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Hepatocellular Carcinoma in the Absence of Cirrhosis in US Veterans is Associated with Non-Alcoholic Fatty Liver Disease

Sahil Mittal, MD, MS[1,3], **Hashem B. El-Serag, MD, MPH**[1,2,3], **Yvonne H. Sada, MD**[1], **Fasiha Kanwal, MD, MS**[1,2,3], **Zhigang Duan, MD, MS**[1], **Sarah Temple, BA**[1], **Sarah B. May, MS**[1], **Jennifer R. Kramer, PhD, MPH**[1], **Peter A. Richardson, PhD**[1], and **Jessica A. Davila, PhD**[1]

[1]Center of Innovation, Effectiveness and Quality, Sections of Health Services Research, Section of Gastroenterology and Hepatology, Houston, Texas

[2]Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas

[3]Baylor College of Medicine, Houston, Texas

Abstract

Background & Aims—Hepatocellular carcinoma (HCC) can develop in individuals without cirrhosis. We investigated risk factors for development of HCC in the absence of cirrhosis in a US population.

Methods—We identified a national cohort of 1500 patients with verified HCC during 2005–2010 in the US Veterans Administration (VA), and reviewed their full VA medical records for evidence of cirrhosis and risk factors for HCC. Patients without cirrhosis were assigned to categories of level 1 evidence for no cirrhosis (very high probability) or level 2 evidence for no cirrhosis (high probability), based on findings from histologic analyses, laboratory test results, markers of fibrosis from non-invasive tests, and imaging features.

Corresponding Author: Sahil Mittal, MD, MS. The Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd. (152), Houston, TX 77030, Phone 713-873-3503 Fax 713-873-3505 (smittal@bcm.edu).

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Data Sources

Administrative data included the Medical SAS (MedSAS) Outpatient and Inpatient files, and the VA Vital Status File. The MedSAS files contain patient demographic data as well as diagnoses according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and procedures according to Common Procedural Terminology (CPT) codes. We determined date of death, if any, in the Vital Status File that uses an algorithm to select the most accurate date of death using the VA MedSAS Inpatient file, Beneficiary Identification & Records Locator System Death File, Medicare Vital Status file, and Social Security Administration death file.16 Patient EMR information were obtained by accessing the Compensation and Pension Records Interchange (CAPRI), which is a VA application that provides access to the EMR found in the Computerized Patient Record System (CPRS) at any VA facility nationwide.

Results—A total of 43 (2.9%) of the 1500 patients with HCC had level 1 evidence for no cirrhosis and 151 (10.1%) had level 2 evidence for no cirrhosis; the remaining 1203 patients (80.1%) had confirmed cirrhosis. Compared to patients with HCC in presence of cirrhosis, greater proportions of patients with HCC without evidence of cirrhosis had metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), or no identifiable risk factors. Patients with HCC without evidence of cirrhosis were less likely to have abused alcohol or have HCV infection than patients with cirrhosis. Patients with HCC and NAFLD (unadjusted odds ratio, 5.4; 95% confidence interval, 3.4–8.5) or metabolic syndrome (unadjusted odds ratio, 5.0; 95% confidence interval, 3.1–7.8) had more than a 5-fold risk of having HCC in the absence of cirrhosis, compared to patients with HCV-related HCC.

Conclusions—Approximately 13% of patients with HCC in the VA system do not appear to have cirrhosis. NAFLD and metabolic syndrome are the main risk factors HCC in the absence of cirrhosis.

Keywords

Liver cancer; Fatty liver; NASH; steatosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of liver.[1] Cirrhosis is the precursor lesion for most HCC cases. Nevertheless HCC is known to occur in the absence of cirrhosis. Among the major etiological risk factors for HCC, hepatitis B virus (HBV) is known to be involved directly in liver mutagenesis. A recent study of patients treated with entecavir reported that up to 44.6% of HBV-related HCC developed in the absence of cirrhosis.[2] Outside the US, a multicenter study conducted in Italy among all HCC patients diagnosed during a 1-year period reported that only 6.9% of patients developed HCC in the absence of cirrhosis.[3] Although some studies have reported that hepatitis C virus (HCV) and alcohol can be associated with development of HCC in the absence of cirrhosis, the causal relationship between HCV, alcohol, and development of HCC in the absence of cirrhosis remains controversial.[4–6] Recent literature has documented non-alcoholic fatty liver disease (NAFLD) associated HCC in the absence of cirrhosis or advanced hepatic fibrosis.[7]

There is a lack of systematic studies examining the epidemiologic and etiologic risk profile of HCC in the absence of cirrhosis. The majority of published studies on HCC in the absence of cirrhosis included patients undergoing either resection or liver transplantation.[5, 8–10] Furthermore, most studies reported data from tertiary referral centers[11–12] and may not be representative of the actual prevalence and risk factors of HCC in the absence of cirrhosis in the general population. Given that most strategies for preventing HCC, including surveillance and chemoprevention, have targeted individuals with cirrhosis, it is important to obtain a better understanding about the development of HCC in the absence of cirrhosis because of its potential implications on current clinical paradigms.

Using automated as well as medical record data obtained from the national Veterans Health Administration (VA) system, we conducted a retrospective cohort study among HCC patients diagnosed during 2005–2011. The aims of our study were to 1) to estimate the frequency of HCC that developed in the absence of cirrhosis, and 2) to examine and compare the etiological risk factor distribution between HCC patients without cirrhosis to those with cirrhosis.

METHODS

Study population

Data were obtained from VA administrative data files combined with review of patient electronic medical records (EMR) and relevant data abstracted using a structured data abstraction tools by trained medical record abstractors (ST and SM) (details in supplement 1). We identified a cohort of 10,695 patients who had a HCC diagnosis across VA hospitals between October 1, 2004 and September 30, 2011 (fiscal years 2005–2010). Patients with possible HCC were initially identified based on the presence of ICD-9 CM code 155.0 (malignant neoplasm of liver) in the absence of code 155.1 (intrahepatic cholangiocarcinoma).[14] Based on a desired sample size of 1500, we selected a random computer generated sample of patients for chart review to determine the study eligibility criteria. We included patients in the study if they had a diagnosis of HCC confirmed either by histopathology or imaging criteria according to the 2005 American Association for the Study of Liver Disease or European Association for the Study of Liver Disease guidelines.[15] We reviewed charts 2,719 patients with possible HCC to arrive at 1500 study subjects. We excluded 830 patients due to insufficient evidence for HCC diagnosis. We further excluded 389 patients without recent VA healthcare utilization (defined as at least one inpatient or outpatient encounter at any VA facility within the 1-year prior to the date of HCC diagnosis); cases with HCC recurrence and first diagnosis of HCC prior to study period, or those who recieved treatment before establishing guideline based diagnosis. Thus our final study cohort included 1,500 patients with verified HCC.

Categorization of cirrhosis status

Patients with HCC were categorized into 3 mutually exclusive groups as either 1) level 1 evidence of no cirrhosis (very high probability) or 2) level 2 evidence of no cirrhosis (high probability) or 3) confirmed cirrhosis (Table 1).

Risk factors for HCC

HCV status was determined by the presence of positive anti-HCV or HCV ribonucleic acid (RNA) tests detected any time before or after HCC diagnosis. HBV was defined by a positive surface antigen (HBsAg) detected any time before or after HCC diagnosis. Alcohol abuse was defined as history of more than 3 drinks a day, documentation of alcoholism/ alcohol abuse in a physician progress notes, enrollment in a substance abuse treatment program, or history of alcoholic hepatitis. NAFLD was determined based on documented evidence of hepatic steatosis on liver biopsy, or in the absence of liver biopsy, by the presence of metabolic syndrome in the *absence* of other causes of chronic liver disease (HCV, HBV, alcohol abuse, and no documentation of primary biliary cirrhosis, primary

sclerosing cholangitis, autoimmune hepatitis, hemochromatosis or Wilson disease) prior to HCC diagnosis. Metabolic syndrome was defined using U.S. National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines[16], except for replacing elevated waist circumference with body mass index (BMI) > 28.8 kg/m2 in both men and women.[17] Less common causes of HCC such as hemochromatosis, Wilson's disease, alpha-1 anti-trypsin deficiency or autoimmune hepatitis were captured when diagnostic laboratory tests results were positive (e.g., homozygosity for C282Y) or diagnoses were listed in the problem list or progress notes. Patients having none of the above risk factors were classified as idiopathic HCC.

Patient characteristics

Patient characteristics such as demographics, Model for End Stag Liver Disease (MELD) score liver disease 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, medical comorbidities and mental health disorders were manually extracted from EMR.

Statistical analysis

Demographic features, HCC risk factors, clinical factors and tumor characteristics were compared among the three groups of HCC patients: Level 1 evidence of no cirrhosis (very high probability), Level 2 evidence of no cirrhosis (high probability), and confirmed cirrhosis using chi-square test for discrete variables and t-test for continuous variables. Logistic regression models were used to identify variables independently associated with HCC in the absence of cirrhosis. Patient with level 1 and level 2 evidence of no cirrhosis (very high probability or high probability) were combined for these analyses. Patient and clinical factors that were significant at a p-value < 0.10 in the univariate analysis were retained in the final multivariable model, except for co-morbidities which were excluded to avoid multicollinearity as they are part of the definition of NAFLD and metabolic syndrome. Odds ratios (OR) and their accompanying 95% CI were calculated. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

The mean age of the study cohort at the time of HCC diagnosis was 63.7 years (standard deviation=9.5) and the vast majority were men (99.8%). The greatest proportions of patients were white non-Hispanic (59.8%), followed by blacks (26.1%) and Hispanics (11.9%). As compared to race distribution in the whole VA population, a higher proportion of HCC patients in our cohort were either blacks or Hispanics and lesser proportion were white. HCV testing was performed in 96.1%, HBV testing in 89.5% and liver biopsy in 52.4% of the study cohort. Among patients in the cohort, 67.5% had HCV, 4.6% HBV, 80.6% alcoholic liver disease, 8% NAFLD, 1.7% had other risk factors (hemochromatosis, alpha-1 anti-trypsin deficiency or autoimmune hepatitis) and 2.6% were idiopathic with no identifiable risk factor.

A total of 43 (2.9%) had level 1 evidence of no cirrhosis (very high probability), 151 (10.1%) had level 2 evidence of no cirrhosis (high probability), 1203 (80.1%) had confirmed cirrhosis, and in 105 (6.7%) there was insufficient information to classify these patients into any of the above categories. Among HCC patients with level 1 evidence of no cirrhosis, the hepatic fibrosis stage was 0 in 4 (9.3%), 1 in 13 (30.2%), 2 in 21 (48.9 %) and 3 in 5 patients (11.6%) according to the Metavir scoring system.

HCC risk factor distribution stratified by cirrhosis status is presented in Table 2. Among patients with NAFLD related HCC, 34.6% had level 1 or level 2 evidence of no cirrhosis and only 65.4% patients had confirmed cirrhosis at time of HCC diagnosis. HCC patients having metabolic syndrome irrespective of presence of other risk factors, 88.9% of them had confirmed cirrhosis and only 19% had no evidence of cirrhosis. However among patients with HCC and metabolic syndrome as the only risk factor (excluding HCV, HBV and alcohol abuse) 32.7% had level 1 or level 2 evidence of no cirrhosis and only 67.3% had confirmed cirrhosis at time of HCC diagnosis. On the other hand, among HCC patients with HCV, only 8.9% had level 1 or level 2 evidence of no cirrhosis and most (91.1%) had confirmed cirrhosis at time of HCC diagnosis. Similarly among HCC patients with HBV or alcohol abuse, 92.3% and 88.9% had confirmed cirrhosis respectively at time of HCC diagnosis.

HCC patients with level 1 or level 2 evidence of no cirrhosis were more likely to be older as compared to those with confirmed cirrhosis (Table 3). The mean MELD scores were significantly lower in HCC patients with level 1 (mean score 8.8, SD 3.2) and level 2 evidence of no cirrhosis (mean score 9.0, SD 3.6) compared to HCC patients with confirmed cirrhosis (mean score 12.2, SD 4.8) ($P<0.01$). No significant differences were observed by race. Patients with HCC in the presence of level 1 evidence of no cirrhosis were more likely to have AFP < 20 ng/ml compared to HCC in presence of confirmed cirrhosis (Table 3), while the prevalence of portal vein thrombosis was significantly lower in HCC patient with very high (2.3%) or high (11.9%) probability of no cirrhosis as compared to HCC in presence of cirrhosis (18.5%) ($P<0.01$). At the time of diagnosis, HCC patients with level 1 evidence of no cirrhosis were more likely to have BCLC stage B tumor (vs. C or D) as compared to HCC with cirrhosis. Tumor differentiation was not significantly different by cirrhosis status.

Association between etiologic risk factors and risk of HCC in the absence of cirrhosis

We performed multiple logistic regression to examine the association of etiologic risk factors and risk of HCC in absence of cirrhosis. For this analysis we combined HCC with very high or high probability of no cirrhosis into single group in one level of the outcome variable (vs. cirrhosis). Model 1 examined NAFLD as the main exposure variable while Model 2 examined metabolic syndrome (Table 4); we did not combine these two variables in one model because of overlap (metabolic syndrome was used to define NAFLD in the absence of liver biopsy). In the unadjusted analysis, HCC patients with NAFLD had more than a five-fold risk (OR 5.4, 95% CI 3.4–8.5) of having HCC in the absence of cirrhosis compared to patients with HCV related HCC. Patients with HCC and underlying metabolic syndrome as the only risk factor for liver disease were also five-fold (OR 5.0, 95% CI 3.1–

7.8) more likely to develop HCC in absence of cirrhosis as compared to patients with HCV related HCC. Patients with HCC with alcohol abuse as the only risk factor had greater than 2-fold risk of having HCC in absence of cirrhosis as compared to HCC with underlying HCV. HCC patients with HBV infection did not have a higher risk of HCC in absence of cirrhosis as compared to HCV related HCC. Adjusting for age, race and BCLC stage, MELD score, AFP and portal vein thrombus did not change the magnitude or direction of the association between etiologic risk factors and risk of HCC in absence of cirrhosis.

DISCUSSION

In a large national cohort of randomly identified US veterans with HCC, we conducted a comprehensive medical record review to confirm diagnosis of cirrhosis and underlying risk factors for HCC, and found that approximately 13% of HCC cases developed in patients without any evidence of cirrhosis. Compared with HCC in the presence of cirrhosis, these patients were more likely to have metabolic syndrome or NAFLD or no identifiable risk factor and less likely to have alcohol abuse or HCV infection. Amongst etiologic risk factors for HCC, patients with metabolic syndrome or NAFLD related HCC had the highest risk, followed by alcohol related HCC of developing HCC in absence of cirrhosis compared to HCV related HCC. HCC patients with HBV infection did not have a higher risk of HCC in absence of cirrhosis as compared to HCV related HCC.

The risk of HCC developing in the absence of cirrhosis varies according to etiology of the liver disease. A systemic review of studies published between 1998 and 2009 reported that among patients with HBV-related HCC who received anti-viral treatment, 9.5% of patients had no evidence of cirrhosis.[18] However, a study that examined at long-term outcomes of chronic hepatitis B among Caucasian patients reported that HCC risk was mostly limited to patients with cirrhosis, findings similar to our study results.[19] In the Hepatitis C Antiviral Long Term Treatment against Cirrhosis (HALT-C) study conducted in the United States, the annual risk of HCV related HCC among non-cirrhotics was 0.8% compared to 2–8% per year in cirrhotics.[15, 20] Among patients with alcohol abuse related HCC, estimates of HCC without evidence of cirrhosis varies widely from 11.5 to 49% depending upon geographical location of study and definition of alcohol abuse.[21] In our study, approximately 10% of those with alcohol abuse or HCV related HCC and 7% of those with HBV related HCC did not have evidence of cirrhosis at time of HCC diagnosis. In contrast, 35% of NAFLD related HCC and 33.8% of idiopathic HCC did not have evidence of cirrhosis at the time of HCC diagnosis (Figure 1). It is however possible that we have missed diagnosis of NAFLD among some patients with idiopathic HCC due to absence of liver biopsy or undiagnosed components of metabolic syndrome.

Studies from other parts of the world have also reported high proportion of NAFLD related HCC occurring in absence of cirrhosis. In a study from Japan, only 51% of 87 cases of NAFLD related HCC had cirrhosis at time of HCC diagnosis.[22] Similarly, among 31 HCC patients with metabolic syndrome as the only risk factor undergoing liver resection in a French hospital only 35% had advanced hepatic fibrosis.[9] In a study from Germany, only 58% of 36 NAFLD related HCC had cirrhosis at time of HCC diagnosis.[12] Another study from US on HCC patients undergoing curative treatment found that only about 73% of 52

cases NAFLD-HCC patients had underlying cirrhosis.[23] A study using health system database found only 46% of patients with NAFLD/NASH and HCC had underlying cirrhosis.[24] However in this study authors relied only on non validated ICD codes to capture diagnosis of NAFLD. In our study we performed manual chart review to confirm diagnosis of HCC, presence or absence of underlying cirrhosis and risk factor. Our study findings extend the findings of these previous and highlight that the sequence of events from steatohepatitis to cirrhosis and finally HCC may not be linear in a substantial proportion of patients with NAFLD or metabolic syndrome related HCC. It seems that the increased risk of HCC in these patients is due to both progression to cirrhosis and oncogenic potential of NAFLD or metabolic syndrome per se.

We used findings on liver biopsy performed within 1 year of HCC diagnosis to evaluate for diagnosis of cirrhosis. Liver biopsy is prone to sampling error and can miss cirrhosis.[25] This is especially true for cases with stage 3 hepatic fibrosis.[26] However among HCC patients with no evidence of cirrhosis on liver biopsy in our study, only a small fraction (< 12%) had stage 3 fibrosis. Moreover, we labelled HCC patients having no evidence of cirrhosis only when biopsy evidence was supplemented by absence of features of cirrhosis on abdominal imaging. Further we used biopsy findings within 1 year of HCC diagnosis thus minimizing the possibility of fibrosis progression in the time interval between biopsy and HCC diagnosis. In absence of liver biopsy we relied upon non-invasive marker AST to platelet ratio (APRI) to rule out cirrhosis. A recent meta-analysis on APRI with cut off 1.0 had summary receiver operating characteristic curve (AUROC) of 0.83 with negative predictive value of 69% in excluding cirrhosis.[27] A diagnostic tool with AUROC of 100% is considered perfect and anything above 80% is considered good. To further reduce the chances of misclassification of cirrhosis status in the absence of liver biopsy, we supplemented APRI score with no evidence of cirrhosis on imaging and absence of any laboratory parameters suggestive of cirrhosis. Thus a patient had to fulfill all three criteria in order to qualify for level 2 evidence of no cirrhosis. HCC patients with no evidence of cirrhosis had significantly lower MELD score and lower prevalence of portal vein thrombosis thus providing internal validity of our findings. We observed that HCC patients without evidence of cirrhosis were older as compared to HCC in presence of cirrhosis. This may be due to the higher prevalence of NAFLD among non-cirrhotic HCC while cirrhotic HC had a higher proportion of HCV or alcohol abuse related HCC.

Our findings have important implications for HCC surveillance practices and paradigms in patients with NAFLD. Current guidelines do not recommend surveillance in patients with NAFLD who do not have evidence of cirrhosis.[15] Studies have shown that HCC screening is under-utilized among cirrhotics who are at the highest risk of developing HCC and most likely to benefit from HCC surveillance.[28] It will be logistically impractical to expand the risk pool by including the large NAFLD population. Although evidence suggests that a substantial proportion of NAFLD patients can develop HCC in absence of cirrhosis the absolute risk of HCC in non-cirrhotics is not known and the strategies and benefits of screening for HCC in NAFLD patients without cirrhosis has not been examined. Chemoprevention may also be a feasible strategy if an intervention has low toxicity and high efficacy. Given the epidemiologic association of diabetes mellitus and obesity with HCC it seems reasonable to seek and treat concomitant metabolic conditions in patients with NASH

to reduce the risk of HCC. There is evidence to suggest that metformin reduces the risk of HCC among diabetics.[29,30] Studies of these and other risk factors of HCC among NAFLD with and without cirrhosis are needed.

Our study has several limitations. The study population was predominantly male and may limit generalizability of results. Large liver specimen obtained during liver transplantation or hepatic resection for HCC treatment provides for more accurate staging of fibrosis and severity of underlying liver disease. However limiting the study to such patients would have introduced considerable selection bias by overestimating the number of patients with preserved liver function and consequently less advanced liver disease and defeated our primary objective to study the prevalence of HCC in absence of cirrhosis and its risk factors among the general population. We used all available VA electronic medical records to identify risk factors including a search of all progress notes for any evidence of alcohol abuse prior to HCC diagnosis. However there is still chance of occult alcohol use and therefore misclassification of risk category between alcohol use and NAFLD. It is also plausible that HCC that we attributed to NAFLD due to the presence of metabolic syndrome in the absence of other risk factors is due to other currently unknown genetic or metabolic causes. However this definition of NAFLD has been successfully employed in several NAFLD studies.[17, 31]

In conclusion, we found that up to 13.0 % of HCC patients had no evidence of cirrhosis at the time of HCC diagnosis. The main risk factors for this entity were NAFLD or metabolic syndrome (vs. HCV, HBV or alcohol abuse). Future research is needed to identify actionable risk factors and/or biomarkers to predict NAFLD patients at higher risk of developing HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NAFLD	Non-alcoholic fatty liver disease
HCC	Hepatocellular carcinoma
VA	Veterans Administration
AFP	Alpha-fetoprotein
HCV	Hepatitis C
EMR	Electronic medical records

ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
CPT	Common Procedural Terminology
CAPRI	Compensation and Pension Records Interchange
CPRS	Computerized Patient Record System
HBV	Hepatitis B
OPC	Outpatient Care File
PTF	Patient Treatment File

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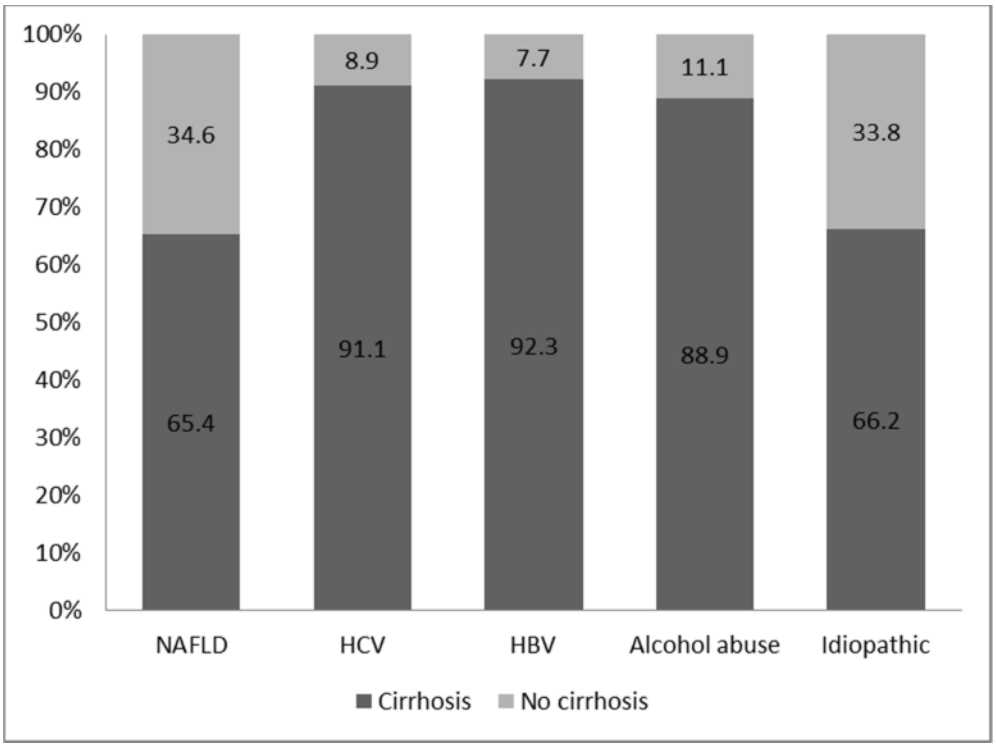

Figure 1.
Proportion of HCC patients with or without evidence of cirrhosis by risk factor

Table 1

Study definition for classification of cirrhosis categories

Cirrhosis Category	Definition
Level 1 evidence of no cirrhosis (very high probability), n= 43	No evidence of cirrhosis on a resection specimen or liver biopsy performed within 1 year prior to or at time of HCC diagnosis AND No features suggestive of cirrhosis on abdominal imaging available nearest to HCC diagnosis within 3 years prior to HCC diagnosis
Level 2 evidence of no cirrhosis (high probability), n=151	Aspartate aminotransferase to platelet ratio index (APRI) <1 based on laboratory results available nearest to HCC diagnosis within 6 months prior and 4 weeks after HCC diagnosis AND No features suggestive of cirrhosis on abdominal imaging performed nearest to HCC diagnosis within 3 years prior to HCC diagnosis AND Two of three tests values in normal range based on laboratory results available nearest to HCC diagnosis within 6 months prior and 4 weeks after HCC diagnosis (albumin > 3.5 g/l, platelets >200,000/microliter or INR <1.1)
Confirmed cirrhosis, n=1201	Documented cirrhosis on a resection specimen or liver biopsy performed any time prior to or at time of HCC diagnosis OR Features suggestive of cirrhosis on abdominal imaging performed nearest to HCC diagnosis within 3 years prior to HCC diagnosis OR Documented presence of ascites, varices, or hepatic encephalopathy OR Abnormal values on two of three laboratory tests available nearest to HCC diagnosis within 6 months prior and 4 weeks after HCC diagnosis (albumin <3.0g/l, platelets <200,000 microliter, INR >1.1)
Unclassified, n=105	Insufficient information to classify in any cirrhosis category

Table 2

Risk factor distribution in the HCC cohort by cirrhosis category (N=1395)*. Risk factor distribution is not mutually exclusive as many patients had more than 1 risk factor.

Risk factor n (%)	Level 1 evidence of no cirrhosis n= 43	Level 2 evidence of no cirrhosis n= 151	Confirmed Cirrhosis n=1201	*P* value
NAFLD	6 (5.6)	31 (28.9)	70 (65.4)	<0.01
HCV	18 (1.9)	67 (7.0)	867 (91.1)	<0.01
HBV	2 (3.1)	3 (4.6)	60 (92.3)	0.25
Alcohol abuse	29 (2.6)	96 (8.5)	1008 (88.9)	<0.01
Metabolic syndrome	14 (3.9)	54 (15.1)	289 (80.9)	<0.01
Others**	2 (8.0)	3 (12.0)	20 (80.0)	0.45
Idiopathic***	2 (5.9)	11 (32.4)	21 (61.8)	<0.01

HCV-hepatitis C virus; HBV-hepatitis B virus; NAFLD-nonalcoholic fatty liver disease

* Of 1500, 105 had insufficient information to classify in any cirrhosis category

** Others – Hemochromatosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency

*** None of the above

Table 3

Comparison of demographics, co-morbidities and tumor characteristics among HCC patients according to cirrhosis status

Variables	Level 1 evidence of no cirrhosis n= 43	Level 2 evidence of no cirrhosis n= 151	Confirmed Cirrhosis n=1201	*P*-value
Age Mean (S.D.)	65.5 (8.5)	69.7 (10.7)	62.6 (9.0)	<0.01
Sex (%)				
Male	43 (100)	150 (99.3)	1199 (99.8)	0.44
Race (%)				0.05
White	23 (53.5)	95 (62.9)	711 (59.2)	
Black	17 (39.5)	44 (29.1)	301 (25.1)	
Hispanic	3 (6.9)	9 (5.9)	160 (13.3)	
Other	0	3 (1.9)	29 (2.4)	
BMI (%)				0.74
<25	10 (23.3)	39 (25.8)	261 (21.7)	
25–29.9	14 (32.6)	56 (37.1)	443 (36.9)	
30+	19 (44.2)	56 (37.1)	497 (41.4)	
Ascites	0 (0)	0 (0)	585 (48.7)	<0.01
Encephalopathy	0 (0)	0 (0)	211 (17.8)	<0.01
Varices	0 (0)	0 (0)	513 (42.7)	<0.01
Medical Comorbidities (%)				
Diabetes	23 (53.5)	68 (45.0)	477 (39.7)	0.10
Hypertension	38 (88.4)	131 (86.8)	872 (72.6)	<0.01
HIV	1 (2.3)	7 (4.6)	37 (3.1)	0.56
Myocardial infarction	5 (11.6)	28 (18.5)	90 (7.5)	<0.01
Peripheral Vascular Disease	5 (11.6)	30 (19.9)	114 (9.5)	<0.01
AFP <20ng/ml (%)	26 (60.5)	53 (35.1)	437 (36.4)	<0.01
Portal vein thrombosis (%)	1 (2.3)	18 (11.9)	222 (18.5)	<0.01
BCLC Stage (%)				<0.01
Stage A	5 (11.6)	6 (3.9)	177 (14.7)	
Stage B	21 (48.8)	42 (27.8)	265 (22.1)	
Stage C	11 (25.6)	72 (47.7)	444 (36.9)	
Stage D	0	15 (9.9)	231 (19.2)	
Missing	6 (13.9)	16 (10.6)	84 (6.9)	
Tumor differentiation (%)				0.63
Well	15 (37.5)	27 (25)	148 (26)	
Moderate	9 (22.5)	24 (22)	122 (21)	
Poorly	4 (10)	8 (7)	55 (10)	
Missing	12 (30)	50 (46)	244 (43)	

Table 4

Association between etiologic risk factors and risk of HCC in absence of cirrhosis – Results of logistic regression analysis examining two models (model 1 contains NAFLD, model 2 contains metabolic syndrome)

Model 1				Model 2		
Variable	**n**	**Unadjusted OR (95% CI)**	*** Adjusted OR (95% CI)**	**Variable**	**Unadjusted OR (95% CI)**	*** Adjusted OR (95% CI)**
Etiology				Etiology		
HCV	952	1.0	1.0	HCV	1.0	1.0
NAFLD	107	5.4 (3.4–8.5)	3.9 (2.1–7.3)	Metabolic syndrome	5.0 (3.1–7.8)	3.4 (1.9–6.4)
Alcohol abuse	280	2.6 (1.8–3.8)	2.5 (1.6–3.9)	Alcohol abuse	2.6 (1.8–3.8)	2.5 (1.5–3.9)
HBV	15	1.6 (0.4–7.1)	1.3 (0.2–7.2)	HBV	1.6 (0.4–7.1)	1.3 (0.2–7.2)
Idiopathic	41	4.7 (2.4–9.5)	3.6 (1.6–8.3)	Idiopathic	6.0 (3.0–11.9)	5.1 (2.2–11.7)
Age	139 5		1.0 (1.0–1.1)			1.0 (1.0–1.1)
Race						
White	829		1.0			1.0
Black	362		2.2 (1.5–3.4)			2.2 (1.5–3.4)
Hispanic	172		0.4 (0.2–0.7)			0.4 (0.2–0.7)
Others	32		0.9 (0.2–3.4)			0.9 (0.2–3.4)
BCLC Stage						
A	188		1.0			1.0
B	328		2.9 (1.4–5.8)			2.9 (1.4–5.9)
C	527		2.5 (1.3–5.2)			2.6 (1.3–5.2)
D	246		1.2 (0.5–2.9)			1.2 (0.5–2.9)
Unknown	106		2.5 (1.0–6.0)			2.5 (1.0–2.9)
MELD score						
< 10	551		1.0			1.0
10–19.9	641		0.2 (0.1–0.3)			0.2 (0.1–0.3)
20+	73		0.1 (0.0–0.5)			0.1 (0.0–0.5)
Unknown	130		0.7 (0.4–1.2)			0.7 (0.4–1.3)
AFP						

		Model 1			Model 2	
Variable	**n**	**Unadjusted OR (95% CI)**	*** Adjusted OR (95% CI)**	**Variable**	**Unadjusted OR (95% CI)**	*** Adjusted OR (95% CI)**
<20	516		1.0			1.0
20+	780		0.8 (0.5–1.2)			0.8 (0.5–1.2)
Unknown	99		1.6 (0.9–2.8)			1.6 (0.9–2.8)
PVT						
Absent	111 3		1.0			1.0
Present	241		0.6 (0.3–1.1)			0.6 (0.3–1.1)
Unknown	41		2.3 (1.1–4.9)			

* Adjusted for age, race, BCLC stage, MELD score, AFP and portal vein thrombus