IJBPAS, June, 2016, 5(6): 1477-1489

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

APPLICATION OF LONG-TERM SURVIVAL MODELS FOR ANALYZING SURVIVAL OF PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Purpose: Liver cirrhosis is one of the most common causes of death in digestive disease with more than one million deaths annually in the world. Liver transplantation is the only treatment of liver cirrhosis and due to shortage of available donor livers prioritizes medically patients who are in waiting list for transplantation is necessary. The aim of this study is to analyze the survival of patients who are in waiting list for liver transplant using mixture cure models.

Method: In this survival study, 305 patients with liver cirrhosis who were on waiting list for liver transplantation and followed for at least 7 years were investigated. Because of high rate of censoring, parametric mixture cure models were used. Data were analyzed using Stata (version12) and R (version 3.2.1) softwares and p-values <0.05 were considered to be significant.

Results: Results showed that the mean age was 39.85 (±14.54) years. During the study, 26.9% patients died due to complications of liver cirrhosis and viral hepatitis (34.8%) was the most common etiology of liver disease. Estimated survival rate at one, three and five years were 85%, 67% and 60%, respectively. It is concluded that among parametric mixture cure models, logistic mixture cure model withLogit link function and the lowest Akaike’s criterionchosen as the best model and variables serum bilirubin, and albumin were significant on long-term of survival.

Conclusion: when the data indicate that the long-lived patientsare available, using long-term models for survival analysis advisable. According to the results, logistic mixture cure model was more efficient than others to predict survival of cirrhotic patents.

Key words: liver cirrhosis, long-term survival, mixture cure model,Akaike's criterion

INTRODUCTION

Liver cirrhosis is one of the most prevalent reasons for mortality resulted due to digestive diseases that possess more than one million deaths across the world annually(1-3).Liver cirrhosis is one of the most important liver diseases and encompasses almost all liver diseases resulting in destruction and loss of Hepatocytes (liver cells) (4). On average, death caused by liver cirrhosis is twice more in male than in female(1). According to Statistics of Iran's Health Ministry for 150 causes of death, 54 out of every hundred thousand deaths are because of liver cirrhosis disease (5).

Hepatitis B, hepatitis C andAutoimmune hepatitis are the main causes of liver cirrhosis in Iran (6). The most important symptoms of liver cirrhosis include ascites, encephalopathy, varices, variceal bleeding and complications created in cardiovascular system, lungs, and kidneys (7). In cirrhosis diseases, the cause of disease should be considered. If the reason is autoimmune or Wilson, probability of improvement of the disease is high and to achieve this condition, it is necessary to diagnose and treat the disease rapidly. Cirrhosis disease has no certain treatment and transplant is the last medical step that it conditions should be provided. An important issue is right time of taking transplant operation in patients. Through ranking patients using two methods of Child and MELD (Model for End Stage Liver Disease), required time to take transplant of liver can be determined (6). According to the rule approved in 2000 by Department of Health and Human Services (DHHS) of the U.S, prioritization of patients waiting in transplant list is an essential action and using MELD model as an optimal prioritization system is required(8).

According to Child ranking table, severity of disease based on its criteria can be ranged from 5 to 15. The method to calculate Child criterion is presented in table 1.

Table 1.Child-Pugh Scores' Calculating Method

CP risk class points			
	A (1 point)	B (2 point)	C (3 point)
Serum bilirubin (mg/dL)	<30	30-50	>50
Serum albumin (g/dL)	>35	28-35	<28
Prothrombin index	>54	44-54	<44
Ascites	none	light	large
Encephalopathy	none	minimal	advanced
Total score	5-6	7-9	10-15

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

In MELD method, severity of disease has been estimated according to the amount of serum bilirubin, creatinine, and international normalized ratio (INR) of prothrombin and was calculated by following formula (6).

In patients with liver cirrhosis, on account to low number of donated livers, high percent of patients fail to receive liver and remain in waiting list till the end of the study. In fact, large number of patients has long-term survival.

The cases that never experience the event of interest are referred to as cured, immune, or non-susceptible.With present of cure fraction in data, standard survival analysis methods such as Cox's proportional hazard model or log-rank test may not be appropriate because they do not account for the possibility of cure (9-12). In such a situation, Cure models(also known as long-term survival models) which are special types of survival analysis models, are used.

Using cure models has been confirmed in survival assessment of patients and factors affecting their long-term survival in other studies. Khoei et al have adopted a study to investigate and compare mixture and non-mixture cure models in 296 patients with major thalassemia. Finally, log-normal non-mixture cure model with lowest Akaike information criterion (AIC) has been selected as the best model to determine risk factors of major thalassemia (13, 14). Therefore, using mixture cure models is suitable for data analysis that some people don't analyze the desired event as time goes. The aim of the current study is assessing and comparing weibull, logistic, log-normal and gamma parametric mixture cure models to determine factors affecting long-term survival of patients with liver cirrhosis waiting in transplant list. Also, to compare the efficiency of these models, and select the best one, we used the AIC.

METHODS AND MATERIALS

This study is survival analysis and an applied research that incorporates data from 305 patients with liver cirrhosis who entered to liver transplant waiting list of Imam Khomeini Hospital during 2008-2009 and were followed up at least for 7 years. Deaths due to liver cirrhosis were regarded as failure and survival time of patients waiting in liver transplant list considered as a response variable. Patients who get liver transplantation or those leaving the study for any reason have been considered as censored. As ratio of censorship is considerable in this study, it would be better to use cure models. Cure models are divided to two major groups of mixture and non-mixture (15). Mixture cure model has been developed for the first time by Boag (1949). In these models, the population includes two heterogeneous groups. The first group contains patients at risks of death who eventually dieand second group includes patients who will not die until the end of the study. Survival function for the individuals in mixture cure models is as follows:

$$\mathbf{S(t|X) = (1 - \theta(X)) + \theta(X)S_0(t|X)} \quad (2)$$

Where; S(t) is survival function of whole population, $(1-\theta(X))$ is ratio of individuals with long-term survival and survival of other individuals is demonstrated with $S_0(t)$ function. Ratio of individuals to long-term survival can be modeled using logistic regression, probit function, log-log amendment link function and linear regression (16). Determining the link function is important because it leads to different assumptions about the joint effect of covariates (17).It should be mentioned that cure models would be changed into standard survival models in absence of people with long-term survival (12).

As a matter of fact, non-mixture cure models are a generalization of mixture cure models that were proposed for the first time by Yakovlev (1996). As it was mentioned, in regard with survival data analysis, the basic assumption is that over the time, all people experience desired event and as a result, accumulative risk function would be increased to infinity; although with presence of individuals with long-term survival and increase in time, survival function would not become zero and hence, accumulative risk function would not be increased to the infinity and survival curve would become flat gradually. In order to limit accumulative risk function, multiplication of a parameter in an accumulative risk function would be applied and increase in time can cause accumulative risk function bounded in non-mixture cure model. Survival function for population individuals in non-mixture cure models would be obtained as follows:

$$\mathbf{S(t|X) = e^{-\theta(X)F(t)}} \quad (3)$$

Where;$\theta(X)$would be related to covariates using a link function like modal link function, logistic and linear function and $F(t)$ is the accumulative distribution function of x stand for non-negative random variable (18).

For data analysis, demographic, clinical, and biochemical characteristics of patients were assessed in the cure models, using STATA (12.0) software and CUREREGR module. The effects of a number of factors on the survival of liver cirrhosis patients were evaluated including, sex, age, BMI (Body Mass Index), marital status, education, blood group, cause of cirrhosis, biochemical factors like levels of albumin, bilirubin, INR and creatinine and clinical factors of as cites and encephalopathy. The significance level was set at $P \leq 0.05$.

RESULTS

Of the 305 patients, 180 people (59%) were male and 125 people (41%) were female. The mean age of the patients was39.85 ±14.54 years. Survival rate at one, two and three years estimated 0.85, .67 and 0.60respectively. During the study, 82 patients (26.9%) died due to complications of liver cirrhosis which comprised 58.5% (48 patients) male and 41.5% (34 patients) female. Totally, 73.1% of patients were censored. Results indicate that majority of patients had blood type O and viral hepatitis (34.8%) followed by cryptogenic (22.6%) were the most prevalent causes of cirrhosis. Demographic information, clinical and biochemical results of liver cirrhosis patients waiting in liver transplant list separated for last vital status of the patients have been presented in table 2. Quantitative results were expressed as mean ± standard deviation.

Before using cure models, it is required to investigate presumptions of model including cure fraction and adequacy of the length of follow up period. This may determine if there isa considerable percentage of long-lived patients and whether the follow up period is long enough or the significance of the long-lived patients in due to a short follow up period. One of the common methods to investigate the presumption is using Kaplan-Meier graph(19, 20).When the survival curve has a stable plateau at the end of the study it is recommended to use cure models for analyzing the survival data(21). Kaplan-Meier graph observed curve with 95% confidence interval has been illustrated in figure 1.As the figure shows, the curve reached a plateau at the right tail, so using the cure model led to more accurate results. Clearly, the ratio of people with long-term survival is more than 0.58.

Table 2: Demographic and clinical characteristics in patients awaiting Liver Transplantation

Factors	Total, (%)	Transplant,(%)	Withdraw,(%)	Death, (%)	Alive, (%)	Value of Statistics (χ^2/Fisher)	Df	P-value
Gender						1.362	3	0.715
Male	59.0	57.5	64.0	58.5	55.7			
Female	41.0	42.5	36.0	41.5	44.3			
Marital status						9.664	3	0.022
Married	71.5	72.5	82.3	72.7	61.1			
Single	28.5	27.5	17.7	27.3	38.9			
Education						18.214	6	0.006
Primary school	54.2	48.7	60.3	62.1	45.3			
Diploma	29.5	17.9	32.9	25.8	34.9			
Academic	16.3	33.4	6.8	12.1	19.8			
Cause of cirrhosis						16.159	9	0.064
Viral Hepatitis	34.8	45.0	41.9	32.9	25.8			
Cryptogenic	22.6	22.5	22.1	22.0	23.7			
Auto Immune	16.4	15.0	15.1	23.2	12.4			
Others	26.2	17.5	20.9	22.0	38.1			
Blood type						4.618	9	0.866
A	27.3	32.5	25.3	27.2	26.8			
B	27.7	30	22.7	29.9	28.9			
AB	9.0	5.0	10.7	11.7	7.2			
O	36.0	32.5	41.3	31.2	37.1			
Clinical factors								
Ascites						9.761	3	0.021
Yes	34.1	30.0	37.2	45.1	23.7			
No	65.9	70.0	62.8	54.9	76.3			
Encephalopathy						8.815	3	0.032
Yes	12.8	10.0	14.0	20.7	6.2			
No	87.2	90.0	86.0	79.3	93.8			
Factors	**Total**	**Transplant**	**Withdraw**	**Death**	**Alive**	**F(ANOVA)**	**Dfs**	**P-value**
BMI, mean(±sd)	23.35 (3.64)	23.68 (2.13)	23.78 (4.08)	23.37 (4.54)	22.80 (2.71)	2.272	3,301	0.080
mean(±sdAge,)	39.85 (14.54)	37.74 (12.98)	43.63 (13.88)	41.3 (15.12)	36.12 (14.4)	4.661	3,293	0.003
Biochemical, mean ± SD								
Serum bilirubin	4.29 (6.25)	4.54 (5.52)	3.52 (3.49)	6.92 (9.86)	2.65 (3.09)	8.022	3,301	<0.001
Serum albumin	3.68 (2.22)	3.37 (0.78)	3.67 (2.35)	3.26 (0.76)	4.18 (3.07)	2.958	3,301	0.033
Serum creatinine	0.99 (1.14)	0.83 (0.23)	0.98 (0.52)	1.04 (1.40)	1.02 (1.48)	0.300	3,301	0.825
INR	1.69 (0.72)	1.75 (0.57)	1.64 (0.65)	1.90 (0.99)	1.53 (0.51)	4.358	3,301	0.005

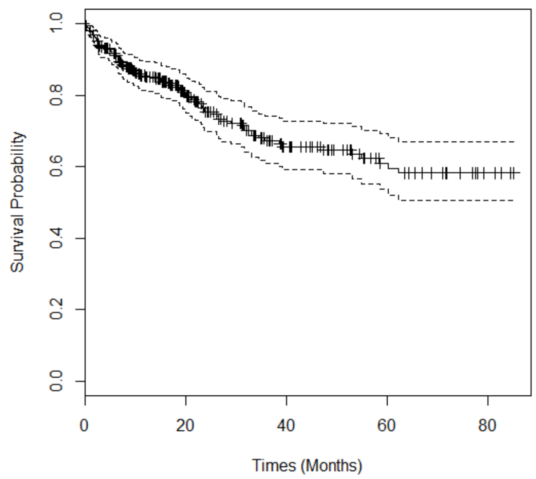

Figure 1.Kaplan-Meier survival curve of the entire study population

For purpose of model fitness, first, univariate mixture cure models have been applied using survival functions of weibull, logistic, log-normal and gamma and to estimate ratio of people with long-term survival, logistic link function is used.

Results of univariate parametric mixture cure models (weibull, logistic, log-normal and gamma) showed thatin all mentioned models, bilirubin, and albumin have been significant effects on the long-term survival of patients, and encephalopathyin gamma model also have been significant correlation. Univariate regression of short-term survival indicated the significant effects of bilirubin, INR on short-term survival. Moreover, age variable in log-normal model and encephalopathy in logistic and log-normal models have been correlated to short-term survival.

After assessment of effect of variables on long-term and short-term survivalin univariate in .2, multivariate mixture cure models was validated using backward elimination procedure. Obtained results from mentioned final models finesses, along withAIC values, have been presented in table 3. It could be observed that lowest value of AIC has been related to logistic cure model and hence, it has had better fitness than other models.

Besides, in univariate as well as multivariate framework, scale parameter was modeled by covariates and shape parameter was considered fixed. In multivariate analysis, variables entered in both the short-term (scale parameter) and long-term (logistic link function).

In table 4, coefficients, standard errors and 95% confidence intervals of variables has been illustrated for logistic mixture cure model. The multivariate analysis showed that the effects of serum bilirubin and albumin level on long-term survival were significant. When using logistic link function for long-term survival, positive variable coefficient indicates that if the variable coefficient is increased, long-term survival would be also increased, so that lower bilirubin level and higher albumin level, improved the long-term survival of the patients. In addition, bilirubin, INR, encephalopathy affected the short-term survival of the patients.

Table 3: Estimation of parametric mixture cure models of patients with liver cirrhosis

Long-term Survival	weibull	logistic	log-normal	gamma
bilirubin	0.046	0.043	0.041	-
albumin	0.003	0.006	0.004	0.006
constant	0.020	0.017	0.011	0.013
Short-term Survival				
bilirubin	0.011	0.002	<0.001	<0.001
INR	0.036	0.029	-	0.049
encephalopathy	-	0.004	-	-
constant	<0.001	<0.001	<0.001	<0.001
shape	0.712	0.186	<0.001	0.379
AIC	1396.775	1390.709	1409.121	1403.498

Table 4.Estimation of logistic multivariate mixture curemodelof patients with liver cirrhosis

Long-term Survival	Coefficients	Standard Error	95% CI
bilirubin	-0.12	0.074	(-0.274 , -0.017)
albumin	1.271	0.465	(0.359 , 2.183)
constant	-4.586	1.927	(-8.364 , -0.809)
Short-term Survival			
bilirubin	0.054	0.017	(0.019 , 0.088)
INR	0.337	0.155	(0.034 , 0.641)
encephalopathy	0.932	0.323	(0.299 , 1.566)
constant	-8.849	0.577	(-9.979 , -7.719)
shape	0.153	0.116	(0.074 , 0.379)

DISCUSSION AND CONCLUSION

Liver cirrhosis is one of the most common reasons for digestive diseases (2, 3). The only curative therapy for end-stage liver disease is transplantation but due to a shortage of available donor livers, high rate of patients remain in list for a long time(6, 22-24),So we are facing with the proportion of patients who do not experience the event under study, i.e. those who are not susceptible to the occurrence of the event under study. The proportion of such observations is known as cure fraction. In addition, survival analysis via considering cure fraction is called cure models or long-term survival models and includes two general types, mixture and non-mixture (25, 26).

Different studies have been adopted till now in field of survival of patients waiting in transplant list in Iran and rest of the world. Results from the investigations indicate that, the majority of studies investigating the factors affecting the survival of cirrhotic patients who are waiting in transplant list, mainly used Log-rank test and Cox analysis(22, 23, 27-30).The presence of long-lived patients among those investigated in survival analysis makes implementing the cure models more adequate (20).On the other hand,number of studies in this field using long-term survival models to determine important factors in long-term survival of these patients is limited. Hence the present study has assessed parametric mixture cure models with log it link function to find factors that may have an effect on the survival of patients waiting in liver transplant list. Preference of final model has been specified through comparing with AIC. Although in studies no certain model can be introduced as the best model, it is concluded that, the logistic mixture cure model with the minimum value of AIC, was more efficient than other models for identification the risk factors of cirrhotic patients. According to the results of logistic mixture cure model, serum bilirubin and albumin are two important factors on long-term survival of patients with logit link function and bilirubin, INR and encephalopathy have had significant effect on short-term survival of patients.

For the past 20 years or more, several studies have been conducted on cure models and they have been well developed in the statistical literature (26, 31-33)

The current data supported the effect of serum bilirub in on long-term survival that in concordant with Sumskiene findings(30). Although it has been said that aging, blood group O and increase in serum creatinine have had significant impact on survival reduction of patients, we found no significant correlation between survival time and these factors.In addition according to their findings, increase of scores in Child and MELD scales had the positive direct correlation with increased mortality in cirrhotic patients (23, 27,30).

Abolghasemi has adopted a study on 305 patients with liver cirrhosis waiting in transplant list and has presented a new prioritization system using fitted risk model based on variables of age, bilirubin logarithm and albumin logarithm. Efficiency of this new model was specified using receive operating characteristics curve for survival predictive model(34).

At the present study, among 305 patients waiting in liver transplant list, the most etiology of liver cirrhosis has beenviral hepatitis, which has been in accordancewith several studies(22, 28, 29, 35, 36).Although this is not in line with the findings of Malek Hosseinin et al. and Saberi Firooziet al. where cryptogenic reported to be the leading cause of liver cirrhosis, also in contrast with results of Malinchoc et al. at a medical center in the U.S.A. where alcoholic liver cirrhosis was the most prevalent (61.9%.) followed by viral hepatitis (10.4%), Sumskiene et al. in Lithuania where alcoholic liver cirrhosis was the most prevalent (48.9%) followed by viral hepatitis (28.9%),and Zapata et al. in Chile with 22% alcohol consumption(23, 30, 37-39). Because of prohibition of using alcohol by Islamic rules and religious beliefs, alcoholic cirrhosis is not a common reason in Iran.

Based on our findings, 26.9% of patients were died. In Sumskiene et al. study, among 45 patients who were placed in waiting list,23 patients (51.1%) were died and only 2 patients could receive liver.In study of Saberi Firoozi et al., 36% of patients and in study of Khademal Hosseini et al., 25.7% of patients waiting in transplant list were died. In study of Zapata, 50% of patients waiting in transplant list with time average of 168 days were operated for liver transplant and only 8 patients (15%) were died (22, 23, 30, 38).

Nevertheless in this study the model converged after a few iterations. It is recommended using semi-parametric or non-mixture cure models in future studies.

Acknowledgement

Authors would like to appreciate all staffs of Liver Transplant Center of Imam Khomeini Hospital (Tehran, Iran) especially Dr. MonavarTalebianfor their kind assistance in collecting the data. This article is a part of M.S thesis of biostatistics under the title of "Application of non-mixture cure survival model with surrogate covariate in cirrhosis patients" with Registration No of 94-02-27-26033. The study is adopted with financial support ofFaculty of Health, Iran University of Medical Sciences.

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