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Original Article

Long-Term Survival of Patient with End-Stage Renal Disease Using Bayesian Mixture Cure Rate Frailty Models

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Abstract

Background: Along with the increasing prevalence of ESRD in developing countries, the use of more up-to-date statistical models is highly recommended. It is crucial to control potential cure pattern and heterogenicity among patients

Methods: In this longitudinal study, the data of 170 hemodialysis patients who visited the dialysis department of Shafa Hospital in Kerman from 2006 to 2016 were collected. To provides robust estimates the time to event data (death) were analyzed with a gamma frailty mixed cure Weibull model (MC-WG) using Bayesian inference.

Results: About 49% of patients experienced the death and median survival time was 37.5 months. Older patients (0.264), female patients (0.269), and patients with higher mean serum urea levels (0.186) had a higher risk of death. Moreover, we observe a decrease in death with increase in Creatine (Cr).

Conclusion: In the MC-WG Bayesian model, the diabetes, AST, calcium, phosphorus and uric acid variables had a significant effect on the survival of hemodialysis patients, while they were not significant in the Cox PH model. The results of MC-WG Bayesian model are more consistent with other studies.

Keywords: Weibull distribution; Long-term survival; Mixture cure; Gamma frailty; Bayesian inference

Introduction

Treatment rates for kidney disease remained stable in developed countries from 2003 to 2016, but increased in East and Southeast Asian countries (1). The overall prevalence of kidney failure

increased approximately 2.3 times from 2017 to 2018. In addition, in Iran, this prevalence was almost 1.56 times higher from 2003 to 2016 (2, 3). One of the most common treatments for ESRD patients in Iran is hemodialysis, accounting for almost half of the treatments for these patients (4). Along with the increasing prevalence of ESRD in developing countries, the use of more up-to-date statistical models such as the cured model instead of the common models is highly recommended. Because by considering the detailed structure of the data, it can provide more accurate evidence for the clinical management of patients.

When we have a cure structure, it is better to use cure models to get more accurate estimates. Therefore, standard survival models such as cox proportional hazard model may not be optimum. Mixture cure (MC) models are designed to capture the characteristics of two distinct subpopulations within the survival model, cured and uncured subpopulation (5). Logit link functions are often used in cure rate models (6, 7). Additionally, some important covariates may be unknown or absent from the model for some reason (8). In these cases, random effects are included in the model to adjust for heterogeneity. In survival analyses, this random effect is commonly referred to as the frailty factor (9).

The Weibull model with gamma frailty is a widely used approach for survival analysis (10). Karamoozian et al. used this model with parametric method by Bayesian approach (11). This model assumes that the underlying distribution follows a Weibull distribution. The Weibull distribution is a practical and appropriate choice for parametric models (10). This model adjusts the heterogeneity and unobserved factors on survival time by adding a gamma frailty term to the Weibull model. Furthermore, the parameters are estimated using a Bayesian inference approach.

Previous studies have used a proportional hazards Cox model, which is a semiparametric model. However, we used a parametric model because this model considers the frailty factor and does not require the assumption of a proportional hazards model. In this study, our aim was to investigate the risk factors for survival of hemodialysis patients with a better approach. We used the parametric Mixture cure Weibull (MC-W) model by gamma frailty factor and used Bayesian inference. This modeling framework allows us to incorporate both the cure factor and the underlying patient heterogeneity. Bayesian inference can be used to estimate model parameters and draw conclusions about important factors influencing survival outcomes in hemodialysis patients.

Methods

Data source and eligibility criteria

This longitudinal study collected information on 170 dialysis patients who visited Shafa Hospital in Kerman from 2007 to 2017. Information on these patients was collected from two sources. Laboratory information for these patients was obtained from the hospital's medical information system "HIS". Other information from patient medical obtained from their reports. The study included patients aged 18 yr and older who had been receiving dialysis for at least 3 months.

Patients who started dialysis in 2017 and patients whose information was not recorded correctly were excluded from the study.

Variables

We investigated the association between risk factors and survival of dialysis patients, using the time to death during the dialysis period as a survival response. Demographic variables involve, age, sex and diabetes status and biological markers in the first session of hemodialysis involve Albumin (g/dl), ALP (IU/l), ALT(U/L), AST(U/L), Ca(mg/dL), Cholesterol(mg/dL), Cr(mg/dL), FBS(mg/dL), Hematocrit(%), Hemoglobin(g/dL), K(mEq/L), MCH(pg), MCHC(g/dL), MCV(fl), Na(mmol/L), P(mg), Platelet(mm3), RBC(mcL), WBC(mcL), TG(mg/dl), urea(mg/dl) and Uric acid(mg/dl) were entered into the model as independent variables.

Survival model

To provide a robust conclusion, we first examine the potential for cure pattern in ESRD patients. In such way, we used Kaplan-Meier to identify possible cure patterns (12). More precisely, if the Kaplan-Meier curve has a straight line to infinity before reaching zero, the data is called cured. To identify the influencing variables, we first performed a univariate mixture cure Weibull (MC-W) model. The variables with *P*-values less than 0.10 were selected for further analysis. In subsequent analyses, urea and uric acid variables were also included in the model. These two variables are correlated with other variables, and the reason they are not significant could be due to the presence of many other variables. Next, the nine variables that were selected in univariate mixture cure model were then fitted by the a multivariate (and univariate) Mixture cure Weibull-gamma (MC-WG) model following a Bayesian approach. Estimation of parameters and regression coefficients was performed using the Metropolis Gibbs algorithm, a technique belonging to the class of Markov chain Monte Carlo methods (MCMC) (13-16). By leveraging Bayesian inference and MCMC approaches, these models provide a framework for estimating parameters and coefficients while accounting for uncertainty and incorporating prior knowledge. Finally, we iterated the model until all parameters converged. We found that all parameters converge in her 200,000 iterations (Fig. 2). We used the AIC criterion to check the accuracy of the model.

Results

Approximately 49% of patients experienced the outcome. Median survival was 37.5 months. The 3-year and 5-year survival rates were reported to be 0.518 and 0.457, respectively. In Fig. 1, the Kaplan-Meier curve approaches infinity before dropping below approximately 0.45.

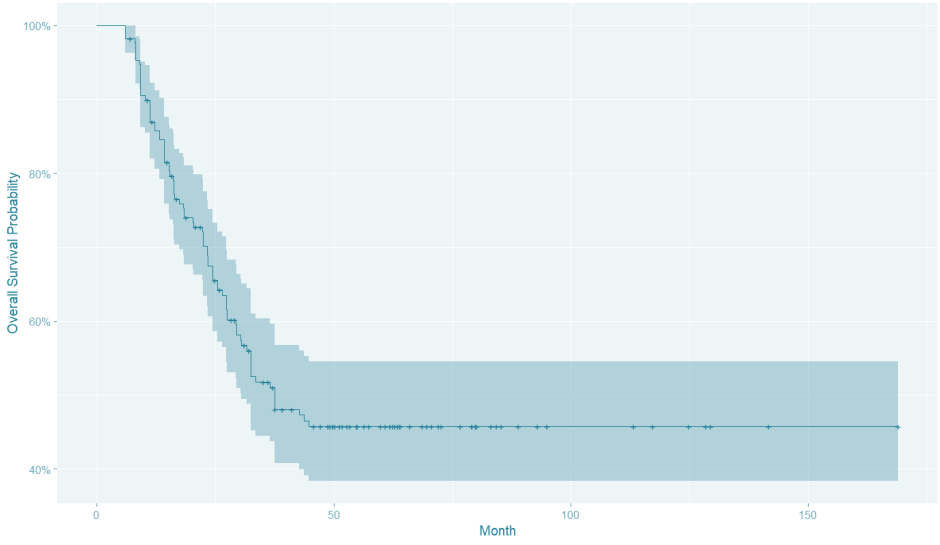

Fig. 1: Kaplan–Meier curve for survival of hemodialyzed patients

Table 1 shows the distribution of demographic variables in the study. Among the patients, 62.3% were male and 37.7% were female. 58.1% of male patients died, while the mortality rate for female patients was 66.7%. Additionally, 58.8% of patients had diabetes at the beginning of hemodialysis, and 46.5% of them died during the study period. Table 1 shows the means and SDs of the variables for hemodialysis patients.

Table 1: Description biological markers and demographic variables of hemodialyzed patients at the beginning of hemodialysis

Variables		***Total***	***Censor***	***Death***
		N (%)	N (%)	N (%)
Sex	Male	106(62.4)	36(41.8)	50(58.1)
	Female	64(37.6)	28(33.3)	56(66.7)
Diabetes	Yes	100(58.8)	46(53.5)	40(46.5)
	No	70(41.2)	54(42.3)	30(35.7)
	Min-max	Mean±Sd	Mean±Sd	Mean±Sd
Age (yr)	22-90	58.17±15.06	53.30±14.84	63.16±13.64
Albumin (g/dl)	2.0-6.2	3.84±0.73	3.92±0.71	3.75±0.76
Log (ALP) (IU/l)	4.5-7.1	5.41±0.47	5.40±0.44	5.41±0.52
Log (ALT)(U/L)	1.09-4.52	2.65±0.60	2.61±0.53	2.70±0.66
Log (AST) (U/L)	1.60-4.67	2.89±0.45	2.81±0.43	2.97±0.45
Ca (mg/dL)	3.0-11.0	8.16±1.10	8.01±1.10	8.31±1.08
Cholesterol(mg/dL)	63.0-311.0	148.99±43.57	146.43±41.29	151.16±48.88
Cr (mg/dL)	1.1-21.6	7.09±3.16	7.73±3.46	6.45± 2.69
Log (FBS) (mg/dL)	3.91-6.25	4.90±0.42	4.81±0.37	5.00±0.44
Hematocrit (%)	5.2-48.2	30.47±6.07	31.68±5.73	30.26±6.42
Hemoglobin (g/dL)	2.5-7.1	9.60±1.85	9.65±1.90	9.56±1.80
K (mEq/L)	2.5-7.1	4.74±0.94	4.64±0.91	4.85±0.98
MCH (pg)	18.8-33.9	27.68±2.72	27.84±2.58	27.50±2.86
MCHC (g/dL)	25.5-37.2	31.39±1.98	31.52±1.80	31.26±2.15
MCV (fl)	65.0-109.1	88.03±7.62	88.51±6.96	87.63±8.27
Na (mmol/L)	123.0-150.0	137.24±4.75	137.76±4.81	136.70±4.67
P (mg)	2.0-13.3	5.66±1.91	5.90±1.77	5.41±1.91
Log (Platelet)(mm^3)	4.2-6.6	5.32±0.38	5.37±0.36	5.27±0.39
RBC (mcL)	1.1-6.0	3.45±0.69	3.46±0.75	3.42±0.66
WBC/100 (mcL)	3.0-18.21	7.21 ±2.69	7.38±54	7.05±2.84
Log (TG) (mg/dl)	3.7-6.5	4.91±0.55	4.86±0.58	4.95±0.53
Urea (mg/dl)	8.0-339.0	118.64±48.8	115.95± 45.12	121.40±45.46
Uric Acid(mg/dl)	0-3.65	1.87±32.8	1.86±0.27	1.89±0.36

Table 2 summarizes the influence of important factors on survival of hemodialysis patients using MC-WG Bayesian model. In the multivariate MC-WG model, increasing age (years) (0.264) and urea (mg/dL) (0.186) increased the risk of death in hemodialysis patients. The risk of death in male patients was 0.269 times lower than female, and increasing Cr (mg/dL) decreased the risk of death by 0.316 times.

In the Univariate MC-WG Bayes model, age(year), diabetes (No), Log (AST) (U/L), Ca (mg/dL), Log(FBS) (mg/dL) and urea(mg/dl) had positive relation by risk of death but Sex (male), Cr(mg/dL), Uric Acid(mg/dl), Cr (mg/dL), Na (mmol/L), P (mg) and Log(Platelet)(mm^3) had negative relation. The AIC value of the multivariate MC-WG Bayesian model was 11.51. In this model, β (scale parameter of gamma distribution), gamma 1 (shape parameter of Weibull distribution), and gamma 2 (scale parameter of Weibull distribution) are 3.24, 1.18, and 3.48, respectively. The final cure rate was 0.128.

Table 2: The effect of important factors on the survival of hemodialyzed patients with Mixture cure model and Bayesian Mixture cure Weibull-gamma model

Variables	***Univariate MC-W***		***Univariate MC-WG Bayes***	***Multivariate MC-WG Bayes***
	Estimate	*P*-value	Percentile (2.5, 97.5)	Percentile (2.5, 97.5)
Intercept	-	-	-	-1.347 (-1.678, -1.033) *
Age(yr)	0.797	<0.001*	0.436 (0.296, 0.583) *	0.264 (0.094, 0.437) *
Sex (male)	-0.506	0.039*	-0.309 (-0.571, -0.013) *	-0.269 (-0.557, -0.016) *
Diabetes (yes)	0.523	0.060	0.245 (0.032, 0.463) *	0.135 (-0.225, 0.434)
Albumin (g/dl)	-0.183	0.289	-0.141 (-0.271, -0.001) *	
ALP (IU/l)	-0.038	0.899	-0.040 (-0.180, 0.102)	
ALT (U/L)	0.183	0.190	0.113 (-0.023, 0.256)	
AST (U/L)	0.041	0.181	0.211 (0.077, 0.346) *	
Ca (mg/dL)	0.287	0.174	0.170 (0.029, 0.308) *	
Cholesterol(mg/dL)	0.110	0.471	0.052 (-0.077, 0.185)	
Cr (mg/dL)	-0.504	0.001*	-0.332 (-0.487, -0.185) *	-0.316 (-0.481, -0.127) *
FBS (mg/dL)	0.516	0.043*	0.257 (0.132, 0.387) *	0.147 (-0.020, 0.302)
Hematocrit (%)	-0.045	0.481	-0.059 (-0.187, 0.082)	
Hemoglobin(g/dL)	-0.023	0.311	-0.052 (-0.178, 0.079)	
K (mEq/L)	0.196	0.134	0.094 (-0.043, 0.231)	
MCH (pg)	-0.108	0.105	-0.106 (-0.228, 0.034)	
MCHC(g/dL)	-0.127	0.187	-0.099 (-0.233, 0.047)	
MCV (fl)	-0.106	0.139	-0.104 (-0.230, 0.035)	
Na(mmol/L)	-0.331	0.018*	-0.183 (-0.309, -0.050) *	-0.069 (-0.217, 0.095)
P (mg)	-0.245	0.936	-0.190 (-0.329, -0.049) *	
Platelet (mm^3)	-0.352	0.015*	-0.205 (-0.340, -0.064) *	-0.102 (-0.259, 0.048)
RBC (mcL)	-0.067	0.877	-0.052 (-0.186, 0.086)	
WBC (mcL)	-0.158	0.188	-0.115 (-0.256, 0.032)	
TG (mg/dl)	0.127	0.345	0.087 (-0.048, 0.223)	
Urea (mg/dl)	0.134	0.403	0.049 (-0.079, 0.180)	0.186 (0.019 ,0.355) *
Uric Acid (mg/dl)	0.120	0.585	-0.089 (-0.194, -0.002) *	-0.078 (-0.247, 0.108)

The Fig. 2 is a Trace plot of the Bayesian results related to the parameters fulfilled by the Bayesian method in the table. According to the Fig. 2, all the parameters have reached convergence.

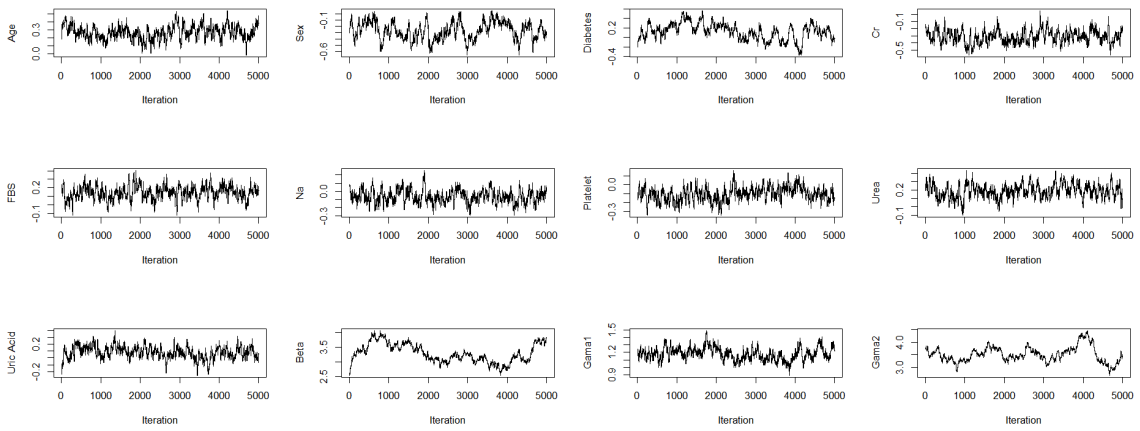

Fig. 2: Trace plot for Bayesian estimates for important variables in dialysis patients

Discussion

The aim of this study was to identify biomarkers that affect the survival of hemodialysis patients. In this section, the results obtained from the MCWG Bayes model are interpreted.

Our findings showed, 5-year survival rate for hemodialysis patients was 36%. Previous studies conducted in different regions of Iran, reported different survival rates of hemodialysis patients. Specifically, the estimated 5-year survival rate is 18.4% in northern Iran, 16% in western Iran, and 48.6% in southern Iran (1). The 5-year survival rate for dialysis patients was 41% in the United States, 60% in Japan, and 48% in Europe (4). Regional differences in survival rates can be influenced by a variety of factors, including: Differences in health care resources, access to care, patient demographics, comorbidities, and quality of care for hemodialysis patients. Survival outcomes for hemodialysis patients may vary depending on geographical location in Iran, so it is important to consider these regional differences when interpreting and generalizing study results. This survival rate is based on the results of previous studies and may not reflect the current situation. Therefore, further research and monitoring of survival rates in different regions is needed to identify changes and trends over time (17).

Similar to our study, older age increases the risk of death in dialysis patients (3). Furthermore, our study found that diabetes increases the risk of mortality and that diabetes is a risk factor for survival in dialysis patients, consistent with other findings (18). The results of this study showed that patients taking male enhancement drugs with high creatinine levels had a lower risk of death. Similar relationships have been observed in other studies (19). Regarding the inverse association between creatinine levels and mortality risk in hemodialysis patients, this may be due to a possible diagnosis of renal failure, fluid overload causing hemodilution of creatinine, or poor nutritional status (20).

In our model, decreased platelet levels increased the risk of death in dialysis patients. To prevent blood clotting, hemodialysis patients are usually prescribed drugs such as heparin. In some cases, heparin can cause side effects such as thrombocytopenia and, in severe cases, intravascular coagulation or microvascular thrombosis. Patients with a high platelet count before starting treatment have a lower risk of coagulopathy or thrombocytopenia and a lower risk of subsequent death. Other studies have also found an inverse association between initial platelet count and mortality risk in hemodialysis patients (21, 22).

A systematic review investigated the relationship between uric acid levels and mortality in dialysis patients. Based on the studies available at the time, the role of uric acid in patient outcomes remains unclear. The authors recommend further research to understand the effects of uric acid on dialysis disease (23). This study found that elevated uric acid levels increase the risk of death in dialysis patients. A 6-year study of patients with end-stage renal disease observed a J-shaped relationship between uric acid levels and mortality in hemodialysis patients. Another study found a U-shaped relationship between uric acid levels and patient mortality A similar association between uric acid levels and patient mortality was also observed in another cohort study that followed 4,132 dialysis patients for 6 years (18). Additionally, uric acid was inversely related to overall mortality in hemodialysis patients (24,25). Also, uric acid was inversely related to risk of disease and are considered a risk factor for mortality in dialysis patients (18, 26).

In survival studies, other independent variables can also be collected over time, which requires the creation of a more efficient system in the registry department of hospitals. It is also suggested to collect data on other types of hemodialysis problems.

Conclusion

In the model used in the article, the results were somewhat different from the classic model, and the new model has provided more detailed results. Therefore, we recommend applying this model specifically to the analysis of data related to hemodialysis patients, as it has several advantages.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

Jarvis WR, Komshian SV (1995). Epidemiology of nosocomial fungal infections. Clin Infect Dis, 20 (6): 1526-30.
The authors declare that there is no conflict of interests.

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