Available online at www.sciencerepository.org

Science Repository

Research Article

Hepatocellular Carcinoma in Cirrhotic Versus Non-Cirrhotic Patients: A Retrospective Study of 483 Patients

Pompilia Radu[1*], Guillaume Aeby[1], Birgit Schwacha-Eipper[2], Philippe Kolly[1], Codruta Mare[3], Vanessa Banz[2] and Jean-François Dufour[1,2]

[1]*Hepatology, Department of Clinical Research, University of Bern, Bern, Switzerland*

[2]*Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, Bern, Switzerland*

[3]*Faculty of Economics and Business administration, Department of Statistics-Forecasts-Mathematics and the Interdisciplinary Centres for Data Science, Babes Bolyai University, Cluj Napoca, Romania*

ARTICLE INFO

Article history:

Received: 11 December, 2020

Accepted: 28 December, 2020

Published: 8 February, 2021

Keywords:

Hepatocellular carcinoma

non-cirrhotic hepatocellular carcinoma

cirrhotic hepatocellular carcinoma

non-alcoholic fatty liver disease

surveillance

survival

ABSTRACT

Background and Aim: Although cirrhosis is a classical risk factor for the development of hepatocellular carcinoma (HCC), its absence does not exclude this risk. We aimed to assess the clinical characteristics and outcomes of cirrhotic HCC (C-HCC) and non-cirrhotic HCC (NC-HCC) patients.

Methods: Patients consecutively included in a prospective HCC cohort (University Hospital Bern) were analysed. They were categorised into two groups, based on the basis of histology or combined radiological and laboratory characteristics.

Results: 20.4% of patients were NC-HCC. This group was characterized by a higher median age and a higher female prevalence compared to the C-HCC group. Non-alcoholic fatty liver disease (NAFLD) (25.7%) and HBV infection (14.9%) were the main risk factors in this group, whereas alcohol abuse (26%) and HCV (21.6%) in C-HCC, P<0.001. 19.4% of them were diagnosed during a screening programme. Resection was performed in 54.5% of NC HCC patients despite the advanced stage (BCLC stage B and C). No statistically significant difference in survival rate was observed between C and NC-HCC patients (24 months vs. 33.9 months, P=0.162). In multivariate analysis, in the NC-HCC group each unit increase in BMI was associated with mortality while liver transplantation and resection were positively associated with survival. In the C-HCC group, the BCLC stage C was negatively associated with survival while all the therapeutic lines were negative factors for mortality.

Conclusion: NC-HCC patients were diagnosed more often outside a screening programme. The patients were older, with a higher female prevalence and despite an advanced stage, were often amenable to surgery.

Introduction

Classically hepatocellular carcinoma (HCC) develops on a cirrhotic liver. In the last few decades, it was reported that a certain number of patients develop HCC in non-cirrhotic liver (NC- HCC) [1]. Occurrence of NC-HCC ranges from 7 to 54%, with significant geographical and etiological variability [2]. Recent data suggests that obesity, diabetes, non-alcoholic liver disease (NAFLD), especially in its progressive form (i.e. NASH), are risk factors associated with HCC development [2-5]. This represents an alarming issue, as the NAFLD prevalence globally is high and increasing (from 15% in 2005 to 25% in 2010), while the global prevalence of NASH among biopsied NAFLD patients during the same timeframe has almost doubled [6]. Therefore, our aim is to evaluate the clinical features of NC-HCCs and to compare them with C-HCCs.

Materials and Methods

All patients diagnosed with HCC and treated at the Department of Visceral Surgery and Medicine, University Hospital of Bern (Inselspital), were asked to participate in the prospective HCC cohort

[*]*Correspondence to: Pompilia Radu, M.D., Ph.D., Hepatology, Department of Clinical Research, Murtenstrasse 35, 3010, Bern, Switzerland; Tel: +41316323391; E-mail: iuliana-pompilia.radu@insel.ch*

http://dx.doi.org/10.31487/j.JSO.2020.06.07

from the University Hospital Bern (Bern HCC Cohort, BHC), Switzerland. The local ethics committee (Kantonale Ethikkommission Bern, Bern, Switzerland) approved collection of patient information and the study protocol (project-ID 2017-00957), which was consistent with the principles of the current version of the Declaration of Helsinki.

Patient characteristics such as demographics, Model for End-Stage Liver Disease (MELD) score, Child Pugh class, complications (ascites, encephalopathy, varices), performance status (Eastern Cooperative Oncology Group performance status 0-5), Barcelona Clinic Liver Cancer (BCLC) HCC stage at diagnosis (A-D), presence of portal vein thrombosis or extrahepatic metastasis, medical comorbidities, were collected on entry into the Bern HCC cohort, which have been previously described by several authors [7-10]. Patients were classified as non-cirrhotic, based on one of the following criteria: histology either in biopsy within 1 year of HCC diagnosis or in a resection specimen in combination with the absence of radiological features of cirrhosis, or endoscopic lack of varices and thrombocytopenia (platelets <150) and radiological absence of splenomegaly (spleen >11 cm) or absence of radiological features of cirrhosis and FibroScan values < 12.5KPa [11].

Alcohol abuse was defined as a chronic alcohol intake exceeding 30 g/day in men and > 20 g/d in women or if a history of chronic alcohol abuse was positive in the past medical history [12]. NAFLD was considered based on either documented steatosis/steatohepatitis on liver biopsy or based on ultrasonographic features of fatty liver if all other known etiologies of liver disease could be ruled out. HCV status was determined by the presence of positive anti-HCV or HCV RNA tests detected any time before or after HCC diagnosis. HBV was defined by a positive surface antigen. Patients having none of the known risk factors (i.e. HCV, HBV, hemochromatosis, Wilson disease, autoimmune hepatitis, alcohol abuse, primary biliary cholangitis, primary sclerosing cholangitis were classified as idiopathic HCC).

The diagnosis and the treatment were performed in line with the current guidelines [13]. Patients were considered screened if they had previous negative screening test (imaging test +/- Alfa-fetoprotein) at 6 months interval within the 18 months preceding the diagnosis of HCC. Measurement of the tumor volume was calculated only for patients, who underwent resection, by using the following mathematical equation: 4/3 πr3, where r is the maximum radius of each tumor. In the case of multiple tumors, the TTV was calculated through the sum of each tumor nodule.

Statistical Analysis

Data was expressed as median and interquartile range or means and standard deviations after testing the normal distribution. Normality of data was tested by Kolmogorov-Smirnov test. When comparing the baseline characteristics, the Student t-test and Mann-Whitney U test were used for continuous data, and Chi-Square test for categorical variables. Overall, survival was defined as the time from HCC diagnosis to the time of death, the time of last follow-up evaluation or the date of data censoring. The Kaplan-Meier survival curves and log-rank tests were used to compare survival rates between the C-HCC and NC-HCC groups and between screened and non-screened C-HCC and NC-HCC group. Univariate and multivariate logistic regression analyses were performed to evaluate patient characteristics (i.e. sex, age, etiology of underlying liver disease, surveillance, extrahepatic metastasis, portal vein tumoral invasion, BCLC stage, therapies) associated with risk of mortality. A P value < 0.05 was considered statistically significant. All analyses were performed with SPSS version 25 (SPSS, Chicago, IL).

Results

Between the 1st of January 2010 and the 31st of August 2020, 483 HCC patients were included in the cohort study, of which 101 (20.9%) presented NC-HCC. Comparison of the baseline characteristics between the two groups revealed several significant differences (Tables 1 & 2).

Table 1: Patient characteristics: comparison between non-cirrhotic and cirrhotic patients.

		Non-cirrhotic n=101		Cirrhotic n=382		*P* value
		N		N		
Age in years (mean, SD)		101	67.16(11.3)	382	63.85(9.14)	**P=0.001**
Gender (males)		101	77(76%)	382	327(86%)	***P*=0.03**
Smoking	Current	98	22(22.4%)	373	123(33%)	**P=0.131**
	Past		17(17.3%)		58(15.5%)	
	Never		59(60%)		192(51.5%)	
BMI (Kg/m2)(mean SD)		101	26.11(5.1)	381	27.53(4.8)	***P*=0.012**
Diabetes	Yes	101	31(30.7%)	382	125(32.7%)	*P*=0.698
Etiology	NAFLD	101	26(25.7%)	382	66(17.3%)	***P*<0.001**
	Alcohol		23(22.8%)		146(38%)	
	HCV		20(19.8%)		85(22.3%)	
	HBV		8(7.9%)		25 (6.5%)	
	HCV+ alcohol		2(2%)		40(10.5%)	
	Other*		10(9.9%)		14(3.7%)	
	Unknown		12(11.9%)		6(1.6%)	
ECOG PS ≥2		101	5(8%)	382	47(16%)	P=0.078

Liver function	Child Pugh	A	91	79 (86.8%)	345	210(60.9%)	***P<0.001***
		B		12 (13.2%)		112(32.5)	
		C		0		23(6.7%)	
	MELD (median and IQR)		100	8 (6-11)	380	9.5 (7-12)	***P<0.02***

Values are presented as n (%), mean (SD, standard deviation), median (IQR, interquartile range).

The p values apply to the cirrhotic versus non-cirrhotic group. P value was assumed to be significant when <0.05.

N represents the patients' number with available data.

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; NAFLD: Non-Alcoholic Liver Disease; Other* include: hemochromatosis, primary biliary cholangitis, and autoimmune hepatitis; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MELD: Model for End-stage Liver Disease.

Table 2: Tumor characteristics and treatment assignment in the cohort population.

Variable			Non-cirrhotic n=101		Cirrhotic n=382	*P* value
		N		N		
Screening program (yes)		98	19(19.4%)	368	167(45.3%)	***P*<0.001**
Tumor characteristics						
BCLC stage	0	99	1(1%)	369	29 (7.9%)	***P*<0.001**
	A		33(33.3%)		160(43.4%)	
	B		39(39.4%)		86(23.3%)	
	C		26(26.3%)		70(19%)	
	D		0(0%)		24 (6.5%)	
First line therapy	Transplant	101	3(3%)	382	30(7.9%)	***P*<0.001**
	Surgery		41(40.6%)		57(14.9%)	
	Microwave ablation		11(10.9%)		57(14.9%)	
	Loco regional therapy		12(11.9%)		80(20.9%)	
	Systemic therapy		16(15.8%)		47(12.3%)	
	Best supportive care		18(17.8%)		111(29.1%)	
TTV, cm^3 (median and IQR)		41	1456(253-10348)	57	179(36-523)	***P*<0.001**

Values are presented as n (%), mean (SD, standard deviation), median (IQR, interquartile range).

The p values apply to the cirrhotic versus non-cirrhotic group. P value was assumed to be significant when <0.05.

N represents the patients' number with available data.

Locoregional therapy included TACE, yttrium-90 radioembolization and external radiotherapy ± TACE, systemic therapy included treatment with Sorafenib and Nivolumab.

SD: Standard Deviation; IQR: Interquartile Range; BCLC: tumor stage according to Barcelona Clinic Liver Cancer staging system; TTV: Total Tumor Volume, applies only for patients who underwent surgery.

Patients with NC- HCC were significantly older (67.2±11 vs. 63.9±9) and had a higher female percentage C-HCC (24% vs. 14%, P<0.001).

The main cause of subjacent hepatic disease in the NC-HCC group was NAFLD (25.7%), whereas in the cirrhotic group, it was alcohol abuse (26%). Despite detailed clinical and laboratory evaluation, 14.9% of NC-HCC and 2.3% of C-HCC had no evident risk factor.

A lower percent of NC-HCC patients was diagnosed during the surveillance programme (19.4% vs 45.3%, p<0.001). Even though the NC-HCC group was diagnosed in more advanced stages, 54.5% of them were assigned to percutaneous ablation or resection compared to 37.3% of C-HCC patients (P<0.001) (Table 2). NC-HCC patients who underwent liver resection had a TTV significantly higher than their counterparts (P<0.001).

I Survival in Cirrhosis Versus No Cirrhosis HCC Patients

Over a median follow-up of 69.4 months, the median survival of NC-HCC patients was longer as compared to C-HCC patients, without reaching the statistical significance (34 months vs. 24 months, P=0.162) (Figure 1).

Overall survival according to inclusion in a screening programme at diagnosis did not differ significantly among the NC-HCC patients (36.4 vs 39.5 months, P=0.519), while in the cirrhotic group the screened

patients show a better overall survival than the non-screened ones (38.4 vs. 15.7 months, P <0.001) (Figure 2).

II Risk Associated with Mortality in Cirrhotic and Non-Cirrhotic HCC Patients

In the survival analysis both HCC group types involve different risk factors. In a univariate Cox regression analysis of the C-HCC group, the presence of portal vein thrombosis, extrahepatic metastases were independently associated with mortality, whereas BCLC stage (0-B) and treatment had a positive effect on survival. In the NC cohort, a unit increase in BMI was found as an independent factor for mortality, while BCLC stage (A-B) and treatment were associated with a good outcome (Table 3).

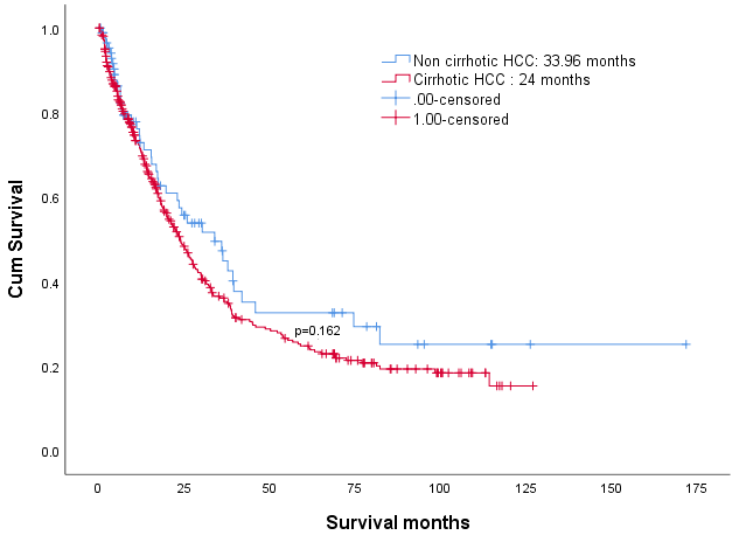

Figure 1: Kaplan-Meier curves for survival in C-HCC versus NC-HCC group. P=0.162.

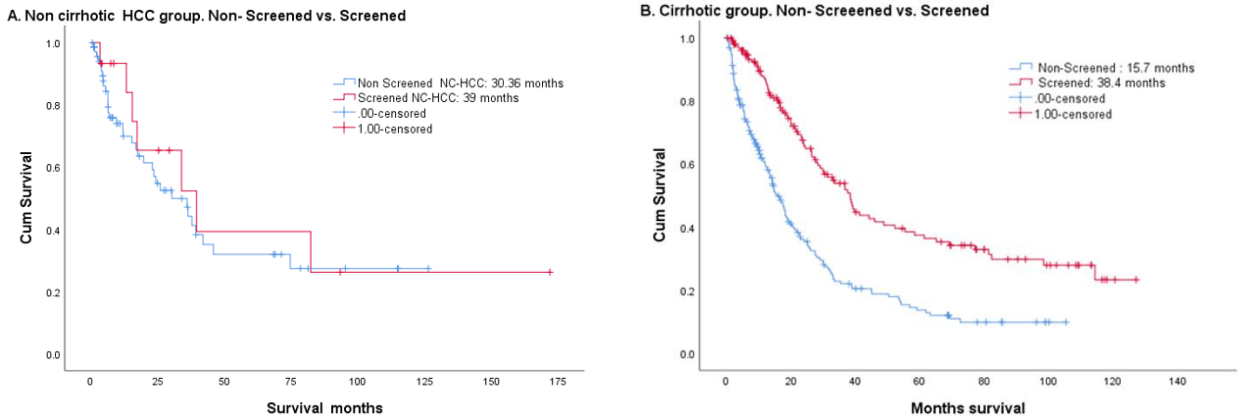

Figure 2: Kaplan Meier estimated overall survival rates of screened and non-screened patients in **A)** NC-HCC group, P= 0.547 and in **B)** C-HCC group, P<0.001.

Table 3: Univariate analysis of overall survival for C-HCC and NC-HCC patients.

Variables	Univariate analysis					
	C-HCC			NC-HCC		
	P value	HR	95%Cl	P value	HR	95% Cl
Age years: <65 vs. >65	0.121	0.815	0.628-1.056	0.915	0.945	0.506-1.840
Gender: male vs. female	0.27	0.821	0.99-1.045	0.883	0.951	0.484-1.867
BMI	0.22	1.017	0.806-1.431	**0.047**	0.929	0.863-0.999
Diabetes: Yes vs. No	0.138	0.813	0.619-1.069	0.377	0.725	0.373-1.408
Surveillance : Yes vs. No	**<0.001**	2.321	1.760-3.061	0.548	0.779	0.344-1.763
Etiology	0.543	1.021	.955-1.091	0.443	1.052	0.925-1.197
Extrahepatic metastasis: Yes vs. No	**<0.001**	0.256	0.173-0.377	0.247	0.631	0.289-1.375

Portal vein invasion: Yes vs. No	**<0.001**	0.153	0.107-.219	0.213	0.549	.214-1.410
BCLC stage	**<0.001**	2.289	2.010-2.607	**0.028**	1.655	1.057-2.591
Treatment	**<0.001**	1.602	1.463-1.756	**<0.001**	1.348	1.143-1.589

C-HCC: Cirrhotic Hepatocellular Carcinoma Group; NC-HCC: Non-Cirrhotic Hepatocellular Carcinoma Group, BMI: Body Mass Index (cm /kg^2); BCLC: Barcelona Clinic Liver Cancer; 95% Cl: Confidence Interval.

In the multivariate analysis of the C-HCC group, only BCLC stage C was associated with mortality, while all the therapeutic lines were associated positively with a good outcome. In the NC-HCC, each unit increase in BMI is associated negatively with survival while therapy (transplant, resection) was associated positively with survival (Table 4).

Table 4: Multivariate analysis of overall survival for C-HCC and NC-HCC patients.

Variables		Multivariate Analysis					
		C-HCC			NC-HCC		
		P value	HR	95%Cl	P value	HR	95% Cl
BMI		-	-	-	**0.048**	0.905	.791-0.953
Surveillance : Yes vs. No		0.64	1.265	0.907-1.764	-	-	-
Extrahepatic metastasis: Yes vs. No		0.71	1.108	0.644-1.36	-	-	-
Portal vein invasion: Yes vs. No		0.056	0.621	0.383-1.019	-	-	-
BCLC stage		<0.001			0.374		
	0	0.056	0.357	0.082-0.121	NA	NA	NA
	A	0.159	0.322	0.162-0.628	0.697	1.545	0.499-4.789
	B	0.952	1.026	0.439-2.410	0.510	0.833	.294-2.362
	C	**0.039**	2.100	1.038-4.248			
Treatment		<0.001			0.013		
	Transplant	**<0.001**	0.042	0.163-0.113	**0.046**	0.109	0.012-0.961
	Resection	**<0.001**	0.125	0.042-0.613	**0.002**	0.044	0.021-0220
	RFA/MWA	**<0.001**	0.260	0.301-0.403	0.972	0.001	0.027-1.101
	Loco-regional	**<0.001**	0.194	0.093-0.473	0.097	0.165	0.02-1.382
	Systemic	**<0.001**	0.249	0.131-0.901	0.079	0.213	0.038-0.642

C-HCC: Cirrhotic Hepatocellular Carcinoma group; NC-HCC: Non-Cirrhotic Hepatocellular Carcinoma group; BMI: Body mass index (cm /kg^2); BCLC: Barcelona Clinic Liver Cancer; 95% Cl: Interval de Confidenta; NA: Not Applicable.

Discussion

In our HCC cohort, the demographic characteristics (age, gender prevalence), risk factors, tumoral stage at diagnosis and treatment approach differed between NC-HCC and C-HCC. We found no statistically significant difference between the overall survival of NC-HCC and C-HCC patients. In survival analysis both HCC groups involved different risk factors. Similar to several previous studies, our NC-HCC group was characterised by an older age and a higher females prevalence compared to the C-HCC group [2, 4, 14-16]. However, this observation was not confirmed by other studies [17, 18]. The main etiological factor in the cohort seems to be reason for the conflicting results, thus the cohorts in which HBV was the main risk factor had a younger population and higher male proportion, while the prevalence of NAFLD was associated with older age and female prevalence [19].

Despite extensive tests, we could not establish the underlying liver disease in 14.9% of NC-HCC and 2.3% of C-HCC cases. Several pathologies have been recognised to be associated with HCC in the subgroup of patients for whom no other classic risk factor could be identified. Previous studies have found that obesity and type 2 diabetes are independent risk factors for HCC occurrence [20-23]. `These risk factors were present in 32% and 40%, respectively of NC-HCC without a classical risk factor. In addition, hypothyroidism, porphyria or other environmental factors have been proposed as possible associated conditions for HCC occurrence [24-26]. In our NC group two patients had hypothyroidism as the only associated pathology. In cirrhotic livers, the "burned-out NASH" was reported as the cause be the for the lack of histological changes [27].

The positive impact of HCC surveillance in cirrhotic patients on an earlier diagnosis, assignment to curative therapy and a long-term survival is universally accepted. A matter of debate still is the benefit of a surveillance programme in NC patients outside the actual EASL guidelines (i.e. chronic HBV at intermediate or high risk of HCC and non-cirrhotic F3 patients, regardless of etiology). Based on EASL recommendation, 19.4% of NC-HCC patients in our cohort were diagnosed during a screening programme [28, 29]. However, it is important to mention that the rate of adherence to a screening programme in cirrhotic population was low, only 43.5%. The relative low adherence to surveillance (52%) is a serious problem and it was reported by Zhao C in recent metanalysis [30].

In terms of survival, in our cohort the difference of survival time between the two groups did not reach the statistical significance. In previous studies, several groups reported that the NC-HCC group had a better

survival rate compared to C- HCC group but are also groups that did not find any significant difference [16, 31]. In contrast with the C-HCC group, in which the screened population had a significantly better survival rate, in the NC-HCC group, we found no statistically significant difference. In this context and considering that the cirrhotic patients showed a relative low adherence to the screening programme, the adherence of NC patients is questionable. In line with previous studies, in our cohort despite an advanced stage at diagnosis, the preserved liver function, allowed to be performed more aggressive therapies with a positive impact on survival [31]. This suggests indirectly that for NC-HCC patients, BCLC staging is not suitable, since a high number of NC-HCC patients could benefit from a more aggressive approach [32]. However, this advantage of a preserved liver function seems to be limited by the associated comorbidities (i.e. obesity).

While the current study included a relatively large number of patients, it is limited by its retrospective nature and single center data. Moreover, since the diagnosis of HCC do not require a biopsy from the tumorous and non-tumorous liver tissue as part of the standard work-up, the number of patients with histology from non-tumorous tissue was rather small. However, a relative high percentage of NC-HCC patients was assigned to resection, which allowed us to have hepatic tissue available. Moreover, in our hospital during percutaneous ablation, biopsy is often performed. Despite available hepatic tissue, a certain degree of misclassification between ASH and NAFLD could not be avoided. Nevertheless, this study provides important overview on the differences between NC- HCC and C- HCC patients in a European cohort.

In conclusion, NAFLD represents an important risk factor for the occurrence of HCC in non-cirrhotic livers. The lack of a screening programme for NC-HCC population results in an incidental and late HCC diagnosis. However, in the absence of cirrhosis, the majority of these patients are able to undergo curative treatment with no statistically significant difference in survival rates between groups.

Acknowledgement

We would like to acknowledge Andrea Cavelti for her dedication and professionalism in assisting HCC patients.

Ethical Approval

Local ethical committees of Inselspital, Bern, approved the study.

Consent

Consents from all of the patients were established prior to submission and all records were confidential.

Conflicts of Interest

Jean-François Dufour: Advisory committees: Abbvie, Bayer, BMS, Falk, Genfit, Genkyotex, Gilead Science, HepaRegenix, Intercept, Lilly, Merck, Novartis. Speaking and teaching: Abbvie, Bayer, BMS, Genfit, Gilead Science, Novartis.

Funding

This study was funded by Swissliver, Stiftung für die Leberkrankheite.

Author Contributions

Literature Research, Manuscript Writing, Formal Analysis: Pompilia Radu; Data Curation: Guillaume Aeby; Data Collection: Birgit Schwacha-Eipper; Formal Analysis: Philippe Kolly, Codruta Mare; Manuscript Preparation (critical review, commentary): Vanessa Banz; Study Conception, Funding Acquisition, Supervision: Jean-François Dufour.

REFERENCES

1. Gaddikeri S, McNeeley MF, Wang CL, Bhargava P, Dighe MK et al. (2014) Hepatocellular carcinoma in the noncirrhotic liver. *Am J Roentgenol* 203: W34-W47. [Crossref]
2. Trevisani F, Frigerio M, Santi V, Grignaschi A, Bernardi M (2010) Hepatocellular carcinoma in non-cirrhotic liver: A reappraisal. *Dig Liver Dis* 42: 341-347. [Crossref]
3. Blonski W, Kotlyar DS, Forde KA (2010) Non-viral causes of hepatocellular carcinoma. *World J Gastroenterol* 16: 3603-3615. [Crossref]
4. Mohamad B, Shah V, Onyshchenko M, Elshamy M, Aucejo F et al. (2016) Characterization of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) patients without cirrhosis. *Hepatol Int* 10: 632-639. [Crossref]
5. Piscaglia F, Svegliati Baroni G, Barchetti A, Pecorelli A, Marinelli S et al. (2016) Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. *Hepatology* 63: 827-838. [Crossref]
6. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L et al. (2016) Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 64: 73-84. [Crossref]
7. Al Hasani F, Knoepfli M, Gemperli A, Kollar A, Banz V et al. (2014) Factors affecting screening for hepatocellular carcinoma. *Ann Hepatol* 13: 204-210. [Crossref]
8. Richani M, Kolly P, Knoepfli M, Herrmann E, Zweifel M et al. (2015) Treatment allocation in hepatocellular carcinoma: Assessment of the BCLC algorithm. *Ann Hepatol* 15: 82-90. [Crossref]
9. Kolly P, Reeves H, Sangro B, Knöpfli M, Candinas D et al. (2016) Assessment of the Hong Kong Liver Cancer Staging System in Europe. *Liver Int* 36: 911-917. [Crossref]
10. Gmür A, Kolly P, Knöpfli M, Dufour JF (2018) FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG Performance Status. *Liver Int* 38: 1468-1474. [Crossref]
11. Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B et al. (2006) Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 55: 403-408. [Crossref]
12. 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) (2016) EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 64: 1388-1402. [Crossref]

13. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer (2012) EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 56: 908-943. [Crossref]
14. Schütte K, Schulz C, Poranzke J, Antweiler K, Bornschein J et al. (2014) Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver. *BMC Gastroenterol* 14: 117. [Crossref]
15. Shimada M, Rikimaru T, Sugimachi K, Hamatsu T, Yamashita Y et al. (2000) The importance of hepatic resection for hepatocellular carcinoma originating from nonfibrotic liver. *J Am Coll Surg* 191: 531-537. [Crossref]
16. Van Meer S, Van Erpecum KJ, Sprengers D, Coenraad MJ, Klümpen HJ et al. (2016) Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: Results from a large cohort in the Netherlands. *Eur J Gastroenterol Hepatol* 28: 352-359. [Crossref]
17. Van Roey G, Fevery J, Van Steenbergen W (2000) Hepatocellular carcinoma in Belgium: clinical and virological characteristics of 154 consecutive cirrhotic and non-cirrhotic patients. *Eur J Gastroenterol Hepatol* 12: 61-66. [Crossref]
18. Chang CH, Chau GY, Lui WY, Tsay SH, King KL et al. (2004) Long-term results of hepatic resection for hepatocellular carcinoma originating from the noncirrhotic liver. *Arch Surg* 139: 320-325. [Crossref]
19. Goh GB, Li JW, Chang PE, Chow KY, Tan CK (2017) Deciphering the epidemiology of hepatocellular carcinoma through the passage of time: A study of 1,401 patients across 3 decades. *Hepatol Commun* 1: 564-571. [Crossref]
20. Larsson SC, Wolk A (2007) Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. *Br J Cancer* 97: 1005-1008. [Crossref]
21. Wang YG, Wang P, Wang B, Fu ZJ, Zhao WJ et al. (2014) Diabetes mellitus and poorer prognosis in hepatocellular carcinoma: a systematic review and meta-analysis. *PLoS One* 9: e95485. [Crossref]
22. Chen Y, Wang X, Wang J, Yan Z, Luo J (2012) Excess body weight and the risk of primary liver cancer: An updated meta-analysis of prospective studies. *Eur J Cancer* 48: 2137-2145. [Crossref]
23. Turati F, Talamini R, Pelucchi C, Polesel J, Franceschi S et al. (2013) Metabolic syndrome and hepatocellular carcinoma risk. *Br J Cancer* 108: 222-228. [Crossref]
24. Mogl MT, Pascher A, Presser SJ, Schwabe M, Neuhaus P et al. (2007) An unhappy triad: Hemochromatosis, porphyria cutanea tarda and hepatocellular carcinoma-A case report. *World J Gastroenterol* 13: 1998-2001. [Crossref]
25. Hamed MA, Ali SA (2013) Non-viral factors contributing to hepatocellular carcinoma. *World J Hepatol* 5: 311-322. [Crossref]
26. Manka P, Coombes JD, Boosman R, Gauthier K, Papa S et al. (2018) Thyroid hormone in the regulation of hepatocellular carcinoma and its microenvironment. *Cancer Lett* 419: 175-186. [Crossref]
27. Mercado Irizarry A, Torres EA (2016) Cryptogenic cirrhosis: Current knowledge and future directions. *Clin Liver Dis* 7: 69-72. [Crossref]
28. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F et al. (2018) EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 69: 182-236. [Crossref]
29. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA et al. (2017) EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 67: 370-398. [Crossref]
30. Zhao C, Jin M, Le RH, Le MH, Chen VL et al. (2018) Poor adherence to hepatocellular carcinoma surveillance: a systematic review and meta-analysis of a complex issue. *Liver Int* 38: 503-514. [Crossref]
31. Liu Y, Li H, Ye N, Luo CJ, Hu YY et al. (2019) Non-Cirrhotic Liver is Associated with Poor Prognosis of Hepatocellular Carcinoma: A Literature Review. *Med Sci Monit* 25: 6615-6623. [Crossref]
32. Desai A, Sandhu S, Lai JP, Sandhu DS (2019) Hepatocellular carcinoma in non-cirrhotic liver: A comprehensive review. *World J Hepatol* 11: 1-18. [Crossref]