

# Host Factors Influences on Treatment Response in Chronic Hepatitis C Patients Treated with pegINF and Ribavirin in Albania

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**Abstract:** ***Introduction:** The impact of viral factors like genotype, HCVRNA at baseline, or viral kinetics during treatment of chronic hepatitis C patients is better defined recently. In contrary different results comes from studies about the impact of age, gender or BMI on treatment response in chronic hepatitis C (CHC) with standard scheme. **Aim:** To evaluate the predictive value of host factors (age, gender, BMI, biochemical and hematological profile) on treatment response in CHC patients in Albania. **Patients and Methods:** A total of 151 patients, diagnosed with CHC in UHC "Mother Tereza" service of Gastro-Hepatology were included in this study. All the patients were treated with PegINF alfa-2a (180 µg s.c/week) and ribavirin 800-1200 mg/day (according to body weight and genotype). The duration of treatment varied from 24-48 to 72 weeks according to genotype and virological response. Patients were assessed for age, gender, BMI, TC (total cholesterol), TGC, Fast blood glucose (FBG), GGT, AST, ALT, WBC, PLT, HB and was evaluated their impact on treatment response in both SVR and Non-SVR group. Data were analyzed statistically by Chi square test and T test.  $P < 0.05$  is considered significant. **Results:** In general patients aged  $< 45$  years/old had a SVR rates of 59.2% and those  $\geq 45$  years/old 64% without significant differences between groups (Chi-square=0.366,  $df=1$ ,  $p=0.545$ ). Female patients had a SVR rate of 63.7% and males 59.7% (Chi-square =0.255,  $df=1$ ,  $p=0.614$ ) without significant differences between groups. The SVR rates of females  $< 45$  years/old, females  $\geq 45$  ys/old, males  $< 45$  ys/old and males  $\geq 45$  ys/old were respectively 66.7%, 61.9%, 55%, 66.7% in all cases without significant differences between groups. Through binary logistic regression technique, is shown that there is a causal link, statistically significant between the non-SVR and BMI  $\geq 27$ kg / m<sup>2</sup>; It can be said that patients with BMI  $> / = 27$  kg / m<sup>2</sup>, are 2.6 times more likely than patients with BMI  $< 27$ kg / m<sup>2</sup>, not to achieve SVR. (OD:2.58, CI 95%: 1.59-5.67). Significant statistical differences in baseline TC, GGT and PLT were found between SVR and non -SVR groups. **Conclusions:** BMI  $\geq 27$ , low level of TC, low level of PLT and high level of GGT at baseline are significant negative baseline predictors of SVR. Age and gender are not predictors of treatment response in CHC patients in Albania.*

**Keywords:** hepatitis C, host factors, treatment, impact

## 1. Introduction

It is estimated that approximately 170 million individuals, i.e. 2.35% of the world population, are chronically infected with HCV. Overall, HCV prevalence across Europe ranges between 0.4% and 3.5%, with wide geographical variation and higher rates in the south and the east (2,3). The genotypes (1, 2, 3, 4, 5, 6 & 7) show differences with regard to their worldwide distribution, transmission and disease progression (4). Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe and 1a in the USA. In Western Europe, HCV prevalence ranges from 0.4% to 3% (5). According studies conducted by Institute of Public Health in Albania the prevalence of hepatitis C varied in the population from 0.9 -1.3 % (6, 7). Genotype 1b is the most prevalent genotype in Albania nearly 65%-70%, followed by genotype 2 and 3 nearly 25-30% and genotype 4 only 1% (8). The objective of antiviral therapy is to obtain a sustained virologic response (SVR), defined as undetectable HCV RNA during treatment and 24 weeks after the end of treatment. In the last decade, treatment of CHC with pegINF 2a or 2b combined with weight-based ribavirin (RBV) for 48 weeks (genotypes 1, 4, 5 and 6) or 24 weeks (genotypes 2 and 3), has been considered the standard of care (SOC) for HCV treatment. Treatment with pegINF/RBV dual therapy is costly and is

associated with side effects. Before initiating treatment, it is useful for patients and physicians to determine the likelihood of achieving a SVR, so that they can decide whether treatment benefits outweigh its costs and risks. The impact of viral factors in pegINF/RBV scheme is better defined. HCV genotype is one of the important baseline predictor for response. Genotype-1 infected patients achieve a SVR ranging from 41-52% after 48 weeks of peg-IFN plus RBV as opposed to 76-84% in genotypes 2 and 3 (9,10,11). Genotype 4 patients treated for 48 weeks showed response rates at an intermediate level compared to genotype 1 and genotypes 2 or 3, with SVR rates between 65% and 72% (12,13). A low baseline viral load ( $< 600,000$ - $800,000$  IU/ml or less) is an independent predictor of SVR regardless to genotype in many studies (11,14,15) and patients with pretreatment high viral loads have lower SVR rates than patients with low viral loads. Once treatment has been initiated, monitoring of HCV RNA decline has become an increasingly important tool for the prediction of SVR (14,16,17). In particular, rapid virological response (RVR) has been recognized as one of the most powerful predictors of SVR and, when assessed in combination with baseline viral load, can be used to identify patients for whom a shortened treatment course is appropriate. Regarded to host factors many studies confirm the impact of race on treatment (18,19,20,21) and the impact of IL28B gene SNPs which are

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strongly associated with HCV clearance, whether spontaneous or treatment-related (22). In general it is believed that younger age, females and low BMI levels have better treatment results but contradictory results come from different studies. For these reason we conducted this study to establish and better define the impact of host factors in our patients with chronic hepatitis C and so better predict the treatment response.

## 2. Aim

To evaluate the predictive value of host factors (age, gender, BMI, biochemical and hematological profile at baseline) on treatment response in CHC patients in Albania.

## 3. Patients and Methods

A total of 151 patients, diagnosed with CHC in UHC "Mother Tereza" service of Gastrohepatology were included in this study. The following were considered to be contraindications for treatment: current liver decompensation, immunosuppressive treatment within the last six months, associated liver diseases (especially autoimmune hepatitis) and other associated serious diseases such as systemic autoimmune disease, neoplasia, cardiac arrhythmias and ischemic vascular disease. All these patients were treated with PegINF alfa-2a (180 µg s.c/week) and Ribavirin 800-1200 mg/day (according to genotype and body weight). Patients with genotype 1 and 4 were treated in general for 48 weeks and for genotypes 2 and 3, 24 weeks but the duration of treatment varied from 24-48 to 72 weeks according EASL recommendations depended also from the virological response during treatment. Success of treatment was considered HCVRNA negative during treatment and 24 weeks after the end of the treatment (SVR). HCVRNA negative were considered levels below 50 IU/ml of HCVRNA. Patients were assessed for age, gender, BMI, TC, TGC, Fast Glucose, GGT, AST, ALT, WBC, PLT, HB and was evaluated their impact on treatment response in both SVR and Non-SVR group. Data were analyzed statistically by Chi square test and T test. Values of  $P < 0.05$  are considered statistically significant.

## 4. Results

The distribution of genotypes among 151 patients was: Genotype 1b (89pt) 59%, 1a (2pt) 1.3%; genotype 2 (48pt) 31.7%; genotype 3 (9pt) 6%; genotype 4 (3pt) 2%. From all patients 93 achieved sustained virological response (SVR) so the SVR rate independently of genotype was 61.5%. In the group with genotypes 1 and 4 the SVR rate was 43.6% while with genotypes 2 and 3 the SVR rate was 88% with significant difference between the groups ( $p < 0.001$ ). The median age  $\pm$  STD of patients enrolled in the study was  $45.5 \pm 13.3$  years/old. From all patients 82 were males (54.3%) and 69 females (45.7%). In general patients aged  $< 45$  years/old had a SVR rates of 59.2% and those  $\geq 45$  years/old 64% without significant differences between groups (Chi-square=0.366,  $df=1$ ,  $p=0.545$ ). Female patients had a SVR rate of 63.7% and males 59.7% (Chi-square=0.255,  $df=1$ ,  $p=0.614$ ) without significant differences between groups (Table 1).

**Table 1:** The impact of age and gender on SVR

Variables		HCVRNA_post terapi		Total	P value
		Non-SVR	SRV		
Gender	f	25	44	69	0.614
		43.1%	47.3%	45.7%	
	m	33	49	82	
		56.9%	52.7%	54.3%	
Age	$\geq 45$ vjec	27	48	75	0.545
		46.6%	51.6%	49.7%	
	$< 45$ vjec	31	45	76	
		53.4%	48.4%	50.3%	

\*Chi square test

Through binary logistic regression technique, is shown that there is a causal link, statistically significant between the Non-SVR and BMI  $\geq 27$  kg / m<sup>2</sup>; It can be said that patients with BMI  $> / = 27$  kg / m<sup>2</sup>, are 2.6 times more likely than patients with BMI  $< 27$  kg / m<sup>2</sup>, not to achieve SVR. (OD:2.58, CI 95%: 1.59-5.67) (Table 2).

**Table 2:** The impact of BMI on SVR

BMI	HCVRNA_pot terapi		OD	CI95%
	Non-SVR n=58 (%)	SRV n=93 (%)		
$\geq 27$ kg/m <sup>2</sup>	40 (69.0)	43 (46.2)	2.58	1.59-5.67
$< 27$ kg/m <sup>2</sup>	18 (31.0)	50 (53.8)	reference	

Significant statistical differences in baseline TC, GGT and PLT were found between Non-SVR and SVR groups (Table 3).

**Table 3:** The impact of biochemical and hematological profile on SVR

Baseline parameters	Non-SVR group(58)	SVR group (93)	P value
TC (mg/dl)	151.71 $\pm$ 31.55	174.30 $\pm$ 37.46	0.005
TGC (mg/dl)	115.14 $\pm$ 68.21	106.48 $\pm$ 52.10	0.5
FBG (mg/dl)	107.32 $\pm$ 41.72	98.72 $\pm$ 30.77	0.5
GGT (UI/l)	82.90 $\pm$ 62.74	56.56 $\pm$ 57.55	0.04
AST (UI/l)	62.8/ml $\pm$ 33.57	66.3 $\pm$ 62.08	0.35
ALT (UI/l)	77,8 $\pm$ 49.14	114.4 $\pm$ 136.4	0.079
WBC/mm <sup>3</sup>	6143.33 $\pm$ 1725.42	6462.35 $\pm$ 1718.63	0.2
HB (g/dl)	13.88 $\pm$ 1.62	13.79 $\pm$ 1.60	0.7
PLT/mm <sup>3</sup>	179145.37 $\pm$ 64504.51	219827.06 $\pm$ 80966.55	0.002

## 5. Discussion

### a) Age

Many study results confirm that patients age is a factor that is associated with responsiveness to Peg-IFN- $\alpha$ /RBV therapy in chronic HCV infection. Generally, it is believed that younger individuals (usually  $< 40$  years of age) respond better to IFN- $\alpha$  treatment than older persons. In large prospective studies of (PEG) IFN and RBV combination therapy younger age correlated significantly with an SVR when assessed by univariate and multivariate analyses and patients younger than 40–45 years showed the best response rates [9,10,11,23]. The explanation is that older HCV patients are likely to have more advanced liver disease, such as fibrosis and cirrhosis (also predictors of poor virological

responses) and also impairments in cellular, humoral, and innate immunity in the elderly may be another important factor that is responsible for decreasing successful responses to IFN- $\alpha$  treatment in older patients. In recent years various studies have been published that have shown that the elderly age is not a negative predictive factor for virological response to therapy with pegylated interferon- $\alpha$  and ribavirin in chronic hepatitis C virus patients, so a study conducted by Frei P. et al. (24) in matched pair analysis, SVR was not different in young and elderly patients (54.2 and 55.9% respectively;  $P = 0.795$  in binominal test). This fact was found also in our study which showed that in general patients aged  $< 45$  years/old had a SVR rates of 59.2% and those  $\geq 45$  years/old 64% without significant differences

between groups (Chi-square=0.366, df=1,  $p=0.545$ ) (Table 1).

When baseline and on treatment characteristics in both groups were compared resulted that although age  $< 45$  years/old had more positive predictive factors in baseline: statistically higher number of patients with BMI  $< 27$ , lower fibrotic scale at baseline (assessed by FIB 4 test), and higher number of PLT at baseline, this group of age had a higher prevalence of genotype 1 and 4 which predicted a comparable treatment response between this group and the group with age  $\geq 45$  years/ old (Table 4).

**Table 4:** Baseline and on treatment data in patients  $< 45$  years/old and  $\geq 45$  years old

Patients baseline and on treatment data	Age $\geq 45$ years/old	Age $< 45$ years/ old	P value
<b>Gender (Male)</b>	33 (44.0)	49 (64.5)	<b>0.012</b>
<b>BMI <math>&lt; 27</math> kg/m<sup>2</sup></b>	27 (36.0)	41 (53.9)	<b>0.027</b>
<b>GGT</b>	79.97 $\pm$ 65.34	57.55 $\pm$ 52.28	0.081
<b>TC</b>	171.28 $\pm$ 37.70	160.93 $\pm$ 35.74	0.191
<b>PLT</b>	184801.45 $\pm$ 74175.94	222969.29 $\pm$ 76241.64	<b>0.003</b>
<b>HCV RNA</b>	2.77 $\times 10^6$ $\pm$ 8.4 $\times 10^6$	3.1 $\times 10^6$ $\pm$ 6.38 $\times 10^6$	0.737
<b>HCV RNA baseline <math>&lt; 400</math> 000</b>	28 (37.3)	30 (39.5)	0.787
<b>Genotype 1 and 4</b>	40 (53.3)	53 (69.7)	<b>0.038</b>
<b>RVR</b>	21 (53.8%)	19 (42.2%)	2.287
<b>FIB 4 test</b>	2.64 $\pm$ 2.26	1.20 $\pm$ 0.92	<b>&lt;0.001</b>

**b) Gender**

A large analysis (n = 1744) of two trials involving standard IFN plus RBV therapy showed a significant positive correlation between female gender and SVR ( $p < 0.004$ ) (24). No such difference has been confirmed in studies involving Peg-IFN plus RBV (10, 11, 25, 26,27). In accordance to these studies female patients had a higher SVR rate (63.7%) than males (59.7%) (Chi-square =0.255, df=1,  $p=0.614$ ) but without significant differences between groups. When the groups male / female were analyzed it was found that although women had significant positive

predictive factors like higher RVR rates, lower GGT levels at baseline compared to males they had higher percentage of age  $\geq 45$  year/olds compared to males (Table 5). The unfavorable effect of treatment in women  $> 45$  years is apparently related to the reduced amount of estrogen after this age. It has been proposed that estrogen may suppress hepatic fibrosis through an effect that depends on its hepatic tissue receptors, and improve the antiviral therapy, in females  $< 45$  years/old (28).

**Table 5:** Baseline and on treatment data in males/females

Baseline and on treatment data	Female group	Male group	P value
<b>Age <math>&lt; 45</math> vjeç</b>	27 (39.1)	49 (59.8)	<b>0.012</b>
<b>BMI <math>&lt; 27</math> kg/m<sup>2</sup></b>	35 (50.7)	33(40.2)	0.197
<b>GGT</b>	49.24 $\pm$ 47.67	81.54 $\pm$ 66.02	<b>0.013</b>
<b>TC</b>	168.39 $\pm$ 34.89	164.47 $\pm$ 39.00	0.621
<b>PLT</b>	206492.06 $\pm$ 85755.63	201975.66 $\pm$ 70160.90	0.733
<b>HCV RNA in baseline</b>	2.93 $\times 10^6$ $\pm$ 8.94 $\times 10^6$	3.02 $\times 10^6$ $\pm$ 5.92 $\times 10^6$	0.948
<b>HCV RNA <math>&lt; 400</math> 000 U/ml</b>	26 (37.7)	32 (39.0)	0.866
<b>Genotype 1 and 4</b>	39 (56.5)	54 (65.9)	0.240
<b>RVR</b>	25 (62.5%)	15 (34.1%)	<b>0.009</b>
<b>FIB 4 test</b>	2.14 $\pm$ 2.28	1.82 $\pm$ 1.42	0.206

The SVR rates of females  $< 45$  years /old, females  $\geq 45$  ys/old, males  $< 45$  ys/old and males  $\geq 45$  ys/old were respectively 66.7%, 61.9%, 55%, 66.7%. When we assessed gender in relation to age resulted that females  $< 45$  ys/old had higher SVR rates than males of the same age (66.7% vs 55%) and older males  $> 45$  years/old had higher SVR rates than younger males (66.7% vs 55%) but in all cases without significant differences between groups. Similar results have been found also from Jian –Wu et al. which in their study

concluded that in the group of patients aged  $< 40$  years, the SVR rate of females was higher than that of males; in the group of patients aged 40–50 years, females and males shared similar SVR rates; in the group of patients aged 51–60 years, the SVR rate of females was lower than that of males (29).

### c) BMI, overweight, obesity

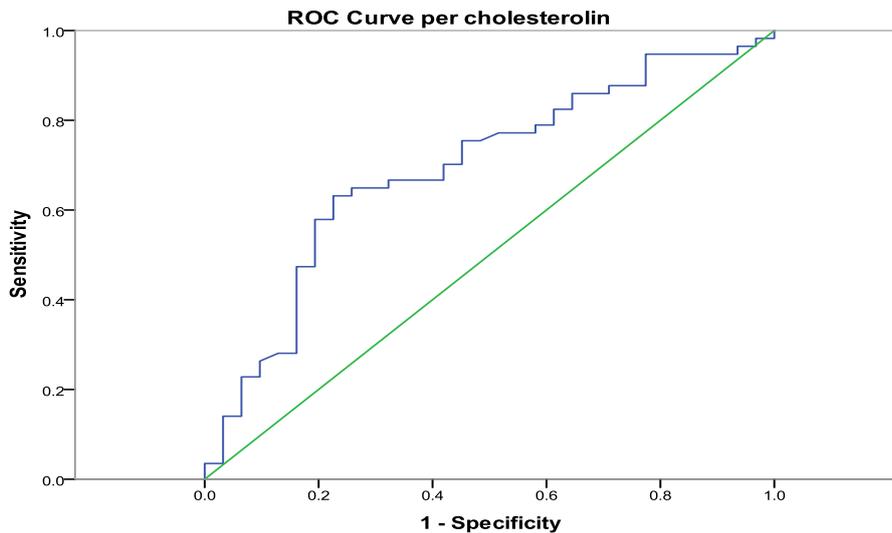
According a study conducted by K-Q. Hu et al. being overweight/obese (BMI >25 kg/m<sup>2</sup>) serves as an independent risk factor for hepatic steatosis in U.S. patients with CHC. Steatosis accelerates activity and progression of CHC, and was independently associated with stage III/IV hepatic fibrosis in these patients (30). Obesity has been reported to be a risk factor of non-response independent of the HCV genotype and the presence of cirrhosis. Obese patients defined as BMI > 30 have approximately a 80% lower chance of achieving SVR compared with non-obese patients (31). As mentioned above obesity and high BMI induces: (1) the metabolic syndrome leading to insulin resistance, hepatic steatosis, and higher baseline viral load, (2) altered cytokine signaling manifested by elevated levels of leptin, adiponectin, and resistin (3) reduced bioavailability of interferon- $\alpha$  (31,32). (4) Certain peg-IFN also may be preferentially absorbed through blood capillaries or the lymphatic circulation. Since obese people are known to have a poor lymphatic circulation (33), this could result in suboptimal serum levels of peg-IFN and a reduced response to antivirals. (5) Obesity may also affect the antiviral response modulating the interferon (IFN) signaling pathway. Normally, interferon  $\alpha$  (IFN- $\alpha$ )-activated cellular signaling is negatively regulated by inhibitory factors such as the suppressor cytokine signaling (SOCS) family. Obese subjects infected with HCV genotype 1 had increased hepatic expression of SOCS-3, a factor that has been shown to inhibit IFN- $\alpha$  signaling. This relationship between obesity and increased SOCS-3 expression remained significant after correction for other factors associated with non-response to treatment. (34). In patients with genotype 3 infection, fatty liver can occur in the absence of obesity and insulin resistance (35,36) suggesting a viral etiology with mechanisms related to how core protein affects lipid oxidation and very low-density lipoprotein assembly (37) while in non genotype 3 infections, steatosis is most common in patients who are obese and insulin resistant (36). However, these results about impact of BMI on SVR were not confirmed in other large studies with PEG/RBV combination therapy in HCV genotypes 1– 3-infected patients in which multilogistic regression analyses including BMI and body weight were conducted (38,39). In our study resulted that median level of BMI was lower in SVR group than Non-SVR 25.1 $\pm$ 4.5 vs 26.5 $\pm$ 3.7 kg/m<sup>2</sup> but without statistical differences. Meanwhile when we compared two groups with a cut-off value of 27 through binary logistic regression technique, resulted that there was a causal link, statistically significant between non-SVR and BMI  $\geq$ 27kg /

m<sup>2</sup>; It can be said that patients with BMI  $> / = 27$  kg / m<sup>2</sup>, are 2.6 times more likely than patients with BMI  $< 27$ kg / m<sup>2</sup>, not to achieve SVR. (OD: 2.58, CI 95%: 1.59-5.67).

### d) Biochemical profile in baseline

Many studies have concluded that the level of ALT in baseline does not predict SVR in multilogistic regression (10,40). We confirmed this result in our study. The median  $\pm$  STD of ALT in SVR group was 114.4 $\pm$ 136.4 and in Non-SVR 77.8 $\pm$ 49.14 without statistical differences between the groups (p=0.079). On the other hand in some studies low pretreatment serum of GGT levels significantly and independently are associated with SVR in multivariate regression analyses due to the relationship between serum GGT levels and hepatic steatosis, advanced fibrosis, and insulin resistance (41, 42). GGT participates in the transfer of amino acids across cell membrane, and also in glutathione (an anti-oxidant) metabolism. The induction of GGT is an adaptive response against oxidative stress elicited by lipid peroxidation in the presence of hepatic steatosis (43). In our study the group with Non- SVR had higher levels of GGT than SVR and these differences were significant (82.9 $\pm$ 62.7 vs 56.56 $\pm$ 57.55; p=0.04)

Several studies indicate that high pretreatment low density lipoprotein cholesterol (LDLc) and TC (Total cholesterol) levels are associated with higher rates of SVR in multivariable analyses (44, 45, 46, 47). In patients with chronic hepatitis C, serum lipid levels have been reported to be correlated with specific cytokines that may have antiviral activity, including tumor necrosis factor- $\alpha$  and interleukin-6 (48). This hyperlipidemia induced increase in cytokine levels may have a favorable and potentially additive effect on antiviral treatment in patients with chronic hepatitis C. Another proposed mechanism may be related to a possible regulatory effect of cholesterol in HCV binding to cell surface receptors, which in turn may be relevant to viral clearance (49). The LDL receptor, a membrane glycoprotein, has been shown to be involved in HCV entry into hepatocytes, and data suggest that HCV RNA levels correlate with LDL receptor expression (50, 51). Elevated serum concentrations of LDL may decrease the number of LDL receptors located on hepatocytes. A cut-off value of total cholesterol of 177 mg/dL was proposed in a study made by Naota Taura et al. (52). This cut-off value of total cholesterol level was lower than other previous studies (46,47). In our study we propose a cut-off value of cholesterol of 150 mg/dl.



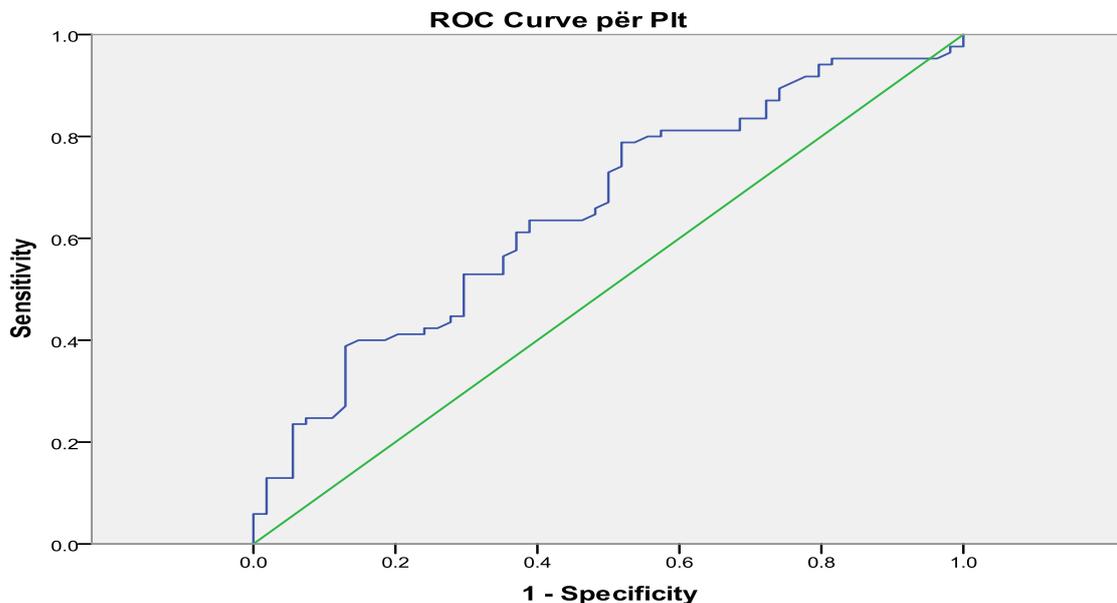
Diagonal segments are produced by ties.

**Graph 1: ROC curve for Cholesterol**  
 (Area under the curve is 0.693;  $p=0.003$ ; Cut-off value is cholesterol=150 mg/dl)

**e) Hematological profile at baseline**

The number of platelets in baseline may predict response to antiviral therapy. Thrombocytopenia occasionally accompanies advanced chronic liver diseases (53), therefore should have a lower response rate to therapy and also is related to antiviral therapy as a serious side effect which

may lead to dose modifications or treatment interruption (54, 55, 56). In our study we confirmed this result and also proposed a cut-off value of PLT of 173000/mm<sup>3</sup>. Regardless to WBC and HB at baseline there were no significant differences between the two groups.



Diagonal segments are produced by ties.

**Graph 1: ROC curve for PLT**  
 (Area under the curve is 0.656;  $p=0.002$ ; Cut-off value is PLT=173000/mm<sup>3</sup>)

**6. Conclusion**

Higher BMI levels at baseline ( $\geq 27$  kg/m<sup>2</sup>), lower level of TC, lower level of PLT and higher level of GGT are significant negative baseline predictors of SVR. Age and gender are not significant predictors of treatment response in CHC patients in Albania although younger female patients < 45 ys/old tend to respond better than males of the same age and older males have greater chances of achieving SVR than

younger males related this to the greater percentage of genotype 1b in younger age in Albania.

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