➡️ **Research Article**

Identification of Effective Factors on the Survival of Hemodialysis Patients Using the LASSO-Cox Approach

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Abstract

Background: Hemodialysis is a method for removing excess fluid and uremic waste from the body of chronic renal failure (CRF) patients. It stops death in patients with CRF. Various factors can affect the survival of patients undergoing hemodialysis treatment. The current study aimed to determine some factors affecting hemodialysis patients' survival using the LASSO-Cox approach.

Methods: This cross-sectional study examined 252 patients undergoing hemodialysis from 2010 to 2016 in all hospitals of Bandar Abbas, Iran, whose data had been recorded in the hemodialysis unit, or it was possible to obtain their files. The Cox model under the LASSO variable selection technique (LASSO-Cox) was applied for data analysis. The collected data were analyzed using SPSS 23.0 (IBM) software and glmnet and survival packages in R software, version 3.5.1.

Results: Overall, 35 (13.9%) death events were observed in this study. The mean follow-up time of 252 patients was equal to 10.93 ± 7.82 years. Based on the results of the Cox-Lasso method, the risk of mortality for patients with a diploma was 49% lower than that of the illiterate group (HR=0.51; 95% CI: 0.02, 0.57; P=0.021). The risk of death for unemployed patients and farmers was 0.66 (HR=1.66; 95% CI: 1.51, 25.79; P=0.004) and 0.29 (HR=1.29; 95% CI: 1.14, 27.40; P=0.005) higher than that of employees, respectively. Further, by an increase in the frequency of dialysis per week, the risk of death was reduced by 0.34 (HR=0.66; 95% CI: 0.04, 0.82; P=0.022), and one unit increase in the duration of dialysis per hour increased the risk of death by 2.23 times (HR=2.23; 95% CI: 1.41, 27.1; P=0.010).

Conclusion: Education level, job, frequency of hemodialysis per week, and duration of hemodialysis per hour were the most important variables in the survival of hemodialysis patients. As a result, it seems that more education for nurses working in hemodialysis wards and the involved patients can be useful to heed the recommendations of physicians in terms of the required duration for hemodialysis per hour and the number of sessions per week.

Keywords: Chronic Kidney Failure, Dialysis, Survival Analysis

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Background

An inappropriate and unhealthy lifestyle is responsible for the occurrence of many types of chronic diseases. Chronic illness is the cause of much mortality throughout the world (1). Chronic renal failure (CRF) is one of the chronic diseases that has risen in recent years and has increased tenfold in the United States in the past 20 years (2). According to the statistics of the Center for the Management of Transplantation and Special Diseases of the Ministry of Health of Iran, the annual growth rate of the disease is nearly 11% in this country (3). Patients with CRF are unable to survive without renal replacement therapy (4). According to a report from the above-mentioned center, the number of patients with kidney failure is equal to 320000 people, 49%, 48%, and 3% of whom use transplantation therapy, hemodialysis, and peritoneal dialysis, respectively (5). Although hemodialysis prevents death in patients with CRF, it does not treat renal disease and does not compensate for the endocrine and metabolic activities of the kidneys, and the patient is exposed to some problems and complications (6, 7). In the US, diabetes mellitus accounts for more than 45% of newly diagnosed cases with end-stage renal disease (ESRD), and it is also the second most common cause of hypertension, which is estimated to account for 28% of ESRD cases. In addition, the results of a study in Iran indicated that hypertension has been reported as the most common cause of ESRD (7, 8). Serum albumin is one of the ways to assess the status of patients with ESRD, and checking changes in serum levels of albumin can help diagnose the progression of the disease and use appropriate treatment to prevent future risks (8, 9). In studies with large sample sizes, it has been shown that a low concentration of albumin is a reliable predictor of mortality in ESRD patients (10, 11). The inadequacy of hemodialysis is one of the main causes of mortality

in patients with ESRD (12). Several factors such as diet, type of filter, device rotation, hemodialysis time, and underlying disease affect hemodialysis adequacy (13). In hemodialysis, uremic removal is calculated by a number used to quantify the hemodialysis and peritoneal dialysis treatment adequacy (Kt/V) formula with a normal level of 1.2. For this purpose, blood urine nitrogen is controlled in the patient to measure urea removal before and after hemodialysis. Therefore, the amount of urea removal in a 4-hour phase of hemodialysis is important in assessing adequacy, and it does not depend on the plasmatic urea level alone (14). One of the important issues in effective hemodialysis is hemodialysis duration. Based on the findings of a study conducted in this regard, mortality in hemodialysis patients had a direct relationship with hemodialysis duration. The mortality rate of hemodialysis patients who underwent hemodialysis below 10.5 hours of hemodialysis in the first week was far more than that of those who underwent hemodialysis every week for more than 12 hours (15).

Survival analysis is a branch of statistics for data analysis where the outcome variable of interest is the time of occurrence of an event. Due to the importance of identifying factors affecting the survival of dialysis patients, the researchers were encouraged to conduct this study.

Objectives

The current study sought to determine some factors affecting the lifespan of hemodialysis patients in Bandar Abbas, Iran using survival analysis.

Methods

In this cross-sectional study, patients' information was collected through a census from the Hemodialysis Department of Shahid Mohammadi, Kodakan, and Khalij-e-Fars Hospitals in Bandar Abbas, Iran. According to studies on the total number of patients who were admitted during 2010-2016, 252 cases were examined, whose data were recorded in the hemodialysis department, and their medical records were available, among whom, only 35 people died by the end of 2016. In the current study, death was considered as the desired event, and excluded cases included live subjects at the end of the study, people missed the follow-up, and kidney transplant recipients. The survival time of patients was calculated from the beginning of hemodialysis to the end of the study in 2016. Data were collected based on a designed checklist which was approved by a specialist. The checklist included variables such as age, gender (female or male), educational status (illiteracy, low literacy, diploma, university graduate, and the number of years of studying), marital status (single, married, or widow), and employment status (housewife, unemployed, civil servant, farmer, retired, or others). The other variables

were smoking status (smoker or non-smoker), the type of underlying disease that leads to hemodialysis (diabetes, hypertension, stones and kidney obstruction, polycystic kidney disease, congenital, unspecified diseases, or others), and age of underlying disease diagnosis. The remaining factors included cardiovascular diseases, family support, age of hemodialysis initiation, mean serum albumin, and serum creatinine. The obtained data were coded and computerized for analysis.

In the present study, excluded cases were live subjects at the end of the study, patients who missed the follow-up, and kidney transplant recipients. The survival time of the patients was calculated by the years from the onset of hemodialysis to the end of the study in 2016. Due to the presence of sparse data (35 cases (13.9%) died and 217 (86.1%) cases were excluded), the performance of ordinary Cox regression is questionable. In such a situation, Cox regression by the Least Absolute Shrinkage and Selection Operator (LASSO) method has been introduced as a suitable approach to finding variables affecting patients' survival.

The collected data were analyzed using SPSS 23.0 (IBM) and installing glmnet and survival packages in R software, version 3.5.1. A two-sided $P < 0.05$ was considered statistically significant. It is worth noting that in the analysis of survival, conclusions are based on the hazard ratio (HR). If its value is greater than one, it indicates that the group is at higher risk for the occurrence of the event compared to the base group. If its value is less than one, compared to the base group, there will be a lower risk for the occurrence of the desired event, and HR-1 is usually used to express such situations.

Results

In the current study, 252 hemodialysis patients were investigated who were referred to Shahid Mohammadi, Kodakan, and Khalij-e-Fars hospitals in Bandar Abbas. Among 252 patients, there were 35 (13.9%) and 217 (86.1%) cases of death and exclusion, respectively. The mean of follow-up time of 252 patients was equal to 10.93 ± 7.82 years, and their mean age was 53.39 ± 18.09 years in death or censoring time. Further, the mean age of hemodialysis initiation in patients was equal to 42.88 ± 17.07 years, and the mean score of their body mass index (BMI) was 22.87 ± 4.24. Most women were housewives (87.1%), and most men were unemployed or retired. No cases with HIV infection were observed in these patients. Hemodialysis lasted 4 hours each time for 194 patients (77%). Overall, 171 (67.9%) patients were hemodialyzed three times a week (Table 1).

The 10-year survival rate of hemodialysis patients was equal to 0.87, implying that 0.87 of the patients will survive more than ten years (Figure 1). The results of the LASSO-Cox model (Table 2) demonstrated that by adjusting other variables, for one unit of increase in BMI, the risk

Table 1. Hemodialysis Patients' Characteristics

Variables		Mean	SD
Follow-up time (y)		10.93	7.82
Body mass index (kg/m²)		22.87	4.24
Age of dialysis initiation (y)		42.88	17.07
Age in death or censoring time (y)		53.39	18.09
		Frequency	**Percent**
Blood group	O	108	42.9
	A	62	24.6
	B	72	28.6
	AB	10	3.9
Education level	Illiterate	87	34.5
	Low literacy	118	46.8
	Diploma	40	15.9
	Academic	7	2.8
Job	Unemployed	46	18.2
	Farmer	44	17.5
	Housewife	101	40.1
	Employed	61	24.2
Gender	Men	136	54
	Women	116	46
Marital	Married	207	82.1
Smoking	Yes	91	36.1
Diabetes	Yes	134	53.2
Hypertension	Yes	152	60.3
Urinary stone	Yes	23	9.1
Kidney cyst	Yes	11	4.4
Cardiac pulmonary disease	Yes	50	19.8
Congenital disease	Yes	4	1.6
Glomerulonephritis	Yes	18	7.1
CRF history in family	Yes	24	9.5
Anemia history	Yes	195	77.4
Take of EPREX	Yes	239	94.8
HCV	Yes	8	3.2
HBV	Yes	3	1.2
Kidney transplantation	Yes	27	10.7
Stopped dialyze in reason of kidney function	Yes	22	8.7

Note. SD: Standard deviation; CRF: Chronic renal failure; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

of mortality is reduced by 0.10. The risk of death for those with a diploma was 0.49 lower than that of the illiterate group. Additionally, the risk of death for unemployed patients and farmers was 0.66 and 0.29 higher than that of employers, respectively. Another significant factor in this study was the duration of each hemodialysis session. The risk of death has fallen by 0.34 for one unit of increase in the number of hemodialyses. Moreover, by controlling other factors, increasing the duration of each hemodialysis session increased the hazard of death 2.23 times.

Discussion

Our study attempted to determine factors affecting the hemodialysis patients' survival using the LASSO-Cox approach. Based on the results of this study, the level of education, occupation, the hemodialysis center, the duration of hemodialysis regarding hours per session, and the frequency of hemodialysis per week were the most important prognostic factors.

The results also represented that by controlling other variables, the risk of death in people with kidney failure was reduced by 10% with one unit increase in the BMI. Weight loss in patients with hemodialysis is the most important goal in every hemodialysis session, and patients are weighed at the beginning and the end of hemodialysis, thus the result of this study suggests a paradox, which has been addressed in previous research (16). It should be noted that BMI reduction is not addressed in patients for two reasons; malnutrition in hemodialysis patients is a major risk in the mortality of patients (17, 18) and depends on receiving insufficient energy. Getting 35 kcal per kg of body weight as the recommended calorie intake will help maintain protein and thus prevent a negative nitrogen balance (19, 20).

Furthermore, the risk of mortality for those with a diploma was 0.49 lower than that of the illiterate group. It may be justified that treatment adherence is higher in these individuals because of higher education or they are more likely to seek information because of their education and even have a better quality of life (21). Literacy by making basic changes in the knowledge of people and attitudes affected health and disease and the other aspects of life, and people with a high level of education have better availability to supportive sources and better control the side effects of diseases, and ultimately have a better quality of life (22). Although it has been proven in some studies, there have been contradictions in this regard (23).

The risk of mortality for unemployed patients and farmers was 0.66 and 0.29 higher than that of employers,
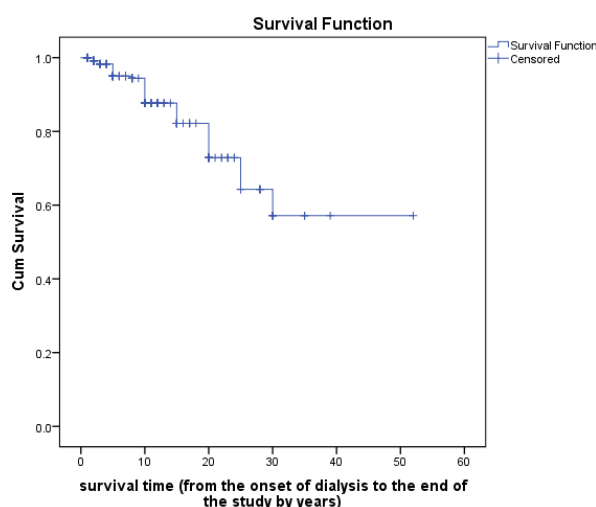

Figure 1. The Kaplan Meier Survival Curve of Patients.

Table 2. The Most Important Variables Selected Based on the LASSO-Cox Model

Variables	Coefficient	*P* Value	95% CI	Hazard Ratio
Body mass index	-0.107	0.045	(-0.182, -0.019)	0.90
Dialyze center[a] (Ref: Center No. 1)				
Dialyze center No. 3	-0.167	0.047	(-2.824, -0.013)	0.85
Level of education (Ref: Illiterate)				
Diploma	-0.673	0.021	(-4.089, -0.563)	0.51
Job (Ref: Employee)				
Unemployed	0.507	0.004	(0.411, 3.250)	1.66
Farmer	0.252	0.005	(0.129, 5.624)	1.29
Number of dialysis sessions per week	-0.421	0.022	(-3.273, -0.202)	0.66
Duration of dialysis sessions	0.802	0.010	(0.341, 3.301)	2.23

Note. CI: Confidence interval.
[a] The name of the centers has been omitted to observe ethics.

respectively. This result may be related to economic issues so that having a job and income plays a more effective role in people feeding, caring, and knowledge. In addition, this issue allows them to have a better quality of life and helps them to adhere to treatment. Given the increased cost of treatment, employees are more successful in meeting their therapeutic needs (22, 24-26).

Additionally, the results showed that with an increase in the frequency of dialysis per week, the risk of death was reduced by 0.34. In other words, increasing the frequency of dialysis leads to increased appetite and food intake and thus improves nutrition. It also has important cardiovascular properties in hemodialysis patients, including lowering blood pressure, reducing environmental resistance, and increasing clearance or reducing endothelial toxins. This justification is also consistent with the findings of several studies (27-29). However, the number of dialysis sessions does not always follow the mentioned justification. In fact, non-adherence to treatment and subsequent electrolyte disturbances in some cases lead to an increase in dialysis sessions. Such a case has been mentioned in some studies (30, 31).

The results further revealed that one unit increase in the duration of hemodialysis was associated with an increased risk of death of 2.23 times. This relationship has been reported in other studies (32, 33). The recent result is probably contrary to our expectations and represents the patient's severe condition; although the duration of hemodialysis is increased, the person is at increased risk of death. It can be explained by the fact that increasing the frequency of hemodialysis increases the risk of hepatitis C virus infection because this infection will be associated with blood transfusions on hemodialysis and can be reduced as much as possible by injecting erythropoietin (34). Even the duration of hemodialysis will be directly related to hepatitis C infection, and the longer the duration of hemodialysis treatment, the greater the need for blood and subsequent hepatitis C infection (35, 36).

Limitations
This study has some limitations. Compared to some other studies, the sample size is small in this study, and we did not have a sample size. We had a census in all hospitals in Bandar Abbas. Thus, the results of this study cannot be generalized to other cities of Iran. The death rate in our study was low; the medical record departments of the hospitals could not supply all patient information, thus we changed our analysis by the Lasso regression method in the Cox proportional hazard model.

Conclusion
Overall, education level, job, frequency of hemodialysis per week, and duration of hemodialysis per hour were the most important parameters contributing to the survival of hemodialysis patients. Accordingly, it seems that more education for nurses working in hemodialysis wards and the involved patients can be useful for heeding the recommendations of physicians regarding the required duration for hemodialysis per hour and the number of sessions per week.

Consent for Publication

Not applicable.

Ethical Approval

The approval was obtained from the Ethics Committee of Hormozgan University of Medical Sciences (Approval number: HUMS.REC.1394.171). Written and informed consent forms were taken from patients to participate in the study. No experimental medical intervention or experimental treatment was used for the particular clinical setting.

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