

Determining Some Factors Affecting the Longevity of Hemodialysis Patients. Using Survival Analysis

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Abstract

Background Dialysis is a method for removing excess fluid and uremic waste from the body of chronic renal-failure patients. In patients with CRF, blood dialysis stops death. Hemodialysis prevents the death of patients with chronic renal failure. Various factors can affect the survival of patients undergoing dialysis treatment. The current study aimed to determine such factors. Methods This descriptive-analytic study examined 252 patients undergoing dialysis from 2010 to 2016 in all of hospitals in Bandar Abbas- Iran, whose data had been recorded in the dialysis unit or it was possible to get their files. The study used Lasso Regression in Cox's proportional hazards model in case with multi variables, background diseases, Body Mass Index,..... The collected data was analyzed using SPSS software and through installing glmnet and survival packages in R software. Results In this study, 35 (13.9%) death events and 217 (86.1%) censored events were observed. The mean survival time of 252 patients was equal to 10.93 ± 7.82 years and the median survival time of these patients was calculated to be ten years. Based on the results of the Cox model under the penalized method of Lasso, The risk of mortality for patients with diploma degree was by 49% lower than that of the illiterate group (HR = 0.51). The risk of death for unemployed patients and farmers was equal to 0.66 (HR = 1.66) and 0.29 (HR = 1.29), respectively, higher than that of employees. Another significant factor in this study is the duration of each dialysis session. The risk of mortality has been reduced by 0.34 (HR = 0.66) for a single increase during dialysis. Conclusions Apart from congenital and underlying diseases which early diagnosis will prevent kidney failure, the risk of mortality will be reduced by training behavioral issues in patients undergoing dialysis such as dialysis at predetermined hours and times and appropriate nutritional behaviors.

Introduction

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, is one of the chronic diseases that has risen in recent years, and it was increased tenfold in the USA in the past 20 years [2]. According to the statistics of the Center for management of transplantation and special diseases of the Ministry of Health, the annual growth rate of the disease is about 11% in Iran [3]. Patients with chronic renal failure are unable to survive without renal replacement therapy [4]. According to a report from the Center for the Management of Transplantation and Special Diseases of the Ministry of Health, the number of patients with kidney failure is equal to 320,000 people, by 49% of whom use transplantation therapy, by 48% use hemodialysis, and by 3% use peritoneal dialysis [5]. Hemodialysis prevents death in patients with chronic renal failure, although it does not treat renal disease and does not compensate for endocrinal and metabolic activities of the kidneys, and the patient is exposed to some problems and complications [6, 7]. In the United States, diabetes mellitus accounts for more than 45% of newly diagnosed cases with ESRD, and it is also the second common cause of hypertension, which is estimated to account for 28% of ESRD cases. Also in a study in Iran, the results indicated that hypertension has been reported as the most common cause in ESRD [7, 8]. Albumin serum is one of the ways to assess the status of patients with ESRD and checking changes in serum levels of albumin can

help to 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 low concentration of albumin is a reliable predictor of mortality in ESRD patients [10, 11]. The inadequacy of dialysis is one of the main causes of mortality in patients with ESRD [12]. Several factors such as diet, type of filter, device rotation, dialysis time, and underlying disease affect dialysis adequacy [13]. In dialysis, uremic removal is calculated by a number used to quantify hemodialysis and peritoneal dialysis treatment adequacy (KT / V) formula with a normal level of 1.2. For this purpose, Blood urine nitrogen (BUN) is controlled in the patient to measure urea removal before and after dialysis. Therefore, what matters are the amount of urea removal in a 4-hour phase of dialysis in assessing adequacy, and it does not depend on the plasmatic urea level alone [14]. One of the important issues in effective dialysis is the dialysis duration, and in a study which has been conducted in this regard, the results showed that mortality in dialysis patients has a direct relationship with dialysis duration. The mortality rate of dialysis patients who underwent dialysis below 10.5 hours of dialysis in the first week was far more than those who underwent dialysis every week for more than 12 hours [15]. In many medical studies, a group of subjects has been studied and followed up during a specified period to have a specific incident. Hence, the researchers of the current study are interested in the time interval from entering the study to the occurrence of the incident and determining its relationship with independent variables for the study of risk factors. The time observations of these studies which have been associated with censored data are called "survival data," and a set of statistical methods for their analysis is called "survival analysis" [16]. The censored event occurs when there is incomplete information about the survival time of some of the subjects. In the study of survival analysis and at the end of the study, some individuals do not experience the incident or researchers have no information about the achievement of the incident to them. Censored Data is data with such feature. The current study was conducted to determine some factors affecting the lifespan of hemodialysis patients in Bandar Abbas using survival analysis.

Methods

In this cross-sectional study, patients' information was collected through a census from the dialysis department of Shahid Mohammadi, Kodakan and Khalij-e-Fars hospitals in Bandar Abbas. According to the studies on the total number of patients who were admitted during 2010–2016, 252 patients were examined whose data was recorded in the dialysis department, and their medical records were available, among whom, only 35 people died at the end of 2016. In the current study, death was considered as a desired event and censored cases included live subjects at the end of the study, people missed in follow up and kidney transplant recipients. The survival time of patients was calculated from the beginning of dialysis to the end of the study in 2016. Data was collected based on a designed checklist which was approved by a specialist. The checklist included variables such as age, sex (female, male), educational status (illiteracy, low literacy, diploma, university graduate, number of years of studying), marital status (single, married, deceased wife/husband, separated wife/husband), employment status (housewife, unemployed, employee, farmer, retired, others), smoking status (smoker, non-smoker), the type of underlying disease that leads to dialysis (diabetes, hypertension, stones and kidney obstruction,

Polycystic Kidney Disease (PKD), congenital, unspecified diseases, others), age of underlying disease diagnosis, cardiovascular disease, family support, age of dialysis initiation, mean serum albumin, serum creatinine, then, data was coded and computerized. One of the applications of the models is to predict the risk of the event in the future. The predictive models that are obtained using survival data are more likely to use Cox proportional hazards model., the use of the classic Cox model is not possible when the number of events is lower than the number of variables. The ratio of the number of people who experienced the event to the number of predictor variables or, more precisely, the number of parameters is defined as Events Per Variable (EPV). Based on simulated studies, EPV has been recommended from 10 to 20. When choosing a variable, the EPV rule applies to the number of candidate variables and not just the variables in the final model [17, 18]. In general, it can be said that, for each independent candidate variable, there should be at least 10 to 20 outcomes in the data to enter the Cox model based on simulated studies for Cox regression analysis. In the present study, due to a low number of mortality (the desired outcome) in the whole sample, Cox regression models which have been obtained by the least squares method are not suitable. Because in this case, the estimated regression coefficients may be obstruct and the predictive models may have poor reliability. Penalized regression methods that shrink the regression coefficients to zero, and include a ridge regression, lasso, and elastic net regressions, which are a combination of the two previous methods, may increase EPV in situations where the number of events is low [19].

We examine the censored survival data $i = 1, \dots, n$, $x_i = (t_i, \delta_i, z_i)$ with the observed time $t_i = \min (T_i, C_i)$. T_i is the time of occurrence of the event and C_i is the time of censorship. If $T_i \leq C_i$, then δ_i takes one, otherwise its value will be zero. Z_i is the vector of the variable p which has been observed at zero time. The Cox proportional hazards model is as follows.

$$h_0(t)\exp(x_i'\beta) = h(t|x_i)$$

In the above model, $h_0(t)$ is the unknown value of the base risk. The vector of the parameter $\beta = (\beta_1, \dots, \beta_p)$ is usually obtained by maximizing the partial log-likelihood function which is shown below.

[Due to technical limitations, this equation is only available as a download in the supplemental files section.]

If $p > n$, direct maximization is not possible. Shrinkage methods overcome this problem. Shrinkage methods maximize the under penalized partial log-likelihood function.

[Due to technical limitations, this equation is only available as a download in the supplemental files section.]

Which is [Due to technical limitations, this equation is only available as a download in the supplemental files section.] in Lasso regression, [Due to technical limitations, this equation is only available as a download in the supplemental files section.] in ridge regression method, and [Due to technical limitations, this equation is only available as a download in the supplemental files section.] in elastic net regression

which is a combination of the two previous methods. $\lambda > 0$ is known as setting when its value is obtained through cross-validation and using data. The setting of λ controls the shrinkage of the regression coefficients to zero, and larger values of λ lead to smaller regression coefficients.

In the present study, censored cases included live subjects at the end of the study; patients missed in the follow-up and kidney transplant recipients. The survival time of the patients was calculated per month from the start of their dialysis. The collected data was analyzed using SPSS and also by installing glmnet and survival packages in R software. It is worth noting that in the analysis of survival, the conclusions are based on the Hazard Ratio (HR). If its value is greater than one, indicating 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, HR-1 is usually used to express such situations.

Results

In the current study, 252 hemodialysis patients were studied who were referring to Shahid Mohammadi, Kodakan and Khalij-e-Fars hospitals in Bandar Abbas. Among 252 patients, 35 (13.9%) cases of death and 217 (86.1%) cases of censor were observed. The mean survival time of 252 patients was equal to 10.93 ± 7.82 years and the median survival time of these patients was calculated to be ten years. The mean age of these patients was equal to 53.39 ± 18.09 years. The mean age of dialysis initiation in patients was equal to 42.88 ± 17.07 years. The mean score of BMI for these patients was equal to 22.87 ± 4.24 . Most of the women were housewives (87.1%), and most men were unemployed or retired. No cases with HIV infection were seen in these patients. Dialysis lasted 4 hours each time for 194 patients (77%). 171 of them were dialyzed three times a week (67.9%)(Table1).

The results of the Cox model under the penalized method of Lasso showed in (Table 2).

Discussion

Based on the results of this study, the 10-year survival rate of dialysis patients was equal to 0.87 according to the Cox model under penalized methods of Lasso. The level of education, occupation, the dialysis center, the duration of dialysis regarding hours per session, and the frequency of dialysis per week as the most important prognostic factors.

The risk of death from kidney failure in diabetics is by 6% higher than that of non-diabetic subjects. This result can explain the kidney failure and death and in many studies, diabetes is the most commonly known cause of chronic renal failure, which caused by 148.8 ESRD cases per million people in the USA in 2004[20, 21]. Since people who have kidney failure due to diabetes, ultimately need to undergo dialysis for their survival, chronic renal failure leads to decrease insulin secretion and resistance to insulin, especially in skeletal muscle and in advanced stages of renal failure, renal clearance and insulin degradation are reduced, which are very important in the treatment of diabetic patients. Insulin resistance,

on the other hand, has led to an increased amount of insulin in these patients and, with decreasing insulin degradation, the need for insulin administration is reduced, and the incidence of hypoglycemia is increased in these patients. Even severe hyperglycemia in patients with ESRD, which becomes anuric or oliguric, may cause the manifestation of hyponatremia, hyperkalemia, and increased acute intravascular volume. Because other organs, such as the eye, heart, and vessels will be damaged, the risk of death is also increased due to the affection of other organs, which has been proved in numerous studies [22, 23].

The results also showed that by controlling other variables the risk of death in people with kidney failure is reduced by 10% with a single increase in Body Mass Index (BMI). Since weight loss in patients with dialysis is the most important goal in every dialysis session and patients are weighed at the beginning and the end of dialysis, the result of this study suggests a paradox which has been addressed in many studies [24]. It should be noted that the BMI index reduction is not addressed in patients for two reasons. First, malnutrition in dialysis patients is a major risk in the mortality of patients [25, 26], and second, the high BMI is associated with survival in dialysis patients [27].

The risk of death for those who received erythropoietin was by 59% lower than those who did not need to receive erythropoietin. The main and primary cause of anemia in patients with renal failure is the reduction of erythropoietin secretion. Hematopoiesis is naturally affected by this hormone, which influences the primary hematopoietic cells through specific receptors and stimulates hematopoiesis. By 90% of the circulating erythropoietin secretes from the interstitial cells of the renal cortex. However, its extra-renal amount that is secreted from the liver can not play a significant role in preventing anemia, and the deficiency of such hormone is compensated by receiving Recombinant Human Erythropoietin (rHuEPO) [28].

Also, the risk of mortality for those with a diploma was by 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 because of their education, they are more likely to seek information and even have a better quality of life [29]. Literacy with by making basic changes in knowledge of people and attitudes had affected in health and disease and other different aspects of life and people with high level of education have better availability to supportive sources and better control the side effects of diseases, then ultimately have better quality of life [3]. However, it has been proven in some studies, but there have been contradictions with this conclusion [30].

The risk of mortality for unemployed patients and farmers was respectively by 0.66 and 0.29 higher than that of employers. This result may be related to economic issues, so that having a job and income play a more effective role in people feeding, caring and knowledge and have better quality of life and help them to treatment adherence and, given the increased cost of treatment, employees are more successful in meeting their therapeutic needs [2, 3].

Also, the results showed that with an increase in the frequency of dialysis per week, the risk of death increased by 2.53 times, and a single increase in the duration of dialysis was associated with an increased risk of death of 0.34 times (maybe these two recent results are contrary to our expectations,

and it shows the patient's severe condition, although the duration of dialysis and the frequency of dialysis are increased, the person is at increased risk of death). It can be explained by the fact that increasing the frequency of dialysis increases the risk of HCV infection, as well as increasing frequency of dialysis can be due to the patient's non-adherence to the treatment, dialysis and its frequencies, and increasing edema increases the number of sessions. An increase in the duration and frequency of dialysis is for dialysis adequacy and removal of accumulated toxins, and therefore it is effective in the outcome of death [31, 32].

Limitation

This study the same as other researches has some problems, for example to compare some other studies the sample size is small, in this study we did not have sample size, and we had census in all of hospital in Bandar Abbas city and we are sure that this results do not have strength to generalize in hole of Iran. The death rate in our study was low, it causes by hospital medical records department that they could not supply all of patient information, for this reason we changed our analysis by Lasso regression method in the Cox proportional hazard model.

Conclusions

The results of the study showed that, apart from congenital and underlying diseases which early diagnosis would prevent kidney failure, the risk of mortality can be reduced by training behavioral issues in patients undergoing dialysis such as dialysis at predetermined hours and frequencies and proper nutritional behaviors.

List Of Abbreviations

CRF: Chronic renal-failure. BMI: Body Mass Index. ESRD: End stage renal disease. HCV: Hepatitis C virus. MCTSD: Management Center for Transplantation and Special Diseases. Kt/V : In medicine, Kt/V is a number used to quantify hemodialysis and peritoneal dialysis treatment adequacy. BUN: Blood urine nitrogen. PKDs: Polycystic kidney disease. EPV: Events per variable. HBV: Hepatitis B virus. HIV: Human immunodeficiency virus. rHuEPO: Recombinant Human Erythropoietin. GFR: glomerular filtration rate

Declarations

“Ethics approval and consent to participate”

The approval was given from the ethics committee of Hormozgan university of medical sciences; approval number: HUMS.REC.1394.171 Written and informed consent was taken by patient to participate. No experimental medical intervention or experimental treatment was used for the particular clinical setting.

‘Consent for publication’

Not applicable

‘Availability of data and materials’

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declared that they had no competing interests.

‘Funding’

None

‘Authors’ contributions’

All authors have contributed to this manuscript and approved this version for submission. LH, SHR, MT designed the study. LH, AS, contributed in recruitment of patients and data collection. LH, SHR processing and analysis of results. LH, SHR, MT and AS wrote the first draft of the manuscript. LH, SHR and MT helped to revise the manuscript.

All authors critically reviewed the manuscript.

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Compliance with Ethical Standards

Ethical Approval

This study was approved by the ethics committee of Hormozgan University of Medical Sciences (Code: HUMS.REC.1394.171). Before the data collection, the purpose of the study was explained to the participants, and an informed consent was obtained verbally from them.

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Tables

Table1. Hemodialysis patients study characteristics

Variable name		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
Sex	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

Table 2. The most important variables selected based on the Cox model under the penalized method of Lasso

Variable name		Coefficient measure	p-value	Confidence interval	Hazard Ratio
N.3 dialyze center		-(0.167)	0.047	(0.013, 2.824)	0.85
Level of education		-(0.673)	0.021	(0.563, 14/089)	0.51
Ref: illiterate					
Job Ref: employee	Unemployed	0.507	0.004	(0.411, 3.250)	1.66
	Farmer	0.252	0.005	(0.429, 5.624)	1.29
A few times a week		-(0.421)	0.022	(0.202, 3.273)	0.66
every time few hours of dialysis		0.802	0.010	(0.341, 3.301)	2.23

Supplementary Files

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