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Prevalence and predictive factors of moderate/severe liver steatosis in chronic hepatitis C (CHC) infected patients evaluated with controlled attenuation parameter (CAP)

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Summary

A novel controlled attenuation parameter (CAP) using FibroScan® has been developed for assessment of liver steatosis. The aim was to evaluate the frequency and associated factors for moderate/severe steatosis evaluated by CAP in CHC patients submitted to transient elastography (TE) by FibroScan®. CHC patients underwent TE with CAP evaluation. The classification of steatosis was defined as: CAP < 222 dB/m = S0; CAP ≥ 222 dB/m and <233dB/m = S1; ≥233 dB/m < 290dB/m = S2 and >= 290 dB/m = S3. The prevalence of moderate/severe steatosis (CAP ≥ S2) and the related independent factors were identified by a logistic regression analysis. A significance level of 5% was adopted. 1104 CHC patients, 85% genotype-1 were included (mean age 55 ± 11 years; 46% male, mean BMI 25 ± 4 Kg/m^2). Systemic arterial hypertension and type 2 diabetes mellitus prevalences were 39% and 17%, respectively. Liver stiffness measurement ≥ 9.5 kPa was observed in 39% of patients and steatosis was identified in 50% (S1 = 7%, S2 = 28% and S3 = 15%). The variables independently associated with moderate/severe steatosis were: male gender (OR=1.35; *P* = .037; 95% CI:1.01-1.81); systemic arterial hypertension (OR=1.57; *P* = .002; 95% CI:1.17-2.10) and BMI (OR=1.17; *P* < .01;95% CI:1.12-1.22). In conclusion, when CAP was adopted as a tool to detect steatosis, genotype 1 CHC patients presented a high prevalence of moderate/advanced steatosis. In these patients, liver steatosis was associated mostly to metabolic factors (arterial hypertension and high BMI).

KEYWORDS
chronic hepatitis C, controlled attenuation parameter, fibroscan, hepatitis C virus, steatosis

1 | INTRODUCTION

The burden of hepatitis C as a progressive disease related to cirrhosis and hepatocellular carcinoma (HCC) is well defined worldwide.[1-3] Although new and efficient drugs that can safely cure hepatitis C with high rates of sustained virological response have been developed, fibrosis still progresses in some patients with a further risk of cirrhosis and HCC development, mainly in those with advanced fibrosis.[4-6] Recently, liver steatosis has been described as an additional risk factor for fibrosis progression and HCC development in patients with and without hepatitis C.[7-9] Hepatic steatosis is defined as excessive fat accumulation in the liver. It is currently the most common cause of chronic liver disease worldwide.[10,11] Over

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; CHC, chronic hepatitis C; DMT2, diabetes mellitus type 2; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; LB, liver biopsy; LSM, liver stiffness measurements; NAFLD, non-alcoholic fatty liver disease; SAH, systemic arterial hypertension; SVR, sustained virological response; TE, transient elastography; UNL, upper limit of normality.

the last decade there has been evidence that liver steatosis in the setting of hepatitis C infection (HCV) is a distinct condition with specific clinical and prognostic features.[12-14] Being considered as the liver component of metabolic syndrome, hepatic steatosis may increase overall morbidity even in patients who had been treated and achieved SVR. In addition, it increases cardiovascular risk as well.[15,16]

Recently, the Controlled Attenuation Parameter (CAP), a non-invasive tool for quantifying steatosis, has been developed on the Fibroscan®. Steatosis quantification by CAP is acquired at the same time of liver transient elastography (TE). It is an accurate method, easy to perform and can quantify low grades of liver steatosis, such as 11%.[17,18] Its accuracy is well established in patients with hepatitis C,[19] as well as in other chronic liver diseases. However, studies with CAP for evaluating steatosis in HCV infected patients are still scarce.[20]

The prevalence of steatosis in a large cohort of exclusively chronic HCV-monoinfected patients evaluated by CAP using Fibroscan® has been hardly described as well as the related risk factors for its diagnosis.[19] Thereby, the aim of this study was to evaluate the frequency and the predictive factors of moderate/severe liver steatosis diagnosed by CAP in a large cohort of patients with chronic hepatitis C submitted to transient elastography by Fibroscan®.

2 | METHODS

2.1 | Study design and patients

This was a retrospective cross-sectional study that included a large cohort of chronically infected HCV outpatients held at two centres which performed transient hepatic elastography in Rio de Janeiro, Brazil: Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro and Hepatoscan, a private clinic also located in the city of Rio de Janeiro, southeast Brazil. In Brazil, according to the National Ministry of Health, only patients with advanced fibrosis are allowed to be treated with DAA agents. This way, all chronic hepatitis C patients needed a pre-treatment evaluation of their fibrosis stage and thus most of them had a Fibroscan® performed.

Patients with the diagnosis of chronic hepatitis C (CHC) with a detected HCV-RNA in serum who had transient elastography performed with CAP by Fibroscan® (Echosens, Paris, France) were included. Demographic (gender, age), anthropometric (BMI, weight, abdominal circumference), clinical (diagnosis of diabetes mellitus, presence of systemic arterial hypertension) laboratory (ALT and AST, gamma-GT, cholesterol, platelet count) and virological (HCV genotype) variables were registered.

HIV and HBV coinfected patients were excluded as those with other etiologies for chronic liver diseases. Patients with aminotransferase levels above 5 times the upper limit of normality (UNL), those with cholestasis or ascites and in whom liver stiffness measurements were not reliable, defined as an IQR> 30% or success rate under 60% were also excluded. In addition, patients with alcohol ingestion higher than 20 g per day were also excluded from the study. The study was approved by the local Ethics Committee and all patients signed an informed consent form.

2.1.1 | Liver stiffness and CAP measurements

Liver stiffness and CAP measurements were performed by the same experienced operator using Fibroscan® 502, as previously described.[19,21] The 3.5 MHz M probe was used for all patients. Final liver stiffness results were expressed in kPa as the median value of 10 measurements performed between 25 and 65 mm depth. Only results with 10 valid shots and IQR/median liver stiffness ratio ≤ 30% were included. Patients with TE ≥ 9.5 kPa were classified as advanced liver fibrosis according to Castéra et al.[22] CAP was registered when there was a valid associated liver stiffness measurement using the same signals as the one used to measure liver stiffness. Both liver stiffness and CAP were obtained simultaneously and in the same volume of liver parenchyma. The final CAP value was the median of individual CAP values and was expressed in dB/m (range 100-400 dB/m). Liver steatosis *cutoffs* evaluated by CAP were classified as previously described: S0 (< 10%) = CAP< 222 dB/m; S1 (11%-32%) = CAP ≥ 222 dB/m and < 233 dB/m; S2 (33%-66%) = CAP ≥ 233 dB/m and < 290 dB/m and S3 (>66%) = CAP ≥ 290 dB/m. Moderate steatosis and severe steatosis were defined as a CAP value ≥ 233 and ≥ 290, respectively.[19]

2.2 | Statistical analysis

Statistical analyses were performed with SPSS software 21.0 (II, Chicago, USA). For descriptive analyses, continuous variables were expressed as mean ± standard deviation (SD), median [min-max] or interquartile range (IQR), and categorical variables as proportions. For univariate analysis, Student *T* Test, Mann-Whitney U-test or Chi-squared test was applied to evaluate the association between each variable and moderate/severe steatosis identified by CAP. Those with a *P*-value <.20 in univariate analysis were selected to be included in a binary regression analysis to evaluate the variables that were independently associated with the outcome variable, which was the presence of moderate/severe steatosis defined by a CAP measurement greater than 233 dB/m.[19] Of note, variables with a *P*-value <.20 but with potential interaction such as weight, BMI and abdominal circumference, and aminotransferase levels (ALT/AST) were not included in the same model. In this case, the variables that entered the model were chosen at the discretion of the authors. A *P* value <.05 was considered significant.

3 | RESULTS

3.1 | Study design and patients

Among all patients who had a Fibroscan® at the two centres (n = 2300), 1132 had other etiology for liver disease and were excluded. Among the patients with chronic hepatitis C (n = 1168),

10 had an unreliable result due to an IQR > 30% and additionally 25 patients had a success rate of the exam < 60% and were also excluded. Thus, overall, Fibroscan® unreliability occurred in 35 patients (3%). In addition, 4 patients were excluded due to morbid obesity in whom it was impossible to perform the exam. Considering alcohol ingestion, 25 patients drank more than 20 g ethanol/day and were excluded as well. Hence, 1104 patients were included in the study. Demographic, clinical and laboratory characteristics are described in Table 1. Mean age was 55 ± 11 years and 46% of patients were male, with a mean BMI of 25 ± 4 Kg/m^2 and mean abdominal circumference of 97 ± 9.8 cm for men and 87 ± 9.7 cm in women. 38% of patients were overweight and 9% obese. The prevalence of systemic arterial hypertension (SAH) and diabetes mellitus type 2 (DMT2) was 39% and 17%, respectively. Most patients were genotype 1 (85%). Liver stiffness measurement equal or above 9.5 kPa, corresponding to presumed advanced liver fibrosis, was observed in 39% of patients.

Steatosis was identified by CAP in 50% of patients; being mild in 7%, moderate in 28% and severe in 15% (Figure 1). Variables associated with moderate/severe steatosis on univariate analysis were: male gender (P = .01), weight (P < .01), BMI (P < .01), abdominal circumference (P < .01 for both genders), DMT2 (P = .003), SAH (P < 0.001), dyslipidemia (P = .005), high ALT (P = .003) and AST (P = .03) levels, mean ALT (P < .001) and mean AST levels (P = .026), advanced fibrosis (P < .01) and TE values (P < .01) (Table 2). There was no significant difference between genotype 1 and 3 patients regarding the diagnosis of steatosis (P = .78).

In the final logistic regression model the variables independently associated with moderate/severe steatosis were: male gender (P = .037; OR=1.35; 95% CI:1.01-1.81) arterial hypertension (P = .002; OR=1.57; 95% CI:1.17-2.10) and BMI (P < .01; OR=1.17; 95% CI:1.12-1.22) (Table 3).

TABLE 1 Demographic, clinical and laboratory characteristics (n = 1104)

Variables	
Male gender (%)	46
Age (yrs ± SD)	55 ± 11
Weight (kg ± SD)	68 ± 12
BMI (kg/m^2 ± SD)	25 ± 4
Abdominal circumference (cm ± SD)	
Male gender	97 ± 9.8
Female gender	87 ± 9.7
Diabetes (%)	17
Systemic arterial hypertension (%)	39
Genotype distribution (%)	
1b	31.7
1a	44.5
1	8.6
2	1.6
3	13.1
4	0.6
Advanced fibrosis (%)	39
ALT levels (U/L)	71 ± 52
Elevated ALT (%)	61
AST levels (U/L)	58 ± 41
Elevated AST (%)	55
Elevated GGT (%)	52
Platelet count (× 10^3)	190 ± 73
Hypercholesterolemia (%)	21
Elastography [Kpa (IQR)]	7.9 (6.4)
CAP mean (dB/m ± SD)	218 ± 50
CAP median (dB/m)	216

4 | DISCUSSION

This study has two major highlights: firstly, it shows that when CAP is adopted as a tool to detect liver steatosis, genotype 1 patients with chronic hepatitis C present a high prevalence of moderate/advanced steatosis. Secondly, it shows that in these patients, liver steatosis is associated mostly with metabolic factors (arterial hypertension and high BMI).

The present study comprises a large cohort of 1104 chronic HCV patients with a predominance of genotype 1 infection. It has evaluated the independent factors associated with moderate/severe liver steatosis identified by the novel controlled attenuation parameter (CAP) by Fibroscan®. In this study, 50% of patients had steatosis, which is similar to the prevalence described by Hwang et al.[23] Other studies have observed that steatosis in HCV patients is higher than in HBV patients, maybe due to the HCV viral impact on metabolic pathways leading to insulin resistance and metabolic syndrome, usually absent in HBV patients.[24] In addition, in the present study the population included is comprised of overweight patients but most without obesity, with a mean BMI of 25 ± 4 kg/m^2, and even this way, BMI was an independent variable related to the presence of steatosis. Although this study was not designed and did not aim to hypothesize about the physiopathologic pathways of steatosis in HCV patients, it is possible to speculate that maybe there is a synergy

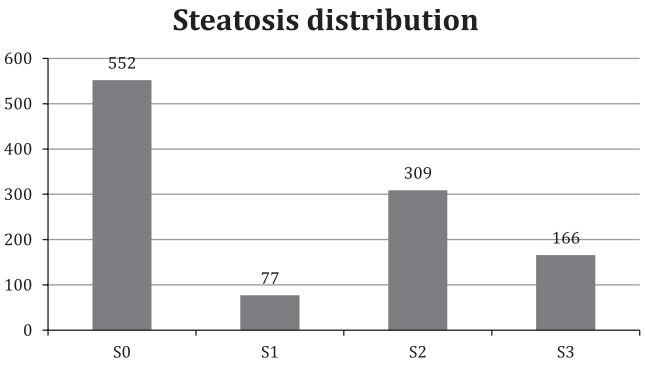

FIGURE 1 Distribution of patients with respect to steatosis grade

TABLE 2 Comparison of patients' characteristics - absence/mild vs moderate/severe steatosis

Variables	S0-S1 (n = 629)	S2-S3 (n = 475)	*P*
Male gender (%)	42	52	.01
Age (ys ± SD)	55 ± 11	56 ± 11	.56
Weight (kg ± SD)	66.2 ± 11.7	73.5 ± 13.4	<.01
BMI (kg/m^2 ± SD)	24 ± 4	27 ± 4	<.01
Abdominal circumference (cm ± SD)	87 ± 9	96 ± 10	<.01
Diabetes (%)	14	21	.003
SAH (%)	35	48	<0.001
Genotype non-1 (%)	16	15	.78
Advanced fibrosis (%)	34	46	<.01
ALT levels (U/L)	66 ± 55	80 ± 56	<.01
Elevated ALT (%)	56	70	.003
AST levels (U/L)	55 ± 41	61 ± 42	.026
Elevated AST (%)	51	61	.03
Elevated GGT (%)	49	54	.59
Platelet count (× 103)	193 ± 75	188 ± 79	.53
Elastography [Kpa (IQR)]	7.4 (6.2)	8.8 (7.5)	<.01
CAP mean (dB/m ± SD)	188 ± 33	269 ± 29	<.001

TABLE 3 Factors associated with moderate/severe steatosis (logistic regression model)

	Univariate analysis		Multivariate analysis	
Variables	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Gender (male)	1.538 [1.203-1.966]	.001	1.359 [1.018-1.815]	.037
BMI	1.190 [1.141-1.241]	<.001	1.177 [1.128-1.228]	<.001
Diabetes mellitus	1.679 [1.189-2.372]	.003		
SAH	1.727 [1.320-2.586]	<.001	1.574 [1.176-2.107]	.002
ALT	1.006 [1.002-1.009]	.003		
Elastography	1.013 [1.001-1.025]	.035		

ALT, alanine aminotransferase; BMI, body mass index; SAH, systemic arterial hypertension.

between the already known effect of HCV on metabolic pathways in patients with a higher BMI, leading to a higher prevalence of steatosis in this group. Unfortunately, these patients did not have a repeat Fibroscan® with CAP evaluation after achieving sustained virological response (SVR) to investigate if steatosis remained with a similar prevalence after achieving HCV infection cure. This would reinforce the hypothesis of HCV-related steatosis and metabolic syndrome in genotype 1 HCV patients.

This is the first time that a large cohort of exclusively HCV infected patients were evaluated by CAP to investigate the related factors for moderate/severe liver steatosis. Recently, de Lédinghen et al[25] have evaluated 4451 individuals, being 32.8% HCV infected. This article, as in the present study, showed that patients with a high CAP had a BMI > 25-30 Kg/m^2, metabolic syndrome, alcohol ingestion higher than 14 drinks/wk and liver stiffness higher than 6 kPa. Another study, from Ferraioli et al,[26] which included 115 patients with viral hepatitis, 71% HCV infected, showed that CAP is directly related to lipid accumulation and could be a useful tool to diagnose steatosis. In their study, there was no correlation with biochemical markers of steatosis, such as triglyceride levels and overall dyslipidemia. Similarly, in our study dyslipidemia was significant only at univariate analysis but was not present in the final regression model.

In our cohort, all patients had detectable HCV-RNA, since elastography with CAP was performed in order to evaluate the indication of HCV treatment according to fibrosis stage as recommended in the Brazilian protocol by the ministry of Health. This way, we were not able to evaluate the impact of SVR in the outcome of liver steatosis. It is well-known that metabolic factors might influence the progression of liver fibrosis in HCV infected patients. After SVR, these factors might still impact HCC development and even liver decompensation.[27] Hence, the identification of factors related to liver steatosis before treatment might help select patients that could need a careful follow-up even after SVR in order to monitor

liver fibrosis progression due to additional metabolic factors and other extra-hepatic complications such as cardiovascular outcomes. Currently, most guidelines suggest that patients who don't have advanced fibrosis should be discharged from the outpatient's clinic after SVR.[28,29] However, those who present with moderate/severe steatosis and the related factors identified in this study might still be followed up regularly until clear evidence is available regarding metabolic factors and the related outcomes in patients who achieved SVR. Recently Serfaty et al[30] suggested an algorithm where patients who still had metabolic factors such as high BMI or diabetes mellitus should be followed annually with noninvasive markers of fibrosis. The outcome of HCV infected patients with steatosis who achieve SVR needs to be better clarified in future longitudinal studies.

Concerning the liver elastography results, in the present study, 39% of patients were diagnosed with advanced fibrosis by Fibroscan®. It is well-known that the diagnostic performance of fibrosis burden by Fibroscan® may be impacted by aminotransferase levels.[31] In our article, the aminotransferase mean levels were in accordance to those usually observed in chronic hepatitis C patients, which are usually less than 5 times the upper limit of normality for both ALT and AST.[32] Thus, we believe that aminotransferase levels did not have an impact on the elastography results. Regarding the impact of fat accumulation on fibrosis evaluation by the Fibroscan®, it has been previously published that liver fat may overestimate fibrosis.[33] Since in this study patients were not submitted to liver biopsy, we cannot precisely say that severe fat accumulation did not have any impact on fibrosis stage evaluation. On the other hand, nowadays, few chronic hepatitis C patients are submitted to liver biopsy to identify either fibrosis stage or liver steatosis. Thus, we have to be cautious on the interpretation of fibrosis stages in patients with severe steatosis, since it might be overestimated.

Steatosis and HCV have been first linked to genotype 3 infected patients. Currently it is not yet clear if the steatosis related to this genotype justify the difficult-to-treat profile related to these patients.[34] In our study, genotype 3 patients have shown equivalent amount of steatosis, as well as body weight and BMI compared to genotype 1 subjects, which might justify the absence of genotype 3 in the final logistic regression model as an independent variable related to moderate/severe steatosis. Of note, genotype 1-related steatosis has a different pathogenic mechanism linked to metabolic syndrome and insulin resistance.[35,36] In this study, we included predominantly genotype 1-infected patients due to its higher prevalence in Brazil.[37] In genotype 1 HCV infection, liver steatosis appears as an additional branch of metabolic factors. This is confirmed by the variables that were independently related to steatosis in the final regression model such as high BMI and arterial hypertension, two components of the metabolic syndrome. These results once again suggest that genotype 1 patients with liver steatosis probably have a dismetabolic pathway that might be different from genotype 3 patients. Surprisingly, in this study, diabetes mellitus was not present in the final regression model. We don't have a clear hypothesis to justify this. Lately, HCV infection has been linked to many extrahepatic manifestations and diabetes mellitus is among them, although there is still some debate about this. In this study, diabetes mellitus was observed in 17% of patients, and was related to steatosis only in univariate analysis.[38]

Although liver biopsy is the gold standard to detect fibrosis and liver steatosis, due to its invasive nature, it cannot be used as a screening tool and is not feasible as a friendly and easy to manage follow up method. Notwithstanding, other noninvasive methods have been developed to diagnose steatosis and quantify fat[17,39-41]. Among image devices, ultrasonography is the most frequently used method for liver imaging and steatosis can be assessed by comparing parenchymal echogenicity with kidney echogenicity.[42] However, ultrasonography, although largely used, is mainly operator and machine dependent and may underdiagnose minor steatosis due to the low sensitivity of the method.[43] Computed tomography is currently considered as an unsuitable imaging modality for NAFLD evaluation since it encompasses the risk of radiation exposure and has limited accuracy for the detection of mild steatosis. Both magnetic resonance spectroscopy and magnetic resonance imaging using chemical shift techniques provide highly accurate and reproducible diagnostic performance for evaluating NAFLD. However, its high cost and difficult availability limit its use in daily routine.[41,44] Mostly, spectroscopy magnetic resonance imaging has been used in clinical trials as a noninvasive reference of the gold standard liver biopsy.[41,44]

CAP can be widely applied to both diagnose and quantify liver steatosis in HCV infected patients helping to identify those that might need further follow-up regarding metabolic optimization to help preclude liver disease progression.[18-20,25] Although it was not available in this study, the XL probe might be an extra device that could be used in difficult patients, such as those with obesity and central adiposity. However, better validation of XL probe cut-offs for liver steatosis is still needed even in chronic hepatitis C patients. In conclusion, as Fibroscan® is currently used worldwide as an easy to operate and a valuable tool to diagnose fibrosis stage, CAP is a novel noninvasive tool to detect and quantify steatosis in patients with chronic HCV infection. The main limitation of this study is that as it is comprised mostly by genotype 1 patients we could have missed the widely described association between genotype 3 HCV infection and liver steatosis. On the other hand, we could show that genotype-1 HCV infected patients also present with steatosis and should be carefully monitored with a noninvasive tool like CAP mainly if they are male, with a high BMI and with the diagnosis of arterial hypertension.

With the high SVR rate available with the new pangenotypic direct antiviral agents, it is possible that fibrosis screening before treatment will no longer be required before treating HCV patients but the presence of male gender, high BMI and arterial hypertension may be important surrogate markers of liver steatosis. The outcome of this special group needs be investigated in longitudinal studies.

CONFLICT OF INTERESTS

None.

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REFERENCES

1. Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol*. 2014;61(1 Suppl):S58-S68.
2. Seeff LB. Natural history of chronic hepatitis C. *Hepatology*. 2002;36(5 Suppl 1):S35-S46Review.
3. Marcellin P. Hepatitis C: the clinical spectrum of the disease. *J Hepatol*. 1999;31(Suppl 1):9-16.
4. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol*. 2010;52:652-657.
5. Ferenci P, Kozbial K, Mandorfer M, Hofer H. HCV targeting of patients with cirrhosis. *J Hepatol*. 2015;63:1015-1022.
6. Chen Yi Mei SLG, Thompson AJ, Christensen B, et al. Sustained virological response halts fibrosis progression: a long-term follow-up study of people with chronic hepatitis C infection. *PLoS ONE*. 2017;12:e0185609.
7. Nirei K, Matsumura H, Kumakawa M, et al. Steatosis influences the clinical profiles and long-term outcomes of interferon-treated chronic hepatitis C and liver cirrhosis patients. *Int J Med Sci*. 2017;14:45-52.
8. Valkov I, Ivanova R, Alexiev A, Antonov K, Mateva L. Association of serum lipids with hepatic steatosis, stage of liver fibrosis and viral load in chronic hepatitis C. *J Clin Diagn Res*. 2017;11:OC15-OC20.
9. Sookoian S, Pirola CJ. Systematic review with meta-analysis: the significance of histological disease severity in lean patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2017;47:1-16.
10. Hu M, Phan F, Bourron O, Ferré P, Foufelle F. Steatosis and NASH in type 2 diabetes. *Biochimie*. 2017;143:37-41pii: S0300-9084(17)30271-7.
11. Bedossa P. Pathology of non-alcoholic fatty liver disease. *Liver Int*. 2017;37(Suppl 1):85-89.
12. Chang ML. Metabolic alterations and hepatitis C: from bench to bedside. *World J Gastroenterol*. 2016;22:1461-1476.
13. Machado MV, Cortez-Pinto H. Insulin resistance and steatosis in chronic hepatitis C. *Ann Hepatol*. 2009;8(Suppl 1):S67-S75.
14. Serfaty L, Capeau J, Hepatitis C. insulin resistance and diabetes: clinical and pathogenic data. *Liver Int*. 2009;29(Suppl 2):13-25.
15. Allen AM, Terry TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. *Hepatology*. 2017;67:1726-1736.
16. Adams LA, Harmsen S, St Sauver JL, et al. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. *Am J Gastroenterol*. 2010;105:1567-1573.
17. Sasso M, Beaugrand M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. *Ultrasound Med Biol*. 2010;36:1825-1835.
18. Sasso M, Miette V, Sandrin L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan. *Clin Res Hepatol Gastroenterol*. 2012;36:13-20.
19. Sasso M, Tengher-Barna I, Ziol M, et al. Novel controlled attenuation parameter for noninvasive assessment of steatosis using Fibroscan®: validation in chronic hepatitis C. *J Viral Hepat*. 2012;19:244-253.
20. Kumar M, Rastogi A, Singh T, et al. Controlled attenuation parameter for non-invasive assessment of hepatic steatosis: does etiology affect performance? *J Gastroenterol Hepatol*. 2013;28:1194-1201.
21. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003;29:1705-1713.
22. Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005;128:343-350.
23. Hwang SJ, Luo JC, Chu CW, et al. Hepatic steatosis in chronic hepatitis C virus infection: prevalence and clinical correlation. *J Gastroenterol Hepatol*. 2001;16:190e195.
24. Thomopoulos KC, Arvaniti V, Tsamantas AC, et al. Prevalence of liver steatosis in patients with chronic hepatitis B: a study of associated factors and of relationship with fibrosis. *Eur J Gastroenterol Hepatol*. 2006;18:233e237.
25. de Lédinghen V, Vergniol J, Capdepont M, et al. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. *J Hepatol*. 2014;60:1026-1031.
26. Ferraioli G, Tinelli C, Lissandrin R, et al. Controlled attenuation parameter for evaluating liver steatosis in chronic viral hepatitis. *World J Gastroenterol*. 2014;20:6626-6631.
27. Persico M, Bruno S, Costantino A, Mazza M, Almasio PL. The impact of antiviral therapy and the influence of metabolic cofactors on the outcome of chronic HCV infection. *Int J Hepatol*. 2011;2011:314301.
28. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62:932-954.
29. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol*. 2015;63:199-236.
30. Serfaty L. Follow-up of patients with chronic hepatitis C and a sustained viral response. *Liver Int*. 2016;36(Suppl 1):67-71.
31. Tapper EB, Cohen EB, Patel K, et al. Levels of alanine aminotransferase confound use of transient elastography to diagnose fibrosis in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol*. 2012;10:932-937.e1..
32. Inglesby TV, Rai R, Astemborski J, et al. A prospective, community-based evaluation of liver enzymes in individuals with hepatitis C after drug use. *Hepatology*. 1999;29:590-596.
33. Petta S, Maida M, Macaluso FS, et al. The severity of steatosis influences liver stiffness measurement in patients with nonalcoholic fatty liver disease. *Hepatology*. 2015;62:1101-1110
34. Martin MT, Deming P. Closing the gap: the challenges of treating hepatitis C virus genotype 3 infection. *Pharmacotherapy*. 2017;37:735-747.
35. Rafiq N, Younossi ZM. Interaction of metabolic syndrome, nonalcoholic fatty liver disease and chronic hepatitis C. *Expert Rev Gastroenterol Hepatol*. 2008;2:207-215.
36. Del Campo JA, Romero-Gómez M. Steatosis and insulin resistance in hepatitis C: a way out for the virus? *World J Gastroenterol*. 2009;15:5014-5019.
37. Campiotto S, Pinho JR, Carrilho FJ, et al. Geographic distribution of hepatitis C virus genotypes in Brazil. *Braz J Med Biol Res*. 2005;38:41-49.
38. Serfaty L. Metabolic manifestations of hepatitis C virus - diabetes mellitus, Dyslipidemia. *Clin Liv Dis*. 2017;21:475-486.

39. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick FJ. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol*. 2009;51:433-445.
40. Nagy G, Munteanu M, Gordan M, et al. Computerized ultrasound image analysis for noninvasive evaluation of hepatic steatosis. *Med Ultrason*. 2015;17:431-436.
41. Lee DH. Imaging evaluation of non-alcoholic fatty liver disease: focused on quantification. *Clin Mol Hepatol*. 2017;23:290-301.
42. Khov N, Sharma A, Riley TR. Bedside ultrasound in the diagnosis of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20:6821-6825.
43. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology*. 2011;54:1082-1090.
44. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. *J Magn Reson Imaging*. 2011;34:729-749.

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