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Survival of Dialysis Patients Using Random Survival Forest Model in Low-Dimensional Data with Few-Events

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Abstract

Background: Dialysis is a process for eliminating extra uremic fluids of patients with chronic renal failure. The present study aimed to determine the variables that influence the survival of dialysis patients using random survival forest model (RSFM) in low-dimensional data with low events per variable (EPV).

Methods: In this historical cohort study, information was collected from 252 dialysis patients in Bandar Abbas hospitals, Iran. The survival time of the patients was calculated in years from the onset of dialysis to death or until the end of the study in 2016. RSFM was used as the number of events per variable (EPV) was low. The data collected from 252 patients were randomly divided into training and testing sets, and this process was repeated 100 times. C-index and Brier Score (BS) were used to assess the performance of the model in the test set.

Results: In this study, 35 (13.9%) mortality cases were observed. Based on the findings, the mean C-index value in training and testing sets was 0.640 and 0.687, and the mean BS value in training and testing sets was 0.017 and 0.023, respectively. The results of the RSFM revealed that BMI, education, occupation, dialysis duration, number of dialysis sessions and age at dialysis onset were the most important factors.

Conclusion: RSFM can be used to determine the survival of dialysis patients and manage low-dimensional data with few-events if the researcher desires to select a nonparametric model.

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Introduction

The full defect and irreversible reduction in renal function lasting more than 3 months is called ‘chronic renal failure’, and its advanced stage, in which survival depends on transplant or dialysis, is called ‘the end-stage renal disease (ESRD)’. The incidence of chronic renal failure has been increasing in recent years; in the US, the prevalence and incidence of ESRD have been doubled in the past decade(1).

The annual growth of chronic renal failure is about 11% in Iran based on the statistics of the Center for Transplant and

Special Disease Management of the Ministry of Health and Medical Education(2). Of all patients with ESRD, 48.5% recieved transplant, 48.5% underwent hemodialysis and 3% received peritoneal dialysis (3). In 2008, approximately 12500 patients with ESRD underwent hemodialysis in Iran (4).

Dialysis is a process to eliminate waste products from the blood when kidneys can no longer function properly. Among the common kidney replacement therapies, hemodialysis is a prevalent method for many patients with ESRD (5).

The negative effects of this disease are as follows: the negative effect on the quality of life of patients due to the chronic and debilitating nature of the disease; reduced social interactions; depression; frustration; reduced ability to independently perform daily activities and an increase in mortality rate.

Considering the problems that patients with dialysis encounter, it seems highly important to determine the variables that affect survival of this group of patients. Thus, this study was conducted to determine the variables that affect the survival of dialysis patients, especially those factors that, if controlled, can increase the survival of patients; factors like the duration of a dialysis session and the frequency of dialysis per week.

Usually data sets have a large enough sample size (n) and limited number of independent variables (p), that is n>p. These are called low dimensional data and the Cox regression is commonly used for such data sets. In contrast, high dimensional data refers to the situations where n<p.

A factor that affects the performance of regression models is the number of Events (known as effective sample size) per number of independent Variables (EPV) (6). EPV of 10 to 20 has been recommended based on the simulated studies. When EPV is low, it is advised not to use the Cox model because the estimated coefficients are not reliable.

In high dimensional data, EPV is always low. Therefore, classical models are not applicable. This may also cause problems when working with low-dimensional data (7). For example, assume a data set where n=150, p=15, n_{event}=30. Here, n>p and EPV=2. A common technique for solving this problem is the random survival forest model (RSFM), a nonparametric strategy which can be applied to construct the model of event occurrence risk prediction in analyzing survival data(8,9). This model has none of the assumptions and limitations of parametric and semi-parametric models.

Considering the importance of this subject and taking into account that only few studies have used RSFM to determine the survival of dialysis patients in low-dimensional data with few-events, the present study examined the performance and predictive power of RSFM. This may be helpful for future studies as well as for the analysis of medical and health-related data. Moreover, it may help to identify the variables that affect dialysis patients.

Materials & Methods

Study Population and Data

In this historical cohort study, the data were collected from the dialysis wards of three hospitals (Shahid Mohammadi; Children's hospital; and Persian Gulf Hospital) in Bandar Abbas, Iran. Of the total patients admitted to the hospitals from 2010 to 2016, only the data of 252 patients were recorded in the dialysis ward. In this study, mortality was considered as the event of interest and those patients who were alive at the end of the study, excluded cases and those treated with kidney transplant were censored. The survival time of the patients was calculated in years from the onset of dialysis to the death or until the end of the study in 2016.

Based on patient records, the first time patients were admitted to the hospital was considered as the time to start dialysis. The data were collected based on the records of patients at the time of admission with a designed checklist that included age, sex, educational status, marital status, smoking, type of disease leading to dialysis (diabetes, hypertension, renal stones and obstruction, renal cysts and congenital diseases), age at the diagnosis, history of cardiac-respiratory diseases, history of anemia, and familial history of chronic renal failure.

Procedures and Evaluations

When the number of events is lower than the number of variables, use of conventional models such as cox regression is questionable. In the present study, because of the low number of mortality cases (the outcome of interest) in the sample, the use of common models, which were based on the least square residuals, was not appropriate. In fact, in this case, the estimated regression coefficients may become biased and the predictive models may have weak reliability. A strategy used in this situation is the application of decision tree models, which includes the root node, middle nodes, and terminal nodes.

In the first step, the population is placed in the root node. Then, members with the maximum difference should be divided into two middle nodes. This is performed by an extensive search among all independent variables to find a variable and cutoff point leading to the largest value of log-rank statistic and the smallest P-value. When the first division is developed, the same process continues for each middle node. Finally, a tree is formed, in which the members are divided into terminal nodes.

Nevertheless, single-tree models suffer from high variance. Thus, the use of bootstrap aggregating (bagging), which includes a large number of decision trees, is suggested. Moreover, it reduces variance and helps to avoid overfitting and improves the predictive performance of single tree.

However, the trees in bagging are not completely independent since all the original predictors should be considered at each split of the tree. It has been shown that when strong predictors exist, the variance of the trees is not that high as strong predictors usually appear at the top of the trees. To provide pictures with higher variability, random survival forest models (RSFM) has been proposed.

RSFM is an ensemble method that introduces two forms of randomization into the tree growing process: First, it draws multiple bootstrap samples from the initial data. Then, a random sample of independent variables is selected and used to construct each tree.

The random forests algorithm is as follows: (1) Draw N bootstrap samples from the original data; (2) Grow a regression tree for each of the bootstrap samples with the following modification: a. Select m variables at random from all p variables, b. Pick the best variable/split-point from among the m variables (Those with the largest value of log-rank statistic and smallest P-value) and (3) Make a new prediction by aggregating the existing predictions of the N trees.

Data collected from 252 patients were randomly divided into training and testing sets, and this process was repeated 100 times. RSFM was used for the training set. The mean concordance index (C-index) as well as the mean Brier Score (BS) statistic were used to assess the prediction accuracy of RSFM in the test set.

To calculate concordance index (C-index), the out-of-bag (OOB) samples of each decision tree that have not been selected for the respective bootstrap sample are used. Then, the probability is estimated according to C-index. It estimates the probability that in a randomly selected pair of OOB samples with an event, the OOB sample with the shorter follow-up time has the worst predictive outcome.

The value of 0.5 for C-index shows the inability of the model in differentiating all people and 1 indicates the full ability of the model in this regard (10). Another index for assessing the accuracy of predictions is BS, which varies from 0 to 1, with a smaller value demonstrating larger prediction precision (11).

In this study, the predictive power of variables in RSFM was evaluated with variable importance (VIMP) and minimal depth scales (8,12,13). VIMP of a variable shows the amount of increase or decrease in misclassification error in the test set if that variable is not present in the model. Any variable with a VIMP larger than 0.002 affects the prediction of survival. To measure the minimal depth for each variable, in each tree of RSFM, the distance from the root node to the middle node where the variable appears for the first time is determined. By averaging these distances in all trees, a valid scale is obtained to measure the importance of a variable. If the minimal depth for a variable is smaller than the cut-off point of 5.54, it is identified as an important variable (14). Therefore, the larger the VIMP and the smaller the minimal depth in a variable, the better the prediction ability would be.

Data were analyzed by R version 3.5.1. The randomForestSRC package was used for fitting the RSFM model. The survival, pec packages were used to calculate the predicted survival probabilities, the BS and the C-index in RSFM.

Results

This study investigated 252 patients with dialysis who were visited at three hospitals (Shahid Mohammadi; Children's hospital; and Persian Gulf Hospital) in Bandar Abbas. Of 252 patients, 35 (13.9%) cases faced the event of death and 217 (86.1%) cases were censored. Findings showed that the one-, three-, five-, 10- and 20-year survival rates of the patients were 100%, 99%, 98%, 94% and 80%, respectively (Figure1). According to Figure1, median survival time is equal to maximum time, namely 52 years, because the survival curve flatted before reaching 0.5. The median survival time as well as the one-, three-, five- and 10-year survival rates calculated by the life-table method, according to BMI, sex, occupation, and education are reported in table 1.

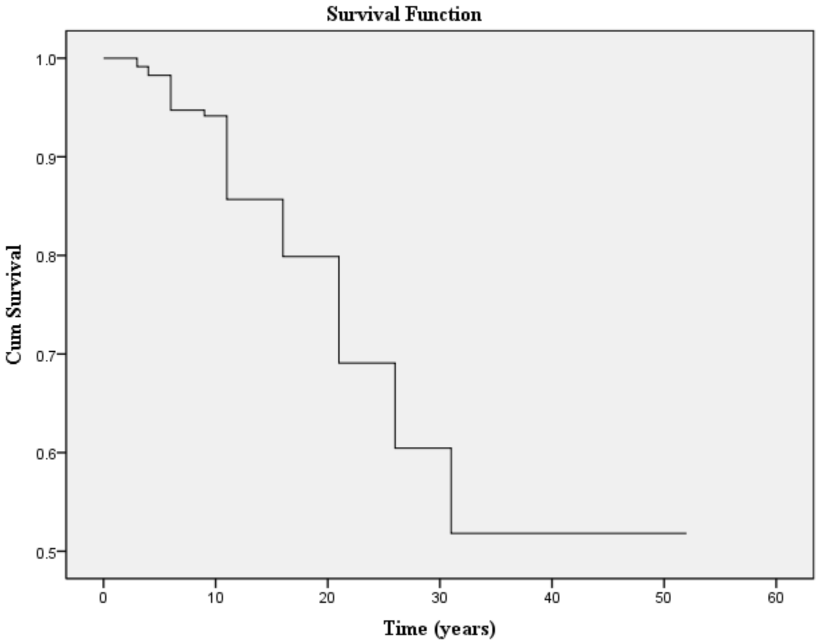

Figure 1. Overall survival rate

Table 1. One-, three-, five- and 10-year survival rates according to important variables

variable	One-year	Three-year	Five-year	10-year	Med time*
Male	100%	99%	98%	92%	31
Female	100%	99%	98%	97%	52
BMI<25	100%	99%	98%	93%	31
BMI≥25	100%	100%	100%	96%	52
illiterate	100%	99%	97%	88%	52
Low literacy	100%	100%	99%	98%	26
Diploma	100%	100%	100%	100%	35
Collegiate	100%	91%	91%	82%	15
Occupied	100%	100%	100%	93%	13
Jobless	100%	95%	90%	85%	30
Housewife	100%	100%	100%	100%	52
Farmer	100%	100%	100%	85%	11
Retired	100%	100%	100%	97%	35

* Median survival time

Over 80% of the participants were illiterate or had low education level. In this study, most of the women were homemakers (87.1%) and most of the men were unemployed or retired (55.9%). About 64% of the patients were nonsmokers. All the patients, except one, had at least one disease that led to dialysis. No case of infection with HIV was observed in the patients. For 194(77%) patients, each session of dialysis took 4 hours. Moreover, 171(67.9%) patients used dialysis three times per week. Table 2 demonstrates patients' characteristics.

Table 2. Patients' Characteristics

Variable		Frequency(percentage)	Mean(SD)
Age			53.39(18.09)
Age at dialysis onset			42.88 (17.07)
Body Mass Index			22.87(4.24)
Blood group			
	O	108(42.9)	
	A	62(24.6)	
	B	72(28.6)	
	AB	10(3.9)	
Level of Education			
	illiterate	87(34.5)	
	Low literacy	118(46.8)	
	Diploma	40(15.9)	
	Collegiate	7(2.8)	
Male		136(54)	
Married		207(82.1)	
Tobacco use		91(36.1)	
Diabetes		134(53.2)	
Hypertension		152(60.3)	
Urinary stones and Kidney obstruction		23(9.1)	
Renal cysts		11(4.4)	
Pulmonary heart disease		50(19.8)	
Congenital disease		4(1.6)	
Glomerulonephritis		18(7.1)	
History of CRF in the family		24(9.5)	
Anemia		195(77.4)	
Receiving erythropoietin		239(94.8)	
HCV		8(3.2)	
HBV		3(1.2)	
Kidney transplantation		27(10.7)	
Stopping dialysis due to kidney function		22(8.7)	

Table 3 shows the most important predictive variables in RSFM based on minimal depth and VIMP. Based on these two indices in RSFM, the predictive power of age, body mass index (BMI), age at dialysis onset, occupation, education level, dialysis duration in each session, and number of dialysis per week were the most important prognostic factors. Figure2 represents the prediction error rate (1 − C-index) for 100 RSFM.

Table 3. The most important variables in RSFM based on minimal depth and VIMP

Variable Name	Value VIMP	Minimal Depth Value
Age	0.016	2.640
Body Mass Index (BMI)	0.031	2.805
Age at Dialysis Onset	0.005	3.162
Occupation	0.009	3.736
Level of Education	0.006	5.154
dialysis duration	0.044	4.106
number of dialysis	0.016	4.563

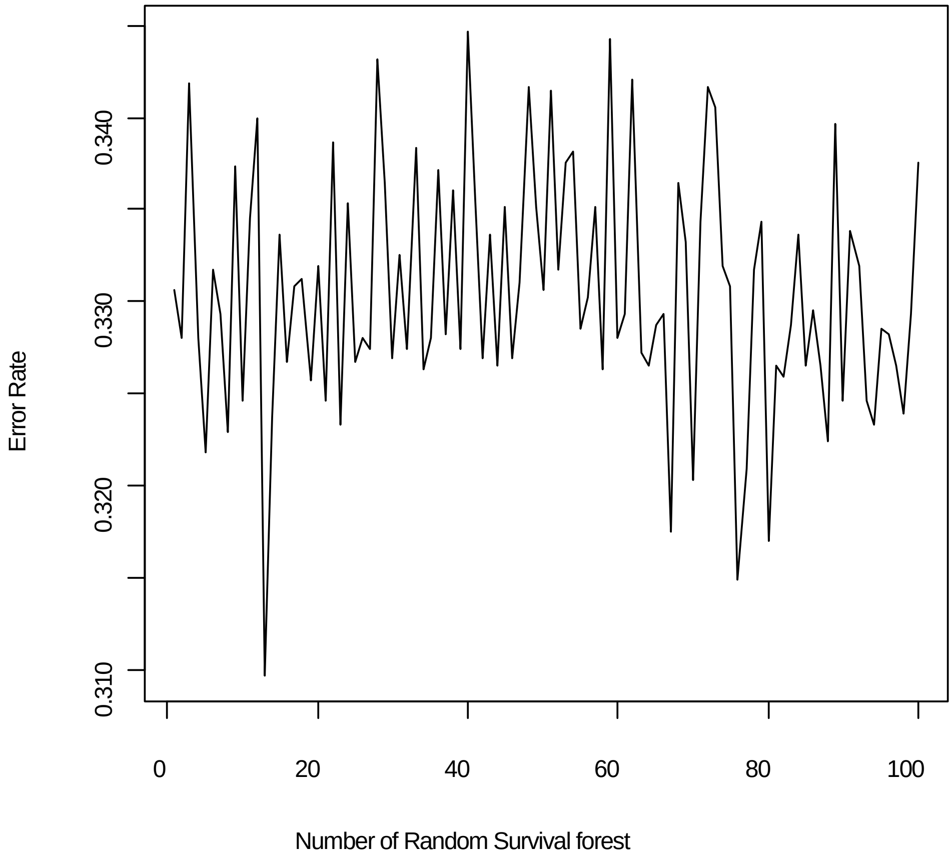

Figure 2. Prediction error rate for 100 Random Survival forests

Table 4 illustrates the prediction accuracy of RSFM in the training and test sets based on C-index and BS. According to Table 4, mean C-index in training and testing sets was 0.640 and 0.687, respectively. Moreover, Findings in Table 4 revealed that mean BS in the training and testing sets was 0.017 and 0.023, respectively.

Table 4. Assessing prediction accuracy of RSFM in ten years

RSFM	C-index	Brier Score
Training set	0.640	0.017
Testing set	0.687	0.023

Discussion

The present study aimed to determine the survival of dialysis patients using RSFM in low-dimensional data with few-events. The results of RSFM indicated that age, BMI, date of dialysis onset, occupation, education level, dialysis duration in each session, and number of dialysis sessions per week were the most important prognostic factors. After assessing the performance of RSFM based on BS and C-index, it was found that RSFM has an acceptable predictive accuracy.

Few previous studies have examined low-dimensional data with few-events, and no similar study has determined the survival of patients undergoing dialysis using RSFM. Therefore, it was difficult to compare the results of the present study with those of the previous researches.

Hamidi et al (2016) used RSFM to identify the risk factors affecting survival in patients with kidney transplant in Iran. They found BS and C-index to be 0.081and 0.965, respectively, for RSFM (15). The present study also confirmed the relatively favorable performance of the RSFM by BS and C-index.

In the study by Mark et al (2019), RSFM was used to build a model that could predict kidney transplant survival and could identify important predictive variables. In the mentioned study, the RSFM had a 5-year C-index of 0.724 (16). In addition, in the present study, RSFM had a good performance in training and testing sets based on BS and C-index. Moreover, the results of the present study on using RSFM to analyze survival data are in agreement with those of the study by Nasejje and Mwambi (17).

Based on the results of the RSFM in the present study, variables of age, BMI, and date of dialysis onset were the most important factors affecting the survival of the patients with dialysis and the importance of these factors has been confirmed in other studies (18-23). An increase in age leads to a decrease in dialysis patients' survival (24,25). Dialysis patients with higher BMI have a lower mortality rate than normal-weight patients, in other words, higher BMI has a protective effect (26). Some studies indicated that the mortality rate of older patients at dialysis onset is greater than that of younger ones (27).

In the present study, the results of RSFM demonstrated the importance of education level and occupation, which has also been confirmed by Kusztal et al (28). In a previous study, it was found that farmers had the lowest median survival rate, which may be due to disparity in access to care centers for farmers in rural and remote areas (29). This was consistent with the results of the present study. Furthermore, it was reported that the increase in literacy level (which has an impact on the level of awareness of individuals) is one of the effective factors in increasing survival rates of hemodialysis patients (29). This finding may be justified by higher adherence of more educated patients to treatment. Perhaps, the risk of mortality was higher in patients with lower education, which is justifiable based on undesirable economic situation; these patients often have poor quality of life. Therefore, by postponing treatment due to its considerable costs, they do not receive treatment in the best possible manner.

In this study, based on the results of RSFM, the duration of dialysis was one of the most important variables to determine the survival of dialysis patients and the importance of this variable was confirmed by Goh et al (30). The positive relationship between the length of the hemodialysis sessions and the survival rate was supported by numerous studies. However, the study by Amini et al revealed that the length of hemodialysis sessions was shorter in Iranian patients than in patients in developed countries. They suggested that increasing the length of hemodialysis sessions may play an important role in improving the outcomes of hemodialysis in Iran (31). There are some obstacles to increase the length of hemodialysis sessions in Iran. Although health care workers in dialysis wards are aware that longer duration of dialysis is associated with higher survival, due to the large number of patients per work shift and inadequate number of dialysis devices per patient, they do not pay much attention to this important factor. From the point of view of the researchers, this is the first and most common barrier.

Based on the results of this study, the number of dialysis sessions per week was important to determine the risk of mortality of dialysis patients; this result is similar to the results of most studies (4,32,33). Patients who underwent incomplete dialysis less than three times in a week, had a higher death risk (34). Therefore, patients and their families need to learn that completing treatment is crucial in such diseases. Moreover, the necessary facilities to visit the dialysis centers should be regularly provided for patients.

To date, no study has assessed the performance of RSFM for low-dimensional data with few events. However, this study had some limitations. Nonparametric RSFM was used in this study and no parametric or semi-parametric models were included for the comparison. Thus, using alternative semi-parametric or parametric models for low-dimensional data with few events are recommended for future studies.

Conclusion

RSFM is the model of choice for managing low-dimensional data with few events to determine the survival of dialysis patients if the researcher desires to select a nonparametric model.

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