Gastroenterology and Hepatology From Bed to Bench.

ORIGINAL ARTICLE

Random effect model for identifying related factors to virological response in HCV patients

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ABSTRACT

Aim: This study aims to employ random effect model to evaluate prognostic factors of hepatitis C.

Background: In recent years, Hepatitis C virus (HCV) infection has been a major cause of liver diseases worldwide and represents a major public health problem. Evaluation of risk factors and a community intervention in order to decrease the problem is one of the solutions which help protect people from the infection.

Patients and methods: The data was collected from a longitudinal study during 2005-2010. The response variable in this study was the viral load of each HCV patient during the treatment, immediately after the treatment and 3 to 4 months after the end of the treatment. The outcome variable of interest is the viral load of HCV patients. For analyzing repeated measure viral load of HCV patients, random effect models were used.

Results: The results obtained from random effect model showed that treatment protocol and time statistically significant. The variance component was statistically differing with zero.

Conclusion: According to the results time had a positive effect on rate of viral load of patient. Combination therapy of Peg-interferon plus Ribavirin increased the rate of virological response.

Keywords: HCV, Viral load, Random effect, Longitudinal data.

(Please site as: **Zayeri F, Chaibakhsh S, Pourhoseingholi A, Akbarzadeh Baghban A, Alavian SM. Random effect model for identifying related factors to virological response in HCV patients. Gastroenterol Hepatol Bed Bench 2013;6(Suppl 1):XX-XX).**

Introduction

Hepatitis C Virus (HCV) infection has been a major cause of liver diseases worldwide and represents a major public health problem in recent years(1-4).Transfusion and contact with infected blood and its products, intravenous drug use and contamination during medical procedures are among different risk factors of HCV(5-7). An estimated 130–170 million people worldwide are infected with hepatitis C and the global prevalence of this infection is approximately 2.2% -3. Apart from few studies that have been done on high-risk groups or in specific locations; no comprehensive and accurate estimate of HCV infection is available in Iran. According to two available studies which examined Iranian population, the prevalence of HCV infection in the general population is less than 1% (8, 9).In the

Received: 15 April 2013 *Accepted*: 18 June 2013
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coming decades, it is expected that the economic burden and mortality associated with hepatitis C rise(6, 10). Unfortunately , the majority of infections do not respond to treatment and lead to chronic diseases; therefore, it seems that controlling HCV infection is an important issue in public health(4, 11). Risk factor evaluation in order to reduce the problem in the community is one solution to protect people from the infection.

In some studies repeated measurements of subjects were recorded. In this situation the correlation between subjects is important and if it is neglected, estimation and results will be misleading. There are different approaches for modeling repeated measure data. Marginal, transition and random effect models are methods of analyzing this kind of data(12, 13). Random effect models are popular approaches in which the regression coefficients measure the more direct influence of explanatory variables on the responses for heterogeneous individuals. The interpretations of these models in contrast of marginal models (population average) are subjected specific(12, 13).

In this paper a random effect approach was used to identify factors related to virological response in HCV patients.

Patients and Methods

This is a longitudinal study and all data for this research were drawn from medical records of 186 patients with hepatitis C, who had been referred to Tehran hepatitis clinic, a clinical clinic of Bagiyatallah Research Center for Gastroenterology and Liver diseases, from 2005 to 2010. The Information concerning186 patients includes viral load (HCV-RNA) before the treatment, during the period of treatment, immediately after this period and 3 to 4 months after end of the treatment. The viral load before treatment has considered for baseline adjusting. The variables included in the study are as follows: demographic information including sex and age, genotypes including genotype 1, 2 and 3, treatment protocol including Combination therapy of standard Interferon (3 MU three times a week) plus Ribavirin (800-1200 mg per day) for 24 weeks or 48 weeks (14-16) as well as Combination therapy of Peg-interferon (Alfa 2a in a fixed dose of 180 micrograms per week) plus Ribavirin (800-1200 mg per day) for 24 weeks or 48 weeks (15, 17) and risk factor which means having one of these three factors including history of blood transfusion, addiction (IV drug user) and contaminated needle stick. All of this information was extracted from the patients' medical records. Therefore five covariates including ages, sex, genotype, protocol of treatment and risk factor were entered in this study. Finally, 558 viral loads of HCV and their related information were extracted; it means that each patient was examined three times (the first time was baseline). So HCV-RNA is considered as response variable and all analyzing was performed on it.

Frequency distribution and descriptive statistics such as mean, standard deviation and percentage were calculated according to standard methods. The outcome variable of interest is the viral load of HCV patients. For analyzing repeated measure viral load of HCV patients, random effect models were used. There are some unobserved factors that cause this heterogeneity between subjects. For counting this heterogeneity random effect models include random coefficients in the model. It means each subject have special coefficient. So it seems difficult to estimate this entire coefficients (there are many coefficients as same as the number of subjects)(18).In fact the random effect models estimate the one variance component for each random coefficient instead of estimation of all random coefficient. If these variance components significantly differ with zero, it will be an unobserved heterogeneity between subjects. All Significance was defined as $p<0.05$.

Results

In general 186 patient were studied, among them 55 patients (29.6%) were female. The mean (SD) age was 42.88 (11.17) years, ranged from 19

to 76 years. Table 1 shows the mean of viral load of different categories of variables. The mean of viral load in women was higher than men. The mean of viral load was increasing over time. The mean in Patients with positive risk factor was higher. Genotype 2 and 3 were the highest and lowest respectively. Patients with Combination therapy of Peg-interferon plus Ribavirin had the highest mean of viral load.

Table 1. The distribution of covariance between patients

Variables	Categories	n	%
Sex			
	Man	55	29.6
	Woman	131	70.4
Risk factor(s)			
	Yes	104	55.9
	No	84	44.1
Genotype			
	1	142	76.3
	2	4	2.2
	3	40	21.5
Protocol of treatment			
	Interferon+ Ribavirin	100	53.8
	Peg-interferon+ Ribavirin	86	46.2

Table 2. The results of univariate analysis

Variable	Categories	Mean(SD)viral load	p-value
Sex			
	Men	182480(767789)	0.702
	Women	208813(668612)	
Time			
	4	113208(605257)	0.013
	7	158369(769511)	
	10	299223(817572)	
Risk Factor (s)			
	No	184709(761821)	0.871
	Yes	194649(722347)	
Genotype			
	1	194697(634472)	0.075
	2	637445(2180182)	
	3	129820(810967)	
Treatment protocol			
	Interferon+ Ribavirin	174922(717761)	0.008
	Peg-interferon+ Ribavirin	206849(767375)	

Each patient had three viral loads for evaluating the treatment process. This viral load was statistically significant difference between two groups of protocol of treatment (p=0.008) and over time (p=0.01). But there is not statistically significant difference of viral load between genotype groups and risk factor group. The result of this univariate analysis is shown in table 2.

Finally, with controlling the effects of sex and age a random effects regression model with log link (assuming a Poisson distribution for the outcome) was used for assessing the impact of genotype, protocol of treatment, risk factor and time on viral load of HCV patients. According to the results of this model time (OR= 1.18, $p<0.0001$) and the treatment protocol (OR= 5.98, p=0.001) was statistically significant. This significant OR shows that the rate of viral load was increasing over time. Also the rate of increasing of viral load of patient with Combination therapy of standard Interferon plus Ribavirin almost 6 times higher than the patient used Combination therapy of Peg-interferon plus Ribavirin. The effect of genotype and risk factor was not significant .In addition to regression parameter in this model, one variance component of random intercept model was estimated and it was statistically differ with zero (σ^2 =13.73, $p<0.001$). Table 3 shows results of random effect model.

Discussion

In this article, a random effect model was used for repeated measure of viral load of HCV patient for accessing their treatment process.

In this model time and protocol of treatment had significant effects on the rate of viral load. Two main protocols of treatment were used in this study based on the genotype of patients. According to the results, Combination therapy of Peg- plus Ribavirin had better results than Combination therapy of standard interferon plus

Table 3. The results of the random effect model

Variables	Category	Estimation	SE	p-value	OR
Age		0.017	0.024	0.480	1.01
Time		0.166	0.001	<0.001	1.18
Sex					
	Men	-1.11	0.612	0.069	0.33
	Women*	-	-	-	-
Risk Factor(s)					
	No	-1.06	0.562	0.06	0.34
	Yes*	-	-	-	-
Genotype					
	1	1.16	0.673	0.085	3.18
	2	0.903	1.976	0.647	2.46
	3*	-	-	-	-
Treatment Protocol					
	Interferon+ Ribavirin	1.797	0.554	0.001	5.98
	Peg-interferon+ Ribavirin*	-	-	-	-

*reference group

Ribavirin. The large number of studies which have been conducted so far showed that Peg- plus Ribavirin had been most responsive to treatment(19-22); therefore, this protocol has been the best choice(23, 24).Unfortunately in Iran, due to high cost of the drug, it is not the first choice for doctors. Usually, when patients did not respond to the treatment, doctors decided to prescribe Peg- plus Ribavirin (24).

On the other hand time had a significant positive effect on rate of viral load. This is a logical result which means with increasing time the rate of viral load increased.

So passing the time had a bad effect on situations of patients. Therefore it seems the time have an important role in treatment process of HCV patients. In addition to regression parameter in this model, parameters of the random effects were estimated. The estimated variance of random effects model was 13.76 indicated the longitudinal correlation between the subjects.

Three methods including transition models, marginal models and random effect models are common in longitudinal studies (12). When heterogeneity between subjects is important random effect models are the best choice (12, 13). In this study each patient was a cluster and the repeated measures of them were correlated. The clusters (each patient) were different because of some unobserved factors. By including a normal random intercept in the random effect model the heterogeneity between subjects was adjusted. Longitudinal studies are increasing in medical research in recent years. Therefore using random effect models is common as a one of approaches for analyzing these types of data recently.

Beets et al were used random effect models for examining the relationship between physical activity and contextual characteristics in 2012. In this study the clusters were subjects as same as our study (25).

To examine the effect of a transitional care program for discharged medical patients and the differential effects of telephone calls only Wong et all in 2013 were used random effect models. The response was measured in two times for each subject so the patients were clusters (26). In all of these studies like present study because of the correlation between subjects using every other models except of longitudinal models causing misleading results.

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