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First Week HCV RNA Level Under the Pegylated Interferon and Ribavirin Treatment Predicts Sustained Virological Response

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This study was planned to investigate whether the decrease in the hepatitis C virus (HCV) RNA levels at the first week of combined pegylated interferon and ribavirin treatment of naive genotype 1 patients with HCV was predicting sustained virologic response (SVR). Fifty-two patients were enrolled into the study. HCV RNA levels were measured at the baseline, first, fourth, and 12th weeks of treatment. Thirty-four patients achieved SVR, which basal, first week, and fourth week HCV RNA levels were log 5.57, log 3.65, and log 1.92, respectively. Eighteen patients could not achieve SVR, which basal, first week, and fourth week HCV RNA levels were log 6.22, log 5.45, and log 3.84, respectively ($P < 0.05$). Patients were distributed in 2 groups according to the amount of decrease in HCV RNA levels at the first week as less or more than 1.5 log. There were 20 patients with ≥1.5 log decrease in the HCV RNA levels at the first week. They were named as patients with very rapid virologic response (VRVR). All patients (100%) with VRVR were achieved SVR. In only 14 (44%) of the 32 patients without VRVR, SVR was achieved. In 16 (84%) of the 19 patients with rapid virologic response and 33 (79%) of the 42 patients with early virologic response, SVR was achieved. A ≥1.5 log decrease (VRVR) in HCV RNA levels of patients with HCV at the first week of combined pegylated interferon and ribavirin treatment predicts SVR very strongly.

Keywords: hepatitis C, HCV RNA, sustained virologic response, very rapid virologic response

INTRODUCTION

Chronic hepatitis due to hepatitis C virus (HCV) is one of the major causes of liver cirrhosis and hepatocellular carcinoma. Nowadays, the treatment of HCV was rapidly changing and improving. The combined pegylated interferon and ribavirin treatment is one of the main treatment modalities, which arrest the progression of the disease by providing sustained virologic response (SVR). Hence, reaching the newly developed antiviral treatments was not universally possible, treatment with pegylated interferon and ribavirin is a treatment modality that can still be used in naive patients.

Using the combined pegylated interferon and ribavirin treatment, an SVR of 40%–60% in HCV genotypes 1 and 4 and an SVR of 70%–90% in patients with HCV genotypes 2 and 3 can be achieved.[1,2] Beside the genotype, the treatment-related decrease rate of HCV RNA levels also affects the SVR rates.[3,4] Rapid virologic response (RVR) is the name given to the HCV RNA negativity at the fourth week of treatment. Early virologic response (EVR) means that

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HCV RNA level has dropped ≥2 logs or is undetectable at the 12th week of therapy, defined as partial EVR or complete EVR, respectively. Both RVR and EVR are known as the factors that can predict SVR.[5,6]

SVR is found to be less than 5% when HCV RNA regressed less than 1 log in the fourth week[7] and is reported as 33% and 75% in patients who achieved partial and complete EVR at the end of 12th week, respectively.[8] Treatment guidelines recommend that the treatment of HCV should be adjusted according to the response of the patient to the treatment. Stopping the pegylated interferon and ribavirin treatment is recommended when 12th week HCV RNA shows less than 2 log decrease or 24th week HCV RNA is still positive.[9]

There are 2 studies in the literature reporting first week HCV RNA decrease under combined pegylated interferon and ribavirin treatment.[10,11] But they do not establish any relation between first week HCV RNA level and SVR. Predicting the possible SVR rate of combined pegylated interferon and ribavirin treatment by the response of the first week can help us to distinguish the patients who would give good response or not give any response to the combined pegylated interferon and ribavirin treatment. Distinguishing patients at the first week of treatment gives us chance to treat only those patients who will achieve SVR and also will prevent ineffective treatment efforts that have many side effects, very early, just at the beginning of the treatment.

This study was planned to detect the predictive value of first week HCV RNA levels under combined pegylated interferon alpha 2a/2b and ribavirin treatment of patients with naive genotype 1 HCV in demonstrating SVR. We planned to investigate whether the decrease in the HCV RNA levels at the first week of treatment was predicting SVR or not and compare with SVR rates of patients with RVR and EVR.

MATERIALS AND METHODS

Study design and selection of patients

Treatment of patients with naive genotype 1 HCV aged between 18 and 70 years who admitted to Gastroenterology Clinic of Sisli Hamidiye Etfal Education and Research Hospital between the years 2010 and 2012 and who had positive for anti-HCV and HCV RNA were enrolled into the study. Patients who have hepatitis B virus and/or HIV coinfection, chronic alcohol consumption, autoimmune, renal, cardiovascular or psychiatric diseases, and decompensated cirrhosis were excluded from the study. A total of 56 patients were enrolled to the study, but there had been 4 patients who begun to the treatment but could not complete the combined treatment of pegylated interferon and ribavirin because of hematologic and psychiatric side effects. These patients were also excluded, and the study was conducted with the remaining 52 patients who completed the treatment.

The selection of pegylated interferon type was performed randomly. The treatment of pegylated interferon alpha 2a 180 mcg or pegylated interferon alpha 2b 1.5 mcg/kg subcutaneous injection per week and weight adjusted ribavirin (>75 kg 1200 mg/d, <75 kg 1000 mg/d) was given to the patients for 48 weeks. All the patients finished the 48 weeks of treatment with pegylated interferon and ribavirin. During the treatment, the dose of ribavirin had been decreased to 800 mg/d in those patients whose hemoglobin levels had decrease to under 10 g/dL. Erythrocyte replacements were used when hemoglobin levels decrease under 8 g/dL. The lowest dose of the ribavirin was 800 mg/d for all of the patients.

Aspartate aminotransferase to platelet ratio index (APRI) score was used to determine the fibrosis levels of the patients at the beginning of the treatment. HCV RNA levels were measured at the baseline and at the first, fourth, 12th, 24th, and 48th week of treatment and 24th week after the end of the treatment. Ethical approval was obtained from the local ethical committee. Written informed consent was taken from all of the patients before the beginning of the treatment. The guidelines issued in Helsinki Declaration by World Medical Association and in Good Clinical Practices and Good Laboratory Practices by World Psychiatry Association were followed during the study.

Laboratory evaluation

Anti-HCV antibody second generation was measured using enzyme-linked immune sorbent assay. HCV RNA level was measured using quantitative real-time polymerase chain reaction (COBAS TaqMan PCR assay amplifier HCV test 2.0; Roche diagnostics); the limit of detection was between 15 IU/mL and 69×10^6 IU/mL. Genotype analysis was performed using a hybridization technique (Inno-LiPA HCV assay Innogenetics SA, Ghent, Belgium).

Statistical analysis

The statistical analysis was performed using SPSS program version 21.0 (IBM Inc, Chicago, IL). The compatibility of the data to normal distribution was evaluated by visual and analytic methods. For the comparison of intergroup categorical rates according to response with the treatment, Pearson χ^2 test and Fisher exact test were used. Mann Whitney U test was used for comparison of nonparametric data.

Spearman correlation analysis was used for the correlation analysis. The capacity of decrease in the first week HCV RNA values in predicting SVR was analyzed using receiver operating characteristic curve analysis. When a significant cutoff value was observed, the sensitivity, specificity, and positive and negative predictive values were presented. Although evaluating the area under the curve, a 5% type I error level was used to accept a statistically significant predictive value of test variables. All assessments were performed at 95% confidence interval, and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 52 patients (31 female and 21 male) were evaluated in this study. Average age of the patients was 50.2 ± 13.2 years. Eight (15.3%) of the patients had diabetes. Pegylated interferon alpha 2a was used in 29 (56%) of the patients and pegylated interferon alpha 2b in 23 (44%) of the patients. The baseline clinical and laboratory data of the patients are given in Table 1.

In 34 (65%) of 52 patients, SVR was achieved (Table 2). The average age of patients who achieved SVR was 48 ± 14.3 years, whereas the average age of patients who had not achieved SVR was 53 ± 10.6 years. SVR was achieved in 61% (19/33) of female patients and in 71% (15/21) of male patients. The body mass index (BMI) of SVR positive group was 25.7 ± 4.1 kg/m^2 and SVR-negative group was 26.9 ± 3.68 kg/m^2. When we evaluate the type of interferon used, we detect 66% (19/29) SVR in the pegylated interferon alpha 2a group and 65% (15/23) SVR in the pegylated interferon alpha 2b group. All of these differences were statistically insignificant. Also APRI score, thrombocyte count, alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) levels were similar. Although fasting blood glucose level of the SVR-negative group (118 ± 48 mg/dL) was higher than the SVR positive group (93 ± 20 mg/dL), it cannot reach statistical significance ($P = 0.06$). Although only 3/8 (38%) of the patients with diabetes achieved SVR, 31/44 (%70) of the patients without diabetes achieved SVR ($P = 0.07$).

Table 1. Clinical features of 52 patients at the beginning of the treatment.

Age	50 ± 13.2
Gender, n (%)	
Male	21 (40)
Female	31 (60)
HCV RNA (log IU/mL)	5.79 ± 0.63
ALT (U/L)	60 ± 39.1
AST (U/L)	46 ± 25.0
GGT (U/L)	49 ± 33.6
Thrombocyte ($10^3/\mu L$)	221 ± 77.2
APRI score	0.60 ± 0.42
Fasting plasma glucose (mg/dL)	101 ± 34
BMI (kg/m^2)	26.1 ± 3.4
Diabetes mellitus, n (%)	
Present	8 (15)
Absent	44 (85)
Pegylated interferon, n (%)	
Alpha 2a	29 (56)
Alpha 2b	23 (44)

Values are given as mean ± SD or number and percentage.

Basal, first, and fourth week HCV RNA levels of the SVR positive and negative groups are shown in Table 3 and Figure 1A. Basal, first, and fourth week HCV RNA levels of the SVR positive group were 5.57 ± 0.52 log, 3.65 ± 1.33 log, and 1.92 ± 1.54 log, respectively and 6.22 ± 0.59 log, 5.46 ± 0.81 log, and 3.84 ± 1.73 log, respectively, for SVR-negative group. The difference between the HCV RNA levels was statistically significant at all time periods ($P = 0.043$, $P < 0.001$, $P < 0.001$, respectively). Decrease in HCV RNA level of the SVR positive group was 1.92 log in the first week and 3.65 log in the fourth week. Same values for SVR-negative group were 0.76 log and 2.33 log, respectively ($P < 0.001$).

We performed receiver operating characteristic analysis for obtaining a cutoff value for first week HCV RNA decrease level in predicting SVR. We detect that, a ≥1.5 log decrease in HCV RNA level at the first week of treatment was predicting SVR with 100% specificity and 58.8% sensitivity. Positive predictive value was 100%, and negative predictive value was 56.3% (area under the curve value was 0.848, $P < 0.001$) (Figure 2). So, we distributed the patients into 2 groups according to the amount of decrease in HCV RNA levels at the first week as less or more than 1.5 log. There were 20 patients with ≥1.5 log decrease in the HCV RNA levels at the first week. They were named as patients with very rapid virologic response (VRVR). All patients (100%) with VRVR were achieved SVR. In only 14 (44%) of the 32 patients without VRVR, SVR was achieved.

The clinical and laboratory values of VRVR-positive and VRVR-negative groups were given at Table 4. HCV RNA levels at the baseline, first, and fourth weeks of treatment of patients with VRVR were 5.67 ± 0.53 log, 3.01 ± 1.36 log, and 1.41 ±

Table 2. Clinical and laboratory features of the SVR (+) and SVR (−) groups.

	SVR (+) (n = 34)	SVR (−) (n = 18)	*P*
Age	48 ± 14.3	53 ± 10.6	0.39
Gender, n (%)			
Female	19 (55)	12 (66)	0.55
Male	15 (45)	6 (34)	
APRI	0.55 ± 0.35	0.70 ± 0.53	0.65
BMI (kg/m^2)	25.7 ± 4.1	26.9 ± 3.68	0.29
ALT (U/L)	60 ± 33	60 ± 30	0.29
Thrombocyte (×10^3/μL)	229 ± 84	205 ± 61	0.51
GGT (U/L)	44 ± 32	57 ± 34	0.13
Pegylated interferon alpha, n (%)			
2a	19 (55)	10 (56)	0.9
2b	15 (45)	8 (44)	
Fasting plasma glucose (mg/dL)	93 ± 20	118 ± 48	0.06
HCV RNA basal (log IU/mL)	5.57 ± 0.52	6.22 ± 0.59	**0.043**
Diabetes mellitus, n (%)			
Present	3 (9)	5 (28)	0.07
Absent	31 (91)	13 (72)	
VRVR, n (%)			
Present	20 (59)	0 (0)	<**0.001**
Absent	14 (31)	18 (100)	
RVR, n (%)			
Present	16 (47)	3 (17)	0.04
Absent	18 (53)	15 (83)	
EVR, n (%)			
Present	33 (97)	9 (50)	<**0.001**
Absent	1 (3)	9 (50)	

Values are given as mean ± SD or number and percentage. Bold values indicate statistical significance.

1.41 log, respectively. Same values for the VRVR-negative group were 5.87 ± 0.8 log, 5.03 ± 0.86 log, and 3.31 ± 1.71 log, respectively (Figure 1B; Table 5). Although the difference between the HCV RNA levels at the baseline was statistically insignificant ($P = 0.09$), the difference was significant both at the first ($P < 0.001$) and fourth week ($P = 0.008$). Decrease in HCV RNA level of the VRVR-positive group was 2.66 log in the first week and 3.75 log in the fourth week. Same values for VRVR-negative group were 0.84 log and 2.56 log, respectively ($P < 0.01$). Age and gender distribution, APRI score, BMI, fasting blood glucose,

Table 3. The change in HCV RNA levels of SVR (+) and SVR (−) groups.

	SVR (+) (n = 34)	SVR (−) (n = 18)	*P*
Baseline HCVRNA (log IU/mL)	5.57 ± 0.52	6.22 ± 0.59	0.043
First week HCVRNA (log IU/mL)	3.65 ± 1.33	5.46 ± 0.81	<**0.001**
Fourth week HCVRNA (log IU/mL)	1.92 ± 1.54	3.84 ± 1.73	<**0.001**

Values are given as mean ± SD or number and percentage. Bold values indicate statistical significance.

thrombocyte count, ALT, and GGT levels of the VRVR-positive and VRVR-negative groups were similar (Table 5). Also, the type of the interferon used shows similar distribution.

There were 19 patients who achieved RVR and 42 patients who achieved complete EVR in our group. In 16 (84%) of the 19 patients with RVR and 33 (79%) of the 42 patients with EVR, SVR was achieved. Although 55% (18/33) of patients with RVR negative achieved SVR, only 10% (1/10) of the patients with EVR negative achieved SVR (Figure 3).

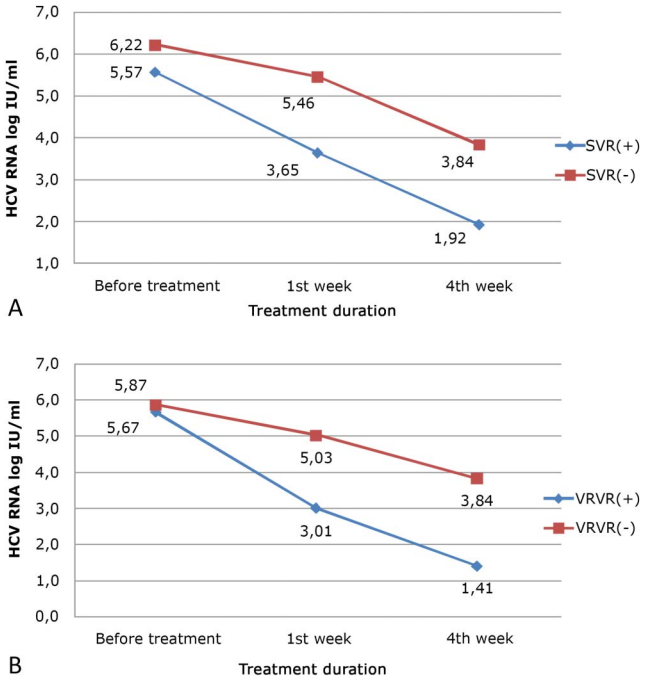

FIGURE 1. (A) Graphic demonstrating the HCV RNA decreases of the SVR-positive and SVR-negative groups. (B) Graphic demonstrating the HCV RNA decreases of the VRVR-positive and VRVR-negative groups.

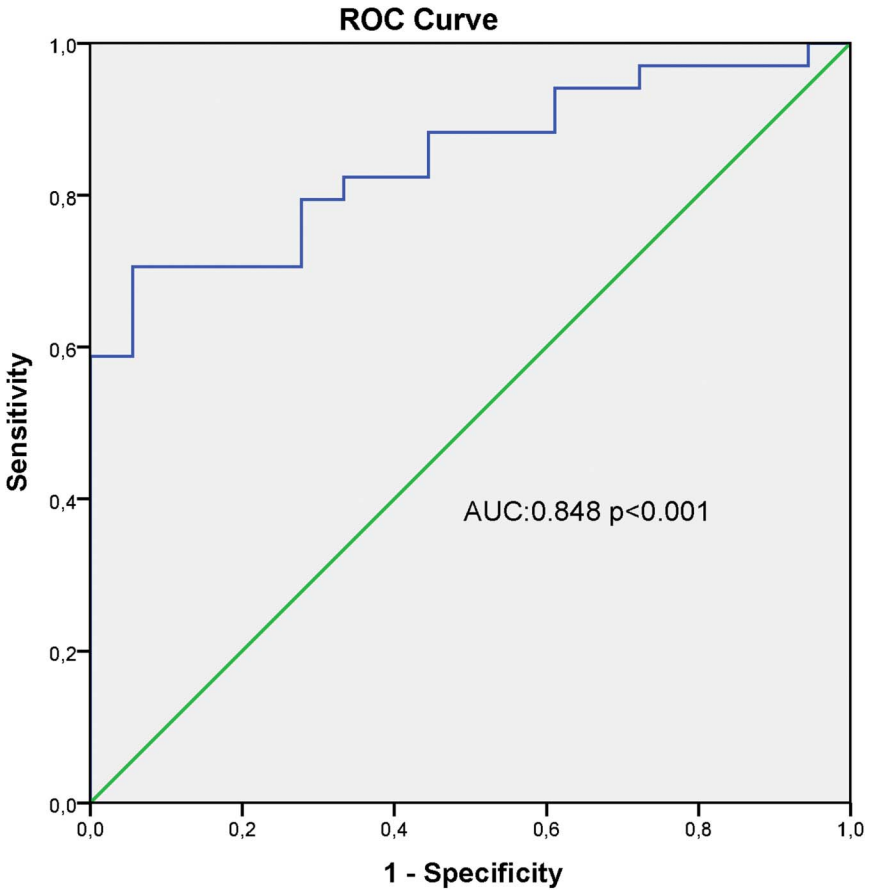

FIGURE 2. Illustration of area under the receiver operating characteristic curves for the prediction of SVR of the first week HCV RNA decrease level.

DISCUSSION

Combined pegylated interferon and ribavirin therapy is being used for curative treatment of chronic HCV for a long time. The expected SVR rate of combined pegylated interferon and ribavirin treatment was between 40% and 60% in patients with genotype 1 HCV.[1,8,12] In our study, we achieved 65% SVR with the same treatment. This rate was a little higher than the literature, which may be due to the ribavirin dose used. We prefer to use higher doses of ribavirin (>75 kg 1200 mg/d, <75 kg 1000 mg/d) and do not allow less than 800 mg ribavirin dose.

The host-related factors that affect SVR in HCV treatment are age, gender, BMI, interleukin (IL) 28 B gene mutation, ALT and GGT levels, thrombocyte count, fibrosis stage, presence of diabetes, and high basal fasting glucose levels.[13,14] In our study, higher fasting glucose level, high BMI, and the presence of diabetes were affecting the response rate negatively, but this difference was not statistically significant. The absence of statistically significant difference in terms of other factors may be due to low number of the patients. Noninvasive APRI score may be the cause of the statistically nonsignificant difference in terms of fibrosis. Lack of IL 28 B gene mutation assessment is one of the limiting parts of this study.

The factors related to HCV that affect the response to treatment are genotype, baseline viral load, and HCV RNA clearance rate with treatment.[15,16] In our study, all patients were genotype 1, and basal viral load was found significantly lower in the SVR group compatible with the literature.

It is known that the occurrence of RVR in the fourth week and/or EVR in 12th week predicts SVR.[17] In our study, complete EVR was achieved in 42 (80%) of 52 patients and SVR was achieved by 33 (79%) of patients with complete EVR. According to the literature, expected SVR rate was 68%–83% in complete EVR and 21%–29% in partial EVR, which was similar to our findings.[2] The reported RVR rate was between 15.1% and 43.5% in patients with genotype 1 HCV and in

Table 4. Clinical and laboratory features of the VRVR (+) and VRVR (−) groups.

	VRVR (+) (n = 20)	VRVR (−) (n = 32)	*P*
Age	48 ± 13.4	51 ± 13.1	0.96
Gender, n (%)			
Female	8 (40)	13 (40)	1.0
Male	12 (60)	19 (60)	
APRI	0.58 ± 0.43	0.61 ± 0.42	0.79
BMI (kg/m^2)	26.5 ± 3.9	25.9 ± 4.0	0.55
ALT (U/L)	61 ± 40	59 ± 39	0.25
Thrombocyte ($\times 10^3/\mu$L)	227 ± 85	217 ± 72	0.42
GGT level (U/L)	45 ± 38	51 ± 3.0	0.13
Pegylated interferon alpha, n (%)			
2a	11 (55)	18 (56)	1.0
2b	9 (45)	14 (44)	
HCV RNA (log IU/mL)	5.67 ± 0.53	5.87 ± 0.68	0.27
Fasting plasma glucose (mg/dL)	95 ± 25	105 ± 39	0.49
Diabetes mellitus, n (%)			
Present	3 (15)	5 (16)	1.0
Absent	17 (85)	27 (84)	

Values are given as mean ± SD or number and percentage.

patients who achieved RVR and SVR between 88% and 91% was expected.[18,19] Similarly, we detected 36% (19/52) RVR and 84% SVR in those patients who had achieved RVR in this study.

Suzuki et al[10] is one of the studies reporting the decrease in HCV RNA levels in the first week of combined pegylated interferon and ribavirin treatment. They found 1.3 log decrease in the first week and 1.6 log decrease in the fourth week in the responder group and 0.5 log and 0.7 log decrease, respectively, in the null-responder group. The differences between the responder and null-responder groups were reported as statistically significant. In another study, 1.8 log decrease in HCV RNA level at the first week and 2.8 log decrease at the second week of combined pegylated interferon and ribavirin treatment were detected in the responder group. Corresponding HCV RNA decrements were both 0.3 log at the first and second weeks in the null-responder group. The authors also showed that second week HCV RNA decrease value had similar predictive value with IL 28B gene mutation and mutant type of amino acid 70 substitution in the core region for predicting SVR.[11] In the study reported by Jeong et al, the authors use the term "very rapid virological response-VRVR" for the second week HCV RNA negativity. At this study, in which patients with genotype 1 with high viral load were excluded, the authors reported that patients who reached VRVR (HCV RNA negativity at second week) had achieved an 89% SVR with 12-week pegylated interferon monotherapy treatment and a 100% SVR with 24-week pegylated interferon monotherapy.[20] Similar to these studies, we detect 38% VRVR (≥1.5 log decrease in the HCV RNA levels at the first week) in which all of them (100% of patients with VRVR) achieved SVR.

The decrease in HCV RNA levels of patients with naive genotype 1 HCV at the first week of combined pegylated interferon alpha 2a/2b and ribavirin therapy strongly predicts the SVR. Predicting the SVR very early may help us to distinguish the patients who would not give any response to combined treatment and should wait for treatment modalities without interferon. Also, we can prevent unneeded treatment

Table 5. The change in the HCV RNA levels of the VRVR (+) and VRVR (−) groups.

	VRVR (+) (n = 20)	VRVR (−) (n = 32)	*P*
Baseline HCV RNA (log IU/mL)	5.67 ± 0.53	5.87 ± 0.68	0.09
First week HCV RNA (log IU/mL)	3.01 ± 1.36	5.03 ± 0.86	**<0.001**
Fourth week HCV RNA (log IU/mL)	1.41 ± 1.41	3.31 ± 171	**0.008**

Values are given as mean ± SD or number and percentage.
Bold values indicate statistical significance.

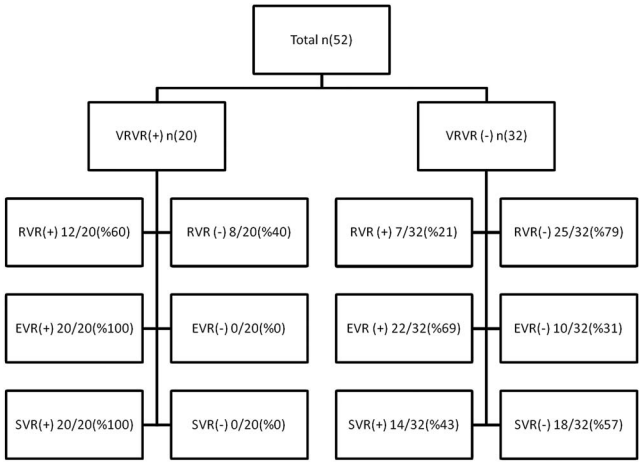

FIGURE 3. Graphic demonstrating SVR rates of the patients based on the development of VRVR.

with highly costing new oral antiviral agents in a special patient group who will respond very well to combined pegylated interferon and ribavirin treatment.

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