Research Square

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High values of liver stiffness play an important role in stratifying the risk of hepatocellular carcinoma in cirrhotic hepatitis C patients.

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Abstract

Background: The identification and selection of patients at-risk for HCC is a recognized challenge in outpatient clinical practice. Limited data on risk factors and the impact of HCC on cirrhotic patients stratified by the elasticity imaging technique are still a potential promise. Aim: To evaluate the clinical contribution of liver stiffness measurement by transient elastography, as a risk factor for Hepatocellular Carcinoma (HCC) occurrence in a prospective cohort of (HCV) patients with cirrhosis.

Method: A cohort of 99 consecutive HCV patients was included between 2011 and 2016 with baseline liver stiffness equal or above 12 kPa. We evaluated the patients with serum and mechanical liver tests. Kaplan-Meier method with the log-rank test and the use of Cox Univariate and multivariate analysis assessed the association between variables and clinical results.

Results: The mean age was 57.8±10.6 years. In a follow-up over a mean of 3.3 years, 20 (20.2%) patients developed HCC, of which 65% were male and 40% had diabetes. The median time to diagnosis of HCC was 2.6 years. In univariate logistic regression analysis, variables associated with HCC occurrence were: lower platelet count (p=0.0446), higher serum alpha-fetoprotein (p=0.0041) and bilirubin (p=0.0008) values, higher MELD score (p=0.0068) and higher liver stiffness measurement (p=0.0354). High LSM evaluated by TE was independently associated with HCC development, and the best cut-off value for HCC risk was > 21.1kPa (HR: 4.7695; 95%CI: 1.0470-21.7274; p=0.0435).

Conclusion: High value of liver stiffness relates substantially to the increased risk for HCC in selected patients with HCV cirrhosis.

Introduction

Liver cancer is a common fatal malignancy that afflicts over 1 million people per year[1], and it is the fourth most common cause of cancer-related deaths in 2018, accounting for 781,631 cases. Hepatocellular carcinoma (HCC) corresponds to the majority of primary liver tumors.[2]The annual incidence of HCC has increased worldwide, affecting 2 to 3% of patients with cirrhosis in the West and up to 11% in Asian countries.[3, 4]

A recent demographic study in South America reported that the most common risk factor for HCC was hepatitis C virus (HCV) infection (48%), followed by alcoholic cirrhosis (22%). In Brazil, HCV is the main etiology of cirrhosis. Of the total population with cirrhosis, 60% was related to HCV etiology.[5] The cumulative incidence rate of HCC in cirrhotic patients was 16.9% over 5 years.[6]

A previous study has pointed out the association between portal hypertension and HCC development in cirrhosis. Hepatic venous pressure gradient (HVPG) > 10 mmHg was associated with a 6-fold increase in HCC risk in patients with compensated cirrhosis.[7] Interestingly, transient elastography (TE), a pioneer elasticity imaging technique as noninvasive test for liver fibrosis evaluation, correlates it to HVPG for detecting portal hypertension.[8] In fact, the use of TE in chronic liver disease allows the stratification of

the degree of fibrosis, which over time, is also associated with hepatic complications, including the risk of development of HCC.[9] However, the vast majority of elasticity imaging studies on at risk HCC occurrence held in Asian patients, heterogeneous and different etiologies, grouping together cirrhotic an non-cirrhotic cases and rare observational studies are from western countries [10–15].

Currently, the rational basis for the HCC surveillance in patients with cirrhosis is supported by abdominal ultrasonography exams (US) every six months, strongly recommended by Hepatology Societies worldwide but elasticity-imaging techniques are only limited to some clinical indications.[16–19] However, despite benefits from surveillance are reported, [20–22]in real life practice, implementation and adherence to HCC screening strategies may be difficult.[23] Recently, Abara et al presented a study held in the USA with 2,933 HCV cirrhotic patients in which only 10.9% were consistently HCC screened every 6 months, and 21.4% of the patients were never screened.[24] In Latin America, HCC surveillance programs are reportedly applied in less than 50% of patients.[25]

In this way, strategies that could promptly identify patients at high-risk for HCC development among all patients with cirrhosis is an important challenge. This approach could potentially lead to HCC early detection providing implements for effective treatments. Therefore, the aim of this study is to evaluate the best evidence of liver fibrosis degree related to the value of TE as a risk factor for HCC occurrence in western countries, in a prospective cohort of HCV cirrhotic patients.

Materials And Methods

Clinical design and patient selection: A prospective study was conducted in a cohort of patients with HCV- related cirrhosis followed up at the Division of Clinical Gastroenterology and Hepatology, Hospital das Clínicas of the Department of Gastroenterology, University of São Paulo School of Medicine(HCFMUSP), Brazil, a tertiary healthcare center, between 2011 and 2016. Inclusion criteria: HCV polymerase chain reaction RNA positivity for at least 6 months, and clinical or histopathological diagnosis of chronic HCV with a minimum baseline liver stiffness measument (LSM) of 12 kPa by TE. Exclusion criteria: patient under 18 years of age; hepatitis B virus or human immunodeficiency virus co-infection, significant and current alcohol intake (> 100 g/week),other chronic liver disease, non-cirrhotic portal hypertension, history of liver transplantation, or refusal to participate in the study.

Study protocol and variables evaluated: We collected the anthropometric and clinical data at inclusion to the study: sex, age, weight, height, body mass index (BMI), presence of diabetes mellitus, past alcohol ingestion and smoking status. Also, these patients were evaluated with serum biochemistry and scores, including: HCV genotype, alpha-fetoprotein (AFP), alanine aminotransferase (ALT), alkaline phosphatase (AP), aspartate aminotransferase (AST), total bilirubin (TB), gamma-glutamyltranspeptidase (γGT), platelet count, international normalized ratio (INR), albumin, urea, glucose and creatinine and Child-Pugh and MELD scores.

Patients were submitted to abdominal ultrasound examination (ACUSON S2000®, Siemens), with transducer 4V1 at the same time as TE evaluation, both performed by a skilled operator, at inclusion. The

absence of focal suspected malignant liver lesions was also registered. We also included in the clinical evaluation the non-invasive liver fibrosis characterization by APRI and FIB-4. LSM and steatosis grade with Controlled attenuation parameter were both obtained using the FibroScan 402 device powered by VCTE (EchoSens, Paris, France), equipped with the standard M probe. TE examination was performed according to previous description.[26]

After study inclusion, we systematically followed these patients every 6 months for HCC detection with US and serum AFP measurements, in accordance with routine institutional clinical practice. During the study period, we documented the HCV therapy and viral eradication. We also analyzed these variables in respect to the study outcome of HCC occurrence.

We followed the international guidelines to the diagnosis of HCC based on radiological criteria by multiphase contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) scan and/or liver biopsy.[17, 16]

Besides HCC development analysis, the following outcomes were provided: HCC stage in relation to Milan criteria, tumor therapy, and evolution to mortality.

Ethical considerations: The Ethics Committee of the HCFMUSP (number 6570) approved the study according to the ethical guidelines of the 1975 Declaration of Helsinki. We obtained from all participants the authorization of informed consent.

Statistical analysis: The Descriptive statistics (mean, standard deviation, minimum and maximum, and median values) were calculated. Univariate (continuous and binary with log rank) and multivariate Cox logistic regression analysis were performed, and hazard ratio (HR) for HCC occurrence was calculated, in addition to a 95% confidence interval (CI). To avoid collinearity among the significant variables mentioned on univariable analysis, we built models including LSM cutoff > 21.1 kPa in all of them, that was almost exclusive independently associated with HCC development. The routine liver function markers as MELD score and the fibrosis methods like FIB-4, APRI score and TE composed the final selected multivariable model. We used the Lausen's test to find the best cutoff point for HCC occurrence. In order to estimate the incidence of HCC and survival rate we applied the log rank test and Kaplan-Meier. Two-tailed test was used and a probability value of < 0.05 was considered significant. A biomedical statistician (João Italo França) using IBM Corp. Released 2010 conducted all statistical analyses (IBM SPSS Statistics for Windows Version 19.0).

Results

We evaluated 111 patients for study recruitment, and 99 subjects were included after exclusion criteria were applied: incomplete clinical and laboratory data at baseline, n = 4; lost in follow-up, n = 7, significant and current alcohol intake, n = 1. Figure 1 shows the flowchart of the study population enrollment.

The mean age was 57.8 ± 10.6 years, and 45.5% were male (n = 49). Most of the included patients were overweight (mean BMI: 28.6 ± 4.8), and 31.1% presented diabetes mellitus. Regarding liver function, 80.8% (80/99) of the patients were Child-Pugh A, and 19.2% (19/99) were Child-Pugh B, with a mean MELD score of 9.7 ± 3.1. The mean LSM of this cohort was 27.3 ± 13.3 kPa. Table 1 presents the clinical characteristics baseline, laboratory variables and non-invasive liver fibrosis markers of the study population.

Table 1
Clinical characteristics, laboratory data and liver fibrosis markers of the included patients (n = 99).

Variables	median (min-max)
Number of patients	99
Age (years)	59 (27–82)
Gender, Male (%)	49 (49.5%)
BMI	28 (18.5–48.4)
Tobacco use, n(%)	30 (30.3%)
Diabetes mellitus, n(%)	31 (31.3%)
Past alcohol ingestion	20 (20.2%)
HCV genotype 1 / non-1, n (%)	81 (81.8%) / 18 (18.2%)
AST (U/L)	74 (12–457)
ALT (U/L)	61 (14–393)
Platelets (x10³ /mm³)	94 (33–257)
GGT (U/L)	86 (11 -1068)
Alkaline phosphatase (U/L)	101 (41–267)
Albumin (g/L)	4.1 (2.5–5.2)
Alpha-fetoprotein (ng/mL)	8.2 (1.6–151.2)
Creatinine (mg/dL)	0.8 (0.4–3.5)
INR	1.6 (0.7–2.19)
Total bilirubin (mg/dL)	0.9 (0.3–5.4)
Child-Pugh score A/B, n(%)	80 (80.8%) /19 (19.2%)
MELD score	9 (6–19)
APRI score	1 (0.2–6.5)
FIB-4 score	4.9 (1.4–32.3)
Transient elastography (kPa)	22.8 (12–75)
IQR	3.8 (0.1–18)

Abbreviations: BMI: body mass index; HCV: hepatitis C virus; AST: aspartate amino transferase; ALT: alanine amino transferase;GGT: gamma glutamyltransferase; INR:international normalized ratio;IQR: interquartile range of measurements; CAP: controlled attenuation parameter;TE: transient elastography.

Variables	median (min-max)
CAP (dB/m)	221 (100–354)
TE Sucess rate (%)	100 (60–100)

Abbreviations: BMI: body mass index; HCV: hepatitis C virus; AST: aspartate amino transferase; ALT: alanine amino transferase;GGT: gamma glutamyltransferase; INR:international normalized ratio;IQR: interquartile range of measurements; CAP: controlled attenuation parameter;TE: transient elastography.

During the study period (mean follow up of 5 years), twenty (20.2%) patients developed HCC, of these, 65% were male. Median time from baseline to diagnosis of HCC was 2.6 years (0.02–4.74). In addition, twenty-eight (28.3%) patients evolved to death. Among them, 7/28 (25%) were caused by complications in HCC therapy / evolution (chemoembolization and liver transplantation) and 21/28 (75%) due to complications of cirrhosis (portal hypertensive bleeding, hepatorenal syndrome and infections). Seven patients died of HCC progression. The prevalence of diabetes in patients with HCC was 40% (8/20), and 25% (8/31) of the diabetics developed HCC during the study period.

In the univariate logistic regression analysis, the baseline variables associated with HCC occurrence over time were lower platelet count ($p = 0.0446$), higher serum alpha-fetoprotein ($p = 0.0041$) and total bilirubin ($p = 0.0008$) values, higher MELD scores ($p = 0.0068$) and higher LSM by TE ($p = 0.0354$), as shown in Table 2. The best cut-off values for these variables as risk factors for HCC prediction in the univariate analysis were: platelet count $< 114 \times 10^3$ /mm³,alpha-fetoprotein ≥ 11.2 ng/mL, total bilirubin ≥ 2.04 mg/dL, MELD Score ≥ 11 and TE > 21.1 kPa ($p < 0.05$).

Table 2
Characteristics among the groups with and without hepatocellular carcinoma.

Variables (median, min – max)	**Non-HCC (n = 79)**	**HCC (n = 20)**	**HR - CI 95%**	***p value***
Males n,(%)	36 (45.6%)	13 (65%)	2.425 (0.965–6.091)	0.0595
Diabetes mellitus	23 (29.1%)	8 (40.0%)	1.525 (0.623–3.734)	0.3521
Child-Pugh score B	12 (15.2%)	7 (35.0%)	1.896 (0.755–4.761)	0.1660
Age (years)	59 (33–82)	61.5 (27–70)	0.995 (0.957–1.035)	0.8174
BMI	28.5 (18.5–48.4)	26.5 (22.2–39)	0.955 (0.865–1.054)	0.3556
Tobacco use	25(31.6%)	5(25%)	0.762(0.277–2.099)	0.59
AST (U/L)	74 (12–457)	77.5 (26–185)	0.999 (0.991–1.006)	0.7116
ALT (U/L)	60 (14–393)	63 (19–147)	0.995 (0.988–1.003)	0.2554
Platelets (x10³ /mm3)	**99 (33–257)**	**88 (36–150)**	**0.989 (0.978–0.999)**	**0.0446***
GGT (U/L)	81 (11-1068)	106.5 (29–685)	1.000 (0.997–1.002)	0.9319
Alkaline phosphatase (U/L)	90 (41–267)	112.5(59–215)	1.008 (1.000-1.016)	0.0504
Albumin (g/L)	4.1(2.5–5.1)	3.9 (2.7–5.2)	0.491 (0.235–1.026)	0.0585
Alpha-fetoprotein (ng/mL)	**7.70 (1.6-151.5)**	**14.8(2.2-119.7)**	**1.017 (1.005–1.028)**	**0.0041***
Creatinine (mg/dL)	0.8 (0.4–3.5)	0.9 (0.5–1.47)	1.435 (0.435–4.737)	0.5529
INR	1.1 (0.7–2.1)	1.2 (1.0-1.8)	3.477 (0.801–15.099)	0.0963
Total bilirubin (mg/dL)	**0.9 (0.3–4.3)**	**1.1(0.4–5.4)**	**1.763 (1.267–2.454)**	**0.0008***

Univariate logistic regression analysis. Abbreviations: HCC:hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval; BMI: Body mass index; AST: aspartate amino transferase; ALT: alanine amino transferase; GGT: gamma glutamyltransferase; INR: international normalized ratio; TE: Transient elastography; mm: millimeters.*** p < 0.05**

Variables (median, min – max)	Non-HCC (n = 79)	HCC (n = 20)	HR - CI 95%	*p value*
MELD score	**9 (6–19)**	**11 (7–18)**	**1.182 (1.047–1.334)**	**0.0068***
APRI score	0.9 (0.2–6.5)	1.3(0.7–3.7)	1.205 (0.886–1.638)	0.2351
FIB-4 score	4.8 (1.4–32.3)	6.2 (2.6–15.6)	1.072 (0.985–1.167)	0.1081
TE (kPa)	**21.9 (12.0-67.8)**	**25.8(17.6–75.0)**	**1.031 (1.002–1.060)**	**0.0354***
HCC diagnostic presentation				
Multiple		5 (25%)		
Single tumor nodule (n, %)		15 (75%)		
≤ 20 mm —		2 (10%)		
> 20 and ≤ 30 mm — —		13 (65%)		
> 30 and ≤ 50 mm —		3 (15%)		
> 50 mm — —		2–10%		
HCC within Milan Criteria, yes/no (n, %)		15 (75%) / 5 (25%)		

Univariate logistic regression analysis. Abbreviations: HCC:hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval; BMI: Body mass index; AST: aspartate amino transferase; ALT: alanine amino transferase; GGT: gamma glutamyltransferase; INR: international normalized ratio; TE: Transient elastography; mm: millimeters.*** p < 0.05**

At admission, all patients were HCV treatment naïve, but during the follow up, 87 (87.9%) patients were treated with interferon based regimens and/or direct antiviral agents (DAA), and 58 (58.6%) achieved sustained virological response (SVR). We analyzed some potential confounder variables for HCC occurrence: hepatitis C treatment (p = 0.9474), response to HCV treatment (p = 0.6248), past alcohol ingestion (p = 0.5510), tobacco use (p = 0.7050), diabetes mellitus (p = 0.3521), and gender (p = 0.0517). These variables were not associated with HCC development in this cohort.

In the multivariate logistic regression analysis, comparing TE, MELD score, and the non-invasive serum fibrosis score APRI and FIB-4, we observed that only the LSM > 21.1 kPa by TE was an independent HCC predictor (p = 0.0435), as shown in Table 3.

Table 3
Variables independently associated with hepatocellular carcinoma occurrence

	HR - CI 95%	***p-value***
TE (> 21.1 kPa)	**4.7695 (1.0470-21.7274)**	**0.0435***
MELD score (> 11)	2.1137 (0.8128–5.4963)	0.1248
FIB-4 score (> 5.7)	1.9656 (0.6704–5.7630)	0.2182
APRI score (> 0.66)	0.8715 (0.5651–1.3439)	0.5336

Multivariate logistic regression analysis. Abbreviations: HR: hazard ratio;CI:confidence interval;TE: Transient elastography.*** p < 0.05**

In fact, those patients with LSM > 21.1 kPa by TE presented a 4.76 times higher chance of developing HCC (Table 3). The general annual incidence rate of HCC was 6.3%, 13.3%, 22.6% and 27.4%. By comparison, the annual incidence rate for HCC in patients with LSM > 21.1 kPa was much higher: 10.7%, 22.6%, 35.8 and 39.2%, as compared to below this cutoff: 2.5%, 2.5%, 2.5% and 9.5%, p = 0.0026. (Fig. 2)

Discussion

Through this prospective cohort study in cirrhotic HCV patients, we could identify high risk factors for HCC occurrence over time related to low platelet count, high serum alpha-fetoprotein and bilirubin values, high MELD scores, and high liver stiffness measurement.LSM by TE was independently associated with HCC development and poor survival prognosis with the best cutoff value more than21.1 kPa. At a follow up, those patients had 4.76 times chance of developing HCC in comparison with observed patients at very low risk, about 10% in 4 years.(Fig. 2).

Nevertheless, we have to consider the lack of consensus in literature regarding the use of FibroScan in predicting HCC risk according to the grade of the liver stiffness. One pioneer study did not present any appropriate cutoff value.[10] Interestingly, our patients with LSM higher than 21.1 kPa showed a significant elevated cumulative HCC incidence up to 35.8% in 3 years (Fig. 2), the same as reported by Masuzaki et al. when taking into account the grade zone of LSM up to 25.1 kPa. In addition, these authors stratified different HCC risks according to LSM during the interferon era, but recently Poynard et al. described higher values of LSM with HCC risk with DAA HCV therapies.[27] In that scenario, even after SVR, LSM could give weight for HCC risk stratification. Indeed Vutien et al. recently demonstrated that in the subsequent HCV treatment, liver stiffness values up to 20 kPa were also independently associated with the development of decompensate cirrhosis, including HCC occurrence.[28] In addition, Rinaldi et al. suggested that the baseline LSM and US could assess the risk for HCC in RVS cirrhotic patients submitted to DAA regime treatment.[12] Even when their best cutoff value to predict HCC was above 27 kPa, our patients was quite comparable, except because they are clinically worse with more diabetes mellitus and Child-Pugh B score patients. The low age range that compromised our patients who developed HCC was another contrast when compared to the other series.[10, 12, 11] Besides, Ravaioli et

al. demonstrated that the HCC risk over time with a LSM of less than 30% reduction after SVR was another possibility to select the worse scenario for HCC occurrence.[29]

The evaluation of HCC prediction in HCV patients with other elasticity imaging techniques for liver fibrosis assessment also demonstrates the medical effort in care response of this group of patients. Hamada et al. reported that after SVR, Shear Wave Elastography above 11 kPa, age above 75 years and alpha-fetoprotein levels more than 6 ng/mg were independently associated with HCC development.[30] Ichikawa et al. described Magnetic Resonance Elastography in patients with chronic liver disease in which the higher the liver stiffness the higher the risk for HCC.[31] Tamaki et al. also recently described liver stiffness by resonance above 3.75 kPa after 12 weeks of successful HCV response as being an independent predictive factor for HCC occurrence.[32]

The present study came upon a correlation of total bilirubin values and MELD score, markers of liver function with HCC occurrence, as previously reported. [33] In addition to the risk for developing HCC over time, some of these parameters (such as bilirubin levels, AFP, platelet count and MELD score) may be associated with the presence of HCC at the time of assessing patients with cirrhosis due to hepatitis C. [34] Although some evidence of association between tobacco consumption and HCC is recognized,[35–38] we could not demonstrate this correspondence in our population. In order to avoid bias, the study recruitment policy excluded patients with significant and current alcohol intake, also an important risk factor for HCC emergence.[37, 39] In our sample, the prevalence of DM in patients with HCC was 40% (8/20) and the prevalence of 25% (20/79) in patients without HCC. DM is highly prevalent in HCC patients, and a well-known risk factor for HCC development.[40–42] However, despite the lack of association between diabetes and HCC occurrence in our sample, a close monitoring is imperative to these high-risk patients. Obesity was also not associated with HCC prediction in our population, contradicting previous findings.[35, 36] However, the majority of our patients were overweight, which may have attenuated this association.

Liver stiffness measurement over 21.1 kPa was a strongly sensitive manner to discriminate patients at high risk of developing HCC, yet it is not specific. Identifying high-risk patients among the general cirrhotic population could concentrate efforts in early HCC diagnosis and consequently in curative treatments. Even though it is tempting to shorten the time between ultrasound exams, in such patients may not improve the detection of small HCC, as previously described.[43] Instead, such those patients with LSM by TE above 21.1 kPa should especially be rigorously included on HCC surveillance programs and followed actively for adherence.

The present study has some limitations. We enrolled a relatively small cohort of patients from only a single center; therefore, the validation in large trials is necessary. Furthermore, we did not collect systematically the complete metabolic profile during the study period. In addition, PNPLA3 polymorphisms data in these patients could add in HCC risk stratification.[44] The qualities of this study include the well-characterized cohort of patients prospectively followed up over five years under a stringent HCC surveillance program.

Conclusion

In this cohort of Brazilian patients with HCV related cirrhosis, we could demonstrate that high risk factors for HCC occurrence were low platelet count, high serum alpha-fetoprotein and total bilirubin values, high MELD score, and high liver stiffness values evaluated by one type of elasticity imaging technique. Moreover, high LSM evaluated by TE was independently factor associated with HCC development. These results will potentially influence clinical practice guidelines on strategy of HCC surveillance for patients with liver stiffness above 21.1kPa.

List Of Abbreviations

AFP Alpha-fetoprotein

ALT: Alanine aminotransferase

APRI: [(AST/LSN) X 100] / Platelets x 10^9/ L

AST: Aspartate aminotransferase

BMI: Body mass index

CAP: Controlled attenuation parameter

CI: Confidence interval

DAA: Direct antiviral agents

DM: Diabetes mellitus

FIB-4: Age (years) x AST (IU/L) / Platelets (10^9/L) x *(*IU/L*)*

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

HR: Hazard ratio

HVPG: Hepatic venous pressure gradient

IQR: interquartile range

kPa: Kilo Pascal

LSM: Liver stiffness measurement

MELD: Model for end stage liver disease

PNPLA3: Patatin Like Phospholipase Domain Containing 3

SVR: Sustained virological response

US: Abdominal ultrasonography

VCTE: Vibration controlled transient elastography

TE: Transient elastography

Declarations

Ethics approval and consent to participate The Ethics Committee of the HCFMUSP (number 6570) approved the study according to the ethical guidelines of the 1975 Declaration of Helsinki. The informed consent was waived since it was completely observational study without any intervention and the methods applied in the population were noninvasive. The names of the patients were also deleted.

Consent for publication: The authors authorize and consent for publication.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The authors declare that that this is an original article which has not been previously published elsewhere.

Competing interests: The authors had no conflicts of interest to declare.

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Figures

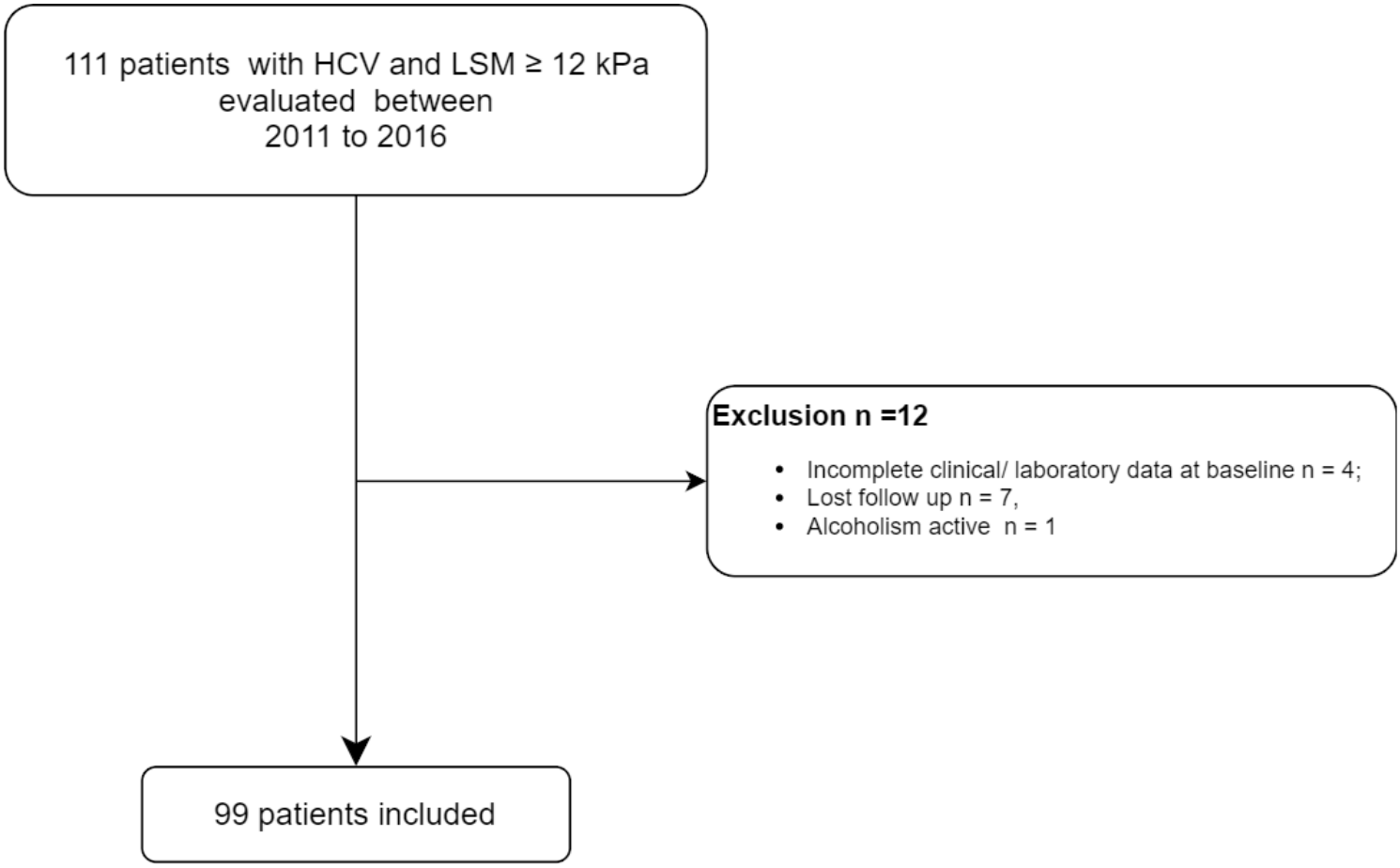

Figure 1

Flowchart of study population enrollment

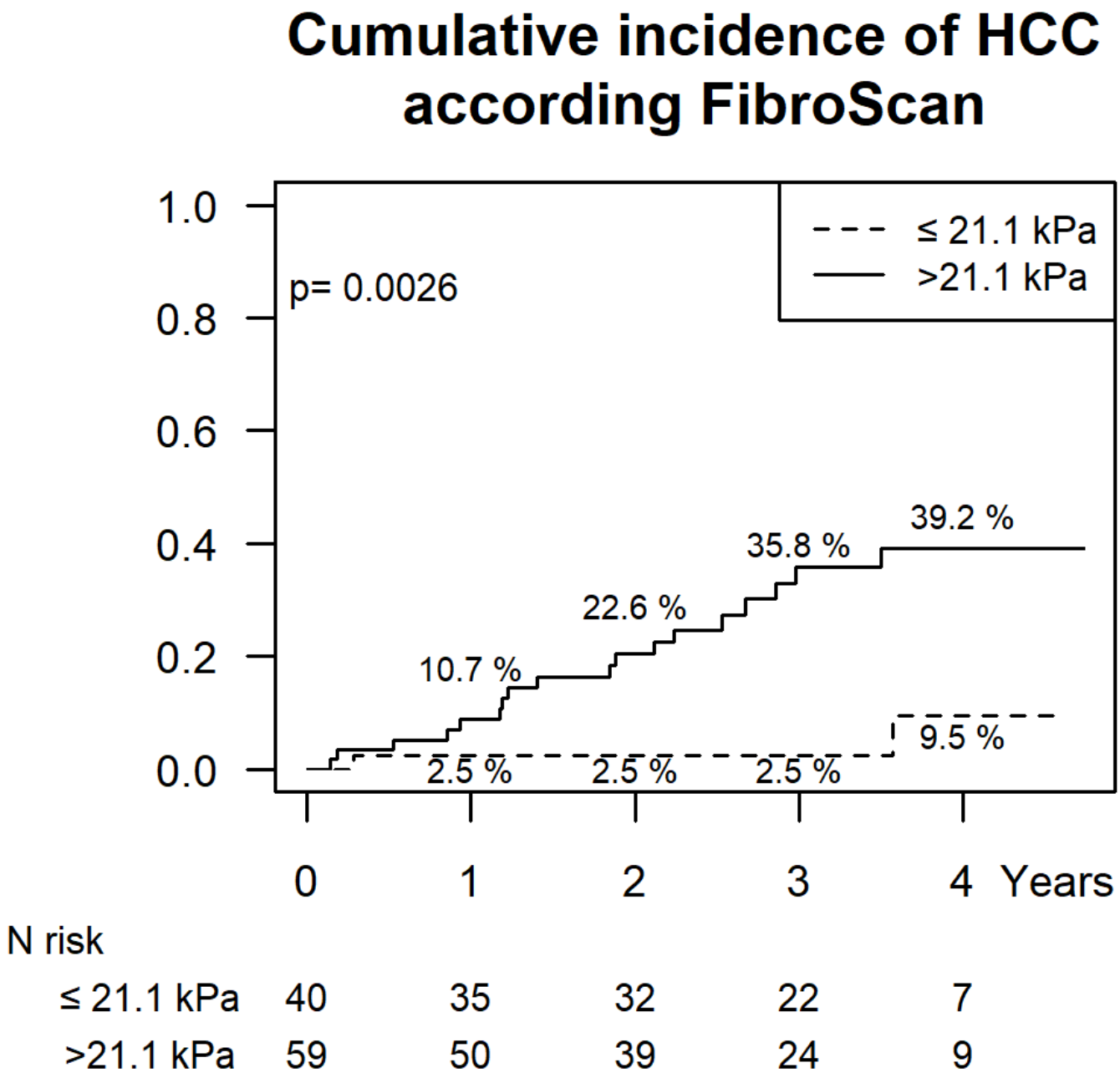

Figure 2

Comparison of two cumulative hepatocellular carcinoma incidence rates, significantly worse in cirrhotic patients with a cut-off higher than 21.1kPa, p=0.0026.