International Journal of Medical, Medicine and Health Sciences
ISSN: 2517-9969
Vol:11, No:5, 2017

Application of Gamma Frailty Model in Survival of Liver Cirrhosis Patients

Elnaz Saeedi, Jamileh Abolaghasemi, Mohsen Nasiri Tousi, Saeedeh Khosravi

***Abstract*—**Goals and Objectives: A typical analysis of survival data involves the modeling of time-to-event data, such as the time till death. A frailty model is a random effect model for time-to-event data, where the random effect has a multiplicative influence on the baseline hazard function. This article aims to investigate the use of gamma frailty model with concomitant variable in order to individualize the prognostic factors that influence the liver cirrhosis patients' survival times. Methods: During the one-year study period (May 2008-May 2009), data have been used from the recorded information of patients with liver cirrhosis who were scheduled for liver transplantation and were followed up for at least seven years in Imam Khomeini Hospital in Iran. In order to determine the effective factors for cirrhotic patients' survival in the presence of latent variables, the gamma frailty distribution has been applied. In this article, it was considering the parametric model, such as Exponential and Weibull distributions for survival time. Data analysis is performed using R software, and the error level of 0.05 was considered for all tests. Results: 305 patients with liver cirrhosis including 180 (59%) men and 125 (41%) women were studied. The age average of patients was 39.8 years. At the end of the study, 82 (26%) patients died, among them 48 (58%) were men and 34 (42%) women. The main cause of liver cirrhosis was found hepatitis 'B' with 23%, followed by cryptogenic with 22.6% were identified as the second factor. Generally, 7-year's survival was 28.44 months, for dead patients and for censoring was 19.33 and 31.79 months, respectively. Using multi-parametric survival models of progressive and regressive, Exponential and Weibull models with regard to the gamma frailty distribution were fitted to the cirrhosis data. In both models, factors including, age, bilirubin serum, albumin serum, and encephalopathy had a significant effect on survival time of cirrhotic patients. Conclusion: To investigate the effective factors for the time of patients' death with liver cirrhosis in the presence of latent variables, gamma frailty model with parametric distributions seems desirable.

***Keywords*—**Frailty model, latent variables, liver cirrhosis, parametric distribution.

I. Background

LIVER as the largest body gland, which is responsible for important duties in the vital performances such as necessary changes on absorbed nutrients and detoxification, plays the most important role in body health maintaining. Therefore, studying and identifying liver diseases and abnormalities is vitally important. Liver cirrhosis is a serious and progressive disorder which is the response of liver to the waste and scar tissue (fibrosis) as a result of chronic liver diseases.

Various factors cause liver cirrhosis, and the most important reasons are viral hepatitis type "B" and "C" and alcohol consumption. Also, diseases such as Wilson and diabetes, consuming some medicines and disorders like autoimmune hepatitis disease can cause liver cirrhosis [1].

Different studies on the liver cirrhosis reasons have been performed around the global, and results are different according to the geographic regions. In Europe and the United States, excessive alcohol consumption is the most common cause of liver cirrhosis, while in Asian and African countries, viral hepatitis types "B" and "C" are most important causes for this disease [2], [3]. In Iran, due to the large number of hepatitis type "B" patients, it is the main cause of liver cirrhosis [4]-[6].

Liver transplantation is the final treatment way for patients of liver cirrhosis, and the critical subject is to identify liver transplant surgery in proper time [7]. Liver cirrhosis patients are exposed to liver cancer, and the risk is higher in cases caused by hepatitis type "B" and "C". Therefore, to be informed about effective factors on survival and risk of mortality, for liver cirrhosis patients, it is an important criterion in prioritizing patients for receiving liver transplantation, and in-time treatment that prevents the early death [8].

In many studies, there may exist some other factors apart from the explanatory variables which influence survival and hazard functions, because these variables are not easily measured, so we cannot put them in the model. Variables such as genetics, economic, social situation and many other factors which they need to be considered in the study by quantitative variables. If we do not put them into the consideration, the parameter estimation will be biased. These variables are nominated as frailty [9]-[11]. The goal of this study was to investigate the effective criteria on liver cirrhosis patients' survival in the presence of frailty variable.

II. Method

In this study, we have used the information of 305 liver cirrhosis patients who joined the liver transplantation waiting list of Imam Khomeini hospital during May 2008- May 2009. The vital situation and other medical information of their disease in the period of at least seven years are investigated. The understudy variables included sex, age, education, marital status, blood group, and cause of cirrhosis. Diagnostic and

Elnaz Saeedi and Saeedeh Khosravi are Master students, Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran.

Jamileh Abolaghasemi is Assistant professor, Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran (corresponding author, fax: + 98 21 86704774, e-mail: Abolghasemi1347@yahoo.com).

Mohsen Nasiri Tousi is Associate professor, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

laboratory variables include ascites, encephalopathy, bilirubin, albumin, creatinine, prothrombin serums, and INR index. In addition to the aforementioned variables, there exist other invisible variables that are set in the model as frailty variables. Considering these variables in the model, it holds the assumption of homogeneity between people, which causes biased results and associates results with frailty corrections [9], [12].

One of the most common models in survival data analysis is the Cox proportional hazard model. It is not possible to set latent variables into this model. Therefore, it seems to be efficient to utilize the frailty model which is the extension of Cox model [13]. The Cox hazard function is given in (1) in which *t* is the event occurrence time, $h_0(t)$ is the basic hazard function, β is the vector of regression coefficients, x is the vector of secondary variable or independent variables and *n* is the number of existing independent variables in the study.

$$h_i(t) = h_0(t)\exp(\sum_{i=1}^{n}\beta_i x_i) \quad i = 1,2,\dots.,n \qquad (1)$$

In semi-parametric Cox model, no special distribution is assumed for the basic hazard function, but in the present investigation, parametric methods were used for modelling. Therefore, Exponential and Weibull distributions with Gamma frailty model were fit to data. In this model, a random effect (frailty variable) was introduced for every individual which represents the demographic and genetic characteristics in susceptibility to the desired event.

Suppose that **z** is a frailty variable; this variable is put in terms of a multiplicative in the basic hazard function and is defined as:

$$h_i(t) = z_i h_0(t)\exp(\sum_{i=1}^{n}\beta_i x_i) \qquad i = 1,2,\dots,n \qquad (2)$$

No precise method is considered for choosing the frailty variable distribution, but due to the flexibility and various applications of gamma distribution, one can choose this distribution for frailty variable [14]-[16]. If the frailty variable is assumed to have gamma distribution with $(\frac{1}{\theta},\frac{1}{\theta})$ parameters, then the following results will be occurred:

$$Z\sim Gamma\left(\frac{1}{\theta},\frac{1}{\theta}\right) \rightarrow E(Z) = 1\ ,\ Var(Z) = \theta \qquad (3)$$

The frailty variance can demonstrate the society heterogeneity. If the frailty variable is less than one, then the risk value for individuals will be less than the society average risk. On the other hand, if the frailty variable is more than one, then the risk value for individuals will be more than the society average risk. Therefore, the ones with higher frailty values are exposed to a greater risk rather than the ones with lower frailty values [17].

Ultimately, gamma frailty model fitting and data analysis have been performed by R software (version 3.2.3), and all the tests have been done under error level of 0.05.

III. Results

The 305 liver cirrhosis patients who enrolled the study were formed by 180 (59%) men and 125 (41%) women. The mean age of enrolling the study was 39.8 (± 14.54) years. In this study, viral hepatitis types "B" and "C", with the sum of 34.8%, received the highest percentage for cause of liver cirrhosis. Hepatitis type "B" with the percentage of 23% was identified as the first and the most important cause for liver cirrhosis, afterwards cryptogenic, autoimmune hepatitis, hepatitis C, PSC, PBC and alcoholic cirrhosis, by 22.6%, 16.4%, 11.8%, 8.5%, 3%, and 0.7%, respectively, were observed as the main causes in the liver cirrhosis patients. In this investigation, 34% had ascites and 12.8% encephalopathy.

Table I shows the patients' mean survival by separating them into different states, and Table II demonstrates frequency distribution of patients' demographic characteristics.

TABLE I
The Survival Means of 1, 3, 5 and 7 Years (Per Month) Understudy Patients

Survival Mean (± SD)	Death	Censored	Total
1 Year Survival	8.7(± 4.1)	10.0(± 3.8)	9.6(± 3.9)
3 Years Survival	16.7(± 12.3)	21.8(± 13.1)	20.4(± 13.1)
5 Years Survival	18.8(± 16.6)	28.1(± 21.2)	25.6(± 20.4)
7 Years Survival	19.3(± 18.1)	31.7(± 27.3)	28.4(± 25.7)

According to Table I, it was concluded that the survival average of the patients who died was less than who had withdrawn the study or have performed liver transplant surgery (were censored).

The results of univariate analysis based on gamma frailty model showed that sex, education, marital status, and blood group had no significant effect in the death time of liver cirrhosis patients. Besides, creatinine in the blood was not an effective factor. However, in Exponential and Weibull distributions, the variables of age, bilirubin, albumin, prothrombin, ascites, encephalopathy and INR index have had a significant impact (p-value<0.05). In the next stage, the significant variables as the result of univariate test, enrolled in multivariate analysis and in Table III, the regression coefficients, standard deviation and p-values according to each one of the variables have been provided. According to the multivariate analysis results, it was observed that age, bilirubin, albumin and encephalopathy have had a significant effect on death time of cirrhotic patients in exponential distribution. In Weibull distribution, age, bilirubin and albumin had a significant effect.

In Exponential and Weibull fitted models, the frailty variable estimations respectively were 1.11 and 2.79, which means that, in addition to explanatory variables, there are existence of other effective criteria for death of liver Cirrhosis patients.

IV. Conclusion

The present investigation expressed that, sex had no significant effect on the death time of cirrhotic patients. Many studies confirmed this emphasis [18]-[20].

TABLE II
FREQUENCY DISTRIBUTION OF DEMOGRAPHIC VARIABLES AND DIAGNOSTIC RESULTS OF UNDERSTUDY PATIENTS

Variables	Death (%)	Censored (%)	Total (%)	x^2	P-Value
Gender					
Male	48(58.5)	132(59.2)	180(59)	0.05	**0.82**
Female	34(41.5)	91(40.8)	125(41)		
Education					
illiterate	9(11)	18(8.1)	27(8.9)		
less than diploma	32(39)	84(37.7)	116(38.1)	6.15	**0.18**
Diploma	17(20.7)	61(27.4)	78(25.6)		
Academic	8(9.8)	35(15.7)	43(14.1)		
Missing	16(19.5)	25(11.2)	41(13.4)		
Marital Status					
Married	52(63.4)	150(67.3)	202(66.2)		
Single	21(25.6)	62(27.8)	83(27.2)	5.08	**0.15**
Divorced	4(4.9)	2(0.9)	6(2.0)		
Missing	5(6.1)	4(9)	14(4.6)		
Blood group					
A	21(25.6)	58(26)	79(25.9)		
B	23(28)	57(25.6)	80(26.2)	0.77	**0.94**
AB	9(11)	17(7.6)	26(8.5)		
O	24(29.3)	80(35.9)	104(34.1)		
Missing	5(6.1)	11(4.9)	16(5.2)		
Ascites					
No	45(54.9)	156(70)	201(66.0)	6.75	**0.009**
Yes	37(45.1)	67(30)	104(34.0)		
Encephalopathy					
No	65(79.3)	201(90.1)	266(87.2)	6.48	**0.01**
Yes	17(20.7)	22(9.9)	39(12.8)		
Cause Cirrhosis					
Hepatitis B	21(25.6)	49(22)	70(23.0)		
Hepatitis C	6(7.3)	30(13.5)	36(11.8)		
PSC	6(7.3)	20(9)	26(8.5)		
PBC	3(3.7)	6(2.7)	9(3.0)	7.86	**0.35**
Cryptogenic	18(22)	51(22.9)	69(22.6)		
Autoimmune	19(23.2)	31(13.9)	50(16.4)		
Alcoholic	0(0)	2(0.9)	2(0.7)		
Other	9(11)	34(15.2)	43(14.1)		
Total	**82(26.9)**	**223(73.1)**	**305(100)**		

TABLE III
THE RESULT OF MULTIVARIATE ANALYSIS OF GAMMA FRAILTY MODEL FOR UNDERSTUDY PATIENTS

	Exponential			Weibull		
Variables	β	SD	P-value	β	SD	P-value
Age	0.02	0.01	0.01*	0.02	0.01	0.02*
Bilirubin	0.13	0.03	0.001*	0.13	0.04	0.002*
Albumin	0.46	0.18	0.01*	0.52	0.19	0.008*
Prothrombin	0.07	0.05	0.22	0.09	0.06	0.12
Ascites	0.31	0.27	0.24	0.42	0.28	0.13
Encephalopathy	1.06	0.32	0.001*	1.07	0.35	0.002
INR	0.07	0.33	0.83	-0.02	0.34	0.93
θ	1.11	1.35		2.79	2.82	

***(p-value<0.05)**

Based on the results of univariate and multivariate analysis, age was an effective factor on the death time of liver cirrhosis patients. In the study of Fazeli et al., age was an effective factor on patients' death [21]. Besides, Khamneh et al. showed that age could be a predictive variable for liver cancer [22]. The mean age of patients enrolled the study was 39.8 years old which was almost the same as an average age of patients in the study of Firuzi et al. [23].

The most common cause of liver cirrhosis in the present study was hepatitis B, while many studies in Iran have observed the same result [4]-[6]. In some studies, the main reason for cirrhosis was cryptogenic disease [24], [25]. In numerous western countries, excessive alcohol consumption is a major cause of liver cirrhosis [2], [3].

The present investigation considered the main effective criteria on the death time of cirrhosis patients by applying the frailty model. In univariate gamma frailty model with Exponential and Weibull distributions, age, bilirubin, albumin, prothrombin, ascites, encephalopathy, and INR had effective impact on death time of cirrhotic patients.

In the analysis of multivariate exponential model, variables such as age, bilirubin, albumin and encephalopathy were identified as influencing criteria on the survival time of liver cirrhosis patients. In Weibull model variables age, bilirubin and albumin had a significant effect on death time of liver cirrhosis patients.

In the study by Bustamante et al. on liver cirrhosis patients, it was observed that increasing of bilirubin, decreasing of albumin and prothrombin time had significant effect [26]. In the investigation of Hui et al., bilirubin, albumin, and INR were known as significant impact [20].

In another study, in order to consider the effective criteria on liver cirrhosis patients, albumin and prothrombin had significant impact and bilirubin was not significant [27]. In the study of Velazquez et al., bilirubin, albumin, ascites and encephalopathy had no significant effect and the only significant variable was prothrombin. The results of an aforementioned study are different from the present investigation [18]. Besides, other studies were conducted to evaluate the factors affecting biliary cirrhosis in which bilirubin and prothrombin had no significant effect, but albumin was a significant factor [28], [29]. In numerous studies including the present one, creatinine is the only variable which had no significant effect in none of univariate and multivariate models [17].

Since hepatitis B is the most common cause of liver cirrhosis in Iran, the easy and low-risk solution of vaccination can be considered in order to control this disease (hepatitis B) in the society [30], [31]. In advanced cases of the liver cirrhosis disease, liver transplant is a satisfactory treatment for most of individuals [7], [32], [33]. The results of the current study can be useful to be referred to the countries in where viral hepatitis is the most common cause of liver cirrhosis.

ACKNOWLEDGEMENT

This article was part of a research project of Master of Science thesis which was sponsored by the School of Public Health at Iran University of Medical Sciences in 2015 and the code of 94-03-27-26534. The authors are grateful to all personnel of Transplant section of Tehran Imam Khomeini Hospital, specifically, Dr. Monaver Talebiyan.

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