Annals of Digestive and Liver Disease

Research Article
Published: 27 Mar, 2019

A Predictive Scoring Model for Relapse in Chronic HCV Patients with Rapid Virologic Response to PEG Interferon/ Ribavirin Treatment

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Abstract

Background: Chronic hepatitis C is a major health problem in Taiwan, treatment is costly and has multiple side effects, identifying the predictors of relapse of the disease after achieving Rapid Virological Responses (RVR) to PEG Interferon/Ribavirin (PEG-IFN/RBV) treatment will help in better selection of patients and avoidance of unnecessary side effects.

Methods: This retrospective study was done on 818 chronic HCV patients, treatment-naive patients receiving PEG-IFN/RBV. Demographic and laboratory data were analyzed against relapse by univariate and logistic regression analysis. The feasibility of predicting treatment failure was using the baseline to build a risk scoring model for HCV patients with a RVR.

Results: The multi-variable logistic regression analysis showed that independent predictors of relapse were AST ≤ 40 IU/L, low platelet count, HCV genotype 1, high viral load, and clinical liver cirrhosis. A scoring model for prediction of relapse was calculated based on the regression coefficients of each predictor. The ROC curve for prediction of relapse by the score showed that the Area under the Curve (AUC) is 71.2. A cut off value of 15% had 73.49% sensitivity, 60.62% specificity, 92.57% negative predictive value and 25.52% positive predictive value.

Conclusion: A scoring model using AST ≤ 40 IU/L, low platelet count, HCV genotype 1, high viral load, and clinical liver cirrhosis during therapy can efficiently predict relapse.

Keywords: Risk scoring; Hepatitis C virus; PEG-interferon; Relapse; Rapid virological response

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Received Date: *04 Mar 2019*
Accepted Date: *21 Mar 2019*
Published Date: *27 Mar 2019*

Citation:
Chang K-C, Hu T-H, Lin M-T, Wu Y-Y, Yen Y-H, Tsaia M-C, et al. A Predictive Scoring Model for Relapse in Chronic HCV Patients with Rapid Virologic Response to PEG Interferon/Ribavirin Treatment. Ann Digest Liver Dis. 2019; 2(1): 1016.

Introduction

Chronic Hepatitis C Virus (HCV) infection is a common health problem affecting more than 180 million people infected in the worldwide [1,2]. Hepatitis C remains a challenge for mankind, because it's increasing the prevalence rate and potentially fatal long-term complications [3]. The virus have been identification, the efforts to find effective treatment are underway and a lot has been achieved i.e., combination therapy, pegylated Interferon with Ribavirin (PEG-IFN/RBV) to Directly Acting Antiviral (DAA) agents, introduced only recently [4].

Although the new therapeutic options are now available, the indications are usually restricted in the several categories of patients and the DAA agents cost is too high [5-10]. The PEG-IFN/RBV is likely to continue as the standard treatment available to patients with hepatitis C patients in Asia area [9]. However, the combination therapeutic regimens do not always furnish adequate rates of Sustained Virological Response (SVR) in all patient categories, showing large differences across HCV genotypes [11-14]. In addition, both drugs have some adverse side effects, which may lead to discontinue the treatment [11-15]. Moreover, any attempt to reduce the side effect and costs of antiviral treatment must be consideration. Therefore, the ideal therapeutic regimen should be based on optimize treatment duration and costs.

A Response-Guided Therapy (RGT) approach, where the optimized treatment duration is on the basis of early viral kinetics during the treatment, has been proposed as the best method to adjust treatment duration to the actual patient response probability [16-19]. Treatment duration can be reduced to 24 weeks in genotype 1 and to 12-16 weeks in genotypes 2 and 3 naïve patients, when baseline viremia is low than 400.000 IU/ml and a Rapid Virological Response (RVR) is observed [16-

20]. No treatment reduction can be considered in patients with HCV genotype 1and high baseline HCV RNA levels, advanced fibrosis or cirrhosis [20-23]. However, the relapse rate was about 0% to 18.8 % for HCV genotype 1 [21,22] and 0% to 15.5% for the genotype 2/3 who achieved RVR [21-23]. The shortening of therapy duration for HCV-infected patients with RVR is still controversial [21-23]. Early detection of relapse patients and continuing treatment for patients who are more likely to respond is of major importance in improving the outcome of patients with chronic HCV infection. Hence, accurate prediction of treatment response has become a major factor in the management algorithm for chronic HCV infection. Therefore, the objective of this analysis was to develop a model that used to identify more accurately the subset of RVR patients who may be candidates for intensified treatment and can potentially reduce their chance of relapse after 24 weeks of therapy.

The aim of the present study was to establish the risk score of failure among our treatment patients with chronic HCV treated with a combination therapy, and to identify any predictors of failure among patients with RVR.

Patients and Methods

The Bureau of National Health Insurance in Taiwan reimbursed HCV treatment with a universal 24-week regimen of peg-IFN/RBV, regardless of viral genotype and according the on-treatment responses, from November 2009 to December 2013. Eight hundred and eighteen patients who maintained 24-week treatment duration were included for analysis retrospectively and consecutively. Eligible subjects were treatment-naive and Serum Alanine Aminotransferase (ALT) levels were more than 40 IU/ml and were seropositive for HCV antibodies (Ax SYM HCV 3.0; Abbott's Laboratories, Chicago, IL, USA) and had detectable HCVRNA (Amplicor™; Roche Diagnostics, Branchburg, NJ, USA) for more than 6 months. Patients were excluded in case of following concurrent diseases or conditions: HBV co-infection, HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, α1-antitrypsindeficiency, decompensate cirrhosis, overt hepatic failure, a current or past history of alcohol abuse (≥ 20 g daily), psychiatric condition, previous liver transplantation, or with evidence of hepatocellular carcinoma. A liver biopsy was not obligatory. Liver Cirrhosis (LC) was diagnosed by ultrasound. All patients received either pegylated-IFN alfa-2a (Pegasys, F. Hoffmann-La Roche, Basel, Switzerland; 180 μg/week subcutaneously), or pegylated-IFN alfa-2b (Peg-Intron, Schering-Plough, Kenilworth, NJ; 1-1.5 μg/kg/week subcutaneously) for 24 weeks. RBV was given at a total daily dose of 1,000 mg for patients who weighed 75 kg or less and 1,200 mg for patients who weighed more than 75 kg. RBV dosing was modified based on the drop of hemoglobin. Serum levels of HCV RNA at the baseline, treatment weeks 4, the end-of-treatment, and 24 weeks after therapy were determined by a standardized Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay (Amplicor™; Roche Diagnostics), using biotinylated primers for the 5′ non-coding region. The lowest detection limit of this assay was 15 IU/mL. The study was approved by the ethics committees at the participating hospitals and carried out according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients gave written informed consent before enrollment.

Assessment of Efficacy

The endpoint of the study was achievement of an SVR, defined as seronegative of HCV RNA throughout 24 weeks of post-treatment follow-up period. RVR was defined by seronegative of HCV RNA at 4 weeks of therapy.

DNA Extraction and IL-28B Genotyping

The genomic region associated with HCV treatment response lies on chromosome 19 and contains multiple SNPs in linkage disequilibrium around the IL28B gene.

Primers used are available on request. Four hundred and eighty-three patients were genotyped for rs12979860 using direct sequencing (AmpliTaq gold® DNA polymerase and BigDye® terminator v1.1 cycle sequencing kit, Applied Biosystems, Warrington, United Kingdom). Free circulating DNA was extracted from 560 ul serum samples (QIAamp Circulating Nucleic Acid Kit; Qiagen Inc., Valencia, CA, USA). The IL28B genotyping was retrospectively performed using the ABI Custom TaqMan SNP Genotyping Assays and performed on Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems, Framingham, MA, USA).

Statistical Analysis

We divided the full dataset into the two parts, 2/3 training dataset for estimating parameters and 1/3 subjects for validation. The association between continuous/categorical variables was tested with independent t-test/chi-square test. The univariate logistic regression model was used for identifying risk factors for the failure of treatment (non-SVR). The multi-variable logistic regression model was further performed to incorporate significant risk factors identified from univariate analyses. The summation of products of regression coefficients in the final model and their associated values of covariates were treated as risk score for non-SVR. The regression coefficients of covariates can be considered as clinical weights for the contribution of covariates to the risk of non-SVR. The estimated probability of treatment failure for each subject according to his/her specific risk profile, i.e. the value of covariates, in the training dataset can be calculated. Given different cut-off values for the estimated probability for predicting non-SVR, we had a series of sensitivity and specificity of our predictive model. Receiver Operating Characteristic (ROC) curve in the form of a plot of sensitivity by one minus specificity is presented for the performance of the predictive model. The Area under ROC Curve (AUC) was computed. The above-mentioned procedure was applied to the validation datasets, except that the clinical weights were directly borrowed from the estimated regression coefficients based on training dataset. All hypothesis tests were two-sided taking alpha-level of 5% as the threshold of statistical significance.

Results

Table 1 lists the clinical and laboratory data of the training and validation cohorts. There were no significant differences in baseline characteristics between patients in both cohorts. Patients in the two cohorts had similar age, gender, BMI, AST, ALT levels bilirubin, platelet count, AFP, HCV genotypes, HCV viral load, Ribavirin, diabetes mellitus, liver cirrhosis, and IL-28 B polymorphisms.

Predictors of SVR in Training Cohort

In total, 86 RVR patients did not achieve the SVR. The SVR rate for the 545 patients in the training cohort was 84.2% (459/545). Table 2 presents the frequencies of SVR among different demographic and characteristic factors. Odds ratio for the association between factors and the occurrence of non-SVR patients were showed in Table 2.

Table 1: Demographics and Clinical Characteristics of Training Dataset and Validation Dataset.

	Training dataset (n=545)	Validation dataset (n=273)	
Characteristic	**No. (%)**	**No. (%)**	**P value**
Age (years)			
<40	58 (10.64)	25 (9.16)	0.1064
40-49	106 (19.45)	37(13.55)	
50-59	163 (29.91)	103 (37.73)	
60-69	167 (30.64)	85 (31.14)	
≥ 70	51 (9.36)	23 (8.42)	
Gender			
Female	247 (45.32)	124 (45.42)	0.9784
Male	298 (54.68)	149 (54.58)	
BMI(kg/m^2)			
<27	426 (78.17)	205 (75.09)	0.3236
≥ 27	119 (21.83)	68 (24.91)	
AST(IU/L)			
≤ 40	105 (19.52)	47 (17.87)	0.5769
>40	433 (80.48)	216 (82.13)	
ALT(IU/L)			
<45	105(19.52)	47(17.87)	0.5769
≥ 45	433(80.48)	216(82.13)	
Bilirubin (mg/dL)			
<1	53 (9.72)	23 (8.42)	0.5459
≥ 1	492 (90.28)	250 (91.58)	
Platelet (×10^9/L)			
<15	394 (72.29)	184 (67.4)	0.1471
≥ 15	151 (27.71)	89 (32.6)	
AFP (ng/mL)			
<20	177 (32.48)	95 (34.8)	0.5063
≥ 20	368 (67.52)	178 (65.2)	
HCV Genotype			
Non-1	366 (67.16)	197 (72.16)	0.145
1	179 (32.84)	76 (27.84)	
HCV viral load (×10^5 IU/L)			
<2	307 (56.64)	146 (53.48)	0.1676
2-8	97 (17.9)	64 (23.44)	
≥ 8	138 (25.46)	63 (23.08)	
DM			
No	484 (88.81)	245 (89.74)	0.6851
Yes	61 (11.19)	28 (10.26)	
Liver cirrhosis			
No	454 (83.3)	224(82.05)	0.6541
Yes	91 (16.7)	49 (17.95)	
IL28B rs12979860			
CC	499 (91.56)	246 (90.11)	0.4928
CT/TT	46 (8.44)	27 (9.89)	

BMI: Body Mass Index; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; HCV: Hepatitis C Virus; DM: Diabetes Mellitus

Table 2: Demographics and Clinical Characteristics associated with Non-SVR in the Training Dataset.

Characteristic	SVR No. (%)	Non-SVR No. (%)	Crude OR	95% CI
Age (years)				
<40	52 (89.66)	6 (10.34)	1	
40-49	90 (84.91)	16 (15.09)	1.54	(0.57, 4.18)
50-59	133 (81.6)	30 (18.4)	1.96	(0.77, 4.97)
60-69	143 (85.63)	24 (14.37)	1.46	(0.56,3.76)
≥ 70	41 (80.39)	10 (19.61)	2.11	(0.71, 6.3)
Gender				
Female	210 (85.02)	37 (14.98)	1	
Male	249 (83.56)	49 (16.44)	1.12	(0.7, 1.78)
BMI (kg/m^2)				
<27	362 (84.98)	64 (15.02)	1	
≥ 27	97 (81.51)	22 (18.49)	1.28	(0.75, 2.19)
AST(IU/L)				
≤ 40	82 (78.1)	23 (21.9)	1.71	(1.00, 2.92)
>40	372 (85.91)	61 (14.09)	1	
ALT (IU/L)				
<45	38 (71.7)	15 (28.3)	1	
≥ 45	421 (85.57)	71 (14.43)	0.43	(0.22, 0.82)
Bilirubin				
<1	339 (86.04)	55 (13.96)	1	
≥ 1	120 (79.47)	31 (20.53)	1.59	(0.98, 2.59)
Platelet (×10^9/L)				
<15	137 (77.4)	40 (22.6)	2.04	(1.28,3.27)
≥ 15	322 (87.5)	46 (12.5)	1	
AFP				
<20	422 (84.57)	77 (15.43)	1	
≥ 20	37 (80.43)	9 (19.57)	1.33	(0.62, 2.87)
HCV Genotype				
Non-1	317 (86.61)	49 (13.39)	1	
11	142 (79.33)	37 (20.67)	1.69	(1.05, 2.7)
HCV viral load (×10^5 IU/L)				
<2	274 (89.25)	33 (10.75)	1	
2-8	78 (80.41)	19 (19.59)	2.02	(1.09, 3.75)
≥ 8	105 (76.09)	33 (23.91)	2.61	(1.53, 4.44)
DM				
No	412 (85.12)	72 (14.88)	1	
Yes	47 (77.05)	14 (22.95)	1.7	(0.89, 3.26)
Liver cirrhosis				
No	395 87)	59 (13)	1	
Yes	64 (70.33)	27 (29.67)	2.82	(1.67, 4.78)
IL28B rs12979860				
CC	419 (83.97)	80 (16.03)	1	
CT/TT	40 (86.96)	6 (13.04)	0.79	(0.32, 1.91)

BMI: Body Mass Index; ALT, Alanine Aminotransferase; AST: Aspartate Aminotransferase; HCV: Hepatitis C Virus; DM: Diabetes Mellitus

Table 3: Regression coefficients (Risk score) of factors for Non-SVR in Multiple factors model.

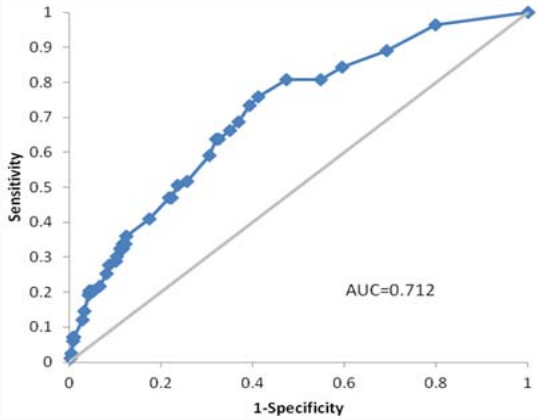
	Multivariate Model			
Factor	**Regression coefficients (Risk score)**	**SE**	**OR**	**95% CI**
Intercept	-2.4735	0.242		
AST(IU/L)				
≤ 40	0.7804	0.3026	2.2	(1.521, 3.95)
>40	0			
Platelet (×10^9/L)				
<15	0.7248	0.2854	2.1	(1.18, 3.61)
≥ 15	0			
HCV genotype				
Non-1	0			
G1	0.6566	0.2854	1.9	(1.16, 3.21)
HCV viral load (×10^5 IU/L)				
<2	0			
2-8	0.2243	0.2036	2.2	(1.15, 4.17)
≥ 8	0.3348	0.1819	2.5	(1.39, 4.31)
Liver cirrhosis				
No	0			
Yes	0.9721	0.3127	2.6	(1.43, 4.88)

Score = -2.4735+0.7804* (if AST ≤ 40) +0.7248* (if Platelet <15) +0.6566* (G1 genotype) +0.2243* (if 200000 ≥ HCV viral load <800000) +0.3348* (if HCV Viral load ≥ 800000) +0.9721* (if liver cirrhosis)
Failure probability =1/(1+exp$^{(-score)}$)

By univariate analysis, low AST (≤ 40 IU/L), high ALT (>45 IU/L), low platelet count (<150 × 10^9/L), HCV genotype 1, high HCV viral load and clinical liver cirrhosis were associated with subsequent non-SVR who receiving peg-IFN/RBV combination therapy. The crude ORs for AST levels, ALT levels, platelet count, HCV genotype 1, and clinical liver cirrhosis were 1.71 (95%, CI=1.00-2.92), 1.71 (95%, CI=1.00-2.92), 0.43 (95%, CI=0.22-0.82), 2.04 (95%, CI=1.28-3.27), 1.69 (95%, CI=1.05-2.7), 2.82 (95%, CI=1.67-4.78), respectively. The risk of non-SVR was increased among patients with higher viral load (OR=2.02, 95% CI=1.09-3.75 among HCV viral load 2-8 × 105 IU/mL and OR=2.61, 95%, CI=1.53-4.44 among HCV viral load ≥ 8 × 105 IU/mL). By multi-variable analysis, the following five independent variables were found to be significant in predicting the non-SVR: AST ≤ 40 IU/L, low platelet count (<150 × 109/L), HCV genotype 1, high HCV viral load and clinical liver cirrhosis. The ORs for AST levels, platelet count, HCV genotype 1, and clinical liver cirrhosis were 2.18 (95%, CI=1.52-3.95), 2.06 (95%, CI=1.18-3.61), 1.93 (95%, CI=1.16-3.61), and 2.64 (95%, CI=1.43-4.88), respectively. The risk of non-SVR was increased among patients with higher viral load (OR=2.19, 95%, CI=1.15-4.17 among HCV viral load 2-8 × 105 IU/mL and OR=2.45, 95%, CI=1.39-4.31 among HCV viral load ≥ 8 × 105 IU/mL) (Table 3).

Model Development

Logistic regression analysis was performed on each of the candidate predictors as an initial evaluation of a relationship with relapse. The risk scores were derived by using significant factors obtained from the regression coefficients of multivariable logistic regression model. The risk scores were calculated as Score = -2.4735+0.7804* (if AST ≤ 40) +0.7248* (if Platelet <15) +0.6566* (HCV genotype 1) +0.2243* (if 200000 ≤ HCV viral load <800000) +0.3348* (if HCV Viral load ≥ 800000) +0.9721* (if liver cirrhosis). The failure probability is equal to 1/(1+exp(-score)).



Figures 1: ROC curve with simplified risk score to predict the treatment failure trained group.

Here, -2.4735 (failure probability equal to 0.07) represented the baseline risk of occurrence the non-SVR. We further illustrated patient with combination of risk factors and the corresponding risks of non-SVR were shown in (Table 4). Patients with AST ≤ 40 IU/L, low platelet count (<15 × 10^9/L), HCV genotype 1, HCVRNA level ≥ 8 × 105 IU/mL and liver cirrhosis had the highest risk score and the treatment failure rate was 73.01%. Compared with participants with AST >40 IU/L, platelet count ≥ 15 × 10^9/L, HCV non-genotype 1, HCVRNA level <2 × 10^5 IU/mL and non-LC who had lowest risk score and the treatment failure rate was 7.77% (Table 4). This table could be easily used in the clinical practice.

In the Table 5 showed the probability of treatment failure and the percentage of all treated patients. For instance, the probability of treatment failure is 10% to 20%, the 47.24% patients need to retreatment. If the probability of treatment failure is more than 40%, the 2.26% patients need to retreatment.

The ROC curve was showed in Figure 1. The area under ROC was 71.2%. The higher cutoff value was used to classify patients as high-risk groups of non-SVR, the lower sensitivity but higher specificity can be achieved. By applying the cut-off point predicted failure probability ≥ 15%, there were 27.07 % patients would be classified as high-risk group of treatment failure. Under such situation, the sensitivity and specificity for prediction of non-SVR was 73.49% and 60.62%. The positive and negative predictive values were 25.52% and 92.57%. The result disclosed that 27.07% patients were needed the other treatment.

When we applied the estimated regression coefficients derived from the training dataset on the validation cohort, the sensitivity and specificity was 80.00% and 62.39%. The positive and the negative predictive value were 30.51% and 93.79%. These results demonstrated the availability of the proposed model.

Discussion

In the present study, we performed the simple risk score analysis and built a simple decision model for the pre-treatment prediction of non-response to PEG-IFN/RBV who achieved the RVR patients. The analysis highlighted five variables relevant to non-response: AST ≤ 40

Table 4: An illustration treatment failure rate of high, intermediate and low risk of patient achieved RVR.

Subjects	Description	Risk score	Failure probability
A (High risk)	AST ≤ 40, platelet <15,	-2.4735+0.7804+	73.01%
	G1, HCV viral	0.7248+0.6566+	
	Load >800000, Liver cirrhosis	0.3348+0.9721=0.9952	
B (Intermediate risk)	AST >40, platelet ≥ 15,	-2.4735+0.6566+0.3348+	37.52%
	G1, HCV viral	0.9721= -0.5100	
	Load >800000, Liver cirrhosis		
C (Low risk)	AST >40, platelet ≥ 15,	-2.4735	7.77%
	non-G1, HCV viral		
	Load <200000, no liver cirrhosis		

Lowest failure probability= 1/(1+exp(-2.5201))=7.77%
Median failure probability= 1/(1+exp(0.1726))=37.52%
Highest failure probability= 1/(1+exp(-1.4091))=73.01%

Table 5: The failure probability in the validation group.

Failure probability	Percentage
0-10	47.24
Oct-20	27.07
20-30	11.03
30-40	12.41
≥ 40	2.26

IU/L, low platelet count (<150 × 10^9/L), HCV genotype 1, high HCV viral load and clinical LC. Classification of patients based on these variables identified the patients with high probabilities treatment failure who achieving the RVR. The reproducibility of the model was confirmed by the independent validation datasets.

Despite the coming emergence of new Direct Anti-Viral Agents (DAAs), the standard combination therapy with PEG-IFN/RBV is still largely used in the treatment of chronic hepatitis C. However, it has become clear that fixed treatment duration is not the optimal regimen for patients in many circumstances, regardless of genotypes, and that personalized schedules are warranted [24-27]. Nevertheless, the host and viral factors can be integrated to predict the response to therapy in future clinical practice is an important question because various host and viral factors interact in the same patients [26]; the predictive analysis should consider these factors in combination [26].

Using the regression coefficients of multivariable logistic regression analysis, we constructed a simple scoring model for the pre-treatment prediction of non-SVR to PEG-IFN/RBV therapy. The classification of patients based on the AST levels, HCV genotype 1, liver cirrhosis, serum levels of HCV-RNA, and platelet counts, identified subgroups of patients who have the lowest probabilities of non-SVR (7.77%) with the highest probabilities of non-SVR (73.01%). The reproducibility of the model was confirmed by the independent validation based on a second group of patients. Using this model, we can rapidly develop an estimate of the response before treatment, by simply allocating patients to subgroups by following the score, which may facilitate clinical decision-making. These results support the evidence based approach of selecting the optimum treatment strategy for individual patients, such as treating patients with a highly probability of non-SVR with current peg-IFN/RBV combination therapy or advising those with a high probability of non-SVR to wait for more effective future therapies. Patients with a low probability of relapse may be treated for a longer duration to avoid a relapse.

Patients with HCV genotype 1 infection and baseline high HCV RNA level were significant risk factors for relapse after PEG-IFN/RVB treatment [14,27-31]. The HCV genotype 1 was difficult to treat compared with non-genotype1 in large randomized controlled studies evaluating the efficacy of IFN-based combination therapy [14,27,28]. Baseline high HCV RNA level has been repeatedly identified as an important prognostic factor for treatment outcome [13,14,23-27]. Recently one study has reported a higher base viral titer (≥ 200,000 IU/ml) as an independent risk factor for higher relapse rate [32]. In another study low pretreatment viral load was pointed out as predictor of the achievement of improved SVR rate as SVR was significantly higher in patients that had baseline viral load less than 200,000 IU/ml [32]. However, we also observed such an association between pre-treatment viral load and treatment response. Relapse rate decreased to only 7.7% in our patients with baseline viral titer lower than 200,000 IU/ml.

Another important the predictors are low platelet count and liver cirrhosis. Previous studies reported that patients with low platelet counts was achieved lower SVR rates than patients with normal platelet counts even in the case of patients with the same category of liver fibrosis treated by PEG-IFN/ribavirin combination therapy [33,34]. Extent of fibrosis/cirrhosis had also been shown to be a strong negative predictor of SVR [28]. Baseline factors that might be useful to predict non-SVR were evaluated in the present study. In our study, significant independent predictor for non-SVR was lower AST levels. HCV genotype 2/3 is already established as an independent predictive factor for RVR and SVR [34] but lower pretreatment AST levels have not previously been reported as a predictor of the treatment outcome, and this may warrant further investigation.

In conclusion, we built a pre-treatment model for the prediction of virological response in PEG-IFN plus RBV therapy. Because this risk score model was made up of simple host and viral factors such as AST level, low platelet count, liver cirrhosis, viral genotypes and baseline viral loads, it can be easily applied to clinical practice. This model may have the potential to support decisions in patient selection for PEG-IFN/RBV therapy based on the possibility of response against a potential risk of adverse events or costs, and may provide a rationale to improve the efficacy of antiviral therapy.

Grant Support

The work is partially supported by the grant from Chang Gung Memorial Hospital, CMRPG8C1251.

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