



Statistical Prediction Model for Relapse Rate in Chronic Hepatitis C Patients Treated with Conventional Interferon and Ribavirin Therapy

Muhammad Irfan^{1*}, Muhammad Arif Nadeem¹, Huda Ghulam Mirza²,
Muhammad Ghias³, Aftab Mohsin¹ and Mutee Ullah Khan Muttee¹

¹Services Institute of Medical Sciences/Services Hospital, Lahore, Pakistan

²Lahore University Medical College, Lahore, Pakistan

³Department of Statistics, Government College University, Lahore, Pakistan.

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ABSTRACT

Objective: To determine the significantly associated factors with the relapse rate in chronic hepatitis C patients treated with conventional interferon and their predictive strength through the regression model.

Material & Methods: In a retrospective analysis of 244 patients, result of PCR, gender, fatty liver, diabetes, abnormal ALT at start and end of treatment were the qualitative variables. Age, weight, ALT at start and end of treatment, hemoglobin, platelets and WBC at start of treatment were quantitative variables. Bivariate, multivariate analysis and odds ratio were computed to verify statistically significant association with relapse rate by running binary logistic regression model.

Results: Out of total 244 patients there were 54.1% male and 45.9% female. Eighty two (33.6%) patients had weight ≥ 70 Kg, 30 (12.3%) had fatty liver, 18 were (7.4%) diabetic, 12 (4.9%) had normal ALT at start of therapy and 140 (57.4%) had abnormal ALT at the end. Eighty four (34.4%) patients relapsed while 160 (65.6%) maintained SVR after 6 month to 2 years of completion. In bivariate analysis, age, weight, fatty liver, high fever, decrease and increase in Hb were found significant. The binary logistic regression revealed the significant association of weight (OR=84.813; $p=0.000$), high fever (OR=4.478; $p=0.038$) and Hb increase at 1st month (OR=0.037; $p=0.013$) with relapse rate. Nagelkerke R Square and Cox & Snell R Square statistics explained 71.1% and 51.1% variation in the model respectively and 93.1% area under the curve gave it very good prediction strength.

Conclusion: The relapse rate to conventional interferon and ribavirin treatment is high in Pakistan. The assessment of predictors of response, like body weight may help in individualizing the treatment, patient selection and to decrease an ever expanding pool of non-responders and re-lapsers. Hence, our prediction model can help us to predict the chances of being relapse in advance

Keywords: HCV; End of Treatment Response; Relapse rate, Interferon therapy; Logistic Regression; Odds ratio; ROC;

1. INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a Tsunami for public health in Pakistan. According to World Health Organization (WHO), 3% of the world's population i.e., 180 million people are infected with hepatitis C virus (WHO, 2010) while 6% Pakistani population is infected with it, (Ali et al., 2009) and genotype 3 is the most prevalent virus (Jafri et al., Idrees et al., 2008, 2009).

Pegylated interferon is the better option than conventional interferon for treatment of chronic hepatitis C and now considered as the standard of care for these patients. Due to marked difference in cost, standard interferon combination therapy is still the preferred therapy for genotype 2 and 3, especially in developing countries like Pakistan (Hamid et al., 2004).

Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred as an End of Treatment Response (ETR). The Sustained Virological Response (SVR) is defined as the absence of HCV RNA (ribonucleic acid) from serum by a sensitive Polymerase Chain Reaction (PCR) assay 24 weeks after the completion of therapy. Person who failed to clear HCV RNA from his/her serum after 24 weeks of therapy is Non-responder. Relapse is defined as reappearance of HCV RNA in serum after therapy is discontinued. Therefore, HCV testing should be performed annually for at least 2 years after completion of therapy to see the relapse (Ghany et al., 2009). If patient relapses or is non responder to conventional interferon, then re-treatment with pegylated interferon is required (Jacobson et al., Shiffman et al., Taliani et al., 2005, 2004, 2006).

A large number of relapsers and non responder patients to conventional interferon and ribavirin therapy provided by Prime Minister Program for Prevention and Control of Hepatitis in Pakistan (PMP) are seeking help from Pakistan Bait ul mal for their expensive retreatment with pegylated interferon. Even the large expenditures bearded by Pakistan Bait ul mal on pegylated interferon, response rate will be only up to 20% (Cheng et al., 2001) in comparison to 93% for treating naïve patients with it (Zeuzem et al., 2004).

Already known factors, predictive of response to treatment in chronic hepatitis C include low serum HCV RNA level, non genotype 1, absence of cirrhosis, age younger than 40 years, lack of steatosis or obesity, mode of acquisition of infection and white race (Strader et al., Alberti et al., 2003, 2004).

A body mass index higher than 30 has been associated with poor response to therapy. Weight reduction, in turn, leads to improved outcome (McCullough et al., 2003).

This study was carried out to assess predictive power of some additional factors prevailing in our population taking conventional interferon, massively provided by the Government free of cost. So, that we can decrease the relapse rate and hence improve SVR. National consensus can be suggested to treat these patients with conventional interferon or Pegylated interferon as initial therapy on the basis of these factors predictive of response and therefore, the health resources can be saved as it is not possible to provide pegylated interferon to all the patients.

The significance of our study is that we will suggest a final prediction model to predict the probability of being relapsed based on certain significant factors. According to our best knowledge there is no known study in literature available, giving such prediction model.

2. EXPERIMENTAL DETAILS

This was a retrospective cohort study carried out at Department of Medicine, Gastroenterology and Hepatology, Services Hospital, Lahore, Pakistan, from January 2007 to December 2010.

A total 1175 patients were treated with conventional interferon and ribavirin provided by Prime Minister Program for Prevention and Control of Hepatitis in Pakistan during this period. Out of these, 700 patients who had completed the treatment with regular visits were called for further follow up during July 2010 to December 2010. Among them only 314 patients responded to our call, and finally 244 patient were recruited under the following inclusion criteria:

1. Patients with genotype 2 and 3
2. Achievement of ETR
3. The time from end of treatment to their visit between 6 months to 2 years
4. Patient not taking any re-treatment

The serum of these patients was tested for HCV RNA quantitatively by Real Time Amplification method of PCR with lower limit of detection 125 IU per ml. The available data about different variables during their 6 month interferon therapy was evaluated retrospectively on SPSS version 15.

The result of PCR test, gender, fatty liver on ultrasound, history of diabetes, abnormal Alanine Aminotransferase (ALT) at start of treatment and at the end of treatment were the qualitative variables. Age, weight, ALT at start of treatment, ALT at end of treatment, hemoglobin (Hb) at start of treatment, white blood cells (WBC) at start of treatment and initial platelet count were quantitative variables. The whole data was interpreted in negative or positive values. Frequencies and ranges were computed for presentation of qualitative variables and means and standard deviations were calculated for quantitative variables. Bivariate and multivariate analysis was performed in order to find the significant factors associated with relapse rate.

In bivariate analysis chi-square test of independence was used to find any association of factors at 5% level of significance. Moreover, odds ratio along with their 95% confidence interval (CI) were also computed. Statistically significant factors associated with relapse rate were then found.

Multivariate analysis was performed to further verify these factors by running binary logistic regression model. Our response variable has only two categories i.e., Relapsed and Not-relapsed and other covariates were either categorical or continuous. Every covariate assigned a base category which indicates minimum risk. Forward likely hood ratio criterion was taken for further variable selection in the model (David, 2003).

3. RESULTS AND DISCUSSION

A total of 1175 patients received interferon therapy along with ribavirin and 700 were called, but only 314 came for follow up. Out of these 314, 244 patients who had achieved ETR were included. One hundred thirty two patients (54.1%) were male and 112 (45.9%) female. Eighty two (33.6%) patients had weight equal or more than 70 Kg, 30 (12.3%) had fatty liver on ultrasound and 18 (7.4%) were diabetic. Only 12 (4.9%) patients had their ALT within normal limit at the start of interferon therapy, while 140 (57.4%) patients had abnormal ALT at the end of interferon therapy even though they achieved ETR (Table 1).

Table 1. Descriptive analyses of quantitative variables (n=244)

Result of PCR test	Age (years)	Weight (Kg)	ALT at start of treatment	ALT at end of treatment	Initial Hb	Initial TLC	Initial PLT count/mm ³
			(U/L)	(U/L)			
Relapsed (n=84)							
Mean	37.12	74.86	64.98	33.05	13.005	7751.9	224.45x10 ³
Standard Deviation	9.764	9.953	38.18	15.08	1.5347	1635.556	41.0x10 ³
Minimum	10	44	16	14	10.1	3700	124x10 ³
Maximum	59	97	181	91	17.2	10600	308x10 ³
Not relapsed (n=160)							
Mean	35.96	59.54	75.72	29.13	12.7	7655	237.39x10 ³
Standard Deviation	8.002	8.619	54.44	13.67	1.5983	1331.751	40.0x10 ³
Minimum	20	42	19	12	9.5	3700	120x10 ³
Maximum	60	80	150	82	21.1	10400	435x10 ³

The mean age of patients was 36.36 ± 8.65 years and mean weight 64.81 ± 11.65 kg. The mean value of ALT was 72.02 ± 49.63 IU/L with a range of 16 - 350 IU/L. The mean value of hemoglobin was 12.80 ± 1.58 gram/dl with a range of 9.5 – 21.1 gram/dl. The mean value of WBC count was 7688.36 ± 1440.94/ mm³ with a range of 3700 - 10600/ mm³. The mean platelets count was 232,934.43 ± 40,714.96/mm³ with a range of 120,000 – 435,000/mm³ (Table 2).

Table 2. Bivariate analysis of risk factors of Hepatitis C virus (Relapsed/Not-relapsed) (n=244)

Predictors/ Categories	Results of PCR		Total	p- value	Odd ratio with 95% Confidence interval
	Not- relapsed	Relapsed			
Gender:					
Male	90 (56%)	42(50%)	132(54%)	0.417	1.29 (0.757-2.183)
Female	70 (44%)	42(50%)	112(46%)		
Age (years):					
<40	128 (80%)	54(64%)	182(75%)	0.009	2.22 (1.231-4.013)
≥40	32 (20%)	30(36%)	62(25%)		
Weight (Kg):					
<70	148 (92%)	70(83%)	162(66%)	0.000	61.67 (27-140.266)
≥70	12 (8%)	14(17%)	82(34%)		
Fatty Liver on Ultrasound:					
No	156 (97%)	58(%69)	214(88%)	0.000	17.48 (5.849-52.258)
Yes	4 (3%)	26(31%)	30(12%)		
History of Diabetes:					
No	152 (95%)	74(88%)	226(93%)	0.069	2.57 (0.973-6.775)
Yes	8 (5%)	10(12%)	18(7%)		
History of Fever:					
No	78 (49%)	22(26%)	100(41%)	0.001	2.68 (1.506-4.772)
Yes	82 (51%)	62(74%)	144(59%)		
ALT at start of treatment:					
Abnormal	156 (98%)	76(90%)	232(95%)	0.26	4.11 (1.199-14.061)
Normal	4 (2%)	8(10%)	12(5%)		
ALT at start of treatment ≥ twice of UNL:					
No	56 (35%)	36(43%)	92(3%)	0.266	0.718 (0.418-1.233)
Yes	104 (65%)	48(57%)	152(97%)		
ALT normalization at 1st month of treatment:					
No	134 (84%)	68 (81%)	202(83%)	0.596	1.213(0.610- 2.412)
Yes	26 (16%)	16 (19%)	42(17%)		
Decrease in Hb≥ 1g/dl in 1st month:					
No	118 (74%)	40 (48%)	158(65%)	0.000	3.09 (1.1775-5.380)
Yes	42 (26%)	44 (52%)	86(35%)		
Increase in Hb≥ 1g/dl in 1st month:					
No	122 (76%)	82 (98%)	204(84%)	0.000	0.078 (0.018-0.334)
Yes	38 (24%)	2 (2%)	40(16%)		

Among 244 patients who achieved ETR, 84 (34.4%) relapsed and 160 (65.6%) remained HCV free within 6 month to 2 years after the completion of therapy. Bivariate and multivariate analysis was performed in order to find the significant factors associated with relapse rate. In bivariate analysis, results elucidate that among all the given factors age, weight, fatty liver, high fever, decrease in Hb and increase in Hb were found significant.

On running the binary logistic regression it was finally found that weight, high fever and Hb at 1st month were significantly associated with relapse rate. Odds ratios along with their 95% CI were also included in the results and weight greater than 70Kg contributed the highest risk to relapse rate. From the coefficient signs, weight and high fever had positive association while Hb increase at 1st month had negative association. Results indicate that about 85 times risk of being relapse increases in those patients who have weight greater than 70 Kg than others, alarmingly requiring very strong attention to overcome the situation. Similarly high fever increases the risk about 5 times more than others and increase in Hb at 1st month reduces the risk of relapse about 0.037 times (Table 3).

Table 3. Multiple Logistic Regression Output with Co-efficient, Odds Ratio and their 95% CI

Risk Factors	B	S.E.	Wald-Statistic	p-value	Odds Ratio	95% C.I. for EXP(B)	
						Lower	Upper
Weight:							
<70kg	4.440	0.723	37.678	0.000	84.813	20.545	350.125
≥ 70kg							
High Fever:							
No	1.499	0.723	4.295	0.038	4.478	1.085	18.484
Yes							
Increase in Hb ≥ 1g/dl in 1st month:							
No	-3.288	1.329	6.120	0.013	0.037	0.003	0.505
Yes							
Constant	-3.095	0.696	19.775	0.000	0.045	-	-

Nagelkerke R Square = 71.1%; Cox & Snell R Square = 51.1%

Wald test applied and it gave the significance of every individual factor in the model. Nagelkerke R Square and Cox & Snell R Square statistics illustrate that about 71.1% and 51.1% variation being explained in the model respectively (Hosmer and Lemeshow, 1989). In the figure (1) overall adequacy of the fitted model was checked by Receiver operating curve (ROC) and it was found that area under the curve is 93.1% which gave the very good prediction. ROC curve plotted with 1-specificity along x-axis and sensitivity along y-axis. Sensitivity means, correct classification of true positive cases and specificity measures the correct classification of true negative cases.

3.1 Logit Model

$$Z = -3.095 + 4.440 (\text{Weight}) + 1.499 (\text{High Fever}) - 3.288 (\text{Hb increase})$$

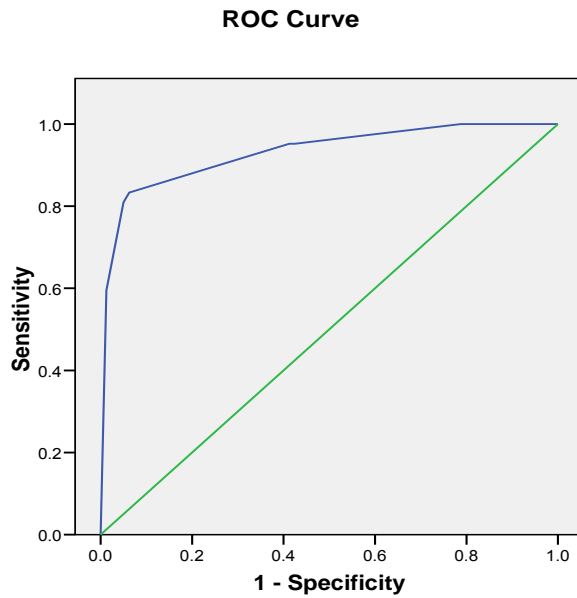
Hence,

$$\text{Probability of Relapse} = 1/(1+e^{-Z})$$

Table 4. Predicted probabilities for relapse of HCV in patients treated with conventional interferon therapy

Weight	High fever	Hb Increase	Z	Probability of (Relapse)
0	0	0	-3.095	0.043314
1	0	0	1.345	0.793311
0	1	0	-1.646	0.16165
0	0	1	-6.383	0.001687
1	1	0	2.794	0.942351
1	0	1	-1.943	0.125319
0	1	1	-4.934	0.007146
1	1	1	-0.494	0.378952

*Weight < 70Kg → 0; ≥ 70Kg → 1. High Fever → No=0; Yes=1.
Hb Increase → No=0; Yes =1*



Diagonal segments are produced by ties.

Fig. 1. ROC representing the overall adequacy of the fitted Mode

In Table 4 predicted probabilities of being relapsed have been calculated based on significant factors in the model under the presence or absence of different situations. Consider the first case, where it is assumed that all factors are negative. Thus, the corresponding estimated probability will be about 0.0433. Similarly, when it is assumed that only weight is positive (>70Kg) and other factors are negative, then this probability goes to 0.793. Maximum risk of being relapsed is 94.2% when weight and high fever are both positive.

In this retrospective analysis of chronic hepatitis C patients receiving interferon therapy with their record maintained at the Department of Gastroenterology and Hepatology, Services Hospital Lahore, a large number of patients (386 out of 700 i.e. 55%) were lost to follow-up, either due to financial problem or lack of interest and awareness about their health issues.

Waqar ud Din Ahmed and his colleagues from Karachi in a large study revealed 74.5% ETR and 26.5% non responders with conventional interferon (Ahmed et al., 2011). In our study 34.4% were re-lapsers, with an overall SVR of 49.6%. Therefore, remaining 51.4 % non responders/re-lapsers will seek pegylated interferon for their retreatment and it will benefit only up to 20% (Cheng et al., 2001) cases in comparison to 93% (Zeuzem et al., 2004) for treatment naïve patients. Our study revealed better treatment response in patients with age <40 years, body weight <70 Kg and non-diabetic as already known. However, we have come across some additional factors like history of fever during 1st month of interferon therapy requiring vigorous antipyretics, increase and decrease of Hemoglobin > 1gram/dl during 1st month of interferon therapy showing statistically significant association with relapse rate.

Our study also provided a model in which weight equal or greater than 70 Kg increases about 85 times risk of relapse to conventional therapy. Similarly high fever during 1st month of therapy increases about 5 times the risk to relapse and Hb at 1st month if increases > 1gram/dl, then it reduces the risk of relapse about 0.037 times. This model has pointed that the patient weight need very strong attention before selecting the treatment type for him/her. It means overweight patient should not be treated with conventional interferon even if they cannot afford pegylated interferon as they are likely to relapse. This fact was similarly shown in earlier studies (Rubbia et al., 2001; Qureshi et al., 2009; Manns et al., 2001) that the less body weight is a good predictor to response to treatment.

Schiffman and his colleagues had already explained better outcome in patients with age < 45 years, weight <80 kg, viral load less than 400,000 IU/ml and genotype 2 (Shiffman et al., 2007). Similarly a meta- analysis by Strader et al. (2004) showed the same results.

It leads us to suggest that the conventional interferon may not be used solely in Prime Minister Program in Pakistan, as it not only increasing the relapse rate but also produces resistance to re-treatment as well. If it is not practicable due to cost, then national consensus should be made on the basis of predictive factors to group the patients into two categories: one who may be provided conventional interferon and others who should never be treated with it to decrease non-responders and relapse rate and in this way SVR could be improved and the resistant pool to re-treatment can be decreased.

4. CONCLUSION

The relapse rate to standard interferon and Ribavirin treatment is high in Pakistan. The assessment of predictors of response, like body weight may help in individualizing the treatment, patient selection and decrease in an ever expanding pool of non-responders and

re-lapsers. Finally our prediction model can give the prediction of relapse under the presence or absence of certain significant factors.

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