Diabetes impacts liver stiffness in chronic hepatitis C patients with and without virological cure: a longitudinal study

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Research article

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Abstract

Background: Transient elastography is controversial as a follow-up tool in chronic hepatitis C (CHC) patients. The aim was to assess the variation of liver stiffness measures and its associated factors on a cohort of CHC individuals composed of naïve, sustained virological response (SVR) and non-responder patients (NR).

Methods: This was a longitudinal study in CHC patients who were followed with clinical, laboratorial and serial elastography (Fibroscan®). The rate of progression of liver stiffness was calculated and the associated factors for progression were assessed by multiple linear regression analysis.

Results: Four hundred and six patients were included: 29% naïve, 24% NR and 47% SVR who were followed for 44 (35-53) months. There was a significant decrease in liver stiffness among SVR patients [11.8 (9.2) kPa *vs* 8.8 (8.4) kPa (p<0.001)], a trend for liver stiffness increasing in NR group [6.6 (5.2) kPa *vs* 7.1 (4.5) kPa; p=0.069)] and no change of liver stiffness in naïve group [6.3 (3.0) *vs* 6.0 (3.8); p=0.22]. The related factors for liver stiffness progression were lack of SVR (p=0.002) and diabetes (p=0.05). In non-diabetic SVR group, a negative rate of progression (- 0.047 kPa/month) was found compared to the highest rate in diabetic non-responder patients (+ 0.044 kPa/month). Diabetics with SVR showed a rate of (+) 0.037 kPa/month while in non-diabetic non-responder patients the ratio was (+) 0.028 kPA/month.

Conclusion: Despite SVR, liver stiffness in diabetic patients progresses, suggesting that a close follow-up of diabetic patients should remain even after SVR.

Background

Recently, in several chronic liver diseases, liver biopsy has been replaced by serological or physical non-invasive methods for the diagnosis of fibrosis [1, 2]. Amongst physical non-invasive methods, transient hepatic elastography (TE) is the most widely validated method mainly in chronic hepatitis C (CHC). TE is a bedside, painless and effective method for assessing liver fibrosis and has well validated cut-off points in CHC[3].

Although TE has been largely validated and considered an accurate tool for the diagnosis of fibrosis stage before HCV treatmen [4][5], its role as a follow-up method is still under debate as well as its interpretation and applicability after sustained virological response in CHC patients. Several studies have demonstrated that liver stiffness measures (LSM) assessed by TE decrease in patients with chronic hepatitis C after sustained virological response (SVR)[6][7][8][9][10]. However, although most studies show a decrease in liver stiffness in SVR patients, LSM changes are scarcely evaluated in naïve and NR in direct acting antiviral (DAA) treatment era. In addition, the associated factors that are related to the rate of progression/regression of liver stiffness in hepatitis C patients independent of SVR has been barely evaluated. Therefore, the aim of the present study was to analyze the changes in liver stiffness and its associated factors over a long-term follow-up on a large cohort of chronic naïve, non-responders (NR), and sustained virological response (SVR) HCV infected patients.

Methods

Study design and patients

Chronic hepatitis C patients who attended the outpatient liver clinic at the University Hospital of the Federal University of Rio de Janeiro, Brazil, were prospectively included. Diagnosis of chronic hepatitis C was based on the presence of a positive anti-HCV and detectable HCV-RNA in serum. Patients with other chronic liver diseases, HCV positive patients ongoing antiviral treatment, those with diagnosis of hepatocellular carcinoma and those who underwent any solid organ transplantation, including liver and kidney, were excluded as well as those with cholestasis, ascites or aminotransferases higher than five times the upper normal limit of normal due to the impact on the reliability of TE. In addition, patients with alcohol ingestion higher than 20 g per day were also excluded from the study. The local Ethics Committee approved the study and all patients signed an informed consent form.

Demographic, Clinical And Laboratory Data

Demographic, anthropometric, clinical and laboratory data from all included patients were registered at the time of first LSM as follows: gender, age (years), BMI (kg/m^2); weight (Kg); abdominal circumference (cm), diagnosis of type 2 diabetes mellitus (DM2)[11], presence of systemic arterial hypertension (SAH)[12], aspartate aminotransferase (AST, UI/L), alanine aminotransferase (ALT, UI/L), gamma glutamyl-transpeptidase (GGT, UI/L), platelet count (x 10^3 per liter), prothrombin time (seconds) and albumin (g/dL). Alcohol consumption and laboratorial parameters were also registered at baseline and at each LSM.

Liver Stiffness Measurement

Liver stiffness was measured by transient hepatic elastography with the FibroScan® Touch 502 equipment (Echosens, Paris, France), whose technique has been previously described[13]. Serial LSM with TE from each included patient at a minimum interval of 6 months either with M-probe or XL-probe. XL probe was adopted when LSM was unreliable with M probe. The same probe was used for all measurements for each patient. Individuals who underwent treatment during the study had at least one LSM at baseline, before treatment, and at least another TE evaluation six months after the end of therapy.

The fasting interval between the last food intake and TE was at least 3 hours. Ten measurements were obtained; final liver stiffness results were expressed in kPa. Unreliable measurements were defined as an interquartile range (IQR) to median value ratio greater than 30% or a success rate (SR) less than 60%[13]. The fibrosis stages based on the obtained LSM were defined according to Castéra et al [2] as follows: LSM under 7.1 kPa was defined as absence of fibrosis or minimum fibrosis (F0/F1); LSM between 7.1 and 9.4 as moderate fibrosis (F2); LSM between 9.5 and 12.4 kPa as advanced fibrosis (F3) and LSM equal or higher than 12.5 kPa as cirrhosis (F4). The same cut-offs were adopted for XL probe. In addition to LSM, steatosis was evaluated by the Controlled Attenuation Parameter (CAP). Both liver stiffness and CAP were obtained simultaneously and in the same volume of liver parenchyma.

Statistical analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics, V.24.0. Armonk, NY). Continuous variables with parametric distribution were expressed as mean ± SD and non-parametric variables were

expressed by median and respective interquartile range. Categorical variables were depicted as absolute numbers and percentages. Continuous variables were compared using Anova or Wilcoxon tests. Categorical variables were compared by chi-squared test. Simple linear regression was applied to calculate the rate of progression regarding the different patient groups. To identify the variables independently associated with the rate of progression altogether, multiple linear regression analysis was performed. The outcome variable was defined as the rate of progression of LSM. A statistical level of 0.5 was adopted.

Results

Study design and patients:

At baseline, a total of 426 chronic HCV patients were enrolled for evaluation of LSM. Twenty patients were excluded after the first LSM due to the following reasons: five patients died due to complications of cirrhosis; four were submitted to liver transplantation; four due to the diagnosis of hepatocellular carcinoma; three due to additional solid organs cancer and four additional patients were lost follow-up. Thus, 406 patients completed the study and were followed for 44 (35–53) months. Patients were categorized according to their status of HCV treatment. This way, 117 (29%) patients were classified as naïve, 96 (24%) were NR (mainly previously non-responders to pegylated interferon and ribavirin) and 193 (47%) patients were treated with direct antiviral drugs and achieved sustained virological response (SVR) during the study. Baseline demographic, anthropometric, clinical and laboratorial characteristics of all patients are shown in Table 1. Regarding each group characteristics, naïve patients were followed during 42 (34–51) months. Among them, 21% had the diagnosis of DM and 5% had liver cirrhosis. The median number of TE that was performed in this group was 3 (2–6). Concerning NR group, the follow-up time was 42 (33–51) months, 25% had DM and 18% were cirrhotic. The median number of TE performed in this group was also 3 (2–6). Finally, the follow-up time of the SVR group was of 17 (6–99) months. Among them, 20% had the diagnosis of DM and 45% were cirrhotic. SVR patients have performed a median of 4 (2–6) TE along the study. A comparative analysis between anthropometric, laboratorial data, LSM and CAP was also performed among the three different groups at baseline and at the last follow-up evaluation (Table 2).

Table 1
Baseline characteristics of chronic HCV-infected patients who were followed- up with transient elastography (n = 406)

Variable	
Age, years	58 ± 11
Female gender, (%)	246 (61)
Weight, Kg	72 ± 14
BMI, Kg/m^2	27 ± 4
DM, (%)	87 (21)
SAH, (%)	195 (48)
HIV, (%)	3 (0.7)
CKD, (%)	14 (3)
ALT (IU/L)	67 (45–97)
AST (IU/L)	47 (32–68)
GGT (IU/L)	69 (42–123)
Albumin (g/dL)	4.0 (3.7–4.3)
Platelets ($x10^3$)	180 (141–217)
HCV Genotypes	n (%)
1b	173 (43)
1a	139 (34)
1	52 (13)
2	02 (0.4)
3	30 (7)
LSM, kPa	8.4 (3.0–61.5)
METAVIR Fibrosis according to LSM	n (%)
F0/F1	161 (40)
F2	70 (17)
F3	66 (16)

Values are given as mean and standard deviation or median and range. BMI: body mass índex; DM: diabetes mellitus; SAH: systemic arterial hypertension; HIV: human immunodefficient vírus; CKD: chronic kidney disease; ALT: alanine aminotransferase; AST : aspartate aminotransferase; GGT: gamma glutamyl transferase; LSM:liver stiffness measurement; CAP: Controlled Attenuation Parameter; NR: previous non-responders to PEG-IFN; SVR: sustained virological response

Variable	
F4	109 (27)
CAP (dB/m)	229 ± 48
Treatment Status	n (%)
Naives	117 (29)
NR	96 (39)
SVR	193 (32)
Follow-up period, months	
All patients	44 (35–53)
Naives	42 (34–51)
Non-responders	42 (33–51)
SVR	17 (6–99)

Values are given as mean and standard deviation or median and range. BMI: body mass índex; DM: diabetes mellitus; SAH: systemic arterial hypertension; HIV: human immunodefficient vírus; CKD: chronic kidney disease; ALT: alanine aminotransferase; AST : aspartate aminotransferase; GGT: gamma glutamyl transferase; LSM:liver stiffness measurement; CAP: Controlled Attenuation Parameter; NR: previous non-responders to PEG-IFN; SVR: sustained virological response

Table 2
Comparative analysis among naïve, NR and SVR HCV infected patients at baseline and at the end of follow-up (n = 406):

	Naives (n = 117)			NR (n = 96)			SVR (n = 193)		
Variables	**baseline**	**end of follow-up 47 (38–56) months**	p	**Baseline**	**end of follow-up 42 (33–51) months**	p	**baseline**	**end of follow-up 17 (6–99) months**	p
Weight (kg)	68.7 ± 12.8	68.8 ± 13.3	0.056	72.2 ± 13.6	74.4 ± 13.7	0.004	72.2 ± 13.3	74.0 ± 14.3	< 0.001
BMI (kg/m^2)	25.9 ± 4.2	26.0 ± 4.4	0.051	26.9 ± 4.3	27.6 ± 3.9	0.012	27.1 ± 4.5	27.7 ± 4.7	< 0.001
ALT (IU/L)	58 (44–83)	56 (38–84)	0.10	61 (47–84)	56 (42–79)	0.06	75 (45–112)	24 (18–38)	< 0.001
AST (IU/L)	40 (30–60)	43 (27–60)	0.95	45 (31–57)	47 (33–64)	0.81	56 (34–87)	26 (21–31)	< 0.001
GGT (IU/L)	60 (36–102)	55 (31–99)	0.54	59 (35–108)	68 (35–122)	0.80	85 (51–142)	30 (22–60)	< 0.001
LSM (kPa)	6.1 (5.1–7.7)	6.1 (4.9–7.9)	0.22	6.6 (5.2–10.4)	7.1 (5.6–10.1)	0.069	11.8 (8.5–17.2)	8,8 (6.0-14.4)	< 0.001
CAP (dB/m)	217 ± 55	220 ± 56	0.68	237 ± 39	234 ± 46	0.26	231 ± 47	236 ± 56	0.39

Values are given as mean and standard deviation or median and interquartile range. NR: previous non-responders; SVR: sustained virological response; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; LSM: liver stiffness measurement; CAP: Controlled Attenuation Parameter

Regarding anthropometric data, patients from both SVR and NR group have gained weight, both groups with a significant increase in BMI, even though CAP values remained stable over time.

Concerning absolute LSM at baseline and last follow-up, except for SVR group that showed a striking reduction of LSM values [11.8 (9.2) kPa *vs*. 8.8 (8.4) kPa; $p < 0.01$], there was a trend for LSM increase in NR group [6.6 (5.2) kPa *vs*. 7.1 (4.5) kPa; $p = 0.069$)] and no change in LSM along the study in the naïve group [6.3 (3.0) *vs*. 6.0 (3.8); $p = 0.22$].

Analysis of serial LSM values amongst the three different groups

Figure 1 shows the variation and change of liver fibrosis stage over the follow-up period in the three studied groups, naïve, NR and SVR. Among the 117 patients included in the naïve group, with a median follow up of 42 (34–51) months, 79 (68%) were considered as F0/F1, according to LSM values at baseline. Overall, 24 patients had a change of fibrosis stage compared to baseline: 14 patients (12%) had increased LSM values changing to higher fibrosis stages and 10 (10%) have decreased LSM values to lower fibrosis stages. The second group was composed of NR patients who were followed along 42 (33–51) months. Among these patients, seventeen patients (18%) increased fibrosis stage and 13 (13%) have decreased fibrosis stage according to baseline and follow-up LSM values. Lastly, the third group composed of SVR patients who were followed for a median of 17 (6–99) months. Among SVR group, there was a significant reduction of LSM values in 83 (43%) of patients, predominantly in 35 patients who have shown at least two-fibrosis stage regression after SVR. In 94 (49%) patients there was no change in fibrosis stage and in 16 (8%) an increase in fibrosis stage was observed. The respective rates of variation based on the serial LSM according to each group were + 0.04 kPa/month for the naïve group, + 0.02 kPa/month for the NR group and – 0.33 kPa/month for the SVR group.

On multivariate linear regression analysis, achievement of SVR and absence of diabetes were independently associated with reduction of LSM as showed in Table 3. When we calculated the rates of variation according to the diagnosis of DM and achievement of SVR, the best scenario was observed in the SVR group in patients without DM, which have shown a negative variation rate (− 0.047 kPa/month). The worst scenario was observed in non-responders diabetic patients who have shown the highest progression rate (+ 0.044 kPa/month). Surprisingly, patients who have achieved SVR but had the diagnosis of DM have shown a positive rate of variation, of + 0.037 kPa/month while among NR patients without diabetes the ratio was + 0.028 kPA/month. The different rates of variation according to the diagnosis of DM and achievement of SVR are shown in Fig. 2.

Table 3
Independent factors related to the progression of liver stiffness measure rate in HCV-infected patients (n = 406)

Variables	Beta- Coefficient	95% CI	p-value
Diabetes Mellitus	0.047	(0.001; 0.094)	0.05
SVR	− 0.062	(− 0.101; − 0.023)	0.002
SVR, sustained virological response; 95% CI, 95% confidence interval			

Discussion

The present study has evaluated changes of LSM values on a large cohort of HCV infected patients with different status of treatment, including naïve, non-responders and sustained virological responders patients. Its main finding was that besides SVR, the diagnosis of diabetes mellitus independently impacts on the improvement of liver stiffness along time. In the present study even patients with SVR had shown worse progression of LSM comparing to those without diabetes. Patients with chronic hepatitis C have an increased risk of diabetes mellitus and insulin resistance (IR) and the finding that diabetes may impact fibrosis evolution is worrisome [14]. Diabetes has clearly been described as risk factor for fibrosis progression in non-alcoholic liver disease patients but its impact on chronic hepatitis C patients has not been prospectively evaluated [15]. Fernandes et al have found a similar impact of diabetes in CHC patients but on a retrospective study that included only SVR patients, without the possibility to compare SVR patients with NR or naïve patients[9]. The prognostic impact of DM observed in our study has great relevance in clinical practice since it might further be the basis to recommend that in daily clinic patients with DM should be kept under care despite virological cure. Serfaty has already suggested that patients with associated metabolic factors should stay in the outpatient clinic even after SVR due to its risk of progression [16], and regarding diabetes patients the main concern was progression of NAFLD-related inflammation. In our study, BMI has a modest increased in SVR group, and, surprisingly, CAP measures stayed stable over time suggesting that the impact of diabetes might be related to other mechanisms such as progression of steatohepatitis not evidenced by elastography and thus not possible to confirm with the present data in this study. However, our study adds evidence that liver fibrosis may not improve as expected in SVR population if diabetes is present.

In the present study, LSM was assessed in HCV-infected patients with different treatment status who were followed for a long period of time ranging from 35 to 53 months. Recent studies have reported a decrease in LSM values after sustained virological response but most of them included only a limited sample or followed patients for a shorter period of time varying from 4 to 13 months compared to the present study[6, 8, 17, 18]. In additional studies, LSM was available only at the end of treatment, with the comparison of different methods at baseline and at the end of follow-up such as TE vs. liver biopsy as the study from Cordero-Ruiz et al that described the LSM changes for 13 years, but only in 66 patients and comparing distinct methods, which was a possible confounder for the results [19]. Our study followed prospectively 193 patients who achieved SVR for a median of 17 months after SVR, with a median of four LSM. We also calculated the ratio for progression/regression of LSM using the serial LSM that were obtained from the included patients, which is also an original data. Although this ratio is not linear, we have shown that in the SVR group, the rate of progression was negative, with a value of – 0.33 kPa/month confirming a decrease in LSM of SVR patients, compared with naïve or NR with respective positive rates of + 0.04 kPa/month and + 0.02 kPa/month showing that there was a trend for the progression of liver fibrosis.

So far, most published studies have focused specifically in the follow-up of SVR patients group[6, 8, 9, 18, 20],describing the straight relationship of SVR and improvement of liver fibrosis with several non-invasive methods like TE and acoustic radiation force impulse. Currently, HCV treatment is effective in most of treated patients, however, assess to treatment is still an issue in many countries, mainly those underdeveloped countries. So, showing that patients who are NR and have diabetes present the worst scenario regarding LSM

progression is of utmost importance in order to make treatment available to this population as fast as possible. This study helped to better understand in the current era of non-invasive methods and DAA treatment how do these diverse group of patients perform on a long-term basis.

Regarding NR patients and LSM changes, few studies with limited samples were published, some regarding patients who were treated with interferon varying from 9 to 52 patients[6, 17, 21, 22]. Our study has evaluated 96 NR patients for a longer period of follow up, with a median of 42 months. The study that has had the longest follow-up time has followed patients for only 20 months, which represents half the time we have followed our patients. Regarding the LSM changes, the results are controversial. The studies from Arima *et al* and Hézode *et al* [6, 21]have found an improvement of LSM but Wang et al did not conform this finding[17]. In addition, Tada et al has shown a steady LSM in NR patients overtime[22]. Our results are related to patients who have been previously treated with pegylated interferon and showed a trend to an increase of LSM values at the end of the study. We can confirm this finding comparing elastography measurements at baseline and at the end of follow up, and also by the positive ratio of progression of + 0.02 kPa/month. We also may hypothesize that the increase in LSM observed in the present study was possible due to the long follow up in our patients, which might increase the evidence of this result. The same way, the long period of follow up for naive patients as presented in this study is rarely described. Erman et al published a meta-analysis where changes in LSM were evaluated in 5874 treatment naive with the majority of patients being HIV co-infected[23]. However, these populations are not comparable with a HCV-monoinfected one due to the faster liver fibrosis progression in HIV coinfected patients as demonstrated in the referred meta-analysis.

Our study had some limitations regarding the absence of a regular interval between LSM, that prevented analysis regarding to the precise moment of LSM improvement in SVR patients, and the absence of pre and post-treatment liver histology due to its invasiveness and risks. So, we may not be able to state if the improvement in LSM was related to an improvement in inflammation or fibrosis and if diabetes could have some impact in maintaining hepatocyte inflammation through activation of other pathways related to glucose metabolism.

In conclusion, our study shows that SVR patients have a significant improvement in LSM, different from NR and naive HCV-infected patients. However, it notably shows that diabetes mellitus contributes to a worse progression of LSM even among patients with SVR. This way, diabetes mellitus is also a marker of bad prognosis in HCV infected patients and these patients should not be discharged from follow up clinic even after attaining SVR.

Declarations

Author's contributions:

CAVN Conceived and designed the study, DMP and ACC followed-up the patients and obtained the data. CAVN drafted the manuscript. CAVN, RRL and RMP analyzed the data and CAVN is the guarantor. All authors helped interpret the results and reviewed the manuscript. All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of data analysis. All authors read an approved the final manuscript.

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Conflict of interest disclosure:

The authors have nothing to declare.

Ethics approval and consent to participate:

The study was approved by the Clementino Fraga Filho University Hospital IRB (approval number CAE 56934416.000.5257, registered at http://www.plataformabrasil.saude.gov).

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Figures

Naïve group (n=117)						Non-responders (n=96);						Sustained virological response (n=193);					
Baseline Liver Fibrosis stage	Final liver fibrosis stage according to LSM					Baseline Liver Fibrosis stage	Final liver fibrosis stage according to LSM					Baseline Liver Fibrosis stage	Final liver fibrosis stage according to LSM				
	F0-F1	F2	F3	F4	TOTAL		F0-F1	F2	F3	F4	TOTAL		F0-F1	F2	F3	F4	TOTAL
F0-F1	69	6	4	0	79	F0-F1	40	7	3	0	50	F0-F1	22	7	0	0	29
F2	8	10	3	1	22	F2	5	8	4	0	17	F2	22	9	4	0	35
F3	2	2	2	0	6	F3	2	2	5	3	12	F3	16	11	14	5	46
F4	0	0	0	10	10	F4	0	1	3	13	17	F4	10	9	15	49	83
TOTAL	79	18	9	11	117	TOTAL	47	18	15	16	96	TOTAL	70	36	33	54	193

Figure 1

Liver fibrosis variation at baseline and at the end of follow-up period in naïve, non-responders (NR) and sustained virological response (SVR) groups

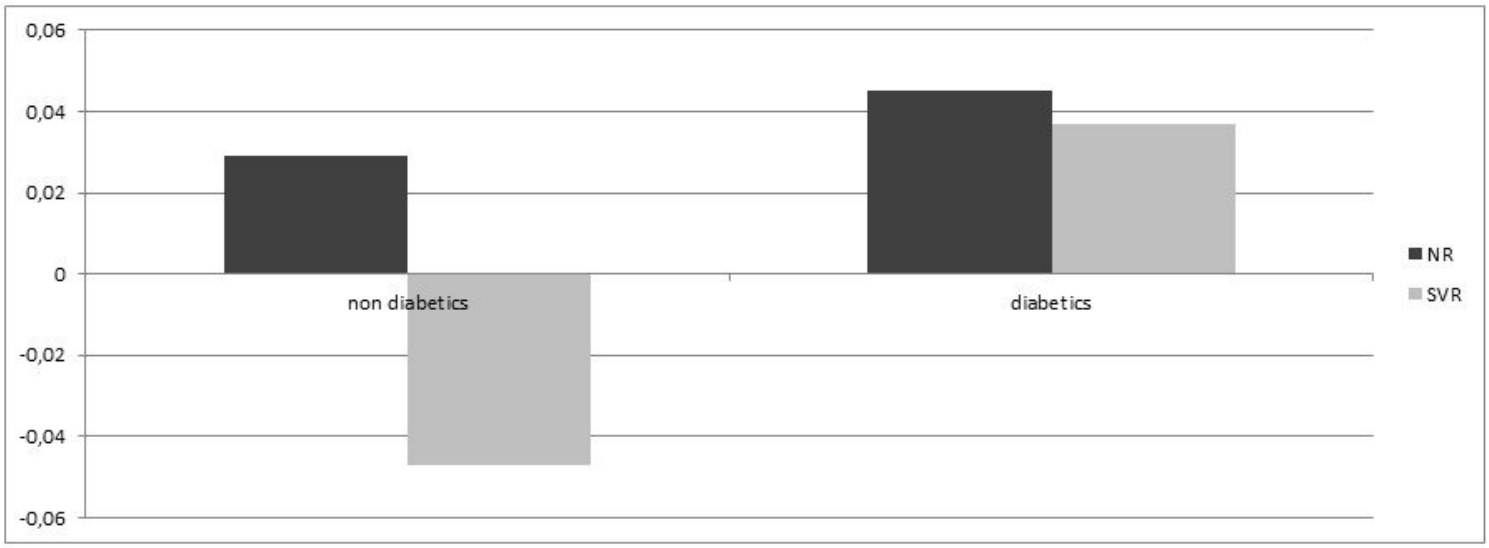

Figure 2

Variation rate of liver stiffness measures according to the diagnosis of diabetes mellitus in sustained virological response (SVR) and in non-responder (NR) patients