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Analyzing the Survival of Patients with Liver Cirrhosis Using Ridge Semiparametric Models

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Abstract: *Introduction and Purpose of the study: Liver cirrhosis is one of the most common causes of death due to gastrointestinal diseases. It accounts for more than one million deaths annually in the world. Liver transplantation is the only way to cure this disease. Given the limited number of donated livers, the prioritization of the patients waiting for the transplantation queue is mandatory. The aim of this study was to analyze the survival of patients who were waiting for the liver transplantation using semi-parametric ridge regression models. Materials and Methodology: This study was a survival research. The data were collected from 305 patients waiting for the liver transplantation that were followed up at least for 7 years. Due to the correlation between the covariates, the ridge semiparametric models were used. Data analysis was performed using R (version 3.2.3) software. Results: In this study, out of 305 patients, 71 (23.3%) patients died because of liver cirrhosis and 51 patients (16.7%) had liver transplantation. The one-year, three-year, and five-year survival of the patients was 0.789, 0.556, and 0.478, respectively. In studying the factors affecting the survival of patients with liver cirrhosis, the variables of albumin logarithm, bilirubin log, age and encephalopathy were found to be statistically significant at the significance level of 0.01 in ridge regression models and Cox proportional hazards model. Using CVL indices, bias and total squared errors, the ridge regression model had better fit than Cox proportional hazards model. Conclusion: Due to the existence of a collinearity between the laboratory variables under study, using a ridge regression model for survival analysis of patients with liver cirrhosis reduced the estimation error and the bias of the fittings. Therefore, it is suggested that in the use of survival models, the collinearity between the covariates should be considered and, if any, some appropriate models should be used for the reduction of bias.*

Keywords: *Liver Cirrhosis, Long-Term Survival, Ridge Regression Model.*

INTRODUCTION

Liver cirrhosis is one of the most common causes of death from digestive diseases and is one of the major causes of the burden of the disease, which accounts for about 1 million deaths annually in the world (Mokdad et al., 2014; Malekzadeh et al., 2015; Ganji et al., 2009). It is one of the most important liver diseases and includes almost all liver diseases that lead to the loss of liver cells (Rajeswari and Reena, 2010). On average, death from liver cirrhosis in men is twice that of women (Mokdad et al., 2014). According to the Ministry of Health of Iran, out of 150 causes of death, 54 deaths from each 100,000 deaths were due to cirrhosis diseases (Aalabaf-Sabaghi, 2010).

The major causes of liver cirrhosis in Iran are hepatitis B, hepatitis C and autoimmune hepatitis (Moyed, 2014). The most important signs of liver cirrhosis include ascites, encephalopathies, esophageal varices, varicose bleeding and complications on the cardiovascular system, lungs and kidneys (Pazouki, Sepehri and Saberifiroozi, 2014). In cirrhosis, one should be aware of the disease, if it is caused by autoimmune disease or Wilson, there is a possibility of recovery, which is urgently needed to meet the requirement for rapid diagnosis and treatment. Cirrhosis does not have a definitive treatment, and the transplantation is the last step of the therapy whose conditions need to be met. What is important is determining the appropriate time for liver transplantation in patients. This time can be determined using the Child Model and MELD (Model for End-stage Liver Disease). According to the approved law of 2000 of US Department of Health and Human Services, the medical prioritization of patients waiting for binding transplantation and the use of the MELD model as an optimal prioritization system has become a compulsory (Abolghasemi et al., 2013).
According to the Child score table, the severity of the disease is ranked from 6 to 15 according to its criteria. The method of calculating the Childe criterion has been shown in Table 1.

Table 1. Calculation of the Child Criterion

Variable	Scores of score class of CP		
	A (1 score)	B (2 scores)	C (3 scores)
Billyrobin	<30	50-30	>50
Albumin	>35	35-28	<28
Prothrombin index	>54	54-44	<44
Ascites	No	slight	high
Encephalopathy	No	slight	high
Total scores	5-6	7-9	10-15

In the MELD method, the severity of the disease is calculated according to the amount of creatinine, bilirubin and the International Normalized Ratio (INR) and according to the following formula (Moyed, 2014).

$$\text{MELD} = 9.6 \times \ln(\text{creatinin mg/dL}) + 11.2 \times \ln(\text{INR}) + 3.8 \times \ln(\text{bilirubin mg/dL}) + 6.43 \quad (1)$$

In this study, due to the correlation between some of the predicting variables, the use of common survival models, like the Cox proportional hazards model, was not suitable since it caused a bias in estimating the parameters. When there is a correlation between the predicting variables, the ridge regression model could be used to estimate the parameters (Xue, Kim and Shore, 2007; Perperoglou, 2014).

Materials and Methodology

This is an applied research and a survival data analysis study. The data of this study were collected from 305 patients having liver cirrhosis, who entered the liver transplantation line of Tehran Imam Khomeini Hospital from June 2008 to June 2009 and were followed up for at least 7 years. The collected data consisted of demographic characteristics including gender, age, weight, height, marital status, educational level, cirrhosis cause and laboratory factors such as albumin levels, bilirubin, blood serum creatinine, and INR, as well as diagnostic factors for ascites and encephalopathy. The response variable in this study included the survival time of patients waiting for liver transplantation. Moreover, any death due to liver cirrhosis was considered as a failure. Patients who underwent liver transplantation during the study or those who were excluded from the study for any reason, were considered censored from right. Considering the fact that in this study, regarding the VIF values, a multiple linear correlation was observed, the Cox regression model was used with the ridge estimation method.
In order to estimate the parameters of the Cox proportional hazards model, a partial likelihood method was utilized. In this method, the time of events is ranked and the likelihood function is formed according to the

number of events. After that, the model parameters are fitted by the staged method so that the likelihood function finds its greatest value.

$$L(\beta) = \prod_{i=1}^{D} \frac{exp\left(\sum_{k=1}^{p} \beta_k Z_{(i)k}\right)}{\sum_{j\in R(t_i)} exp\left(\sum_{k=1}^{p} \beta_k Z_{jk}\right)} \quad (2)$$

The numerator of the above likelihood includes the information of those who have experienced the occurrence of the intended event, and its denominator includes the information of those who have not yet experienced the desired event and are at risk. In this case, the likelihood function logarithm is as follows:

$$l(\beta) = \sum_{i=1}^{D} \sum_{k=1}^{p} \beta_k Z_{(i)k} - \sum_{i=1}^{D} ln\left[\sum_{j\in R(t_i)} exp\left(\sum_{k=1}^{p} \beta_k Z_{jk}\right)\right] \quad (3)$$

In the relation (1), β is the vector of parameters, the vector of covariates, where the risk set R (t_i) for time t_i includes all persons who have been studied and survived before the time t_i, irrespective of censorship or occurrence.

Ridge regression

The ridge estimator is a linear combination of the least squares estimator such that:

$$\hat{\beta}_r = (X'X + kI)^{-1}X'Y = (X'X + kI)^{-1}(X'X)\hat{\beta} = Z_k\hat{\beta} \quad (4)$$

Different values for K are considered. If K=0, then the ridge estimator would be equal to the least squares error estimators. For K, other values such as $\frac{1}{\hat{\beta}'\hat{\beta}}$ and $\frac{p}{\hat{\beta}'\hat{\beta}}$ can be used, where p is the number of independent variables of the model. Each one that produces a lower bias would be selected as the selected K.

In the case of multiple collinearity, the likelihood function is as follows:

For Cox proportional hazards model with relationship

$$\lambda(t|Z) = \lambda_0(t)\exp\left(\sum_{k=1}^{p} \beta_k Z_k\right) \quad (5)$$

Where $\lambda_0(t)$ is called the model`s baseline hazard. So, the maximum likelihood estimator is obtained as follows:

$$\hat{\beta} = (\hat{D}'\hat{D})^{-1}\hat{D}'\hat{U} \quad (6)$$

In the above formula, $\hat{D}$ and $\hat{U}$ are a function of $\hat{\beta}$, the matrix of independent variables, the survival time and, of course, censorship. Similarly, $\hat{\beta}^R$, which is a ridge estimator for the Cox model, is obtained as follows:

$$\hat{\beta}^R = (\hat{D}'\hat{D} + KI)^{-1}\hat{D}'\hat{U}\hat{\beta} \quad (7)$$

Where K is the constant value in the Cox model in the presence of a collinearity of values of ${}^{1}/_{\hat{\beta}'\hat{\beta}}$, ${}^{p}/_{\hat{\beta}'\hat{\beta}}$ or ${}^{(p+1)}/_{\hat{\beta}'\hat{\beta}}$ and p is the number of covariates in the model.

Contrary to the maximum likelihood estimators for the hazard regression models, the partial likelihood estimators are only asymptotically non-bias. Therefore, for the ridge estimators in the survival data analysis, there is no need for non-bias establishment. Furthermore, for comparing ridge estimators with commonly maximum used estimators of the total squared error (MSE) the cross validation values (cvl) are used which are defined as follows:

$$cvl = \sum_{i=1}^{n} lp_i(\hat{\beta}_{-i}^R) \quad (8)$$

$$lp_i(\beta) = l(\beta) - lp_{-i}(\beta) \qquad (9)$$

Where $lp_{-i}(\beta)$ is the maximum value of the likelihood. If the person i is excluded from the analysis, then similarly, $\hat{\beta}_{-i}^{R}$ would be the ridge estimation of the parameter β when the person i is excluded from the analysis.
To calculate the confidence interval for the ridge parameters, since the variance of the ridge estimator is defined as:

$$\widehat{Var}(\hat{\beta}^{R}) \approx \left(\widehat{D}'\widehat{D} + KI\right)^{-1}\widehat{D}'\widehat{D}\left(\widehat{D}'\widehat{D} + KI\right)^{-1} \qquad (9)$$

A confidence interval of $1-\alpha$ percent with $\hat{\beta}_j^R \pm Z_{1-\alpha/2}\sqrt{\widehat{Var}_{jj}^{R}}$ is obtained (Xue, Kim and Shore, 2007; Perperoglou, 2014).

Multiple collinear Detection

If VIF is defined as follows.

$$(10) VIF_j = C_{jj} = \frac{1}{1-R_j^2}, c = (X'X)^{-1}$$

In the formula above, R_j^2 is designated as the coefficient of determination.
If there be linear dependencies between the independent variables, the coefficient of determination would be close to ±1 and large C_{jj}. If $VIF_j s$ exceed 5 or 10, there would be multiple collinearity.

Findings

In this research, 305 patients having liver cirrhosis waiting for the transplantation line, with a mean age of 47.7 and a standard deviation of 14.32 years, were studied. Out of these pateients, 180 (59%) were men and 125 (41%) were women. One-year, three-year and five-year survival of the patients was 0.85, 0.67, and 0.60, respectively. During the study, 82 patients (26.9%) died due to liver cirrhosis complications, out of which 58.5% (48 patients) were males and 41.5% (34 patients) were female. A total of 73.1% patients were considered as censored from the right. The findings of this research showed that the majority of patients had a blood type of O and hepatitis B with 23% and cryptogenic disease with 22.6% were the most important causes of cirrhosis. Demographic characteristics, diagnostic and laboratory results of liver cirrhosis patients waiting for the transplantation line have been given in Table 2 according to their last vital condition.

Table 2: Demographic characteristics, diagnostic and laboratory results of patients with liver cirrhosis waiting for the transplantation according to the vital status

Demographic characteristics / Vital status		Living (frequency/ percentage)	Died (frequency/ percentage)	Withdrawal (frequency/ percentage)	Transplantation (frequency/ percentage)	Total
Gender	Man	54 (55.7)	48 (58.5)	55 (64.0)	23 (57.5)	180 (59.0)
	Woman	43 (44.3)	34 (41.5)	31 (36.0)	17 (42.5)	125 (41.0)
Marital status	Married	57 (58.8)	52 (63.4)	64 (74.4)	29 (72.5)	202 (66.2)
	Single	37 (38.1)	21 (25.6)	14 (16.3)	11 (27.5)	83 (27.2)
	Divorced or widow	1 (1.0)	4 (4.9)	1 (1.2)	0 (0.0)	6 (2.0)
	Non-specified	2 (2.1)	5 (6.1)	7 (8.1)	0 (0.0)	14 (4.6)
education	Illiterate	10 (10.3)	9 (11.0)	6 (7.0)	2 (5.0)	27 (8.9)
	Under diploma	29 (29.9)	32 (39.0)	38 (44.2)	17 (42.5)	116 (38.0)

	Diploma	30 (30.9)	17 (20.7)	24 (27.9)	7 (17.5)	78 (25.6)
	Academic	17 (17.5)	8 (9.8)	5 (5.8)	13 (32.5)	43 (14.1)
	Non-specified	11 (11.3)	16 (19.5)	13 (15.1)	1 (2.5)	41 (13.4)
BMI	mean (±sd)	22.80 (2.71)	23.37 (4.54)	23.78 (4.08)	23.68 (2.13)	(3.64) 23.35
Age	mean (±sd)	43.50 (14.10)	49.18 (14.68)	51.84 (13.81)	45.72 (12.48)	(14.32) 47.67
Cirrhosis cause		15 (15.5)	21 (25.6)	21 (24.4)	13 (32.5)	70 (23.0)
		10 (10.3)	6 (7.3)	15 (17.4)	5 (12.5)	36 (11.8)
		12 (12.4)	6 (7.3)	4 (4.7)	4 (10.0)	26 (8.5)
		2 (2.1)	3 (3.7)	4 (4.7)	0 (0.0)	9 (3.0)
		23 (23.7)	18 (22)	19 (22.1)	9 (22.5)	69 (22.6)
		12 (12.4)	19 (23.2)	13 (15.1)	16 (15)	50 (16.4)
		1 (1.0)	0 (0.0)	1 (1.2)	0 (0.0)	2 (0.7)
		22 (22.7)	9 (11.0)	9 (10.5)	3 (7.5)	43 (14.1)
Blood group	A	26 (26.8)	21 (25.6)	19 (22.1)	13 (32.5)	79 (25.9)
	B	28 (28.9)	23 (28.0)	17 (19.8)	12 (30.0)	80 (26.2)
	AB	7 (7.2)	9 (11.0)	8 (9.3)	2 (5.0)	26 (8.5)
	O	36 (37.1)	24 (29.3)	31 (36.0)	13 (32.5)	104 (34.1)
	Non-specified	0 (0.0)	5 (6.1)	11 (12.8)	0 (0.0)	16 (5.2)
Laboratory and diagnostic results of ascites	Yes	23 (23.7)	37 (45.1)	32(37.2)	12 (30.0)	104 (34.1)
	No	74 (76.3)	45 (54.9)	54(62.8)	28 (70.0)	201 (65.9)
Encephalopathy	Yes	6 (6.2)	17 (20.7)	12 (14.0)	4 (10.0)	39 (12.8)
	No	91 (93.8)	65 (79.3)	74 (86.0)	36 (90.0)	266 (87.2)
Blood serum bilirubin	mean (±sd)	2.65 (3.09)	6.92 (9.86)	3.52 (3.49)	4.54 (5.52)	(6.25) 4.29
Blood serum albumin	mean (±sd)	4.18 (3.07)	3.26 (0.76)	3.67 (2.35)	3.37 (0.78)	(2.22) 3.68
Blood serum creatinine	mean (±sd)	1.02 (1.48)	1.04 (1.40)	0.98 (0.52)	0.83 (0.23)	(1.14) 0.99
Blood serum INR	mean (±sd)	1.53 (0.51)	1.90 (0.99)	1.64 (0.65)	1.75 (0.57)	(0.72) 1.69

Using the non-parametric Kaplan-Meier method, the survival of patients waiting for the liver transplantation has been shown in Table 3.

Table 3. Survival rates of three months, six months, one year, three years and five years of patients waiting for transplantation

Survival	Survival ratio	Standard deviation	Confidence distance of 95%	
			Lower limit	Upper limit
three months	0.924	0.924	0.893	0.955
six months	0.898	0.898	0.861	0.935
one year	0.793	0.793	0.744	0.842
three years	0.556	0.556	0.487	0.627
five years	0.480	0.480	0.403	0.556

As shown in Table 3, the survival ratio decreased dramatically in the first year, and the survival ratio of five years to one year was approximately 60% and the median survival rate for these patients was 4.3 years. Figure 4-1 shows the survival function per days.

Table 4. Multiple regression model`s results for the Cox proportional hazards in analyzing the survival of patients with liver cirrhosis

Variable	Coefficient variable	Coefficient variable Exp	Standard deviation	Z	P
Albumin logarithm	-1.4650	0.2311	0.4380	-3.340	0.001
Bilirubin algorithm	0.6868	1.9873	0.1238	5.550	<0.001
Age	0.0279	1.0283	0.0091	3.000	0.002
Encephalopathy	1.2533	3.5018	0.2909	4.310	<0.001

As seen in Tables 4 and 5, the logarithmic variables of albumin, bilirubin, INR logarithm, encephalopathy, ascites, gender and age in the simple analysis and log variables of albumin, bilirubin, encephalopathy and age in the multiple analysis showed Cox proportional hazards for Patients survival with the liver cirrhosis.

Table 5- Results of ridge regression model in analyzing the survival of patients with liver cirrhosis

Variable	Coefficient variable	Coefficient variable Exp	Standard deviation	P
Albumin logarithm	-1.4460	0.2355	0.4345	0.0009
Bilirubin algorithm	0.6779	1.9697	0.1230	<0.0001
Age	0.0274	1.0277	0.0090	0.0024
Encephalopathy	1.2406	3.4576	0.2901	<0.0001

Table 6: Comparison of CVl and MSE values based on Cox and ridge proportional hazards models in predicting the risk function of patients with liver cirrhosis

	Cox	Ridge		
		$\boldsymbol{k} = \mathbf{1}/\widehat{\boldsymbol{\beta}}'\widehat{\boldsymbol{\beta}}$	$\boldsymbol{k} = \boldsymbol{p}/\widehat{\boldsymbol{\beta}}'\widehat{\boldsymbol{\beta}}$	$\boldsymbol{k} = (\boldsymbol{p}+\mathbf{1})/\widehat{\boldsymbol{\beta}}'\widehat{\boldsymbol{\beta}}$
Bias	0.67	0.63	0.58	0.57
Bias relative to Cox	1.00	0.94	0.87	0.85
MSE	0.061	0.054	0.051	0.050
MSE relative to Cox	1.00	0.86	0.84	0.82
Cv1	-70.1	-69.9	-69.7	-69.7
Difference with Cox model	0.0	0.2	0.4	0.4

Regarding the results of regression models and ridge regression model, it was found that the ridge regression model was of bias with respect to $\boldsymbol{k} = (\boldsymbol{p}+\mathbf{1})/\widehat{\boldsymbol{\beta}}'\widehat{\boldsymbol{\beta}}$, so that its bias was 85% of the Cox model bias and the total error squared error was 82% relative to the Cox model. Moreover, CVl varied with Cox 0.4 model.

Discussion and Conclusion

Liver cirrhosis is one of the most common causes of gastrointestinal diseases (Malekzadeh et al., 2015; Ganji et al., 2009). So far, several studies have been conducted regarding the survival of patients waiting for liver transplantation in Iran and elsewhere in the world. In Australia, Michael examined the survival of patients awaiting transplantation line using Kaplan Meier diagram and a logarithmic rank test, and used the proportional hazards in a multivariate analysis. According to the findings of this study, the survival of patients awaiting transplantation in women, the patients with acute liver failure, blood type O, Childe score greater than and equal to 10, MELD score greater than and equal to 20 was significantly worse (Fink et al., 2007).

In the study of Sumskiene, out of 236 patients diagnosed with liver cirrhosis, 45 patients had a Child score greater than and equal to 10, and waited for transplantation. Out of these patients, 23 (51.1%) patients died, and only two patients received liver. The mean survival time was 17.93 months. 48.9% of patients had liver cirrhosis due to alcoholic cirrhosis and 28.9% of patients had it due to viral hepatitis. Increasing the age and bilirubin, creatinine and urea, as well as increased Child score and MELD, had a significant effect on the decreased survival of patients waiting for the transplantation line (Sumskienė et al., 2005).

In a study, Khadem al-Hosseini estimated the survival of 646 patients waiting for liver transplantation in Shiraz Namazi Hospital using the Kaplan Meier method and compared the results with a logarithmic rank test. The mean waiting time for transplantation was 6.6 months and the mean survival time was 22.8 months for patients not undergoing liver transplantation. In this study, hepatitis B (31.2%) and cryptogenic disease (26.9%) were the most common causes of liver cirrhosis. According to the results of this study, the gender and the blood group were not associated with receiving transplantation but were in relation with the cause of the disease and the RH of the blood group ($p < 0.05$). Through classifying patients who did not undergo liver transplantation, based on the MELD criteria, it was observed that the individuals with a MELD score less than 15 had higher survival and a significant difference ($p < 0.001$).

Using Cox regression model in the presence of age, gender, Child score, MELD score and having or not having complications, Saber Firouzi concluded that MELD as an independent risk factor ($p = 0.001$) and increased age and gender were the risk factors for death in 480 patients with liver cirrhosis, waiting for the liver in the queue of liver transplantation of the Namazi Hospital in Shiraz. Cryptogenic disease (29.9%) and hepatitis B (26.5%) were the most common causes of liver cirrhosis in these patients (Saberifiroozi et al., 2006).

In a study on 305 patients with liver cirrhosis waiting in the transplantation line, Abolghasemi provided a new prioritization system through using proportional hazards model based on the variables of age, logarithm bilirubin and logarithm albumin. He showed its efficacy`s superiority with the MELD prioritization system, by Area Under the Curve (AUC) of Receiver Operating Characteristic of survival performance (Abolghasemi, 2012).

Ebrahimi Khamenei et al. used a data mining and decision tree to predict liver cancer in 258 cirrhosis patients referred to the gastrointestinal and liver Institute of Shariati Hospital, which had been monitored for 4 years. According to the results of decision tree categorization, the variables of age, body mass index, cause of disease, placket, bilirubin, INR, creatinine, alpha-fytoprotein and albumin were predictors of the likelihood of liver cancer in the cirrhosis patients (Khameneh, Sepehri and Saberifiroozi, 2014).

In the present study, out of 305 patients waiting for the transplantation, the most common cause of liver cirrhosis has been hepatitis B which was consistent with the studies of Zorzi, Mathur, Khadem al-Hosseini, Azimi and Hajiani. The results of the current study were not in line with the study of Malekhosseini and Saberi Firouzi, in which the most important cause was the cryptogenic disease. Due to the Islamic law and religious beliefs, the alcoholic cirrhosis is not a common cause in Iran. In the study of Saber Firouzi, 36% and in the study of Khadem al-Hosseini, 25.7% of patients waiting for the transplantation died. In the current study 26.9% of patients waiting for the transplantation died, while in the Zapata's study, 50% of patients waiting for the transplantation with a mean time of 168 days underwent liver transplantation, and only 8 (15%) patients died (Sumskienė et al., 2005; Zapata et al., 2004; Malinchoc et al., 2000; Zorzi et al., 2012; Mathur et al., 2011; Hajiani et al., 2012; Azimi et al., 2000).

In this study, the variables of bilirubin logarithm, albumin logarithm, age and encephalopathy were found to be effective on the survival of patients waiting for liver transplantation in Cox and ridge regression models. However, in fitting these two model, the ridge regression model had better fit due to having less bias and error as well as the superiority of cvl.

Regarding the high prevalence of gastrointestinal and liver diseases and the need of advanced liver patients for transplantation and thus the establishment of transplantation line based on medical provisions, it is recommended to use the methods controlling collinearity such as the ridge regression model based on the collinearity between laboratory variables.

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