

Case Control Study

Risk factors for hepatocellular carcinoma in cirrhosis due to nonalcoholic fatty liver disease: A multicenter, case-control study

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Abstract

AIM

To identify risk factors associated with hepatocellular

carcinoma (HCC), describe tumor characteristics and treatments pursued for a cohort of individuals with nonalcoholic steatohepatitis (NASH) cirrhosis.

METHODS

We conducted a retrospective case-control study of a well-characterized cohort of patients among five liver transplant centers with NASH cirrhosis with (cases) and without HCC (controls).

RESULTS

Ninety-four cases and 150 controls were included. Cases were significantly more likely to be male than controls (67% *vs* 45%, $P < 0.001$) and of older age (61.9 years *vs* 58 years, $P = 0.002$). In addition, cases were more likely to have had complications of end stage liver disease (83% *vs* 71%, $P = 0.032$). On multivariate analysis, the strongest association with the presence of HCC were male gender (OR 4.3, 95%CI: 1.83-10.3, $P = 0.001$) and age (OR = 1.082, 95%CI: 1.03-1.13, $P = 0.001$). Hispanic ethnicity was associated with a decreased prevalence of HCC (OR = 0.3, 95%CI: 0.09-0.994, $P = 0.048$). HCC was predominantly in the form of a single lesion with regional lymph node(s) and distant metastasis in only 2.6% and 6.3%, respectively. Fifty-nine point three percent of individuals with HCC underwent locoregional therapy and 61.5% underwent liver transplantation for HCC.

CONCLUSION

Male gender, increased age and non-Hispanic ethnicity are associated with HCC in NASH cirrhosis. NASH cirrhosis associated HCC in this cohort was characterized by early stage disease at diagnosis and treatment with locoregional therapy and transplant.

Key words: Hepatocellular carcinoma; Nonalcoholic fatty liver disease; Cirrhosis, Gender; Ethnicity

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Core tip: The present paper identifies male gender, increased age and non-Hispanic ethnicity as factors associated with hepatocellular carcinoma (HCC) in nonalcoholic steatohepatitis cirrhosis. In this series, HCC in nonalcoholic fatty liver disease cirrhosis was diagnosed at an early stage and treated predominantly with locoregional therapy and liver transplantation.

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INTRODUCTION

The burden of nonalcoholic fatty liver disease (NAFLD) is substantial. Estimates suggest 75-100 million people in the United States have NAFLD, and alarmingly, many of these patients are not aware of or evaluated for this condition^[1,2]. A subset of individuals with NAFLD will develop nonalcoholic steatohepatitis (NASH), the inflammatory phenotype of NAFLD. Hepatic fibrosis and eventual cirrhosis is a consequence of NASH progression, particularly in genetically predisposed individuals. NASH cirrhosis is projected to be the leading indication for liver transplantation in the next 10-20 years^[3].

Hepatocellular carcinoma (HCC), like NAFLD, is also underrecognized. In fact, a recent retrospective study suggested that only 20% of patients received appropriate surveillance before their HCC diagnosis^[4]. Inadequate screening is a serious concern for patients with cirrhosis of any type. However, recent data suggests that a deficiency in screening may be particularly problematic for patients with NAFLD HCC who present at a later tumor stage, have shorter survival times, and lower rates of liver transplantation^[5].

Thus, the convergence of NAFLD and HCC uniquely focuses the narrative for providers caring for these patients to enhance the screening and diagnosis of both diseases. Simultaneously, identifying risk factors for HCC development in patients with underlying NASH cirrhosis is critically important to improve screening and treatment. We have conducted a retrospective case-control study of a well-characterized cohort of patients with NASH cirrhosis with and without HCC in order to identify risk factors associated with HCC. We also provide tumor characteristics and survival data for this cohort. Our data, derived from five academic liver transplant centers, highlights patient characteristics associated with HCC and enhances the growing body of evidence on HCC in the setting NAFLD.

MATERIALS AND METHODS

We conducted a case-control study of individuals with NAFLD cirrhosis with and without HCC from five academic medical centers in the United States. NAFLD was diagnosed between 1991-2015 and all HCC cases were diagnosed between 2004-2015. This study was approved by the Institutional Review Boards at the respective institutions.

A diagnosis of NAFLD cirrhosis was made either (1) by histology; or (2) clinically. Clinical NAFLD was defined by the exclusion of other causes of chronic liver disease and the presence of one or more risk factors for NAFLD including diabetes, obesity or ≥ 1 component of the metabolic syndrome. The diagnosis of cirrhosis was made either by histology or by imaging suggestive of cirrhosis (nodular liver, splenomegaly, ascites or varices) in combination with laboratory values suggesting portal hypertension or impaired synthetic function (platelet count

< 150000/ μ L, albumin < 3.5 g/dL) or complications of end-stage liver disease. Characteristic liver histology for NASH served as one diagnostic modality; NAFLD Activity Score values were not available for all subjects.

Definition of cases

Cases were individuals with NAFLD cirrhosis and well-characterized HCC. HCC was defined by histology or imaging consistent with Organ Procurement and Transplantation Network criteria^[6].

Definition of controls

Controls were defined as individuals meeting criteria for NASH cirrhosis but without evidence of HCC on imaging within one year following the diagnosis of cirrhosis. For each case, depending on the availability, we enrolled 1-3 controls from the same institution. Cases and controls were matched for the year of enrollment, *i.e.*, ascertainment of absence of HCC by imaging in the controls was in the same year as the HCC diagnosis in the cases.

Data collection

Charts were reviewed for weight, height, body mass index (BMI) and co-morbid disease including diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnea, polycystic ovary syndrome and obesity. Complications of liver disease were also recorded including the presence of ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy and gastroesophageal varices. These complications were combined in to a composite cirrhosis complication variable. Use of medications including metformin, pioglitazone, vitamin E, HMG-CoA reductase inhibitors ("statins") was also collected. Laboratory values for platelet count, INR, fasting insulin, fasting glucose, creatinine, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, albumin, total cholesterol, low-density lipoprotein level, high-density lipoprotein level, triglycerides, glycosylated hemoglobin (A1C), ferritin, alpha-fetoprotein, and model for end-stage liver disease (MELD) score. MELD score was calculated according to the published formula^[7].

Pathology reports were reviewed for the presence of HCC as well as TMN classification of malignant tumor status, differentiation status, vascular and/or perineural invasion and lymph node involvement. Imaging including ultrasound, computerized tomography scan or magnetic resonance imaging was reviewed for tumor number, size and location.

Statistical analysis

All statistical analyses were performed using SAS software, version V.9.2 (SAS Institute, Cary, NC). Continuous variables were analyzed using a Student's *t*-test for normally distributed variables and a Wilcoxon rank sum test for variables that were not normally distributed. Categorical variables were analyzed using a χ^2 test or Fisher's exact test as appropriate. Nominal, two-sided

P values were used and were considered statistically significant if *P* < 0.05. The final model was selected by combining clinical judgment and statistical assessment. We included variables with *P* < 0.1 in univariate analysis and variables that are considered as known confounders. All analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC) and Stata 13.1 (Stata Corp., College Station, TX).

RESULTS

Baseline characteristics

Two hundred and forty-four individuals (94 cases and 150 controls) were included. Individuals were predominantly male (54.7%), and Caucasian (81.8%) with a mean age of 59 years. Diabetes (69.5%), dyslipidemia (47.9%) and hypertension (60.1%) were frequent. Mean BMI was 33.5 kg/m² and mean MELD score was 12.

Seventy-five point four percent had a complication of cirrhosis with the most frequent being gastroesophageal varices (58.0%), ascites (48.6%) and encephalopathy (39.6%). Hepatorenal syndrome and spontaneous bacterial peritonitis were infrequent (3.3% and 4.2%, respectively).

Characteristics of cases and controls: Univariate analysis

Ninety-four cases and 150 controls were included in the present study. Cases were significantly more likely to be male than controls (67% vs 45%, *P* < 0.001) and be of older age (mean, 61.9 \pm 9.4 vs 58.0 \pm 9.9, *P* = 0.002). In addition, cases were more likely to have had complications of end-stage liver disease including ascites, SBP, HRS, gastroesophageal varices or encephalopathy (composite 83% vs 71%, *P* = 0.032). There was no difference between cases and controls by comorbidities, medication use including statins or vitamin E, or biochemical markers such as ALT or MELD score (Table 1).

Characteristics of cases and controls: Multivariate analysis

On multivariate analysis, after adjustment for the relevant confounders, the strongest association with the presence of HCC among those with NASH cirrhosis was male gender (OR = 4.3, 95%CI: 1.83-10.3, *P* = 0.001). In addition, age (OR = 1.082, 95%CI: 1.03-1.13, *P* = 0.001) was associated with HCC. Hispanic ethnicity was associated with a decreased prevalence of HCC (OR = 0.3, 95%CI: 0.09-0.994, *P* = 0.048) (Table 2).

Characteristics of HCC in NAFLD cirrhosis

HCC diagnosed in this cohort of individuals with NASH cirrhosis was predominantly in the form of a single lesion (median 1.0, IQR 1.0) with a median size of 2.7 cm (IQR 2.5) (Table 3). Regional lymph node and distant metastasis were recorded in only 2.6% and 6.3%, respectively. Vascular or perineural invasion was documented in

Table 1 Characteristics of cases and controls

Characteristic		Case (n = 94)	Control (n = 150)	P value
Age, yr (mean ± SD)		61.9 ± 9.4	58.0 ± 9.9	0.002
Gender	Female	33%	55%	< 0.001
	Male	67%	45%	
Race	White	85%	80.0%	0.605
	Black	1%	17%	
	Other	14%	3%	
Ethnicity	Not Hispanic	82%	90%	0.149
	Hispanic	18%	10%	
Diabetes mellitus	Yes	74%	67%	0.237
	No	26%	33%	
Hypertension	Yes	61%	60%	0.888
	No	39%	40%	
Dyslipidemia	Yes	50%	47%	0.609
	No	50%	53%	
Cardiovascular disease	Yes	28%	19%	0.093
	No	72%	81%	
Metformin use	Yes	40%	37%	0.660
	No	60%	63%	
Statin use	Yes	25%	21%	0.401
	No	75%	79%	
Vitamin E use	Yes	11%	9%	0.620
	No	89%	91%	
Ascites	Yes	51%	47%	0.628
	No	49%	53%	
Gastroesophageal varices	Yes	66%	53%	0.072
	No	34%	47%	
Hepatic encephalopathy	Yes	40%	40%	0.995
	No	60%	60%	
Complications of cirrhosis	Yes	83%	71%	0.032
	No	17%	29%	
BMI (kg/m ²)		32.8 ± 5.8	33.9 ± 7.3	0.222
ALT (IU/L) (mean ± SD)		43.3 ± 25.4	42.18 ± 37.3	0.819
MELD score (mean ± SD)		11.6 ± 4.4	12.39 ± 4.8	0.382

BMI: Body mass index; ALT: Alanine aminotransferase; MELD: Model for end-stage liver disease.

13.9% and 1.3%, respectively. Fifty-five percent of tumors involved a single lobe of the liver, 25.6% were bilobar, while the lobar distribution was unknown in 32.4%.

Treatment for HCC

In this cohort, 59.3% of individuals with HCC underwent either locoregional therapy with radiofrequency ablation, transarterial chemoembolization or radiation. In addition, 61.5% of the entire cohort underwent liver transplantation for HCC. Resection was infrequent and took place in only 10% of the HCC cohort. Sorafenib and/or palliative care was administered in 10% of patients.

DISCUSSION

NASH cirrhosis is projected to become the leading indication for liver transplantation by 2020, surpassing alcohol and chronic hepatitis C infection^[3]. Despite its public health impact, however, relatively little is known about the risk factors for HCC development in NASH cirrhosis. The present case-control study sought to address this gap by evaluating individuals with NASH

Table 2 Variables associated with presence of hepatocellular carcinoma on multivariate analysis¹

Variable	Univariate P value	Multivariate OR 95%CI	Multivariate P value
Age	0.002	1.08 (1.032-1.13)	0.001
Gender	< 0.001	4.34 (1.83-10.31)	< 0.001
BMI	0.22	0.96 (0.90-1.02)	0.20
Ethnicity	0.15	0.300 (0.090-0.994)	0.045
Platelet count	0.14	1.004 (1.00-1.01)	0.14
CVD	0.09	1.21 (0.61-2.41)	0.58
Gastroesophageal varices	0.07	1.43 (0.63-3.21)	0.39
Complications of cirrhosis	0.03	1.15 (0.43-3.02)	0.78

¹The final model was selected by combining clinical judgment and statistical assessment. We included variables with P < 0.1 in univariate analysis and variables that are considered as known confounders. CVD: Cardiovascular disease; BMI: Body mass index.

cirrhosis with and without HCC.

We found that HCC was associated with male gender and older age. There was no difference between cases and controls with regards to comorbidities, prescription medications, vitamin E use, or biochemical markers such as ALT or MELD score. Surprisingly, the Hispanic ethnicity conferred a decreased risk of HCC.

The observed differences in sex and age are consistent with prior studies. Ascha *et al*^[8] compared patients with HCC secondary to NASH cirrhosis to those with HCV cirrhosis and HCC. Compared to those with HCV, individuals with NASH and HCC were significantly older and had a trend toward an increased risk of HCC in men. Bugianesi *et al*^[9] also evaluated risk factors for HCC in a cohort of 641 individuals with chronic liver disease of varying etiologies. Six point nine percent of the cohort had cryptogenic cirrhosis largely attributed to NASH. HCC in cryptogenic cirrhosis was associated with older age although no difference in gender was seen. These studies also found that HCC in NASH cirrhosis/cryptogenic cirrhosis was associated with BMI, obesity and diabetes mellitus. The present study did not find associations between diabetes, obesity, BMI or insulin resistance. Our use of NASH cirrhosis controls with high prevalence of diabetes and obesity may account for this difference as prior studies have compared NASH patients who are often characterized by diabetes and obesity to those with other forms of chronic liver disease among whom these comorbidities are less frequent.

Metabolic stress including development of the metabolic syndrome is not only associated with increased risk of cancer in general, but with risk for HCC. Presumably, most NAFLD patients meet criteria for diagnosis of the metabolic syndrome, yet a great proportion of these patients do not develop HCC. The present study did not find a significant difference in comorbidities between cases and controls. Just as only a subset of NAFLD patients progress to NASH, this lends further support to a genetic determinant for development of HCC within NAFLD. Investigation of genetic alterations in insulin signaling including the PI3K-AKT-PTEN pathway and other factors

Table 3 Tumor characteristics of hepatocellular carcinoma

Characteristics of HCC	n (%)
Primary tumor (T)	
1	27 (42.86)
2	28 (44.44)
3	8 (12.70)
Regional lymph nodes (N)	
Yes	2 (2.63)
No	43 (56.58)
Unknown	31 (40.79)
Distant metastasis (M)	
Yes	5 (6.33)
No	45 (56.96)
Unknown	29 (36.71)
Tumor size, median (IQR)	2.7 (2.5)
Number of lesions, median (IQR)	1.0 (1.0)
Vascular invasion	
Yes	11 (13.92)
No	56 (70.89)
Unknown	12 (15.19)
Perineural invasion	
Yes	1 (1.30)
No	51 (66.23)
Unknown	25 (32.47)
Bilobar involvement of tumor	
Yes	21 (25.61)
No	45 (54.88)
Unknown	16 (19.51)

HCC: Hepatocellular carcinoma.

in inflammatory pathways including NF-KB may be promising^[10-12] and possible with a prospective study in a similar cohort of subjects.

Genetic variation may explain reported racial/ethnic disparities. Racial/ethnic disparities have been reported both in NAFLD and HCC: Hispanics tend to have a more progressive course in NAFLD; and have lower rates of curative therapies for HCC^[13]. Our finding that Hispanic ethnicity was associated with a decreased risk of development of HCC within NAFLD is surprising and needs confirmation with a larger cohort of individuals with NASH and other etiologies of chronic liver disease. Indeed among other causes of chronic liver disease, specifically hepatitis C, Hispanics are more likely to progress to cirrhosis and HCC^[14]. The present study is limited by a small number of Hispanic patients among both cases and controls and further evaluation of this relationship between ethnicity and HCC among those with NASH cirrhosis is needed.

The tumors observed in our study were typically a single lesion, confined to a single lobe and without any invasion to adjacent structures. This is in contrast with a recent study by Piscaglia *et al*^[15] who found that NAFLD-HCC tended to be more advanced when compared to HCC in the background of HCV cirrhosis (HCV-HCC). The authors concluded that this was a result of delayed diagnosis of NAFLD and subsequent lack of screening in advanced fibrosis. There was no significant difference in mortality when propensity score analysis was performed. Certainly, detection of early stage HCC centers around

appropriate screening. Our patients were established in our respective clinics and routinely followed. Resection was infrequent and the majority of our patients (61.5%) underwent orthotopic liver transplantation. The earlier stage observed in our study may be a product of referral and/or selection bias, as this cohort was selected from tertiary care and transplant medical center populations.

The limitations of our study include its retrospective nature; only cirrhotic patients were included in the study by design, thus limiting our ability to add to the body of data of HCC in the absence of advanced fibrosis. Similarly, we did not include HCC arising within other etiologies of cirrhosis, and therefore, cannot report that our findings are unique to NAFLD but that these characteristics play a role in the development of HCC in the context of NAFLD cirrhosis. The duration of cirrhosis is not known in this cohort given the case-control design and absence of longitudinal data.

In conclusion, the present study found that male gender and advanced age were associated with increased risk for the development of HCC among individuals with NASH cirrhosis whereas Hispanic ethnicity was associated with lower risk. Larger cohorts of individuals with HCC, from NASH and other etiologies are needed to further explore these associations. Additionally, prospective studies will help address these factors as predictors of HCC development and to risk stratify patients with NAFLD at increased risk for HCC who may benefit from more intense surveillance for HCC.

COMMENTS

Background

Both nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) are rising in prevalence worldwide. Recent data suggest that HCC surveillance rates are poor in those with nonalcoholic fatty liver disease (NAFLD) cirrhosis.

Research frontiers

The authors sought to identify risk factors for HCC in NAFLD cirrhosis to identify individuals at highest risk for HCC.

Innovations and breakthroughs

Male gender, increased age and non-Hispanic ethnicity are associated with HCC in NASH cirrhosis. NASH cirrhosis associated HCC in this cohort was characterized by early stage disease at diagnosis and treatment with locoregional therapy and transplant.

Applications

The present study suggests that among those with NAFLD cirrhosis, men with increased age and of non-Hispanic ethnicity are at highest risk of HCC and should be targeted for screening.

Terminology

NAFLD is a chronic liver disease characterized by hepatic steatosis and can lead to the development of cirrhosis in a subset of patients.

Peer-review

Kathleen *et al* found male gender, increased age, and non-Hispanic ethnicity are associated with HCC in NASH cirrhosis, and suggested that these parameters may be useful for diagnosis and treatment of NASH cirrhosis associated HCC.

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