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Liver Steatosis Replaced with Non-Invasive Viral and Host Parametars Can Serve as Negative Predictive Model in Patients with Chronic Hepatitis-C

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A B S T R A C T

Almost 70% of chronic hepatitis C (CHC) patients will have concomitant hepatic steatosis (HS) usually determined with invasive method. HS serve as negative predictive factor for lower sustained viral response (SVR) in CHC patients treated with standard of care (SOC) (PEG-IFN and Rib). Retrospective analysis of biochemical, virological and histological data in CHC patients treated with PEG-IFN and Ribavarin. Statistical analysis was carried out by Biometrika Healthcare Research. Level of significance was set to 95% ($p<0.05$). 72 patients (43 M; 29 F; median age 41y) with CHC (60 G1; 12 G3) with no concomitant metabolic syndrome were analyzed. HS ranged from 5 to 30% (median 15%). Overall accuracy of prediction of SVR based on the levels of HS was AUC=0.71 (95% CI=0.58–0.84; p=0.005). When HS was split regarding cut-off value of 5% significant difference was found between responders and non-responders to treatment ($\chi^2=10.025$; df=1; p=0.002). Overall sensitivity was 48% and specificity 91%. Conventional predictive variables (gender, age, fibrosis and genotype) where combined with HS (>5%) and all together achieved Nagelkerke R squared of 34.0% in prediction of SVR, with accuracy rate of 75.0%. Further, invasive variables (fibrosis and HS) where replaced with viremia and body mass index (BMI). All noninvasive variables together achieved Nagelkerke R squared of 26.5% in prediction of SVR with 74% accuracy rate of the logistic regression model. Very low HS (<5%) is negative predictor of SVR and can be replaced with noninvasive variables (gender, age, viremia and BMI) with same accuracy rate of the logistic regression model.

***Key words**: chronic hepatitis c, hepatic steatosis, hepatitis c chronic/pathology, noninvasive parameters, adult*

Introduction

Chronic hepatitis C virus (HCV) infection is a global health problem with an estimated prevalence of 2%, representing 120 to 130 million people[1]. Polyethylene glycol interferon-α (PegIFN-α) combined with ribavirin (RBV) is the standard of care (SOC) regimen for HCV, except for patients with HCV genotype 1 where direct-acting antiviral drug (DAA), telaprevir or boceprevir, combined with PegIFN-α and RBV is the SOC. The main factors influencing the efficacy of HCV antiviral treatments are divided into two categories: viral and host-related. The viral category includes the HCV genotype, baseline viral load, and virological response during treatment. On the other hand host category includes age, gender, race, drinking habits, obesity, degree of liver fibrosis, and IL28B gene polymorphisms. Some host factors including age ≥40 years old[2], insulin resistance[3,4], liver cirrhosis[5], metabolic syndrome[6,7] and liver steatosis, can serve as a predictor to poor response to SOC.

Approximately 50% of patients chronically infected with hepatitis C virus have fatty infiltration of the liver also referred to as liver steatosis[8,9]. This complication is not just associated with the failure of interferon therapy but also with progression of liver fibrosis[10–12]. The patho-

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genesis of HCV-related steatosis is likely to be multifactorial and three predominant forms have been proposed: viral, metabolic and alcohol-induced steatosis. In patients infected with genotype 3, steatosis is mostly virus-induced and often severe. It has been suggested that HCV genotype 3 core protein could inhibit very-low-density lipoprotein (VLDL) secretion and induce liver steatosis[13]. This type of steatosis correlates with high viral load and resolves after successful antiviral therapy[12,14,15]. In contrast, in patients infected with genotypes other then 3, steatosis is mainly linked to obesity and metabolic disorders including peripheral insulin resistance[2,6]. In these patients, the steatosis resembles nonalcoholic steato-hepatitis, is unrelated to viral load, and does not necessarily improve following successful eradication of HCV[16].

The value of steatosis as a negative predictor of response to anti-HCV therapy was confirmed in two large clinical trials. In one study, 574 HCV patients treated with the SOC were evaluated, and the results showed that the presence of steatosis reduces the likelihood of achieving EVR and SVR in genotype-1 infected patients[17]. In another study, 231 HCV patients treated with the SOC were evaluated[18]. The results showed that steatosis negatively affected SVR in HCV genotype non-3-infected patients.

The aim of this study was to confirm hepatic steatosis (HS) as negative predictive factor for lower sustained viral response (SVR) in cohort of chronic hepatitis C (CHC) patients treated with SOC.

Subjects and Methods

Subjects

This research was conducted as a retrospective study which involved one hundred and three CHC patients. All patients were interferon naive, had positive anti-HCV and detectable HCV-RNA. Patients were treated with PegIFN-α and ribavirin in University Hospital Centre Zagreb in 2011. Treatment duration was adjusted according to genotype, 24 weeks for patients infected with genotype 3 and 48 weeks for patients infected with genotype 1. Epidemiological data such as, sex, age, alcohol intake, weight, height, BMI and history of smoking and hypertension were collected prior to treatment. BMI was calculated as the weight divided by the square of height (kg/m^2). All patients underwent liver biopsy prior the treatment together with laboratory assessment done within one week prior to biopsy. Baseline laboratory assessment included AST, ALT, GGT, cholesterol and triglycerides.

Assessment of HCV-RNA

HCV-RNA was detected using commercial assay kits: qualitative PCR test (COBAS Amplicor HCV RNA test, v2.0, Roche Diagnostic Systems, Branchburg, NJ); viral load by quantitative RT-PCR test (COBAS Amplicor TM–HCV Monitor test, v2.0, Roche Diagnostic Systems, Branchburg, NJ) and genotypes by INNO-LIPA HCV II (Innogenetics N.V., Ghent, Belgium).

All patients had HCV genotype 1 or 3. Viral load was determined at baseline, after the 12^{th} week of therapy for genotype 1 patients and for all patients at the end of therapy and 6 months after the therapy was stopped. Definition of virological responses were: 1) end-of-treatment virological response (ETVR) if the HCV RNA was undetectable at the end of treatment; 2) sustained virological response (SVR) if the HCV RNA remained undetectable 6 months after cessation the therapy; 3) relapse = patients who achieved ETVR and become positive after the therapy was stopped and 4) non-response = patients who did not achieved ETVR.

Histopathology

A pathological assessment was made on sections from formalin-fixed and paraffin-embedded liver biopsy stained with hematoxylin-eosin. All specimens were centrally evaluated by single pathologist. Histological activity and stage of fibrosis were scored according to Ishak model[19]. Hepatic steatosis (HS) was graded as the percentage of hepatocytes containing macrovesicular fat droplets: grade 0 (<5%); grade 1 (5–33%); grade 2 (34–66%); and grade 3 (>66%).

Histology activity index (HAI) was determined by the combining the scores for portal inflammation, lobular degeneration and necrosis, and periportal necrosis. The stage was defined according to the Ishak fibrosis score: 0 = absence; 1 = fibrous expansion of some portal areas; 2= fibrous expansion of most portal areas; 3 = fibrous expansion of most portal areas with occasional portal to portal bridging; 4 = fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central); 5 = marked bridging with occasional nodules (incomplete cirrhosis); 6 = cirrhosis, probable or definite.

Statistical analysis

Level of significance was set to 95% ($p<0.05$), and all confidence intervals were given on the 95% level. In all instances two-tailed tests of statistical significance were used. Since sample size was small, normality of continuous variables distributions was tested with Shapiro-Wilk test. Median and interquartile range were used as measures of central tendency and variability when the distribution statistically significantly deviated from the normal one. Statistical significance of differences in categorical variables' frequencies between groups were analyzed by Chi-square (χ^2) test and phi coefficient (φ) of association was used as the standardized measure of effect size in case of statistically significant difference. Group difference in continuous, but not normally distributed variable was analyzed using Mann-Whitney U test. The analyses were carried out using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical software package. Confidence intervals for proportions were determined using Statistics Calculator 3.0 (StatPac Inc., Bloomingtom, MN, USA).

Results

General characteristics

Of 103 retrospectively analyzed CHC patients only 72 of them were included in statistical analysis. Excluded patients were those with possible signs of metabolic syndrome (obesity, hypertension and diabetes mellitus). Median age was 41 (IQR 29.3–54). Overall SVR was observed in 69.4%. All baseline characteristics for analyzed patients are summarized in Table 1.

TABLE 1
DEMOGRAPHIC CHARACTERISTICS (N=72)

	N	(%)
Gender		
Male	43	(59.7)
Female	29	(40.3)
Body mass index (median; IQR)	24.2	(22.8–25.8)
Body mass index (N; %)		
Normal (<24.9)	43	(59.7)
Overweight (25.0+)	29	(40.3)
Body weight, kg (median; IQR)	73	(66.3–79)
Body height, m (median; IQR)	1.7	(1.7–1.8)
Alcohol		
No	56	(77.8)
Appositely	16	(22.2)
Genotype		
1	60	(83.3)
3	12	(16.7)

IQR – interquartile range

Viral, biochemical and histological features

Majority of patients (58.3%) had high viral load (>600.000 IU/L). Liver enzymes were normal in minor patients: ALT in 4 patients; AST in 26 patients and GGT in 26 of 72 patients. Median level for liver enzymes were: for ALT 67 IU/L (IQR 48.3–91), AST 40.5 IU/L (IQR 32–56) and for GGT 48 IU/L (IQR 36–76.3). Different ratio between liver enzymes was calculated due to fact that some of liver enzymes (AST and GGT) are known as steatotic enzymes. Median AST/ALT ratio was 0.60 (IQR 0.50–0.80) while median GGT/ALT ratio was 0.82 (0.37–1.16).

Liver histological examination showed that among 72 patients median of liver cylinder size was 2 cm (IQR 1.4–3) with median number of portal spaces of 16 (IQR 14–18) what was good enough to include them in statistical analysis. Summary of histological findings is showed in Table 2.

Determination of cut-off values for hepatocytes steatosis

HS ranged from 5 to 30% (median 15%). Proportion of patients with different severity of HS was: 48.6% with grade 0; 19.4% with grade 1; 23.6% with grade 2 and 8.3% with grade 4.

TABLE 2
HISTOLOGICAL FINDING (N=72)

Piecemeal necrosis (median; IQR)	2	(2–3)
Confluent necrosis (median; IQR)	1	(0–3)
Focal necrosis (median; IQR)	2	(2–3)
Portal inflammation (median; IQR)	3	(2–3)
Activity (median; IQR)	8.5	(7–11)
Fibrosis (median; IQR)	4	(3–4.8)

IQR – interquartile range

Overall accuracy of prediction of SVR (area under the ROC curve, Picture 1) based on the levels of hepatocytes steatosis was AUC=0.71 (95% CI=0.58–0.84; p=0.005). Area under the curve was statistically significant, meaning that level of hepatocytes steatosis was statistically significant predictor of sustained virological response.

Youden index calculated as:

$$J = \max\{\text{sensitivity} + \text{specificity} - 1\}$$

where c ranges over all possible hepatocytes steatosis values, was J=0.39 (95% CI=0.13–0.50) with corresponding value of hepatocytes steatosis = 5%. Youden index calculator at value of hepatocytes steatosis = 20%, was 0.33 (95% CI=0.06–0.57), and at value of hepatocytes steatosis = 25%, was 0.37 (95% CI=0.10–0.50). All data were shown in Table 3.

Relationship of hepatic steatosis and sustained virological response

Statistically significant difference was found in level of HS when it was split as ≤5% and >5% (χ^2=10.025; df=1; p=0.002; phi coefficient=0.373); as ≤20% and >20% (χ^2=7.444; df=1; p=0.006; φ=0.322); and as ≤25% and >25% (χ^2=9.876; df=1; p=0.002; φ=0.370). Participants

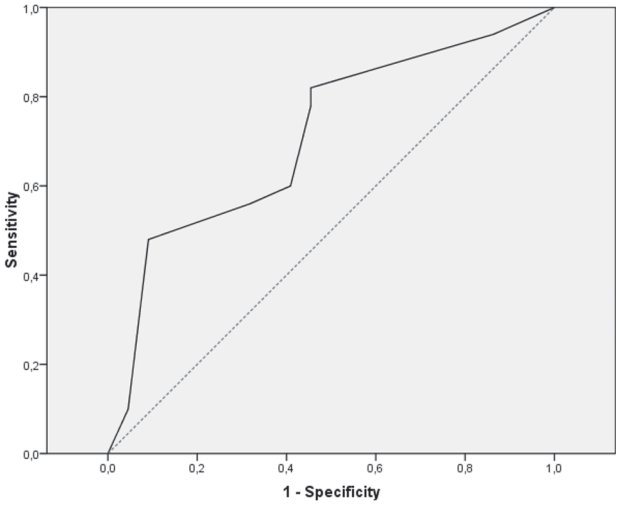

Fig. 1. ROC levels of hepatocytes steatosis, in prediction if sustained virological response with 95% confidence interval (N=72).

TABLE 3
CRITERION VALUES AND COORDINATES OF THE ROC CURVE OF HAPATOCYTES STEATOSIS IN PREDICTION OF SUSTAIND VIRAL RESPONSE (N=72)

HS	Sensitivity	Specificity	+LR	95% CI	–LR	95% CI	+PV	–PV
<0	0.0	100.0			1.0	1.0–1.0		30.6
≤0	10.0	95.5	2.20	0.3–49.6	0.94	0.9–1.2	83.3	38.1
≤5	48.0	90.9	5.28	1.5–31.7	0.57	0.5–0.8	92.3	43.5
≤10	56.0	68.2	1.76	0.9–4.0	0.65	0.4–1.1	80.0	40.5
≤15	60.0	59.1	1.47	0.9–2.9	0.68	0.4–1.2	76.9	39.4
≤20	78.0	54.5	1.72	1.1–3.0	0.40	0.2–0.9	79.6	52.2
≤25	82.0	54.5	1.80	1.2–3.0	0.33	0.2–0.7	80.4	57.1
≤30	94.0	13.6	1.09	0.9–1.3	0.44	0.1–2.6	71.2	50.0
≤40	100.0	0.0	1.00	1.0–1.0			69.4	

HS – hepatocytes steatosis; LR+ – positive likelihood ratio, ratio between the probability of a lower level of HS given the presence of the SVR and the probability of a lower level of HS given the absence of SVR; +PV – positive predictive value, probability of SVR if HS is lower or equal to the given value

TABLE 4
PREDICTION OF SVR REGARDING HS

	SVR		No SVR		p; effect	OR_{uv}	95% CI
	N	(%)	N	(%)			
Hepatic steatosis							
0–10%	28	(80.0)	7	(20.0)		1.0	
11–20%	11	(78.6)	3	(21.4)	0.058	0.9	(0.20–4.20)
21–30%	8	(47.1)	9	(52.9)		0.2	(0.63–0.79)
31–40%	3	(50.0)	3	(50.0)		0.3	(0.04–1.52)
Hepatic steatosis							
<5%	24	(92.3)	2	(7.7)	0.002; 0.373	1.0	
>5%	26	(56.5)	20	(43.5)		0.1	(0.02–0.51)
Hepatic steatosis							
<20%	39	(79.6)	10	(20.4)	0.006; 0.322	1.0	
>20%	11	(47.8)	12	(52.2)		0.2	(0.08–0.69)
Hepatic steatosis							
<25%	41	(80.4)	10	(19.6)	0.002; 0.370	1.0	
>25%	9	(42.9)	12	(57.1)		0.2	(0.06–0.55)
Hepatic steatosis*	10	(5–20)	30	(10–10)	0.003; 0.29	0.94	(0.90–0.99)

p – χ^2-test for nominal variables, Mann-Whitney test for numeric; the level of statistical significance, or probability of type I error (alpha); effect – standardized effect size given by statistically significant results; phi coefficient for χ^2; AUC for Mann-Whitney test; OR – odds ratio; 95% CI-95% confidence interval for odds ratio; uv – univariate logistic regression; * Median (interquartile range)

who have SVR had statistically significantly lower HS (Mann-Whitney U=864, Z=–1.958; p=0.049; AUC=0.38).

Participants with 21–30% of HS had 0.8 times smaller odds for achieving SVR (OR=0.2; 95% CI=0.63–0.79), compared to participants with 0–10% of HS. Also, participants with HS >5% had 0.9 times smaller odds for achieving SVR (OR=0.1; 95% CI=0.02–0.51), compared to participants with HS ≤5%. Participants with HS >20% had 0.8 times smaller odds for achieving SVR (OR =0.2; 95% CI=0.08–0.69), compared to participants with HS ≤20%. Those with HS >25% had 0.8 times smaller odds for achieving SVR (OR=0.2; 95% CI=0.06–0.55), compared to participants with HS ≤25%. Regarding numeric HS variable, with each unit HS increase odds for achieving SVR are 0.06 times smaller (OR=0.94; 95% CI=0.90–0.99) (Table 4).

Relationship of demographic, virological and histological characteristics with sustained virological response

When all demographic, virological and histological variables were entered in the multivariate logistic re-

gression model, included variables together achieved Nagelkerke R squared of 41.6% in prediction of SVR. The accuracy rate of the logistic regression model was 76.4%, meaning that 76.4% of participants were correctly classified as those with or without SVR, by mentioned variables.

In the next step, HS was added to the model. Firstly, HS was included as grouped into four categories (0–10%; 11–20%; 21–30%; 31–40%). Secondly, original, numeric HS was added into the model instead of the grouped one. Thirdly, HS split by newly determined cut-off values (≤5%) was added into the model; fourthly, HS split by newly determined cut-off values of 20% was added into the model, and finally, HS split by newly determined cut-off values of 25% was added into the model.

When HS (grouped into four categories) was included into the model, there was no statistically significant enhancement to prediction of SVR (χ^2=2.485; df=3; p=0.478), although Nagelkerke R squared increased to 45.0%, and accuracy rate increased to 80.6%. When original, numeric HS was included into the model, statistically significant enhancement to prediction of SVR was found (χ^2=3.886; df=1; p=0.049). Nagalkerke R squared increased from 41.6% to 46.9%, and the accuracy rate increased from 76.4% to 83.3%. When HS split by cut-off of 5% was included into the model statistically significant enhancement to prediction of SVR was found (χ^2=11.720; df=1; p=0.001). Nagalkerke R squared increased from 41.6% to 56.6%, and the accuracy rate increased from 76.4% to 83.3%. When HS split by cut-off of 20% was included into the model, there was no statistically significant enhancement to prediction of SVR (χ^2=2.375; df=1; p=0.123), although Nagalkerke R squared increased from 41.6% to 44.9%, and the accuracy rate increased from 76.4% to 79.2%. Finally, HS split as ≤25% and >25% was included into the model, statistically significant enhancement to prediction of SVR was found (χ^2=4.784; df=1; p=0.029). Nagalkerke R squared increased from 41.6% to 48.0%, and the accuracy rate increased from 76.4% to 81.9%.

Discussion

The findings in the current study evaluating steatosis in 72 chronic hepatitis C patients represent the single center cohort study. Whilst retrospective, this study explored the relationships between steatosis and possibility to achieve sustained viral response among patients with chronic hepatitis C infected with genotype 1 and 3. Hepatic steatosis was graded as the percentage of hepatocytes containing macrovesicular fat droplets. Majority of our patients had 5% or less hepatocytes affected with steatosis. Interestingly, when hepatic steatosis was split at the cut-off value of 5%, significant difference was found between responders and non-responders to treatment. Area under the curve was statistically significant, meaning that level of hepatocytes steatosis was statistically significant predictor of sustained virological response.

Steatosis has been identified as a negative predictor factor of response to antiviral therapy in many studies and still controversies exists. Steatosis appears to have a greater clinical impact on patients with genotype 1 infection where it decreases sustained response rates and is associated with fibrosis. The mechanism is not completely understood. In contrast, hepatitis c virus genotype 3 has been shown to be more sensitive to interferon-based therapy perhaps related to its unique interaction with host lipid metabolism. Some authors propose that interventions aiming at reducing hepatic steatosis prior to the onset of antiviral therapy may be of benefit to patients infected with genotype 1.

Problem with hepatic steatosis is in fact that is mainly confirmed by invasive method in majority of countries. Among clinicians tendency to find non-invasive and specific method of evaluating hepatic steatosis should be priority. Available radiographic methods are mainly operator dependent.

In conclusion we can say that steatosis induced by HCV infection has been confirmed as crucial factor that influence the outcome of antiviral treatments. Having in mind that some countries, like Croatia, still have pegylated interferon and ribavirin as standard of care in first line treatment, patients with high percentage of hepatic steatosis should be excluded from that treatment algorithm. Noninvasive methods for determination of hepatic steatosis or combination of laboratory parameters that can replace degree of hepatic steatosis are needed.

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STEATOZA JETRE ZAMIJENJENA NEINVAZIVNIM PARAMETRIMA DOMAĆINA I VIRUSA MOŽE POSLUŽITI KAO NEGATIVNI PREDIKTIVNI MODEL U PACIJENTA S KRONIČNIM HEPATITISOM C

S A Ž E T A K

Gotovo 70% bolesnika s kroničnim hepatitisom C (KHC) imat će prateću steatozu jetre (SJ) uglavnom utvrđenu invazivnom metodom. SJ služi kao negativni prediktivni čimbenik za sniženi trajni virološki odgovor (SVR, eng. sustained viral responce) u bolesnika s KHC liječenih standardnom terapijom (PEG IFN-α i Rib). Statistička analiza provedena je u Biometrika Healthcare Research. Razina statističke značajnosti određena je na 95% ($p<0,05$). Analizirano je 72 bolesnika (43 M; 29 Ž; medijan starosti 41 g) s KHC (60 G1; 12 G3) bez pratećeg MS (metaboličkog sindroma). Raspon SJ bio je od 5 do 30% (medijan 15%). Sveukupna točnost predikcije SVR na temelju razine SJ bila je AUC=0,71 (95% CI=0,58–0,84; p=0,005). Podijelivši SJ s obzirom na graničnu vrijednost od 5% nađena je značajna razlika između bolesnika koji su odgovorili na terapiju i onih koji nisu ($\chi^2=10,025$; df=1; p=0,002). Sveukupna osjetljivost bila je 48% i specifičnost 91%. Uobičajene prediktivne varijable (spol, dob, fibroza i genotip) bile su kombinirane sa SJ (>5%) te su zajednički dosegnuli Nagelkerke R squared od 34,0% u predviđanju SVR s razinom točnosti od 75,0%. Nadalje, invazivne varijable (fibroza i SJ) bile su zamijenjene s viremijom i indeksom tjelesne mase (BMI, eng. body mass index). Sve neinvazivne varijable postigle su zajednički Nagelkerke R squared od 26,5% u predviđanju SVR s razinom točnosti od 74% prema modelu logističke regresije. Jako niska SJ (<5%) je negativan pretkazivač (prediktor) SVR i može biti zamijenjena s neinvazivnim varijablama (spol, dob, viremija i BMI) iste razine točnosti prema modelu logističke regresije.