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Original Article

Identifying Influential Prognostic Factors of Death Hazard Rates in Patients with Chronic Kidney Disease (CKD) Using Weibull Model with Non-Constant Shape Parameter

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ABSTRACT

Introduction: Chronic Kidney Disease (CKD) is a disease in which damaged kidneys could not remove waste material from the blood which could result in other health problems. The aim of this analysis was to identify significant laboratory prognostic factors on death hazard due to CKD.
Methods: There were 109 patients with end-stage renal disease (ESRD) treated at Helal pharmaceutical and clinical complex. The survival time was set as the time interval from starting dialysis until death due to CKD. Age, gender and factors such as creatinine, cholesterol, uric acid, SGOT, SGPT, bilirubin, hemoglobin, potassium, ALP, HbA1C, ferritin, calcium, phosphorus, PTH and albumin were employed in this study. Weibull Distribution with non-Constant Shape Parameter versus constant Shape Parameter for the analysis were used.
Results: Death due to CKD occurred in 29 (26.6%) of the patients. Sixty-seven (61.5%) had uric acid higher than 6.8 (mg/dl) and 39(35%) had phosphorus higher than 4.7 (mg/dl) which were poor prognoses. The incidence of death was 48.4%. Calcium<8.5 (mg/dl) (p=0.002), Calcium > 9.5 (mg/dl) (p=0.003), Albumin 4-6.3 (g/dl) (p=0.034), Phosphorus (p=0.022), hemoglobin<10 (g/dl) (p=0.043), hemoglobin>12.5 (g/dl) (p=0.006) and iPTH (p<0.001) were significant variables which had an effect on death hazard rates.
Conclusion: The Weibull model with Non-Constant shape parameter was suggested to be more accurate for identifying risk factors, leading to more precise results, compared to constant shape parameter. Investigators mostly emphasize on the importance of Calcium, Albumin, Phosphorus, hemoglobin and iPTH for reducing hazard rates in CKD patients.

Introduction

Chronic kidney disease (CKD) irreversibly alters kidney function and structure over months or years, leading to decreased kidney function[1] and diagnosed as glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 for at least 3 months.[2] CKD is a public health issue

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which could result in other health problems such as heart disease and high blood pressure.[3] Because of marked changes in bone mineral metabolism, diseases such as cardiovascular and high blood pressure, risk for fractures and overall mortality increases, as a result of damaged kidney function.[4] Although CKD does not appear to be symptomatic in its early stages, the prevalence is estimated to be around 10% to 14% in the world.[5] It has been estimated that more than 500 million people have CKD which 80% of them are living in the less developed countries.[6] Globally, the incidence of CKD increased significantly in the last three decades and it has escalated about 1.3 times from 1990 to 2016.[7] In Iran, prevalence of CKD was increased from 208 (per 10,000) in 2012 to 15.4% in 2018 in higher rate in females compared to males.[8, 9] Worldwide, the deaths rate from CKD was 11.47 in 1990 and 16.05 in 2016; indicating increasing slope in mortality rate during these 27 years.[7] In Iran, based on the Global Burden of Disease (GBD) the mortality rate of this disease has doubled.[10, 11] There is no estimation for survival of CKD patients in Iran. In addition to dialysis and transplantation as main approaches for treatment, increasing awareness of the factors affecting the mortality rate by using valid statistical methods can be beneficial.[12–14] In medical studies, the survival analysis is the analysis of time until certain events occur (such as death due to CKD) and it aims to identify hazard rates of these certain events.[15] Survival time is non-negative which has often a skew distribution and Weibull distribution is generally used in survival time models because it is is very flexible and by changing its parameters, it can be used for survival times that have left or right skewness.[16, 17] Among the various models applied in survival analysis, given the assumptions are met, parametric models lead to more accurate results. Weibull distribution as one of the most important parametric models requires the proportional hazard assumption (PH), in which the shape parameter should be considered constant. However, in some cases that the hazard rate is time dependent, the PH assumption is not established. In these cases, considering that the constant shape parameter leads to distorted results, non-constant shape parameter can lead to better estimation of the results.[18,19] Regarding these points and the increasing trend of CKD incidence in Iran and worldwide, the aim of this study was to determine the prognostic factors on the risk of death in patients with CKD using the Weibull parametric model with unstable shape parameter.

Material and Methods

In this retrospective cohort study, a total of 109 hemodialysis patients were enrolled and registered in the Iran Helal pharmaceutical and clinical complex during 2014-2018. Data were collected from hospital medical records which includes all CKD patients that were given hemodialysis three times a week. The survival time was calculated as the time interval between the time of starting dialysis and time of death due to CKD. The inclusion criteria were men and non-lactating women with negative serum pregnancy test at Screening and CKD with eGFR <60 mL/min at Screening using the 4-variable Modification of Diet in Renal Disease (MDRD) equation (with a limit of up to 20% of the target randomization of 230 subjects with eGFR <15 mL/min). The exclusion criteria were evidence of acute kidney injury or requirement for dialysis within 12 weeks

prior to screening, scheduled kidney transplant or initiation of dialysis planned within 24 weeks of screening, active infection requiring antibiotics at screening and malignancy. The information of all participants in the study was confidential and subjects (or their parents or guardians) have given their written informed consent. Also all the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was confirmed by the ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran with the approval code is IR.SBMU.RETECH.REC.1398.789. Initially, information on demographics was collected. A blood sample was taken after 12–14 h overnight fasting and was centrifuged within 30–45 min of collection. All blood analyses were performed at the research laboratory on the day of blood collection. For oral glucose tolerance test, 82.5 g glucose monohydrate solution (equivalent to 75 g anhydrous glucose) was administered orally to subjects and a blood sample was taken 2 hours later. Total cholesterol (TC) and triglycerides (TG) were assayed using the enzymatic calorimetric method with cholesterol esterase- cholesterol oxidase and glycerol phosphate oxidase, respectively. Serum creatinine (CR) levels were assayed by kinetic colorimetric Jaffe. The sensitivity of the assay was 0.2 mg/dL (range, 18–1330 μmol/L (0.2–15 mg/dL). Reference intervals according to manufacturer's recommendation were 53–97 μmol/L (0.6–1.1 mg/dL) and 80–115 μmol/L (0.9–1.3 mg/dL) in women and men respectively. All biochemical assays were performed using commercial kits (Pars Azmoon Inc, Tehran, Iran) by a Selectra 2 auto analyzer (Vital Scientific, Spankeren, The Netherlands). The risk factors which were assessed in the current analysis were age at diagnosis (years), gender, creatinine (mg/dl), cholesterol (mg/dl), uric acid (mg/dl), serum glutamic oxaloacetic transaminase (SGOT) (U/L), serum glutamic-pyruvic transaminase (SGPT) (U/L), bilirubin (mg/dl), hemoglobin (g/dl), potassium (mEq/L), Alkaline phosphatase (ALP) (U/L), hemoglobin A1c (HbA1C) (mmol/mol), ferritin (ng/ml), calcium (mg/dl), phosphorus (mg/dl), Parathyroid hormone (PTH) (pg/dl) and albumin (g/dl).

Descriptive statistics mean (SD) for continuous variables and frequency (percentage) for categorical factors were used to summarize demographic and prognostic variables of the study population. In this paper, we used the model with constant and non-constant shape parameter and then we chose the best model according to Akaike information criterion (AIC). For data analysis, clinical, pathological and biological characteristics of patients were evaluated in the survival model. A Weibull distribution was proposed for survival time. The statistical analyses were carried out using SAS (SAS Institute Inc, Cary, NC, USA). SAS codes are available upon request. The level of significance was set at $P \leq 0.05$. Weibull distribution has two parameters, shape (α) and location (β), which can be defined as

$$\beta = exp(b_0 + \sum_{j=1}^{p} b_j x_j)$$

and

$$\alpha = exp(a_0 + \sum_{j=1}^{p} a_j x_j)$$

and has a density and hazard functions as

$$f(t|\alpha.\beta) = \alpha\beta t^{\alpha-1} exp(-\beta t^{\alpha}); t > 0.\alpha > 0.\beta > 0$$

and $h(t|\alpha.\beta) = \alpha\beta t^{\alpha-1}$.

In this distribution, if α>1, the risk function is incremental, if α<1 decreasing, and if α=1, the risk is constant, in which case the distribution becomes exponential. We can get hazard rate of any two different levels of covariates by

$$\boldsymbol{HR = \frac{h(t|x)}{h(t|x^*)}}.$$

A key point is that in Weibull distribution with non-constant shape parameter HR will not be constant over time.

Results

Overall, 26.6% of the patients experienced death due to CKD and others were censored. Out of 109 hemodialysis patients 71.6% were male, 33.9% had hemoglobin lower than 10 (g/dl) and 88.1% of patients had HbA1C less than 7 (mmol/mol) with mean age of 57.80 years (Table1). We explored the property of Weibull model by plotting the log {-log (survival probability)} against log (time). It shows that our dataset satisfies the Weibull distribution because all the points allies on a line (Figure1). Kaplan Meier survival curve of total population shows that the survival rate decreases over time (Figure 2). Therefore, it is wise to find time dependent covariates. The AIC of Weibull distribution with Constant Shape Parameter was 255.2 and AIC of Weibull distribution with non-Constant Shape Parameter was 186.7 (Tables 1 and 2), so Weibull distribution with non-Constant Shape Parameter is the superior model. Scale parameters which were significant based on Weibull distribution with non-Constant Shape Parameter, were calcium less than 8.5 (mg/dl) compared with 8.5-9.5 (mg/dl) (p=0.002), Albumin 4-6.3 (g/dl) compared to less than 4 (g/dl) (p=0.034) and Phosphorus (p=0.022) (Table 2). Significant parameters based on Weibull distribution with non-Constant Shape, were hemoglobin less than 10 (g/dl) compared to 10-12.5 (g/dl) (p=0.043) and hemoglobin more than 12.5 (g/dl) compared with 10-12.5 (g/dl) (p=0.006), calcium more than 9.5 (mg/dl) compared with 8.5-9.5 (mg/dl) (p=0.003), and iPTH (p<0.001) (Table 2). Based on significant prognostic factors, the fitted hazard function according to our superior model (Weibull distribution with non-Constant Shape Parameter) would be:

For instance, hazard ratio for calcium>9.5

$$\boldsymbol{h(t|\alpha.\beta) = \alpha\beta t^{\alpha-1}}$$

Where $\hat{\beta} = exp(\hat{b}_0 + \sum_{j=1}^{p} \hat{b}_j x_j) = \exp\{-80.81(Calcium < 8.5) + 6.208(Calcium > 9.5) - 8.35(Albumin) - 0.09(Phosphorus)\}$ and

$\hat{\alpha} = exp(\hat{a}_0 + \sum_{j=1}^{p} \hat{a}_j x_j) = \exp\{0.30(Hemoglobin < 10) - .55(Hemoglobin > 12.5) - .18(Calcium < 8.5) + 0.62(Calcium > 9.5) + 0.0004(\text{iPTH})\}$

For instance, hazard ratio for calcium>9.5 compared to calcium<8.5 is:

$$\boldsymbol{HR = \frac{h(t|x)}{h(t|x^*)}} = \frac{t^{\exp\{0.30(Hemoglobin<10)-.55(Hemoglobin>12.5)+0.62(1)+0.0004(\text{iPTH})\}-1}}{\exp\{0.30(Hemoglobin<10)-.55(Hemoglobin>12.5)-.18(1)+0.0004(\text{iPTH})-80.81(1)-8.35(Albumin)-0.09(Phosphorus)\}}$$

$$= e^{87.80} t^{87.01}$$

Table 1. Identified Risk Factors of death hazard rates Based on Weibull Distribution with Constant Shape Parameter and Demographic and prognostic factors of the study population.

	Variables	Constant Shape and scale Parameters model[$]			Frequency (%)
		Categories	Estimates parameters	P-value	
α	a_0		4.375	0.0002*	
β	b_0		-6.926	0.620	
	Gender	Male	6.997	0.017*	78 (71.6)
		Female[&]	-	-	31 (28.4)
	Hemoglobin (g/dl)	<10	7.765	0.014*	37 (33.9)
		>12.5	-1.763	0.483	25 (22.9)
		10-12.5[&]	-	-	47 (43.1)
	Potassium (mEq/L)	>5	-0.705	0.455	73 (67.0)
		3.5-5[&]	-	-	36 (33.0)
	Alkaline phosphatase (U/L)	>300	-4.413	0.052	50 (45.9)
		<300[&]	-	-	59 (54.1)
	HbA1C (mmol/mol)	>7	5.848	0.007*	13 (11.9)
		<7[&]	-	-	96 (88.1)
	Calcium(mg/dl)	<8.5	-1.821	0.560	15 (13.8)
		>9.5	7.036	0.044*	14 (12.8)
		8.5-9.5[&]	-	-	80 (73.4)
	Albumin (g/dl)	4-6.3	4.973	0.093	85 (78)
		<4[&]	-	-	24 (22)
					Mean (SD)
	Age (year)		0.179	0.003*	57.80 (17.26)
	Ferritin (ng/ml)		0.002	0.113	347.90 (32.43)
	Creatinine(mg/dl)		0.118	0.110	8.93 (3.61)
	Cholesterol (mg/dl)		-0.066	0.089	146.64 (36.47)
	Uric acid (mg/dl)		-3.610	0.005*	7.00 (1.33)
	SGOT (U/L)		-0.981	0.030*	18.40 (7.53)
	SGPT (U/L)		0.466	0.041*	21.33 (13.97)
	Bilirubin (mg/dl)		-4.689	0.665	0.68 (0.14)
	Phosphorus (mg/dl)		-0.815	0.168	5.27 (1.24)
	Parathyroid hormone (pg/dl)		-0.008	0.018*	368.64 (224.53)

[&]References category
*Significant at 0.05
[$] AIC: 255.2
SGOT, Serum glutamic oxaloacetic transaminase
SGPT, Serum glutamic-pyruvic transaminase

Table 2. Identified Risk Factors of death hazard rates Based on Weibull Distribution with Non Constant Shape Parameter Model of 109 Cases of Chronic Kidney Disease

	Variables	Categories	Estimates parameters	P-value
	a_0	-	-39.875	0.896
α	Gender	Male	0.331	0.523
		Female[&]	-	-
	Hemoglobin (g/dl)	<10	0.301	0.043*
		>12.5	-0.550	0.006*
		10-12.5[&]	-	-
	Calcium (mg/dl)	<8.5	-0.183	0.414
		>9.5	0.625	0.003*
		8.5-9.5[&]	-	-
	iPTH (pg/dl)	0.0004	<0.001*	0.052
	b_0			
β	Gender	Male	1.627	0.396
		Female[&]	-	-
	Hemoglobin (g/dl)	<10	0.094	0.995
		>12.5	17.834	0.130
		10-12.5[&]	-	-
	Potassium (mEq/L)	>5	-0.015	0.717
		3.5-5[&]	-	-
	Alkaline phosphatase (U/L)	>300	-7.042	0.625
		<300[&]	-	-
	HbA1C (mmol/mol)	>7	27.033	0.525
		<7[&]	-	-
	Calcium(mg/dl)	<8.5	-80.819	0.002*
		>9.5	6.208	0.762
		8.5-9.5[&]	-	-
	Albumin (g/dl)	4-6.3	-8.353	0.034*
		<4[&]	-	-
	Age (year)		1.439	0.184
	Ferritin (ng/ml)		30.638	0.699
	Creatinine(mg/dl)		-0.355	0.704
	Cholesterol (mg/dl)		-7.871	0.191
	Uric acid (mg/dl)		-2.186	0.503
	SGOT (U/L)	-	-0.375	0.828
	SGPT (U/L)	-	-57.339	0.545
	Bilirubin (mg/dl)	-	-31.107	0.480
	Phosphorus (mg/dl)	-	-0.096	0.022*
	Parathyroid hormone (pg/dl)	-	-12.897	0.270

[&]References category
*Significant at 0.05
[$]AIC: 255.2
SGOT, Serum glutamic oxaloacetic transaminase
SGPT, Serum glutamic-pyruvic transaminase

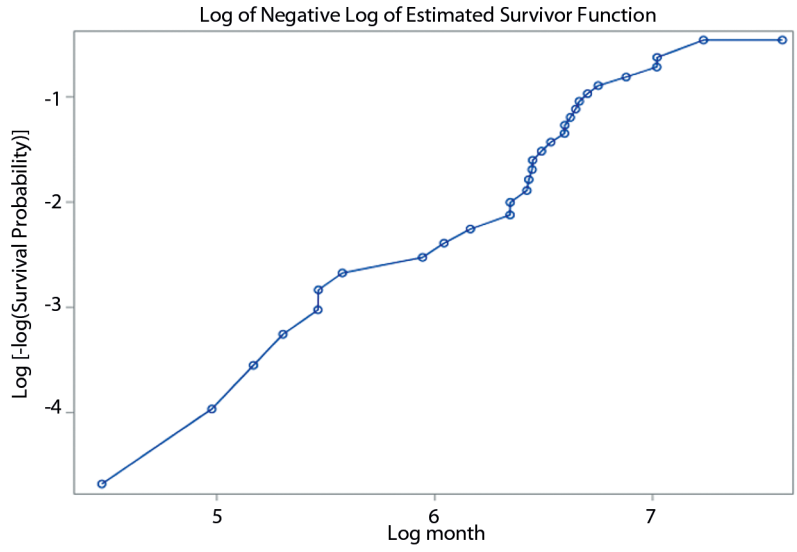

Figure1. The log{-log(survival probality)}

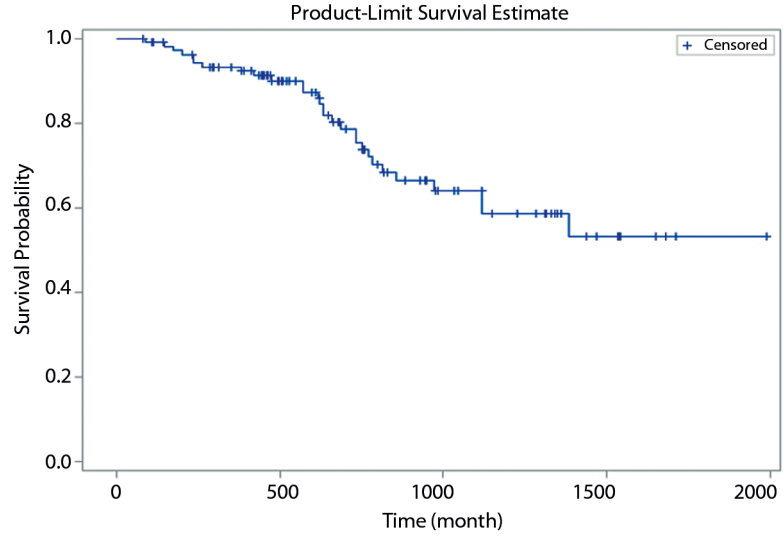

Figure 2. The survival curve (Kaplan Meier) of total population

compared to calcium<8.5 is:

$$HR = \frac{\boldsymbol{h(t|x)}}{\boldsymbol{h(t|x^*)}} = \frac{t^{\exp\{0.30(Hemoglobin<10)-.55(Hemoglobin>12.5)+0.62(1)+0.0004(\text{iPTH})\}-1}}{\begin{array}{c}\exp\{0.30(Hemoglobin<10)-.55(Hemoglobin>12.5)- \\ .18(1)+0.0004(\text{iPTH})-80.81(1) \\ -8.35(Albumin)-0.09(Phosphorus)\}\end{array}}$$

$$= e^{87.80}t^{87.01}$$

It is clear that adjusted HR for calcium>9.5 (mg/dl) compared to calcium<8.5 (mg/dl) is not constant and it increases over time. Hence, according to the results, it is observed that the hazard ratio of calcium, hemoglobin and iPTH is not constant over time. Adjusted HR for hemoglobin<10 (g/dl) compared to hemoglobin>12.5 (g/dl) increases in time. In addition, adjusted HR of iPTH increases in the course of time. On the other hand, the hazard ratio of phosphorus and albumin is constant over time. Adjusted HR of phosphorus and albumin is 0.90 and 0.0002, respectively. So mortality hazard increases as phosphorus and albumin increase.

Discussion

In survival studies, the outcome variable is time until the event occurs. Due to the asymmetry and censorship in survival data, special analysis procedures of statistical methods are required. Weibull model as a flexible function is very advantageous in survival studies.[20] In using the shape parameters, it is important to bear in mind that it is not always constant. The aim of the present research is to show the superiority of non-constant shape parameter against constant shape model in CKD data. Many similar studies were performed using the Weibull model with the unstable shape parameter and have shown that this model is more accurate in estimating the coefficients.[21,22] Some authors through a simulation study, demonstrated that models with stochastic effects and unstable parameters provide a more accurate fit.[23, 24] In our study and based on Weibull distribution with non-Constant Shape Parameter, Calcium, Albumin, Phosphorus, hemoglobin and iPTH are factors that are associated with hazard death rates. Floege et al.[25] also reported that iPTH, Calcium and Phosphorus are factors that are associated with mortality rate of haemodialysis patients. Naves-Díaz et al.[26] who conducted a study on a large number of haemodialysis patients, reported that reduced serum levels of Albumin, Calcium, Phosphorus and PTH were associated with increments in mortality. Although, no parametric survival analysis methods were applied in their study, but the use of a large sample size made the results very accurate. In our study, despite the small sample size, we were able to extract relatively similar results with high accuracy using the correct model except calcium. Increments in mortality by a decrease in calcium level is in contrast with our study. In our research, the mortality rate for Calcium>9.5 (mg/dl) compared to Calcium<8.5 (mg/dl) increases over time. Tentori et al. used adjusted hazard ratio models and reported the highest risk of mortality for calcium or CaAlb levels greater than 10.0 (mg/dL), phosphorus levels greater than 7.0 (mg/dL), and PTH levels greater than 600 (pg/dL).[27] Additionally, in some studies from the USA, it was found that higher levels of iPTH, Calcium and Phosphorus were associated with an increased risk of mortality.[28–30] Cox models have been used in most studies on the survival of CKD patients, in which the main assumption is that the hazard ratio is constant over time. However, the results of the present study indicate that the hazard ratio in Calcium, iPTH and hemoglobin is not constant over time. Therefore, it is necessary to be careful in interpreting the results obtained from these models and to select appropriate models (smaller AIC). According to the results of the previous studies, if patients were diagnosed with these risk factors, it would be beneficial

to treat them with conservative treatment.[31] Some authors reported that low calcium level could reduce all mortality causes,[28, 29] while others found that increased risk of mortality is associated with low serum Calcium levels.[27,32] High serum Calcium level has a negative effect on cardiovascular system and mortality.[30] Consequently, one of the reasons for the relationship between Calcium and mortality in CKD patients is due to cardiovascular diseases. An important point from our study results is that the risk of death increases over time in patients whose calcium is higher than 9.5 (mg/dl). One scientific justification for this important finding could be the increase in calcium deposition in the arteries. Given that other factors such as hypertension, cardiovascular diseases, and malnutrition can also cause death in CKD patients.[33, 34] Designing extensive studies to record and review the complete data on these patients and using competing risk models seems essential. It is also necessary to design clinical trials with several groups in order to evaluate different treatments along with dialysis and evaluate their survival using more accurate models. Other studies also declared that high serum phosphorus was associated with a higher risk of mortality[35, 36] and reducing serum phosphorus with phosphate binders could decreases HR.[37] Aligned results have not been reported in various studies regarding the effect of iPTH on mortality in CKD patients.[38, 39] The mortality due to CKD or cardiovascular diseases is a subject which requires closer examination. Based on the results of this research, further studies about iPTH on the effect of time on increasing the risk of mortality seem necessary.

Ultimately, we found that adjusted HR for Calcium>9.5 (mg/dl) compared to Calcium<8.5 (mg/dl) increases over time. Our study indicated that adjusted HR for hemoglobin<10 (g/dl) compared to hemoglobin>12.5 (g/dl) increases over time. The adjusted HR of iPTH also escalates over the course of time. Moreover, we demonstrated that, the hazard ratio of phosphorus and albumin is constant over time and death hazard increases by an increase in phosphorus and albumin level. Although, the results of this study signifies the appropriateness of Weibull model with Non-Constant shape parameter compared to the Weibull model with Constant shape parameter, more studies are needed with larger sample sizes and wider variables for reaching accurate conclusions.

Limitations

One of the limitations of our study is its retrospective and observational nature. In addition, unmeasured confounding variables could increase or decrease the HR for mortalities and/or hospitalization. Small sample size which could have reduced the power of test was another limitation but it seems that with correct model we could reduce small dataset effect.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare regarding the publication of this article.

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Author Contribution

Seyede Solmaz Taheri and Ahmadreza Baghestani wrote the article and programs in SAS and data analyzing. Farzanehsadat Minoo and Anahita Saeedi collected the data.

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