic findings in 39 U.S. residents. Radiology, 2002; 222(1): 89–94
33. Mohamad B, Shah V, Onyshchenko M et al: Characterization of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) patients without cirrhosis. Hepatol Int, 2016; 10(4): 632–39
34. Tokushige K, Hashimoto E, Kodama K: Hepatocarcinogenesis in non-alcoholic fatty liver disease in Japan. J Gastroenterol Hepatol, 2013; 28(Suppl. 4): 88–92
35. BaffyG, Brunt EM, Caldwell SH: Hepatocellular carcinoma in non-alcoholic fatty liver disease: An emerging menace. J Hepatol, 2012; 56(6): 1384–91
36. Schutte K, Schulz C, Poranzke J et al: Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver. BMC Gastroenterol, 2014; 14: 117
37. Ichikawa T, Yanagi K, Motoyoshi Y et al: Two cases of non-alcoholic steatohepatitis with development of hepatocellular carcinoma without cirrhosis. J Gastroenterol Hepatol, 2006; 21(12): 1865–66
38. Hashizume H, Sato K, Takagi H et al: Primary liver cancers with nonalcoholic steatohepatitis. Eur J Gastroenterol Hepatol, 2007; 19(10): 827–34
39. Hai S, Kubo S, Shuto T et al: Hepatocellular carcinoma arising from nonalcoholic steatohepatitis: Report of two cases. Surg Today, 2006; 36(4): 390–94
40. Sato K, Ueda Y, Ueno K et al: Hepatocellular carcinoma and nonalcoholic steatohepatitis developing during long-term administration of valproic acid. Virchows Arch, 2005; 447(6): 996–99
41. Cuadrado A, Orive A, Garcia-Suarez C et al: Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. Obes Surg, 2005; 15(3): 442–46
42. Bencheqroun R, Duvoux C, Luciani A et al: [Hepatocellular carcinoma without cirrhosis in a patient with nonalcoholic steatohepatitis]. Gastroenterol Clin Biol, 2004; 28(5): 497–99 [in Chinese]
43. Yeh MM, Daniel HD, Torbenson M: Hepatitis C-associated hepatocellular carcinomas in non-cirrhotic livers. Mod Pathol, 2010; 23(2): 276–83
44. Witjes CD, de Man RA, Eskens FA et al: [Hepatocellular carcinoma: the significance of cirrhosis for treatment and prognosis – retrospective study]. Ned Tijdschr Geneeskd, 2010; 154: A1747
45. Trevisani F, Frigerio M, Santi V et al: Hepatocellular carcinoma in non-cirrhotic liver: a reappraisal. Dig Liver Dis, 2010; 42(5): 341–47
46. Lafitte M, Laurent V, Soyer P et al: MDCT features of hepatocellular carcinoma (HCC) in non-cirrhotic liver. Diagn Interv Imaging, 2016; 97(3): 355–60
47. Weinmann A, Alt Y, Koch S et al: Treatment and survival of non-alcoholic steatohepatitis associated hepatocellular carcinoma. BMC Cancer, 2015; 15: 210
48. Alkofer B, Lepennec V, Chiche L: Hepatocellular cancer in the non-cirrhotic liver. J Visc Surg, 2011; 148(1): 3–11
49. An SL, Wang LM, Rong WQ et al: Hepatocellular adenoma with malignant transformation in male patients with non-cirrhotic livers. Chin J Cancer, 2015; 34(5): 217–24
50. Yu J, Shen J, Sun TT et al: Obesity, insulin resistance, NASH and hepatocellular carcinoma. Semin Cancer Biol, 2013; 23(6 Pt B): 483–91
51. Smoot RL, Nagorney DM, Chandan VS et al: Resection of hepatocellular carcinoma in patients without cirrhosis. Br J Surg, 2011; 98(5): 697–703
52. Llovet JM, Ricci S, Mazzaferro V et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med, 2008; 359(4): 378–90
53. Schmelzle M, Krenzien F, Schoning W et al: [Treatment of hepatocellular carcinoma in the cirrhotic and non-cirrhotic liver]. Chirurg, 2018; 89(11): 851–57 [in German]
54. Ono M: Are donors or recipients a more important predictive factor for the development of non-alcoholic fatty liver disease after liver transplantation? Hepatol Res, 2018; 48(3): E6–E8
55. Faber W, Sharafi S, Stockmann M et al: Patient age and extent of liver resection influence outcome of liver resection for hepatocellular carcinoma in non-cirrhotic liver. Hepatogastroenterology, 2014; 61(135): 1925–30
56. Yip VS, Gomez D, Tan CY et al: Tumour size and differentiation predict survival after liver resection for hepatocellular carcinoma arising from non-cirrhotic and non-fibrotic liver: A case-controlled study. Int J Surg, 2013; 11(10): 1078–82
57. Zaydfudim V, Smoot RL, Clark CJ et al: Role of operative therapy in non-cirrhotic patients with metastatic hepatocellular carcinoma. J Gastrointest Surg, 2012; 16(8): 1516–23
58. Bruix J, Sherman M: Practice Guidelines Committee A A f t S o L D: Management of hepatocellular carcinoma. Hepatology, 2005; 42(5): 1208–36
59. Mazzaferro V, Regalia E, Doci R et al: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med, 1996; 334(11): 693–99
60. Worns MA, Bosslet T, Victor A et al: Prognostic factors and outcomes of patients with hepatocellular carcinoma in non-cirrhotic liver. Scand J Gastroenterol, 2012; 47(6): 718–28
61. Giannini E G, Marenco S, Bruzzone L et al: Hepatocellular carcinoma in patients without cirrhosis in Italy. Dig Liver Dis, 2013; 45(2): 164–69
62. Kim JM, Kwon CH, Joh JW et al: Outcomes after curative hepatectomy in patients with non-B non-C hepatocellular carcinoma and hepatitis B virus hepatocellular carcinoma from non-cirrhotic liver. J Surg Oncol, 2014; 110(8): 976–81
63. Chen MF, Tsai HP, Jeng LB et al: Prognostic factors after resection for hepatocellular carcinoma in noncirrhotic livers: Univariate and multivariate analysis. World J Surg, 2003; 27(4): 443–47
64. Dupont-Bierre E, Compagnon P, Raoul JL et al: Resection of hepatocellular carcinoma in noncirrhotic liver: Analysis of risk factors for survival. J Am Coll Surg, 2005; 201(5): 663–70
65. Lang H, Sotiropoulos GC, Brokalaki EI et al: Survival and recurrence rates after resection for hepatocellular carcinoma in noncirrhotic livers. J Am Coll Surg, 2007; 205(1): 27–36
66. Lang H, Sotiropoulos GC, Domland M et al: Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis. Br J Surg, 2005; 92(2): 198–202

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

67. Laurent C, Blanc JF, Nobili S et al: Prognostic factors and longterm survival after hepatic resection for hepatocellular carcinoma originating from non-cirrhotic liver. J Am Coll Surg, 2005; 201(5): 656–62
68. Verhoef C, de Man RA, Zondervan PE et al: Good outcomes after resection of large hepatocellular carcinoma in the non-cirrhotic liver. Dig Surg, 2004; 21(5–6): 380–86
69. Capussotti L, Muratore A, Amisano M et al: Liver resection for large-size hepatocellular carcinomas in 47 non-cirrhotic patients – no mortality and long-term survival. Hepatogastroenterology, 2006; 53(71): 768–72
70. Faber W, Sharafi S, Stockmann M et al: Long-term results of liver resection for hepatocellular carcinoma in noncirrhotic liver. Surgery, 2013; 153(4): 510–17
71. Witjes CD, Polak WG, Verhoef C et al: Increased alpha-fetoprotein serum level is predictive for survival and recurrence of hepatocellular carcinoma in non-cirrhotic livers. Dig Surg, 2012; 29(6): 522–28
72. Vernon G, Baranova A, Younossi ZM: Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther, 2011; 34(3): 274–85
73. Younossi ZM, Stepanova M, Afendy M et al: Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol, 2011; 9(6): 524–30e1; quiz e60
74. Page JM, Harrison SA: NASH and HCC. Clin Liver Dis, 2009; 13(4): 631–47
75. Chalasani N, Younossi Z, Lavine JE et al: The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology, 2012; 55(6): 2005–23
76. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO): EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol, 2016; 64(6): 1388–402
77. Singal A G, Yopp A C, Gupta S et al: Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res, 2012; 5(9): 1124–30
78. Della Corte C, Colombo M: Surveillance for hepatocellular carcinoma. Semin Oncol, 2012; 39(4): 384–98
79. Tanaka S, Miyanishi K, Kobune M et al: Increased hepatic oxidative DNA damage in patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. J Gastroenterol, 2013; 48(11): 1249–58
80. Liu D, Wong CC, Fu L et al: Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target. Sci Transl Med, 2018; 10(437): pii: eaap9840
81. Koyama N, Yamazaki T, Kanetsuki Y et al: Activation of apoptosis inhibitor of macrophage is a sensitive diagnostic marker for NASH-associated hepatocellular carcinoma. J Gastroenterol, 2018; 53(6): 770–79
82. Ki Kim S, Ueda Y, Hatano E et al: TERT promoter mutations and chromosome 8p loss are characteristic of nonalcoholic fatty liver disease-related hepatocellular carcinoma. Int J Cancer, 2016; 139(11): 2512–18
83. Kumar DP, Santhekadur PK, Seneshaw M et al: A novel regulatory role of apoptosis antagonizing transcription factor in the pathogenesis of NAFLD and HCC. Hepatology, 2018 [e-pub ahead of a print]
84. Liu YL, Patman GL, Leathart JB et al: Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol, 2014; 61(1): 75–81
85. Takeda M, Sakaguchi T, Hiraide T et al: Role of caveolin-1 in hepatocellular carcinoma arising from non-alcoholic fatty liver disease. Cancer Sci, 2018; 109(8): 2401–11
86. Wu H, Ng R, Chen X et al: MicroRNA-21 is a potential link between non-alcoholic fatty liver disease and hepatocellular carcinoma via modulation of the HBP1-p53-Srebp1c pathway. Gut, 2016; 65(11): 1850–60
87. Tian Y, Wong VW, Wong GL et al: Histone deacetylase HDAC8 promotes insulin resistance and beta-catenin activation in NAFLD-associated hepatocellular carcinoma. Cancer Res, 2015; 75(22): 4803–16
88. Simon Y, Kessler S M, Bohle R M et al: The insulin-like growth factor 2 (IGF2) mRNA-binding protein p62/IGF2BP2-2 as a promoter of NAFLD and HCC? Gut, 2014; 63(5): 861–63
89. Shen ZQ, Chen YF, Chen JR et al: CISD2 haploinsufficiency disrupts calcium homeostasis, causes nonalcoholic fatty liver disease, and promotes hepatocellular carcinoma. Cell Rep, 2017; 21(8): 2198–211
90. Witjes CD, ten Kate FJ, Verhoef C et al: Immunohistochemical characteristics of hepatocellular carcinoma in non-cirrhotic livers. J Clin Pathol, 2013; 66(8): 687–91
91. Uthamalingam P, Das A, Behra A et al: Diagnostic value of Glypican3, heat shock protein 70 and glutamine synthetase in hepatocellular carcinoma arising in cirrhotic and non-cirrhotic livers. J Clin Exp Hepatol, 2018; 8(2): 173–80
92. Kawanaka M, Tomiyama Y, Hyogo H et al: Wisteria floribunda agglutinin-positive Mac-2 binding protein predicts the development of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. Hepatol Res, 2018; 48(7): 521–28
93. Kwon JH, Ahn KS, Moon YH et al: AROS is a significant biomarker for tumor aggressiveness in non-cirrhotic hepatocellular carcinoma. J Korean Med Sci, 2015; 30(9): 1253–59
94. Mei Y, You Y, Xia J et al: Identifying differentially expressed microRNAs between cirrhotic and non-cirrhotic hepatocellular carcinoma and exploring their functions using bioinformatic analysis. Cell Physiol Biochem, 2018; 48(4): 1443–56
95. Salvi A, Abeni E, Portolani N et al: Human hepatocellular carcinoma cell-specific miRNAs reveal the differential expression of miR-24 and miR-27a in cirrhotic/non-cirrhotic HCC. Int J Oncol, 2013; 42(2): 391–402
96. Jiang CM, Pu CW, Hou YH et al: Non alcoholic steatohepatitis a precursor for hepatocellular carcinoma development. World J Gastroenterol, 2014; 20(44): 16464–73
97. Alexander J, Torbenson M, Wu TT et al: Non-alcoholic fatty liver disease contributes to hepatocarcinogenesis in non-cirrhotic liver: A clinical and pathological study. J Gastroenterol Hepatol, 2013; 28(5): 848–54
98. Chun YS, Parker RJ, Inampudi S et al: Imaging surveillance of hypervascular liver lesions in non-cirrhotic patients. J Gastrointest Surg, 2016; 20(3): 564–67
99. Fu X, Wan S, Hann HW et al: Relative telomere length: A novel non-invasive biomarker for the risk of non-cirrhotic hepatocellular carcinoma in patients with chronic hepatitis B infection. Eur J Cancer, 2012; 48(7): 1014–22

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]