Factors Associated With Short-Term and Long-Term Survival in Patients Undergoing Hemodialysis Using Semi-Parametric Mixture Cure Models

Zahra Shayan,[1] Vahid Ebrahimi,[2] Shahrokh Ezzatzadegan Jahromi[3]

[1]Trauma Research Center, Department of Biostatistics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Biostatistic, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

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Introduction. Understanding the factors affecting the survival of patients undergoing hemodialysis is the mainstay of care in this population. The present study aims at finding these features using novel cure models that discover factors important in both long term and short-term survival of patients undergoing HD.

Methods. Data were retrospectively collected from the database of Shiraz University of Medical Sciences Special Diseases Administration including patients of 34 HD centers during 2011 to 2015. The primary outcome was death. Considering people with no death event as cured, the rest of the patients considered as uncured. To evaluate the factors affecting mortality, we used a mixture cure model (MCM) that model the long-term and short-term survival of patients separately.

Results. Of 506 patients, 68.75% of women and 75.0% of men were long-term survivors. The mean (± SD) age of the patients was 57.5 (± 16.5) years and the empirical value of the cure rate was 72.9%. Sex, age, and Kt/V_{urea} were recognized as important factors in the long-term survival. In other words, lower age, male sex, and $Kt/V_{urea} \geq 1.2$ significantly increased the odds of being cured. The factors effective in short-term survival were mean corpuscular hemoglobin concentration (MCHC) and serum hemoglobin. The serum hemoglobin between 11 and 12.5 and a high MCHC decreased the risk of death.

Conclusion. Using cure model survival analysis, it was found that factors affecting the proportion of the patients with long-term survival might be different from those affecting short-term survival.

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INTRODUCTION

End-stage renal disease (ESRD) is the advanced stage of chronic kidney disease (CKD) requiring dialysis or transplantation.[1] The disease progresses over time during which new complications occur for the patient. Nowadays, despite appropriate dialysis methods, the mortality rate of patients with ESRD is still higher than that of the general population. Therefore, many efforts have been made to improve the quality of life and the survival of patients undergoing hemodialysis (HD), especially in developed countries.[2] Various factors such as infection, cardiovascular diseases, and older age contribute to higher mortality rates in patients with ESRD. Among these factors, cardiovascular diseases are the main cause of death.[3,4]

By the end of 2016, there were approximately 3,920,000 patients with ESRD, of which 2,810,000 (72%) were undergoing HD. The rate of hemodialysis grows 6% per year globally compared to the world population growth of 1.1%.[1] In 2016, studies on ESRD in Iran showed that about 57,800 patients were under treatment with one of the renal replacement therapies, of which 50% were treated with HD.[5] Since patients undergoing HD lose their life after a while or are continuously under dialysis, the identification of the factors affecting survival is of great importance. Survival analysis is a more appropriate method for this aim because it considers patients who have experienced the censoring event. Several studies have been conducted to specify the factors affecting mortality in patients undergoing HD. Most of these studies have applied the Log-rank test and Cox regression in their analyses, which are not appropriate methods for analyzing long-term survival. In many of these studies, death has been the outcome of interest in analyzing the survival of patients.[6-10]

In survival analysis studies, a substantial proportion of the study population will not experience the desired primary outcome, i.e. death. Assuming that the individuals not experiencing death are cured, the rest of the patients are considered uncured.[11,12] In the survival analysis, if we have a high percentage of patients who have not experienced the event of interest at the end of follow-up and the Kaplan-Meier plot of patients has a large plateau, using the cure models may be more appropriate than the traditional survival analysis models (e.g., Cox regression); however, time of follow-up must be long enough. The sufficient follow-up hypothesis is checked via non-parametric α_n-test.[13] Although, cure models have dominated a great portion of statistical literature for more than two decades, they have not been widely used in clinical studies.

Cure models are used in two fundamental categories: mixture cure models (MCMs) and non-mixture cure models (NMCMs).[11,12] MCMs assign individuals into two categories: long-term and short-term survivors. One advantage of MCMs over the Cox model is that we can separately examine the effect of different factors on long-term and short-term survivals. MCMs are offered in parametric and semi-parametric forms.[12] Since, assessing parametric assumption in parametric models is a difficult issue, we will focus on semi-parametric MCMs. Most studies investigated the effect of different factors on overall survival in patients undergoing HD,[6-10] whereas the aim of this study is to evaluate the impact of different factors on mortality of patients with long-term survival (cured patients) and those with short-term survival (uncured patients) separately. To our knowledge, this is one of the earliest studies to investigate the factors associated with long-term and short-term survival separately in patients using semi-parametric MCMs.

MATERIALS AND METHODS

This retrospective cohort study was conducted using data of 506 patients undergoing chronic HD who survived the initial 3 months on maintenance HD in 34 HD centers affiliated to Shiraz University of Medical Sciences (SUMS), Shiraz, Iran, from March 2011 to November 2015. The data were extracted from the database of SUMS Specific Diseases Affairs electronic database that was established in 2011 and included the information of patients on maintenance HD. Exclusion criteria were deficits in data, switch to peritoneal dialysis (PD), kidney transplantation, and loss of follow-up because of being transferred to an HD center not covered by the database. The interval between three months after the first dialysis to the death of the patient was considered as survival time. If the study ends while the patient is still on dialysis, the survival time was considered as censored time.

Demographical and Clinical Factors of Patients

The baseline demographic features of the patients at the time of starting HD (e.g., age and sex) and the laboratory values and body mass index (BMI) that belong to the fourth month of starting HD were considered for the analysis. Because of the existence of a large number of variables and since it was not possible to run the cure model with all of them, we initially applied mixture cure univariate tests and selected the variables with $P < .2$ to be entered into the multivariate analysis.

Statistical Analysis

Survival analysis was performed using KM curves to achieve the standard estimation of the survival function and to compare the survival of patients among different levels of various factors. Semi-parametric MCM was conducted to estimate the percentage of the patients who did not experience the death outcome from HD therapy and calculate the survival probability of the patients who experience the death event. The proportional hazards (PH) model can be used for modeling short-term survivors to achieve the semi-parametric proportional hazards mixture cure (PHMC) model. Different link functions also can be applied to formulate the long-term survivors such as logit, probit, and complementary log-log (cloglog) link functions.[11,12] The estimated cure proportion can be easily found from the estimation of parameters for the long-term survivor portion.

Statistical analyses were performed using SPSS ver. 16.0 software and an R package named 'smcure' in R 3.1.3 software.[14]

RESULTS

Among all 1,060 patients started maintenance HD during March 2011 to November 2015 (56 months), 276 patients underwent kidney transplantation, 12 switched to PD, 17 recovered from HD, and 45 were transferred to an HD center not covered by the database. Also, 204 patients had a high number of missing data and thus were not included in the analysis. Of the remaining 506 eligible patients, 298 (58.9%) were men. Considering that 369 of 506 patients did not experience the event of death, the empirical value of cure rate (i.e., the proportion of patients who did not experience death after the end of study) was 72.9% at 5 years. The mean (± SD) age of the patients on HD was 57.5 (± 16.5) years (18 to 91 years) and the mean of survival time was 684 days (124 to 1610 days). Table 1 presents some characteristics of the patients.

Using the KM plot in Figure 1, the survival probabilities tended to plateau after 500 days of follow-up, suggesting the evidence of long-term survival. In other words, no desired event occurred after 500 days (being plateau in the KM curve at a value much higher than zero, around 70%) and the overall KM plot is almost 1110 days as levels-off. In addition, of the 506 patients, 369 (72.9%) were censored and about 82% of censoring occurs in the plateau portion. Since there is no rejection of the sufficient follow-up hypothesis via α_n-test (.0008 < .05), we could apply the MCM to discover

Table 1. Patients' Characteristics and Laboratory Values (n = 506)

Variables	Mean (± SD)
Demographics	
Male Sex, %	298 (58.90)
Age, y	57.50 (16.50)
BMI, kg/m^2	22.75 (4.40)
Dialysis Factors	
Kt/V$_{urea}$	1.30 (0.30)
Ultrafiltration volume, mL	1950 (1100)
Laboratory Values	
Hemoglobin, g/dL	10.10 (2.05)
HCT, %	32.40 (5.20)
MCH, pg/cell	26.40 (3.10)
MCHC, g/dL	31.00 (1.90)
BUN, mg/dL	56.80 (21.50)
Creatinine, mg/dL	6.85 (3.00)
Sodium, meq/L	139.50 (4.80)
Potassium, meq/L	5.00 (0.80)
Calcium, mg/dL	8.70 (1.00)
Phosphate, mg/dL	5.10 (1.4)
Uric acid, mg/dL	6.60 (1.70)
Albumin, g/dL	3.80 (0.60)
Triglyceride, mg/dL	122.50 (60.00)
Cholesterol, mg/dL	148.00 (41.50)
LDL, mg/dL	85.90 (33.00)
HDL, mg/dL	37.00 (9.90)
FBS, mg/dL	123.50 (71.00)

Abbreviations: BMI, body mass index; Kt/V$_{urea;}$ adequacy of dialysis; HCT, hematocrit; MCH, mean cell hemoglobin concentration; MCHC, mean corpuscular hemoglobin concentration; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBS, fasting blood sugar; BUN, blood urea nitrogen

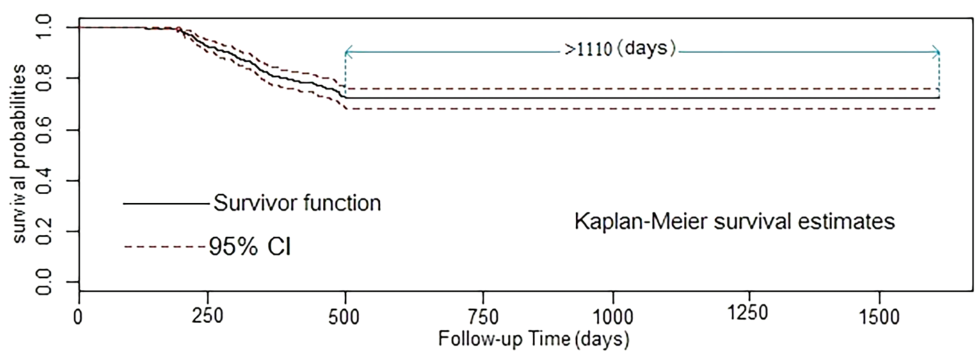

Figure 1. It shows overall Kaplan-Meier survival curve for patients undergoing hemodialysis.

the variables that have a considerable impact on mortality in both long-term and short-term groups. Neither of sexes had different KM survival estimates (log-rank statistic = 2.6, $P > .05$) while there was a significant difference between the overall survival of patients according to the levels of Kt/V_{urea}; i.e., patients with $Kt/V_{urea} \geq 1.2$ had higher survivals (Figure 2a). Furthermore, as shown in Figure 2b, sex was not a confounding factor for survival considering different Kt/V_{urea} levels.

The estimation of parameters for both cured and uncured patients and their associated confidence interval (CI) are presented in Table 2.

Since the results of the PHMC model were the same for different link functions, due to the simplicity of interpretation, we interpreted our findings using logit link function by introducing odds ratio (OR) for long-term survivors and hazard ratio (HR) for short-term survivors. These statistical terms have been used in most of the medical

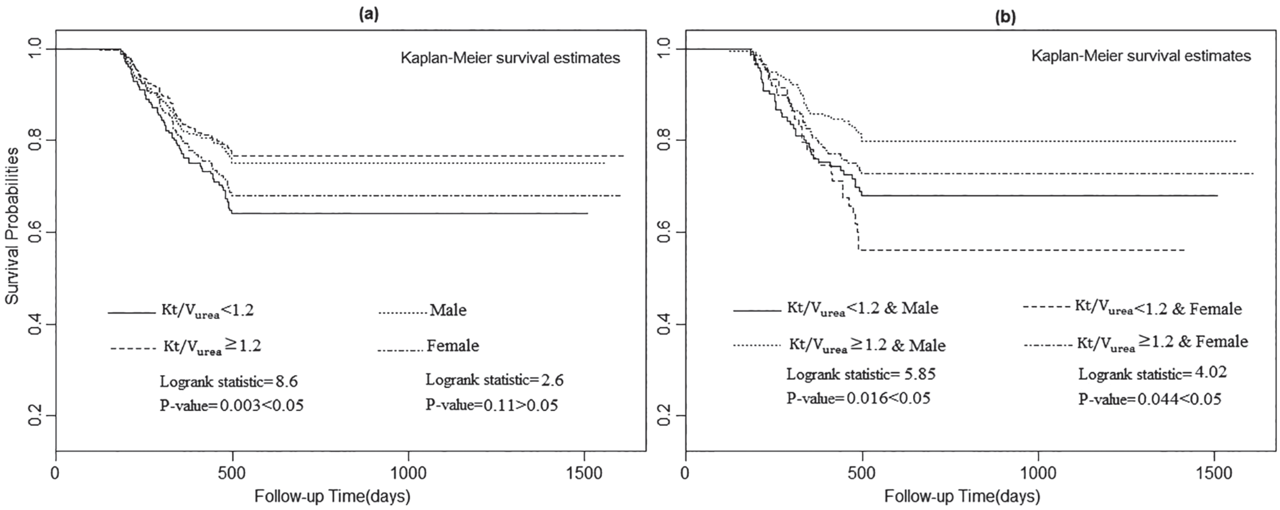

Figure 2. Kaplan-Meier survival estimates plots for the various combinations of sex and Kt/V_{urea} in the study population of patients undergoing hemodialysis.

Table 2. Factors Affecting Survival for the Study Population Using Different Link Function From the Semi-parametric PHMC Model by the EM Algorithm

Long-term Survivor Using Different Link Functions									
Factor	Probit Link Function			Logit Link Function			Cloglog Link Function		
	Coef	95% CI	*P*	Coef	95% CI	*P*	Coef	95% CI	*P*
Intercept	0.42	-2.28 to 3.12	> .05	0.89	-4.27 to 6.06	> .05	0.40	-4.24 to 5.05	> .05
Age	0.01	0.00 to 0.02	< .05	0.02	0.00 to 0.04	< .05	0.02	0.01 to 0.03	< .05
Sex									
Male[R]	-	-	-	-	-	-	-	-	-
Female	0.28	0.05 to 0.52	< .05	0.50	-0.01 to 1.01	> .05	0.42	0.02 to 0.81	< .05
Kt/V_{urea}									
< 1.2[R]	-	-	-	-	-	-	-	-	-
≥ 1.2	-0.42	-0.69 to -0.15	< .05	-0.72	-1.17 to -0.28	< .001	-0.60	-0.94 to -0.27	< .001
Short-term Survivor Using Proportional Hazards (PH) Model									
Factor	Coef	95% CI	*P*	Coef	95% CI	*P*	Coef	95% CI	*P*
MCHC	-0.08	-0.16 to 0.01	> .05	-0.07	-0.16 to 0.01	> .05	-0.07	-0.15 to 0.01	> .05
Hb, mg/dL									
< 11[R]	-	-	-	-	-	-	-	-	-
11 - 12.5	-0.53	-1.01 to -0.05	< .05	-0.53	-1.03 to 0.03	< .05	-0.53	-0.10 to -0.07	< .05
> 12.5	-0.11	-0.77 to 0.55	> .05	-0.11	-0.86 to 0.63	> .05	-0.12	-0.73 to 0.49	> .05

P value < .05 is significant.
[R]**:** Reference Group
Abbreviation: Coef, estimated coefficient; EM, expectation maximization; Hb, hemoglobin; $Kt/V_{urea,}$ adequacy of dialysis; MCHC, mean corpuscular hemoglobin concentration; PHMC, proportional hazard mixture cure

literature and are more familiar to clinicians.

Long-term Survival of Patients Using the PHMC Model

Age had a significant effect on long-term survival (with probit, logit, and cloglog link functions; $P < .05$, $P < .05$, and $P < .05$; respectively) and not on short-term survival. The OR (95% CI) for age was 1.02 (1.004 to 1.038), suggesting that younger patients a higher chance of being cured compared to the older ones (Table 2). Patient's sex was found to be significant only in long-term survivors using three link functions (with probit, logit, and cloglog link functions; $P < .05$, $P > .05$, and $P < .05$; respectively). In other words, males had a higher chance of being cured than females do (OR = 1.65, CI: 0.987 to 2.754). Dialysis adequacy, which was measured by Kt/V_{urea}, had an important and considerable impact on long-term survival (with logit, probit, and cloglog link functions; $P < .05$, $P < .001$, and $P < .001$; respectively). $Kt/V_{urea} \geq 1.2$ significantly increased the odds of being cured than $Kt/V_{urea} < 1.2$ (OR = 0.49, 95% CI: 0.312 to 0.759). Moreover, based on the estimated probabilities plot for the patients with long-term survival in Figure 3, survival rate for patients with the $Kt/V_{urea} \geq 1.2$ was more than those with $Kt/V_{urea} < 1.2$ in both sexes. Based on this stratification, the long-term survival of men was always higher than that of women in the two categories of Kt/V_{urea} (< 1.2 or ≥ 1.2).

Short-term Survival of Patients Using the PHMC Model

MCHC was found to have a borderline significant effect on short-term survival such that with a unit increase in MCHC, the hazard of death decreased by 7% (HR = 0.93, CI: 0.855 to 1.011, $P > .05$). In other words, patients with a lower MCHC level had a higher risk of death than those with higher levels of MCHC.

Our findings revealed that hemoglobin (11 to 12.5 g/dL) had a significant effect on short-term survival of patients (HR = 0.59, CI: 0.356 to 0.972; $P < .05$). The result demonstrates that the death hazard for patients with hemoglobin in the range of 11 to 12.5 g/dL is 0.59 times lower than the hazard for other categories (hemoglobin < 11 or > 12.5 g/dL). To represent these findings intuitively, the estimated short-term survival curves for the different levels of hemoglobin were drawn in Figure 4. Based on this graph, it can be concluded that in the initial ~200 days of HD, the short-term survival of the patient in each hemoglobin levels was approximately the same. Afterward, 11 < Hb < 12.5 g/dL had the highest survival probability (or the lowest hazard of death), Hb < 11 had the lowest survival probability (or the greatest hazard of death), and Hb > 12.5 was in between. The estimated coefficients of all the factors, which were imported to the multivariate analysis, were used to estimate the cure rates (Table 3). The estimated cure proportions using PHMC model

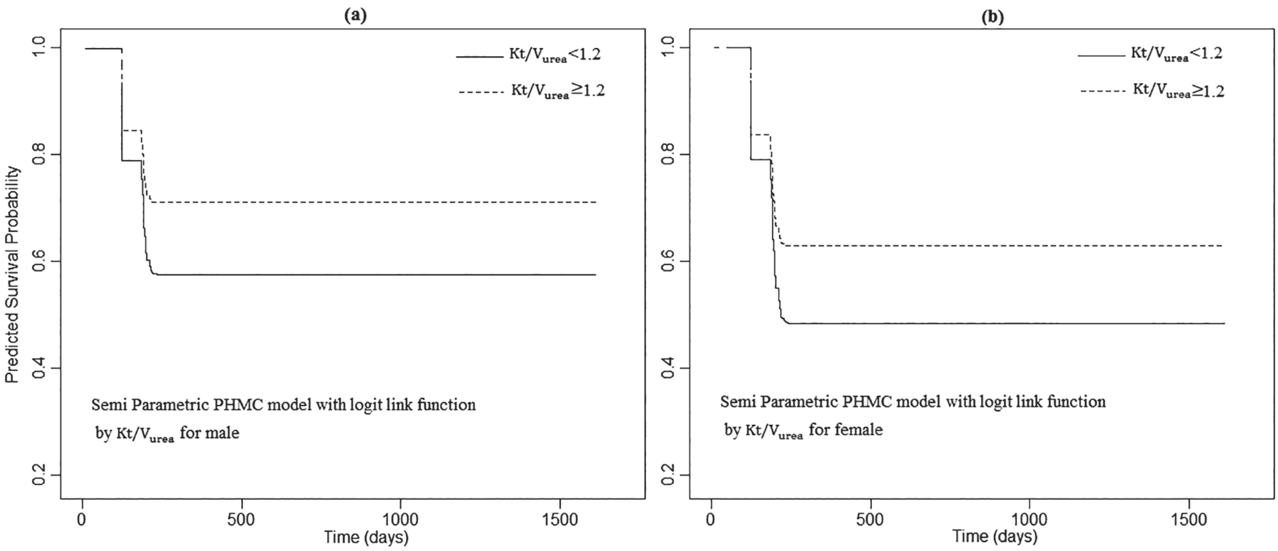

Figure 3. This figure estimated probabilities plot for the two various levels of the adequacy of dialysis (Kt/V_{urea}) in the long-term survived HD patients from semiparametric PHMC model (using the EM algorithm with logit link function), (a) for male and (b) for female.

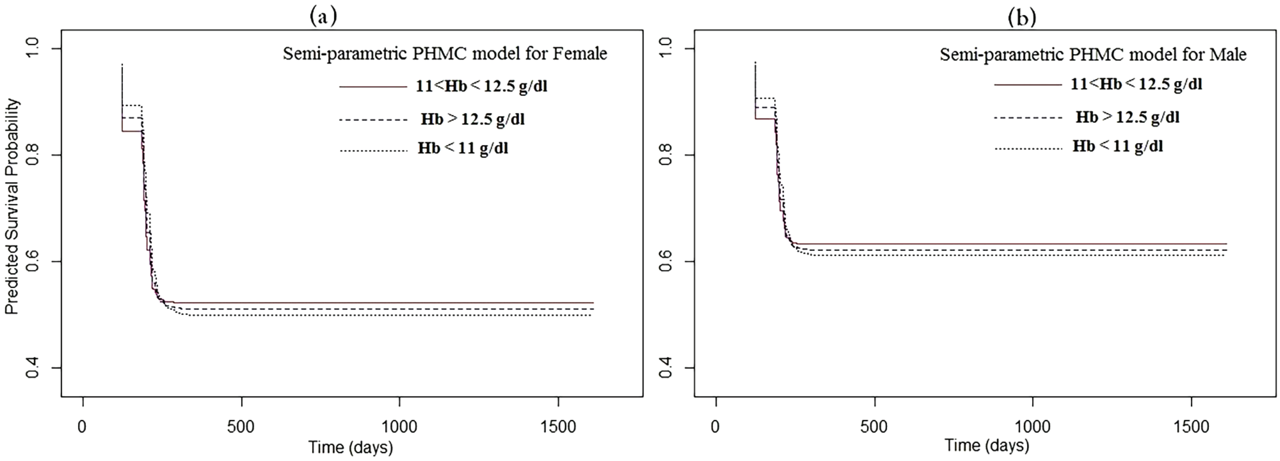

Figure 4. It estimated short-term survival curves of HD patients from semi-parametric PHMC model using the EM algorithm in the three different levels of hemoglobin, (a) for female and (b) for male.

Table 3. The Estimated Cure Rates Using Different Link Functions

Estimation of Cure Rate*	Link Functions		
	Probit	Logit	Cloglog
Sex			
Male	79.25	79.94	80.02
Female	70.24	70.73	71.33
Male			
Kt/V_{urea} < 1.2	65.38	65.97	66.55
Kt/V_{urea} ≥ 1.2	79.18	79.00	79.99
Female			
Kt/V_{urea} < 1.2	54.45	54.03	53.93
Kt/V_{urea} ≥ 1.2	70.01	70.01	71.25

*The estimated coefficients of all the factors, which were applied in multivariate analysis, have been used to calculate the cure rate.

with probit, logit, and cloglog link functions for the male sex (without constraint) were 0.7925, 0.7994, and 0.8002; respectively, suggesting that 79.25%, 79.94%, and 80.02% of the male patients were cured. Comparatively, the cure rate for the female sex with probit, logit, and cloglog link functions was calculated similarly but was found to be 0.7024, 0.7073, and 0.71.33; respectively. Also, the estimated cure rates with considering different levels of Kt/V_{urea} for both men and women are shown in this Table 3. In general, for both levels of Kt/V_{urea} the calculated cure proportions for males were higher than those of females.

DISCUSSION

Considering the growing population of patients with ESRD, particularly in developing countries, several studies have recently investigated the effects of different factors on the morbidity and mortality of patients undergoing HD.[6-10,15] To the best of our knowledge, this study is the first one that investigates the long-term and short-term survival rates of patients undergoing HD separately. Preceding surveys have applied the general Cox PH regression model, which is a suitable approach for analyzing short-term survival.

In certain populations such as HD patients, when the time of follow-up is long enough and the censoring rate (i.e., the proportion of surviving patients) is also high, using cure models is more appropriate than the Cox regression model.[16] In our population, the KM curve levels-off was around 0.7 and a large plateau was observed over time, approximately 1,110 days in the plateau. Since 82% of the censoring times occurred after the last observed event time, MCMs was implemented. The main goal of this study was to determine the factors that have a significant effect on both long-term and short-term survival in a population of Iranian patients undergoing maintenance HD.

To analyze the long-term survival of patients, semi-parametric PHMC model with three link functions (i.e., logit, probit, and cloglog) was used. The statistically significant factors were identified in different link functions. We found three features, age, sex, and Kt/V_{urea} have important impacts on long-term survival while MCHC and serum hemoglobin have affected short-term survival. The current study showed that age had an important effect on long-term survival. Younger patients had more chance of being cured such that many of them experienced long-term survival compared to older patients. The results of a multicenter retrospective study conducted to examine the relationship between different age ranges and mortality in patients undergoing HD was in line with our findings.[7] This finding was also in agreement with some previous reports about the survival of patients.[8,17,18]

In the present study, sex had a significant effect on long-term survival such that a higher proportion of male patients experienced long-term survival than females (Table 3, Figures 3 and 4). Therefore, males were more likely to be cured than females. Several studies have stated that sex plays an important role in determining survival in patients and the mortality proportion in women was less than men;[10,19] inconsistent with the current study. In line with our results, a study showed that female sex is a strong predictor of mortality.[18] We found that an increase in dialysis adequacy by Kt/V_{urea} from the desired threshold level of 1.2 increases the chance of being a long-term survivor. Therefore, the adequacy of dialysis has an important impact on survival of patients (Table 2 and Figure 3). Several investigations have recognized that high quality of dialysis increases the overall survival of patients.[9,10] According to the findings of the present study, a higher MCHC level is associated with a lower hazard of death (Table 3). To the best of authors' knowledge, there is only one study on patients with ESRD that showed low MCHC increases short-term mortality[20]. Iron deficiency, which can lead to low MCHC level, could account for the higher mortality of patients with low MCHC. This finding emphasizes the role of this index as one of the items that could have a remarkable impact on survival patients and should be highlighted as an important item in the laboratory evaluation of patients.

Our results showed that patients with hemoglobin in the range of 11 to 12.5 g/dL have lower mortality rates rather than those with hemoglobin < 11 g/dL. Effect of hemoglobin on survival has been the subject of some studies in patients on maintenance HD. A low hemoglobin level is associated with higher all-cause mortality and serum hemoglobin level of 11 to 12 g/dL is linked to a low risk of death in these patients; therefore, our findings are consistent with these studies.[21,22]

Due to the existence of the bias in the estimation of the parameters through three link functions (Table 2), the calculated cure proportions associated with each of the various link functions were slightly different. The empirical values of cure rate in our HD population (i.e., proportions of the patients who experienced long-term survival for males and females) were 75.09% and 68.75%, respectively. By looking at the estimated cure proportions, it is evident that the semi-parametric PHMC model with probit link function was superior because of its more accurate estimation cure rate (estimated cure rate for men and women 79.25% and 70.24%, respectively). Since the P values for the sex and Kt/V_{urea} factors were significant with three link functions ($P < .05$), it is inferred that there is a significant and considerable difference in cure proportion between male and female sex when implementing semi-parametric PHMC model. The present study has some limitations. Some of the variables with a potential impact on survival, such as iron profile indices (i.e., serum iron and ferritin) and underlying renal diseases, were not considered for the final analysis. As mentioned in the method, due to the existence of a large number of variables, it was not possible to run the cure model with all of them including iron indices. Thus, these variables were excluded in the primary analysis. The other weakness of the present study was unavailability of the cause of mortality in the database.

CONCLUSION

Many attempts have been made to improve short-term survival of patients undergoing HD in several countries via traditional survival model. In this regard, cure models show that factors affect long-term and short-term survival rates separately. Age, sex, and Kt/V_{urea} affected the probability of being a long-term survivor while MCHC and serum hemoglobin affected patients with short-term survivors. According to the findings of the present study, factors affecting the long-term survival might be different from those affecting short-term survival. In this regard, further research is needed to determine the role of cure models in the survival analysis of the patients and to explain the effects of the various factors on survival, which might be different for short-term and long-term survival.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Correspondence to:
Shahrokh Ezzatzadegan Jahromi, MD
Department of Medicine, Nemazee hospital (Postal Code: 7134845794), Shiraz, Iran
Tel: 0098 9173 1380 34
E-mail: shjahromi@sums.ac.ir

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