

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 – Evaluate the role of liver stiffness measurement (LSM) by transient elastography (TE) as a risk factor for hepatocellular carcinoma (HCC) occurrence in a prospective cohort of Brazilian hepatitis C virus (HCV) patients with cirrhosis. **Methods** – A cohort of 99 consecutive HCV patients was included between 2011 and 2016 with baseline LSM ≥ 12 kilopascals (kPa). Baseline variables were evaluated and HCC occurrence was documented. Kaplan-Meier methods with a 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. 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 Model for End-Stage Liver Disease (MELD) score ($P=0.0068$) and higher LSM ($P=0.0354$). LSM evaluated by TE was independently associated with HCC development, and the best cut-off value for higher HCC risk was >21.1 kPa (HR: 5.548; 95%CI: 1.244–24.766; $P=0.025$). **Conclusion** – A high value of liver stiffness relates substantially to an increased risk for HCC occurrence in Brazilian patients with cirrhosis due to HCV.

Keywords – Elasticity imaging techniques; risk factors; carcinoma hepatocellular; mortality, hepatitis C; complications; Brazil-epidemiology.

INTRODUCTION

Liver cancer is a common fatal malignancy that afflicts over 1 million people per year. The annual incidence of hepatocellular carcinoma (HCC) has increased worldwide affecting 2 to 3% of patients with cirrhosis in the West and up to 11% in Asian countries^(1,2).

A previous study suggested the association between portal hypertension and HCC development in cirrhosis⁽³⁾. Hepatic venous pressure gradient (HVPG) >10 mmHg was associated with a 6-fold increase in HCC risk in patients with compensated cirrhosis. The use of TE in chronic liver disease stratifies the degree of fibrosis, which is also associated with hepatic complications over time including the risk of HCC development⁽⁴⁾. However, the vast majority of elasticity imaging studies on subjects at risk of HCC occurrence were held in an Asian population encompassing heterogeneous and different etiologies of liver disease grouping together cirrhotic and non-cirrhotic cases; observational studies from Western countries are rare.

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^(5,6). However, despite the reported benefits from surveillance⁽⁷⁾, implementation and adherence to HCC screening strategies may be difficult in practice⁽⁸⁾.

In this way, strategies that could promptly identify patients at high risk for HCC developments among all patients with cirrhosis

are an important unmet need. This approach could potentially help early HCC detection allowing curative treatments to be implemented. In addition, despite previous reports evaluating HCC risk stratification by TE in hepatitis C virus (HCV) cohorts^(9,10), there is no data in admixed populations such as among Brazilians. Therefore, the aim of this study was to evaluate the liver fibrosis degree related to the value of TE as a risk factor for HCC in a western prospective cohort of Brazilian patients with HCV-related cirrhosis.

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 (tertiary public healthcare center) between 2011 and 2016. Inclusion criteria: HCV polymerase chain reaction RNA positivity for at least 6 months with a minimum baseline liver stiffness measurement (LSM) of 12 kPa by TE. The exclusion criteria were age under 18 years; 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.

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Study protocol and variables evaluated

We collected the anthropometric and clinical data at study inclusion: sex, age, weight, height, body mass index (BMI), presence of type 2 diabetes mellitus (DM), past alcohol ingestion, and smoking status. These patients were also evaluated with serum biochemistry and liver function scores including HCV genotype, alpha-fetoprotein (AFP), alanine aminotransferase (ALT), alkaline phosphatase (AP), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transpeptidase, platelet count, international normalized ratio (INR), albumin, urea, glucose, creatinine, and Child-Pugh and Model for End-Stage Liver Disease (MELD) scores. The APRI score [(AST/ULN) x 100]/platelet count 10⁹/L, ULN: upper limit of normal], and Fibrosis-4 (FIB-4) score {[age (years) x AST (U/L)] / [platelet count (10⁹/L) x ALT (U/L)]}—two serum non-invasive tests for liver fibrosis evaluation—were also calculated at study inclusion.

Patients were submitted to abdominal US (ACUSON S2000®, Siemens, Germany) with transducer 4C1 at the same time as TE evaluation (both were performed by a skilled operator) at study inclusion. The absence of focal suspected malignant liver lesions was also registered. LSM and steatosis grade with controlled attenuation parameter (CAP) were both obtained using the FibroScan® 402 device powered by VCTE (EchoSens, Paris, France) equipped with the standard M probe. The LSM was considered reliable when the following criteria were fulfilled: 10 valid measurements, success rate >60% and the ratio of the interquartile range to the median (IQR/M) ≤30%. TE examination was performed according to the previous description⁽¹¹⁾.

After study inclusion, we systematically followed these patients every 6 months for HCC detection with US and serum AFP measurements following our routine institutional clinical practice. During the study period, we documented HCV therapy and viral eradication. We also analyzed these variables concerning the study outcome of HCC occurrence. The diagnosis of HCC was based on radiological criteria by multiphase contrast-enhanced magnetic resonance imaging or computed tomography scan showing hyperattenuation in the arterial phase, with washout in the portal venous phase. In cases with inconclusive imaging findings, tumor biopsy was performed to confirm the HCC diagnosis. HCC stage according to Milan criteria⁽¹²⁾ (1- single tumor diameter less than 5 cm; 2- not more than three foci of the tumor, each one not exceeding 3 cm; 3- no vascular invasion; 4- no extrahepatic involvement) was described. The study procedures and patient assessment modalities are shown in FIGURE 1.

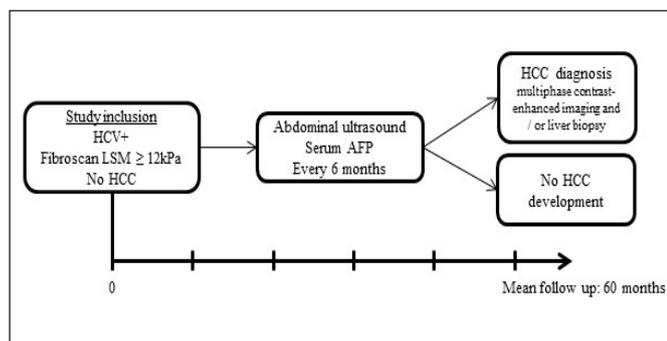


FIGURE 1. Study procedures.
AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; LSM: liver stiffness measurements.

Ethical considerations

The Ethics Committee of the HCFMUSP (number 6570) approved the study, which was conducted under the ethical guidelines of the 2013 World Medical Association Declaration of Helsinki⁽¹³⁾. We obtained informed consent from all participants.

Statistical analysis

We assumed that the rate of those with TE >12 kPa is approximately 30% in our liver outpatient clinic among all chronic hepatitis C patients. Thus, to detect a hazard ratio (HR) above two with an alpha of 5% and study power of 80%, the sample size required would be at least 78 patients. 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 a hazard ratio (HR) for HCC occurrence was calculated in addition to a 95% confidence interval (CI). We avoided collinearity among the significant variables mentioned in the univariate analysis, and we also built six models using Cox analysis, and with C-statistic test applied to select the best model including LSM cutoff >21.1 kPa in all of them. This was almost exclusive independently associated with HCC development. APRI and FIB-4 scores were also included in these models, due to their significance in clinical practice. The FIB-4 score and TE composed the final selected Cox analysis model with the best C-statistic in six months and with stable and high value during the 3 year-evaluation (supplementary data). We used Lausen's test to find the best cutoff point for HCC occurrence. To estimate the incidence of HCC, we applied the log-rank test and Kaplan-Meier. A two-tailed test was used, and a probability value of <0.05 was considered significant. A biomedical statistician (França JI) conducted the statistical analyses using IBM SPSS Statistics for Windows Version 19.0 (IBM Corp, USA).

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.

The mean age was 57.8±10.6 years, and 49.5% were male (n=49). Most of the included patients were overweight (mean BMI: 28.6±4.8), and 31.1% presented DM. 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 shows the baseline clinical characteristics, laboratory variables and non-invasive liver fibrosis markers of the study population.

During the study period (mean follow-up of 5 years), 20 (20.2%) patients developed HCC, and of these, 65% were male. The median time from study inclusion to HCC diagnosis was 2.6 (0.02–4.74) years. In addition, 28 (28.3%) patients evolved to death. Among them, 7/28 (25%) had HCC diagnosis, and deaths were caused by complications in HCC therapy/complications of cirrhosis or after liver transplantation [three patients died due to complications after HCC chemoembolization (two related to liver failure, and one due to infection)], two due to post-liver transplantation complications (one secondary to infection, and one related to gastrointestinal bleeding), and two secondary to complications of cirrhosis (one due to portal hypertensive bleeding, and the other due to spontaneous bacterial peritonitis). The remaining, 21/28 (75%), died due

TABLE 1. Clinical characteristics, laboratory data and liver fibrosis markers (n=99).

Variables	n (%) or median (min–max)
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 (x10 ³ /mm ³)	94 (33–257)
GGT (U/L)	86 (11–1068)
Alkaline phosphatase (U/L)	101 (41–267)
Albumin (g/dL)	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)
CAP (dB/m)	221 (100–354)
TE success rate (%)	100 (60–100)

ALT: alanine amino transferase; AST: aspartate amino transferase; BMI: body mass index; CAP: controlled attenuation parameter; GGT: gamma glutamyl transferase; HCV: hepatitis C virus; INR: international normalized ratio; IQR: interquartile range of measurements; MELD: Model for End-Stage Liver Disease; TE: transient elastography.

to complications of cirrhosis (portal hypertensive bleeding, hepatorenal syndrome, and infections). 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 (TABLE 2), the baseline variables associated with HCC occurrence over time were lower platelet count ($P=0.0446$), higher serum AFP ($P=0.0041$), higher total bilirubin ($P=0.0008$) values, higher MELD scores ($P=0.0068$), and higher LSM by TE ($P=0.0354$). The best cut-off values for these variables as risk factors for HCC prediction in the univariate analysis were: platelet count $<114 \times 10^3 / \text{mm}^3$, AFP $\geq 11.2 \text{ ng/mL}$, total bilirubin $\geq 2.04 \text{ mg/dL}$, MELD Score ≥ 11 and TE $>21.1 \text{ kPa}$.

At admission, all patients were HCV treatment naïve, but during the follow-up, 87 (87.9%) patients were treated. Sustained virological response (SVR) occurred in four patients treated with interferon-based regimens and in 58 patients treated with direct-acting antiviral (DAA) agents. The overall SVR was 73.5%. Twenty-five patients did not achieve SVR. Among them, five patients had HCC diagnosis and 12 evolved to death. 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.

We built six models in Cox analysis among the significant variables mentioned in the univariate analysis, and with APRI and FIB-4 scores due to their significance in clinical practice (TABLE SUPPLEMENTARY). The multivariate logistic regression analysis showed the HCC risk in each model, with TE value above 21.1 kPa, in almost of them. Subsequently, the C-statistical test selected the best of them, considering the short and long HCC occurrence time. In this analysis, comparing TE and FIB-4, we observed that only the LSM $>21.1 \text{ kPa}$ by TE was an independent HCC predictor ($P=0.025$) as shown in TABLE 3. Those patients with LSM $>21.1 \text{ kPa}$ by TE presented a 5.54-fold 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 $>21.1 \text{ kPa}$ was much higher: 10.7%, 22.6%, 35.8%, and 39.2% versus below this cutoff: 2.5%, 2.5%, 2.5%, and 9.5%, $P=0.0026$ (FIGURE 2).

DISCUSSION

This prospective cohort study of patients with HCV-related cirrhosis showed that lower platelet count, higher serum AFP, higher total bilirubin values, higher MELD scores, and higher liver stiffness values evaluated by TE were risk factors for HCC occurrence over time in the univariate logistic regression analysis. Interestingly, LSM evaluated by TE was independently associated with HCC development, and the best cut-off value related to higher HCC risk was 21.1 kPa. Those with TE LSM $>21.1 \text{ kPa}$ had a 5.54-higher chance of developing HCC during follow up versus patients with lower LSM at baseline.

Since the pioneering study from Masuzaki et al.⁽⁹⁾, we recognized the lack of consensus in the literature regarding the grade of the liver stiffness when using FibroScan® for predicting HCC risk. Patients with an LSM higher than 21.1 kPa showed a significantly elevated cumulative HCC incidence up to 35.8% in 3 years similar to Masuzaki et al.⁽⁹⁾ when considering the grade zone of LSM up to 25.1 kPa. These authors stratified different HCC risk according to the LSM during the interferon era; more recently, Poynard et al.⁽¹⁴⁾ described higher values of LSM related to HCC risk, but with DAA HCV therapies. Nakagomi et al.⁽¹⁵⁾ recently reported a retrospective analysis of 1146 Japanese patients with chronic hepatitis C whereby LSM by TE at study enrollment could predict HCC development and also, the overall survival in this cohort. Likewise, Rinaldi et al.⁽¹⁰⁾ reported an Italian study of HCV patients with cirrhosis and showed that the risk of HCC was much higher ($P=0.019$; HR 0.329) when they were classified by LSM $>30 \text{ kPa}$. The patients were quite comparable despite finding a higher cut-off of LSM than our study, and except for the more frequent presence of DM and Child-Pugh

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

Variables	Non-HCC (n=79) n (%) or median (min–max)	HCC (n=20) n (%) or median (min–max)	HR - CI95%	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 (x10 ³ /mm ³)	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/dL)	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*
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%)

ALT: alanine amino transferase; AST: aspartate amino transferase; BMI: body mass index; CI: confidence interval; GGT: gamma glutamyl transferase; HCC: hepatocellular carcinoma; HR: hazard ratio; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease; TE: Transient elastography; mm: millimeters. *P<0.05.

TABLE 3. Variables independently associated with hepatocellular carcinoma occurrence.

	HR (95%CI)	P-value
TE (>21.1 kPa)	5.548 (1.244–24.766)	0.025*
FIB-4 score (>5.7)	1.947 (0.760–4.987)	0.165

CI: confidence interval; HR: hazard ratio; TE: transient elastography. *P<0.05.

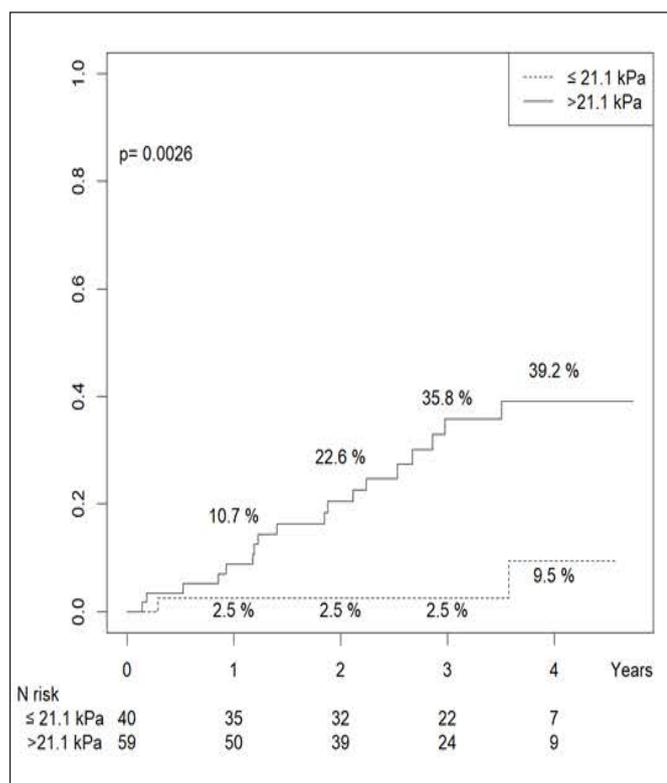


FIGURE 2. Cumulative incidence of hepatocellular carcinoma according to transient elastography LSM.
 HCC: Hepatocellular carcinoma; LSM: liver stiffness measurements.

B score in the Italian cohort. Of note, Singh et al.⁽¹⁶⁾ demonstrated that each kilopascal of increase in LSM in patients with cirrhosis raised the risk of HCC by 4%.

In addition to having a baseline role in predicting HCC risk over time, the evaluation of LSM reduction after successful viral eradication can also be useful for risk stratification in patients with HCV-related cirrhosis as shown by Ravaioli et al.⁽¹⁷⁾ The authors reported that a delta LSM reduction of less than 30% at the end of antiviral treatment in relation to baseline was independently associated with HCC occurrence. Vutien et al.⁽¹⁸⁾ recently demonstrated that after viral eradication with DAA, liver stiffness values >20 kPa were independently associated with the development of decompensated cirrhosis including HCC occurrence.

Other non-invasive mechanical tests for liver fibrosis were evaluated regarding HCC prediction in HCV patients. Hamada et al.⁽¹⁹⁾ reported that after SVR, shear wave elastography ≥11 kPa along with age ≥75 years and alpha-fetoprotein levels more than 6 ng/mg were independently associated with HCC development. Using magnetic resonance elastography (MRE) for patients with chronic liver diseases, Ichikawa et al.⁽²⁰⁾ reported that a higher liver stiffness leads to a higher risk of HCC. In addition, Tamaki et al.⁽²¹⁾ also recently reported that liver stiffness ≥3.75 as evaluated by MRE 12 weeks after successful HCV treatment was an independent predictive factor for HCC occurrence.

We found an association of baseline total bilirubin values and MELD score (markers of liver function) with the occurrence of HCC in the univariate logistic regression analysis, as previously reported⁽²²⁾. 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⁽²³⁾.

Despite some evidence of an association between tobacco smoking and HCC^(24,25), we could not demonstrate this in our population. To avoid bias, the study recruitment policy excluded patients with significant and current alcohol intake because this is also an important risk factor for HCC emergence^(25,26). In addition, significant alcohol consumption may overestimate the results of LSM by FibroScan[®]^(11,27). In our sample, the prevalence of DM in patients with HCC was 40%. DM is highly prevalent in HCC patients and a well-known risk factor for HCC development^(28,29,30). However, we could not find an association between DM and HCC occurrence in our cohort. Obesity was also not associated with HCC prediction in our population in contrast to previous reports⁽²⁴⁾. However, the majority of our patients were overweight, which may have attenuated this association.

The annual incidence of HCC has increased worldwide^(31,32). A previous study from our group⁽³³⁾ reported a cumulative HCC incidence of 16.9% in 5 years, in patients with HCV-cirrhosis evaluated from 1998 to 2008. The presented study enrolled patients from 2011 to 2016 and showed a higher HCC incidence. The mean baseline LSM by TE of our population was 22.8 kPa, above the cut-off value that was associated with a higher HCC risk. The stringent screening protocol and the characteristics of the population could, at least in part, justify the increased HCC cumulative incidence found in the present study.

LSM > 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 all the cirrhotic population could concentrate efforts in early HCC diagnosis and consequently in curative treatments. Despite tempting, shorter US exam intervals in such patients may not improve the detection of small HCC, as previously described⁽³⁴⁾. Instead, patients with LSM by TE >21.1 kPa should be rigorously included on HCC surveillance programs and followed actively for adherence. LSM evaluation in our cohort was undertaken before HCV treatment. After successful HCV eradication, LSM values usually decrease⁽³⁵⁾, and our results might not apply for treated patients.

However, we must recognize that TE is currently not widely available in Brazil, especially in public health services. And for cirrhotic patients, the population included in this study, HCC screening remains based upon ultrasonography and/or AFP at 6-month intervals. On the other hand, with the spread of its use, in addition to facilitating the diagnosis of cirrhosis, it may allow better stratification of patients at greater risk of developing HCC. Indeed, LSM by TE was included in simple algorithms to identify the occurrence of de novo HCC in patients with compensated advanced chronic liver disease after cure of hepatitis C, as recently reported by Semmler et al.⁽³⁶⁾.

The present study has some limitations. We enrolled a relatively small cohort of patients from only a single center; therefore, these results need to be validated in larger trials. Furthermore, complete metabolic profiling was not systematically collected during the study period. In addition, PNPLA3 polymorphisms data in these patients could add to HCC risk stratification⁽³⁷⁾. The strengths of our study include the well-characterized cohort of patients prospectively followed for more than four years under a stringent HCC surveillance program.

CONCLUSION

In this cohort of Brazilian patients with HCV-related cirrhosis, we could demonstrate that lower platelet count, higher serum AFP and total bilirubin values, higher MELD scores, and higher liver stiffness values evaluated by TE were risk factors for HCC occurrence in the univariate logistic regression analysis. LSM evaluated by TE was independently associated with HCC development.

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Authors' contribution

Reinoso-Pereira GL, Paranaguá-Vezozzo DC: data collection. Reinoso-Pereira GL: research execution. Reinoso-Pereira GL, Paranaguá-Vezozzo DC, Mazo DF: Text writing. França JID: statistical Analysis. Carrilho FJ, Mazo DF, Ono SK: final review.

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Supplementary Data

The 6 multiple Cox models were built with significant variables in the univariate logistic regression analysis and also with FIB-4 and APRI due to their significance in clinical practice. The reduction final mode after Stepwise Back-ward method from Model 1 and 2:

	HR (95%CI)	P-value
TE (>21.1 kPa)	4.462 (0.984–20.227)	0.052
Alpha-fetoprotein (>11.2 ng/mL)	2.362 (0.917–6.085)	0.074
Total bilirubin (mg/dL)	5.161 (1.956–13.619)	0.0009*

CI: confidence interval; HR: hazard ratio; TE: transient elastography. * $P < 0.05$.

The reduction final mode after Stepwise Back-ward method from Model 3:

	HR (95%CI)	P-value
TE (>21.1 kPa)	5.675 (1.286–25.034)	0.021*
MELD score (>11)	2.158 (0.881–5.281)	0.092

CI: confidence interval; HR: hazard ratio; MELD: Model for End-Stage Liver Disease; TE: transient elastography. * $P < 0.05$.

Model 4:

	HR (95%CI)	P-value
TE (>21.1 kPa)	5.072 (1.164–22.109)	0.031*
APRI (>0.75)	6.351 (0.837–48.212)	0.074

CI: confidence interval; HR: hazard ratio; TE: transient elastography. * $P < 0.05$.

Model 5:

	HR (95%CI)	P-value
TE (>21.1 kPa)	5.548 (1.244–24.766)	0.025*
FIB-4 score (>5.7)	1.947 (0.760–4.987)	0.165

CI: confidence interval; HR: hazard ratio; TE: transient elastography. * $P < 0.05$.

Model 6:

	HR (95%CI)	P-value
TE (>21.1 kPa)	5.769 (1.295–25.674)	0.021*
Platelets ($< 114 \times 10^3 / \text{mm}^3$)	1.820 (0.593–5.585)	0.295

CI: confidence interval; HR: hazard ratio; TE: transient elastography. * $P < 0.05$.

C-Statistic test comparing the final models.

Model	C-statistic			
	6 months	1 year	2 years	3 years
Model 1+2 (TE + Alpha-fetoprotein + total bilirubin)	0.5538	0.7337	0.7968	0.7997
Model 3 (TE + MELD score)	0.5590	0.6745	0.7208	0.7420
Model 4 (TE + APRI)	0.6441	0.7014	0.7388	0.7616
Model 5 (TE + FIB-4 score)	0.6892	0.7214	0.7195	0.7371
Model 6 (TE + Platelets)	0.6372	0.6129	0.7084	0.7306

TE: transient elastography.

Reinoso-Pereira GL, Paranaguá-Vezozzo DC, Mazo DF, França JID, Ono SK, Carrilho FJ. Altos valores de rigidez hepática desempenham um papel importante na estratificação do risco de carcinoma hepatocelular em pacientes cirróticos com vírus C. *Arq Gastroenterol.* 2022;59(2):204-11.

RESUMO – Contexto – O carcinoma hepatocelular (CHC) é o tumor maligno hepático mais comum, e a cirrose é o principal fator de risco para o seu desenvolvimento. **Objetivo** – Avaliar o papel da medição da rigidez hepática por elastografia transitória (ET) como fator de risco para ocorrência de CHC em uma coorte prospectiva de pacientes brasileiros com cirrose por vírus da hepatite C (VHC). **Métodos** – Um total de 99 pacientes com VHC e medida de rigidez hepática ≥ 12 kilopascals (kPa) foram incluídos consecutivamente, entre 2011 e 2016. As variáveis do *baseline* foram avaliadas e a ocorrência de CHC foi documentada. Os testes de Kaplan-Meier e log-rank, além das análises uni e multivariadas de Cox avaliaram a associação entre as variáveis e os resultados clínicos. **Resultados** – A média de idade foi de $57,8 \pm 10,6$ anos. Vinte (20,2%) pacientes desenvolveram CHC, num período médio de seguimento de 3,3 anos. Na análise de regressão logística univariada, as variáveis associadas à ocorrência de CHC foram: contagem de plaquetas mais baixa ($P=0,0446$), valores séricos mais elevados de alfa-fetoproteína ($P=0,0041$) e de bilirrubina ($P=0,0008$), maior pontuação do escore MELD ($P=0,0068$) e valores mais altos de rigidez hepática por ET ($P=0,0354$). A medição da rigidez hepática por ET foi independentemente associada ao desenvolvimento de CHC, e o melhor valor de corte para maior risco de CHC foi $>21,1$ kPa (HR: 5,548; IC95%: 1,244–24,766; $P=0,025$). **Conclusão** – Um alto valor de rigidez hepática está relacionado substancialmente a um risco aumentado de ocorrência de CHC em pacientes brasileiros com cirrose por HCV.

Palavras-chave – Técnicas de imagem de elasticidade; fatores de risco; carcinoma hepatocelular; mortalidade, hepatite C; complicações; Brasil-epidemiologia.

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