# Predictive factors for achieving sustained virological response among patients with chronic Hepatitis C treated with pegasys interferon and ribavirine

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## Abstract

**Aim**: A number of factors influence response to therapy among chronic hepatitis C patients treated with Peginterferon alfa-2a and Ribavirine. Predictors of treatment success in routine clinical practice remain to be established. The aim of this study was to assess the effects of host and viral related factors during treatment of chronic hepatitis C.

**Methods**: A total of 80 patients, diagnosed with CHC, were included in this prospective study during the period 2008-2012. All the patients were treated with Peginterferon alfa-2a (180 μg s.c/week) and Ribavirine 800-1200 mg/day (according to body weight and genotype). The duration of treatment varied from 24-48 weeks according to the virological response. The primary end point was SVR defined as undetectable HCVRNA level 24 weeks after the end of treatment. We assessed the impact on SVR of age (<40, 40-55 and >55 years), sex (males vs. females), BMI (<27 vs. >27), genotype (1+4 vs. 2+3) and baseline viral load (HCVRNA>800000 UI/ml vs. HCVRNA<800000 UI/ml). Data were analyzed statistically by use of T-test.

**Results:** Regardless the genotype, 47(58.75%) patients had SVR and 33 (41.25%) had non-SVR. 55.3% of females and 44.7% of males achieved SVR, without significant differences between them. The rates of SVR in groups of patients <40, 40-55 and >55 years were 53%, 59% and 73.3%, respectively, with significant differences between group 1 and group 3 (P= 0.03). Conversely, the prevalence of genotype 1b in group 1 was higher than in group 3 (79% vs. 34%, P<0.001). The group of patients with BMI<27 had a SVR rate higher than those with BMI>27 (72% vs. 50 %, P<0.05). The patients with genotypes 2 and 3 had higher

SVR rates than those with genotypes 1 and 4 (83% vs. 48%, P< 0.01). Patients with baseline HCVRNA<800000UI/ml had higher SVR rates than those with HCVRNA>800000 (P<0.01). **Conclusion**: BMI< 27, genotype 2 and 3, and low viral load at baseline (< 800000UI/ ml) should be considered as positive predictive factors in CHC treatment response, whereas there is no significant difference between males and females regarding the SVR rate. Importantly, age < 40 years does not seem to be a positive predictive factor in our country, which may be explained by the high prevalence of genotype 1b in this group of patients.

**Keywords**: hepatitis C, host and viral factors, SVR.

## Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide (1). It is estimated that approximately 130–210 million individuals, i.e. 3% of the world population, are chronically infected with HCV (2). In Western Europe, HCV prevalence ranges from 0.4% to 3.0%. It is higher in Eastern Europe and the Middle East, but the exact numbers are not well-documented. Prior to the 1990s, the principal routes of HCV infection were via blood transfusion, unsafe injection procedures, and intravenous drug use. These modes of acquisition are estimated to account for approximately 70% of cases in industrialized countries. Screening of blood products for HCV by means of enzyme immunoassays and, in a number of European countries, nucleic acid testing, has virtually eradicated transfusion-transmitted hepatitis C. Currently, new HCV infections are primarily due to intravenous or nasal drug use, and to a lesser degree to unsafe medical or surgical procedures. Parenteral transmission via tattooing or acupuncture with unsafe materials is also implicated in occasional transmissions. The risk of perinatal and of heterosexual transmission is low, while recent data indicate that promiscuous male homosexual activity is related to HCV infection (3-5). Acute HCV infection is asymptomatic in 50-90% of the cases. An average of 26% of the patients with acute hepatitis C (range 20%-67%) experience spontaneous clearance of the virus, an event that occurs primarily during the first three months after clinical onset of the disease. It seems that spontaneous resolution occurs more frequently in the presence of symptomatic disease. Interestingly, several reports have now stated that a strong and multi-specific cellular immune response is an important host factor for spontaneous viral eradication. If viremia persists for more than six months, chronic disease should be considered (6).

The severity of the disease associated with HCV infection varies from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma. Liver disease progression takes place over several decades, and is accelerated in the presence of cofactors such as alcohol consumption, diabetes mellitus (to which HCV itself appears to predispose), older age of acquisition, HIV or other hepatotropic virus co-infections. Depending on the presence of co-factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur at an incidence of approximately 4% per year, whereas HCC occurs in this population at an estimated incidence of 1%-5% per year (1).

The combination of pegylated interferon (IFN)-a and ribavirin is the approved and well-accepted standard-of-care (SoC) for chronic hepatitis C (7,8). The primary goal of HCV therapy is to cure the infection, which results in eliminating detectable circulating HCV after cessation of treatment. Sustained virological response (SVR) is defined as an undetectable HCV RNA level (< 50 IU/ ml) 24 weeks after treatment withdrawal. The factors that determine the likelihood of achieving SVR are called predictors of response. They can be classified as viral- or host-related, or as pre- or on-treatment factors depending on the time point of evaluation. In the pegIFN/ RBV dual therapy, predictors of response help the patient and the physician to decide

whether or not to start treatment, because the treatment of this therapy is costly and is associated with several side effects and also can help to predict the chance of each patient to respond to the treatment. Nowadays, where triple therapies and interferon free regimens are present, it is possible, in naive patients, to predict response to dual, triple or other new therapies and choose between them.

***Aim of the study:*** The primary aim of this study was to determine the impact of viral and host factors in predicting SVR rates in HCV treatment in Albania.

## Methods

A total of 80 patients diagnosed with CHC [41(51.2%) females and 39 (48.8%) males with a mean age of 43.3± 12.7 years] were included in this prospective study during the period 2008-2012.

The study was approved by the Albanian Committee of Medical Ethics. All participants who agreed to take part in the study gave written consent after being informed about the aims and procedures of the study.

Chronic HCV infection was defined as both positivity of Anti-HCV and serum HCVRNA > six months. The patients included in the study had no absolute contraindication to long acting interferon and ribavirin therapy i.e. uncontrolled depression, psychosis, or epilepsy; uncontrolled autoimmune diseases; cirrhosis (Child–Pugh B7 or more); pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease and also were not included in the study patients with end stage renal disease and hemoglobinopathies.

All the patients were treated with Peginterferon alfa-2a (180μg s.c/ week) and Ribavirine 800-1200 mg/ day (according to body weight and genotype). The duration of treatment varied from 24-48 weeks according to the virological response. The primary end point was SVR defined as undetectable HCVRNA level 24 weeks after the end of treatment. Patients were evaluated at baseline with AST, ALT, GGT, WBC, Hb, PLT, HCVRNA, age, sex, weight, height, and at weeks 4, 12, 24 (genotype 2/ 3) 48 (gen 1/ 4) and 24 weeks after end of treatment. We divided the patients into three groups according to age (< 40, 40-55, > 55 years) and analyzed the distribution of genotypes in each of the groups and the SVR rates. We also evaluated the impact on SVR rate of gender (males vs. females), BMI (< 27 vs. > 27), genotype (1+ 4 vs. 2+ 3) and baseline viral load (HCVRNA> 800000 UI/ ml vs. HCVRNA< 800000 UI/ ml).

Data were analyzed statistically by T-test and univariate logistic regression. P≤0.05 was considered statistically significant.

## Results

From 80 patients included in the study 41(51.2%) were females and 39 (48.8%) were males with an overall mean age of 43.3± 12.7 years. Regardless the genotype, 47 (58.75%) of the patients had SVR and 33 had non-SVR (41.25%). Female patients had higher SVR rates than males (55.3% vs. 44.7%), but without significant differences between them. The rates of SVR in the groups of patients < 40 years, 40-55 years and > 55 years were 53%, 59% and 73.3%, respectively, with significant differences between the group 1 and group 3 (P= 0.03). The prevalence of genotype 1b in the group 1 was higher than in group 3 (79% vs. 34%, P<0.001). The group of patients with BMI< 27 had a SVR rate of 72%, while in those with BMI>27 this rate was 50%, with significant differences between the groups (P< 0.05). The patients with genotypes 2 and 3 had higher SVR rates than those with genotypes 1 and 4 (83.3% vs. 48.1%, P< 0.01). Patients with baseline HCVRNA< 800000UI/ ml had higher SVR rates than those with HCVRNA> 800000 (72.3% vs. 40.6%, P< 0.01).

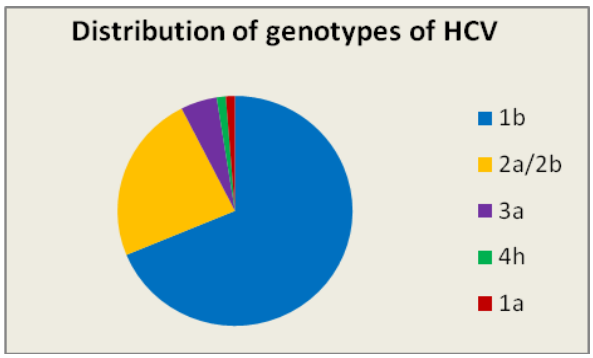
## Discussion

A number of factors influence response to therapy among chronic hepatitis C patients treated with Peginterferon alfa-2a and Ribavirine. We will analyze the specific impact of predictor factors (viral and host) which are assessed in routine clinical HCV treatment in Albania and explain their values for a successful treatment of our patients.

***Viral factors***

***HCV genotype:*** The distribution of genotypes among patients included in the study were: 1b (68.75 %), 2a/ 2c (23.75%), 3a (5%), 4h (1.25%) and 1a (1.25%) [Figure 1].

**Figure 1. Distribution of genotypes of HCV**




It is clear that the most prevalent genotype in Albania is 1b. Genotype 1 (subtypes 1a and 1b) is by far the most prevalent genotype worldwide, with a higher prevalence of 1b in Europe and 1a in the US. Genotype 3a is highly prevalent in European intravenous drug users. This group is currently experiencing an increasing incidence and prevalence of infections related to HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are more rarely found (1). In the pivotal clinical trials for registration of pegylated IFN-a and ribavirin therapy, SVR was achieved in 46%-54% of patients infected with HCV genotype 1 treated with pegylated IFN-a-2a (180 microgram/ week) plus weight-based ribavirin (0.8-1.2 g/day) for 48 weeks. In patients infected with HCV genotypes 2 and 3, SVR was achieved in these trials in 65%-82% of cases treated for 24 weeks (1). Our study confirmed that genotype of HCV is one of the strongest baseline predictors for SVR (83.3% versus 48.1%, P< 0.05; respectively for genotypes 2/ 3 and 1/4).

***Baseline HCV Viral Load:*** HCV RNA levels before initiating treatment predict the likelihood of obtaining SVR with pegIFN/ RBV dual therapy (9). According to EASL guideline there is no current agreement on the most discriminatory HCV RNA level, which ranges between 400,000 and 800,000 IU/ ml. In our study resulted that baseline viremia <800,000 UI/ ml should be considered in the routine clinical assessment as a strong positive predictor factor.

***Virological response during therapy:*** The monitoring of on-treatment viral responses has become a vital aspect of treatment regimens and allows prediction of the treatment response, therapy adjustments, and development of stopping rules governing cessation of therapy. A clear relationship has been established between the time to viral negativity and SVR. The on- treatment monitoring concepts are as follows:

· Rapid virological response (RVR): HCV RNA negative (<50 IU/ mL) after 4 weeks of therapy.

· Early virological response (EVR): viral response at 12 weeks, subdivided into:

· Partial EVR (p-EVR): HCV RNA >2-log drop, but still detectable at week 12.

· Complete EVR (c-EVR): no RVR, but HCV RNA <50 IU/ mL at week 12.

· Non-response: persistent or inadequate reduction in HCV RNA during therapy, subdivided into:

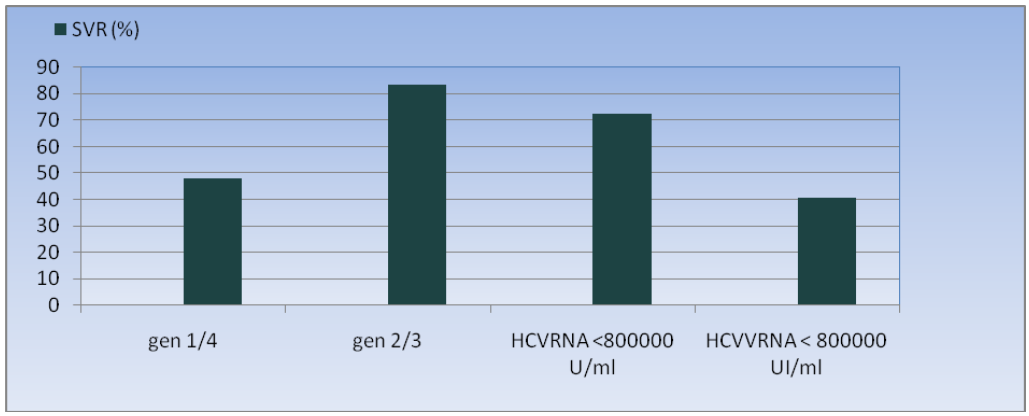
· Null response: either <1-log decrease in HCV RNA at week 4 or <2-log decrease in HCV RNA by week 12.

· Partial response: greater than a 2-log decrease by week 12, but continued viral positivity at week 24.

Patients who initially achieve serum viral negativity by week 4 (RVR) or week 12 (c-EVR) have 91% and 60% to 72% SVR rates. In our study, HCVRNA in week 4 was performed in 44 patients; 50% of them had RVR and 86% of patients with RVR achieved SVR (Figure 2). HCVRNA at week 12 was performed in 72 patients and 78% of those who achieved c-EVR resulted with SVR. Patients who decrease their viral loads by 2 logs following 12 weeks of treatment and who achieve viral negativity by week 24 are referred to as slow responders and have much lower rates of SVR (35% to 45%). Patients who do not achieve a 2-log reduction by week 12 or viral negativity by week 24 have only a 2% chance of achieving SVR with therapy, and treatments are therefore typically stopped. RVR is the best predictor of SVR during treatment of CHC

with peg interferon and ribavirine (1).

**Figure 2. Impact of viral factors on SVR**




***Host factors***

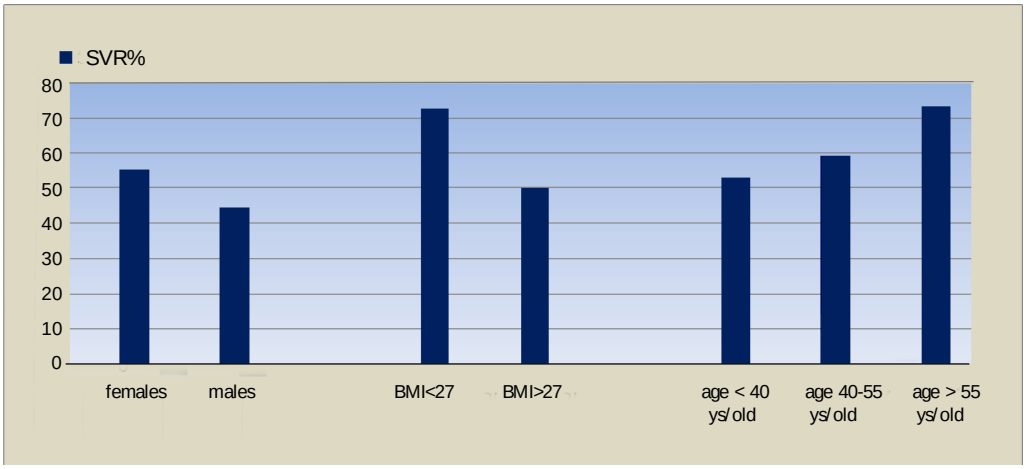
***Age:*** Patient age is another factor that is associated with responsiveness to Peg-IFN-α/ RBV therapy in chronic HCV infection Univariate and multivariate analyses performed in most of the randomized control trials in patients treated with pegIFN/ RBV dual therapy showed that younger age significantly correlated with the likelihood of obtaining SVR. Furthermore, higher SVR rates were obtained in patients younger than 40–45 years (10). One of the most important result in our study was that the prevalence of gen 1b in younger patients (aged < 40 years) was significantly higher than in older patients (>55 years; P<0.001). This is the reason why in HCV treatment in Albania age < 40 years seem to be not a positive predictor factor for SVR. This result emphasizes the importance of preventing HCV infection in youngsters by promoting the information about ways of transmission of HCV, as long as we don't have yet vaccination against HCV infection (1).

***Gender:*** Despite a previous large analysis (N=1744) on two trials involving standard IFN plus RBV therapy that showed a significant positive correlation between female gender and SVR (P< 0.004) (11) no such difference has been confirmed in studies involving Peg-IFN plus RBV (12-16). In accordance to these studies female patients in Albania tend to have greater SVR rates than males for all genotypes but without significant differences. We evaluated the side effects occurred in non SVR patients and resulted that the group of females with non SVR had more side effects during treatment than males with non SVR, especially serious side effects: hematologic (anemia, thrombocytopenia, leucopenia), depression, interstitial pneumonia that lead to treatment suspension in 33.3% of them while in males treatment was interrupted only in one patient.

**BMI***:* Body weight (BMI) adversely influences the response to pegylated IFN-á and ribavirin, even after dose adjustment for IFN and ribavirin (17). According to study conducted by K.-Q. Hu et al being overweight/ obese (BMI > 25) serves as an independent risk factor for hepatic steatosis in U.S. patients with CHC. Steatosis accelerates activity and progression of CHC, and is independently associated with stage III/IV hepatic fibrosis in these patients (18). Studies show that severe fibrosis or cirrhosis seen on liver biopsy is associated with a reduced rate of sustained viral response when treatment with IFN and ribavirin (19). Also this effect of steatosis in SVR, however, is more pronounced in patients with the non-3a genotype (20), implicating insulin resistance (IR) as the mechanism that affects the response to IFN-á and suggesting that viral steatosis (genotype 3a) does not impair the response to treatment (21). IR is known to increase hepatic lipid synthesis (22). Since the lipid droplet is an important organelle for HCV replication (23), the accumulation of hepatic lipid droplets may increase HCV replication and result in poor responses to antiviral treatment. Similarly individuals with T2DM are less likely to achieve SVR

(24). As steatosis correlates with BMI, importantly, our study showed that patient with BMI>27 had significantly lower SVR rates, which emphasizes the recommendation of EASL guidelines that body weight reduction in overweight/obese patients prior to therapy may increase likelihood of SVR (1). Also it is important that patients should be counseled to abstain from alcohol during antiviral therapy because it is known that individuals with chronic hepatitis C who drink more than 30-50 g per day increase their risk of developing fibrosis approximately four-fold (25).

**Figure 3. Host factors impact on SVR**




## Conclusion

During treatment of HCV in Albania we must consider BMI<27, genotype 2 and 3, and low viral load at baseline (<800 000 UI/ml) as positive predictive factors in CHC treatment response. On the other hand, gender does not predict the SVR rate. Importantly, age <40 years does not seem to be a positive predictive factor in Albania, which may be explained by the high prevalence of genotype 1b in this group of patients.

**Conflicts of interest:** None declared.

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