Evaluation of Long-term Survival and Predictors of Mortality in Hemodialysis Patients by Using Time Dependent Variables, A Single Centre Cohort Analysis

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Introduction. Despite significant improvement in End Stage Kidney Disease (ESKD) patient's management, and better availability of dialysis for caregivers, mortality among these patients is unacceptably high.
Methods. We collected the data of 751 incident hemodialysis patients from March 2004 to November 2018. Survival curves was created by using the Kaplan-Meier method. Comorbidities, as well as time-dependent values of laboratory findings, were examined as independent factors by three models of Cox regression analysis.
Results. The median follow-up period was 31.7 months (1.08 to 169.28). Patient survival rates were 88%, 77%, 56%, 32%, 26% ,16% and 12%, at 1, 2, 4,6, 8, 10, 12 and 14 years of follow-up, respectively. The most common cause of mortality was cardiovascular disease. We observed lower survival rates in patients ≥ 65 years (HR = 2.684, 95% CI: 1.133 to 3.377; $P < .001$), diabetes mellitus (HR = 1.729, 95% CI: 1.484 to 2.014; $P < .001$) and walking disability (HR = 2.505; 95% CI: 2.104 to 2.983; $P < .001$). Low hemoglobin level (HR = 1.496; 95% CI: 1.257 to 1.779; $P < .001$), hyperphosphatemia (HR = 1.305, 95% CI: 1.104 to 1.542; $P = 0.002$) and high low-density lipoprotein cholesterol level (HR = 1.933; 95% CI: 1.431 to 2.611; $P < .001$) were predictors of mortality. A single pool Kt/V > 1.2 (HR = 0.743, 95% CI: 0.635 to 0.870; $P < .001$) and high serum creatinine level (HR = 0.842, 95% CI: 0.811 to 0.874; $P < .001$) showed protective effects.
Conclusion. Our study showed a high survival rate in a single center cohort of hemodialysis patients in Iran. Traditional risk factors of mortality in general population, as well as indices of dialysis efficacy and general health status were the main predictors of mortality. Nationwide registries are necessary to investigate the dialysis survival rates and their predictors in our country.

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Original Paper

INTRODUCTION

End stage kidney disease (ESKD) is a universal health burden with the median prevalence of Kidney replacement therapy by 759 per million population (pmp) throughout the world on 2019.[1] The cardiovascular mortality of ESKD patients is estimated to be 10 to 30 times higher than the general population and the metabolic complications induced by ESKD contribute to morbidity and mortality.[2,3]

The significant burden of kidney disease and its exceedingly rising prevalence, particularly in low-middle income countries is posing great challenges the health care system.[4,5]

Data of the national registry of ESKD of Iran in 2016, shows that the number of prevalent ESKD patients was 380 pmp.[6] On the other hand, patient survival rates vary across different countries and also within dialysis centers in the same country.[7,8] The Dialysis Outcomes and Practice Patterns Study (DOPPS) indicated that the survival rate of ESKD patients in the United States was lower compared to Japan and European countries, even after detailed adjustment.[9] The overall outcome is also markedly influenced by individual risk factors including the age, residual renal function, the underlying disease causing ESKD, and comorbid conditions[7]. Moreover, the difference in patient characteristics, environment and health care system can potentially impact the outcome.[10,11]

The aim of this study was to determine the long-term survival rate of patients undergoing maintenance hemodialysis patients, considering time-dependent laboratory values, in one of the largest referral kidney centers in the country.[8] As the national registry of dialysis patients in Iran still lacks the data to analyze the risk factors of long-term patient survival, we believe that well designed single center analyses will help us to build up models for a national registry and improve ESKD management and patient care in our country.

MATERIALS AND METHODS

This retrospective cohort study was done on maintenance hemodialysis patients of Hasheminejad Kidney Center. The baseline demographic data and the regular periodic laboratory results were extracted from the hemodialysis data processor software designed for our hemodialysis ward (AIP Company, 2014, Tehran, Iran). Baseline data included age on admission, gender, walking disability, underlying cause of ESKD, type of vascular access and previous medical history of diabetes mellitus (DM), hypertension, and cardiovascular disease (CVD). Physical disability was defined as the need for assistance in walking or inability to walk. Patients who were affected by at least one the following were considered as high risk: DM, central nervous system diseases, malignancy, walking disability, or an age of 65 years and older.[8]Any vascular access other than arteriovenous fistula (AVF) at the time of data collection was considered as high-risk vascular access.

Laboratory Data

Laboratory data included monthly measurements of blood hemoglobin (Hb) , and plasma levels of calcium, phosphate, potassium, serum iron, ferritin, total iron binding capacity (TIBC), blood urea nitrogen (BUN), creatinine (Cr), seasonal measurement of single-pool Kt/V (SpKt/V), cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and intact parathyroid hormone (iPTH) and twice yearly measurement of serum albumin, and protein (total amount of two classes of albumin and globulin). The average estimates of the repeated measurements of mean values were calculated as the average value during the study follow-up. In addition, the averages of variables were calculated at 6-month intervals from the beginning of study (time-dependent values). The average values were categorized according to their reference target ranges, defined as normal, high or low values.

The target ranges for the laboratory results were defined as the following:

- Hemoglobin (10 to 12 g/dL)
- Calcium (8.4 to 9.5 mg/dL)
- Inorganic phosphate (3.5 to 5.5 mg/dL)
- Intact PTH (150 to 300 pg/mL)
- Potassium (3.5 to 5 mEq/L)
- LDL-C (70 to 130 mg/dL)
- Protein (5.5 to 8 g/ dL)
- Single-pool Kt/V ($\geq$ 1.2)
- Ferritin: 200 to 500 ng/mL

Statistical Analysis

Serum levels of HDL-C, TG, ferritin, and Cr were treated as continuous variables. Events were recorded from the beginning of the study. The duration of time between entering the study and events including death or censor was considered as survival rate. Censor was defined as transfer to another center, kidney transplant, and modality change to peritoneal dialysis (PD) or recovery. The study follow-up period was 14 years starting from March 21, 2004 to November 2, 2018 and

was approved by the ethic committee of the Iran University of Medical Sciences. All statistical analyses were done using the SPSS, 23. *P* values less than .05 was considered significant.

Survival curves were created through Kaplan Meir Method and differences in survival rates were compared between different groups of the incident patients, by log rank test. Predictors of mortality were evaluated by the Cox proportional hazard models and used to estimate the hazard ratios. The average value of laboratory data, as well as six baseline demographic variables including age, sex, walking disability, high-risk vascular access, and previous medical history of DM and CVD were used in the models. Repeated measurements of a particular variable were reported by using either the averaged values or the time-dependent values, as mentioned above. Missing data were less than 10% for each patient. Three models were used for the analysis: 1) Unadjusted Cox regression model for each baseline variable, 2) Adjusted Cox regression model for baseline variables only, and 3) Fully adjusted model for all of the clinical and laboratory measurements including repeated and time averaged data and baseline values.

RESULTS

The data of 751 incident patients were evaluated. The mean age at admission was 56.28 ± 17.5 years, with 37.3% older than 65 years of age and 61.8% of the patients were male. The most common underlying cause of ESKD was DM (37.1%) and CVD was the most common comorbid condition (50%). High-risk patients accounted for 64.2% (Table 1).

The median follow-up period was 31.7 (1.08 to 169.28) months. Three hundred out of 751 patients (39.9%) died during the follow up period, 13.6% were transferred to other centers, 1.5% were switched to PD and 21.7% underwent kidney transplant. The most common cause of mortality was CVD, which was the cause of mortality in 38.2% of the patients (Table 2). Patient survival rates were 88%, 77%, 56%, 32%, 26% ,16% ,12%, and 12%, at 1, 2, 4,6, 8, 10, 12, and 14 years of follow up, respectively (Figure 1).

Mortality increased by 3.9% for each year increase in the age at admission (HR = 1.039, 95% CI: 1.031 to 1.047, $P < .001$). Survival rates were significantly lower in patients with an age of 65 years and older (HR = 2.684, 95% CI: 1.133 to 3.377; $P < .001$), patients with DM (HR = 1.729, 95% CI: 1.484 to 2.014; $P < .001$) and patients with walking disability at admission (HR = 2.505, 95% CI: 2.104 to 2.983; $P < .001$) and the defined high-risk group (HR=4.338; 95% CI, 3.06-6.151; $P < 0.0001$).

Although a remarkable association was found between cardiovascular comorbidity and mortality rate with log-rank test ($P < .001$), there was no significant association after full adjustment

Table 1. Demographic and Baseline Clinical Characteristics of 751 Incident Maintenance Hemodialysis Patients

Characteristic	Value
Age, y (mean ± SD)	56.28 ± 17.5 (11 to 95)
Patients ≥ 65 years old [No. (%)]	280 (37.3)
Male Sex [No. (%)]	464 (61.8)
Smoker [No. (%)]	116 (15.4)
Marital Status	
Married, Living with Partner [No. (%)]	599 (79.8)
Single, Divorced, or Widowed [No. (%)]	149 (21.2)
Dialysis Hours per Session	
< 4 hours [No. (%)]	13 (1.8)
4 [No. (%)]	731 (97.3)
> 4 [No. (%)]	7 (0.9)
Dialysis Sessions per Week	
2 [No. (%)]	25 (3.3)
3 [No. (%)]	720 (95.9)
Walking Ability [No. (%)]	
Walks Without Help	573 (76.3)
Walks With Help	60 (8)
Uses Wheelchair or Walking Stick	92 (12.3)
Unable to Walk	19 (2.6)
Cause of ESKD [No. (%)]	
Diabetes Mellitus	277 (36.9)
Unknown	217 (28.9)
Hypertension	99 (13.2)
Glomerulonephritis	45 (6)
Others	39 (5.2)
Polycystic Kidney Disease	36 (4.8)
Stone	15 (2)
Reflux Nephropathy	13 (1.7)
Obstructive Uropathy	6 (0.8)
Other Comorbidities [No. (%)]	
Cardiovascular Disease	375 (50)
Cerebrovascular Disease	6 (0.8)
Malignancy	2 (0.3)
Last Vascular Access [No. (%)]	
Arteriovenous Fistula	312 (41.5)
Arteriovenous Native Graft	10 (1.2)
Arteriovenous Synthetic Graft	10 (1.2)
Permanent Central Vein Catheter	300 (40)
Temporary Central Vein Catheter	119 (15.7)
High-risk Group [No. (%)]	482 (64.2)
Single-pool Kt/V (Mean Value ± SD)	1.3 ± 0.21 (0.5-2.1)
Single-pool Kt/V > 1.2 [No. (%)]	526 (70)

Values in parentheses are percent for frequencies and range for mean values.

Table 2. The Outcome of 751 Incident Maintenance Hemodialysis Patients

Out come	Value
Median Study Follow-up, Months (Min to Max)	31.7 (1.08 to 169.28)
Last Status [No. (%)]	
Dead	300 (39.9)
Alive	163 (21.7)
Transplanted	163 (21.7)
Transferred	102 (13.6)
Recovered	12 (1.6)
Changed Dialysis Modality	11 (1.5)
Cause of Death [No. (%)]	
Cardiovascular	115 (38.2)
Infectious	41 (13.6)
Other	36 (12)
Not Identified	35 (11.6)
At Home, On the Way, at Trip	23 (7.6)
Cerebrovascular	22 (7.3)
Neoplasm	13 (4.3)
Pulmonary	11 (3.7)
Gastrointestinal	5 (1.7)
Trauma or Accident	3 (1)

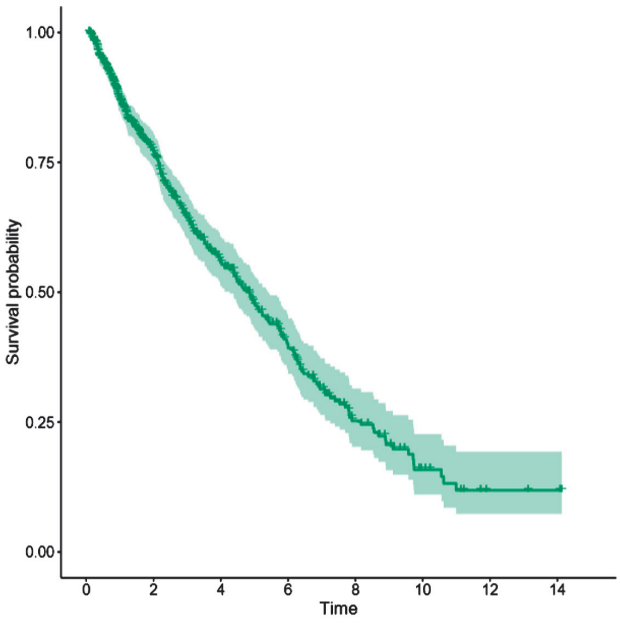

Figure 1. Patient Survival in 751 Incident Maintenance Hemodialysis Patients

(HR = 0.83, 95% CI: 0.69 to 1.01; $P > .05$). Lastly, type of vascular access, i.e., AVF vs. non-AVF and mortality were not associated ($P > .05$) (Figure 2).

Gender did not affect survival rates in unadjusted analysis (HR = 1.004, 95% CI: 0.798 to 1.265; $P > .05$) but after full adjustment, male sex had a relationship with morality (HR = 1.396, 95% CI: 1.218 to 1.576; $P < .0001$).

At the next step, the association between patient survival and laboratory values, treated as averaged values (in 6-month intervals) or time-dependent values, was analyzed (each unadjusted, adjusted for baseline clinical variables, and fully adjusted for laboratory and baseline cyclical variables) (Tables 3 to 5).

Low Hemoglobin levels was a significant risk factor for mortality in all three models. (Tables 4 and 5). Likewise, low phosphorus levels were significantly associated with mortality in both unadjusted models and the model adjusted for baseline variables, but not after full adjustment. On the other hand, high phosphorus levels were significantly associated with mortality in the fully adjusted model.

Low calcium level was associated with mortality as an averaged-value variable in the model adjusted for baseline variables and marginally as a time-dependent variable, but this effect was not found in fully adjusted models. Similarly, the effect of high calcium level on mortality was observed in the model adjusted for baseline variables only as an averaged-value and also in unadjusted model, but there was no association between high calcium levels and mortality after full adjustment.

Low serum iPTH level was a risk factor for mortality in all three models only as an averaged-value. In contrast, high iPTH level had a protective effect in time dependent value after full adjustment. Likewise, high ferritin levels seemed to be a protective factor after full adjustment for time dependent values.

Increments in HDL-C showed protective effect against mortality in the unadjusted model and after adjustment for baseline variables, only with averaged-value and maintained its significance after full adjustment in both time-dependent and averaged-value models. In addition, serum triglyceride had limited protective effect only found with the time-dependent values after full adjustment. No protective effect was observed for low LDL-C levels. Low of serum protein level was a risk factor in all three models only as an averaged-value. On the other hand, high protein level did not exert any significant protective effect.

Both high SpKt/V and serum Cr levels significantly decreased mortality in all three models.

Overall, in the fully adjusted model, increased age, male sex, diabetes mellitus, walking disability at admission, low HDL-C, low serum Cr and potassium, high serum phosphorus and

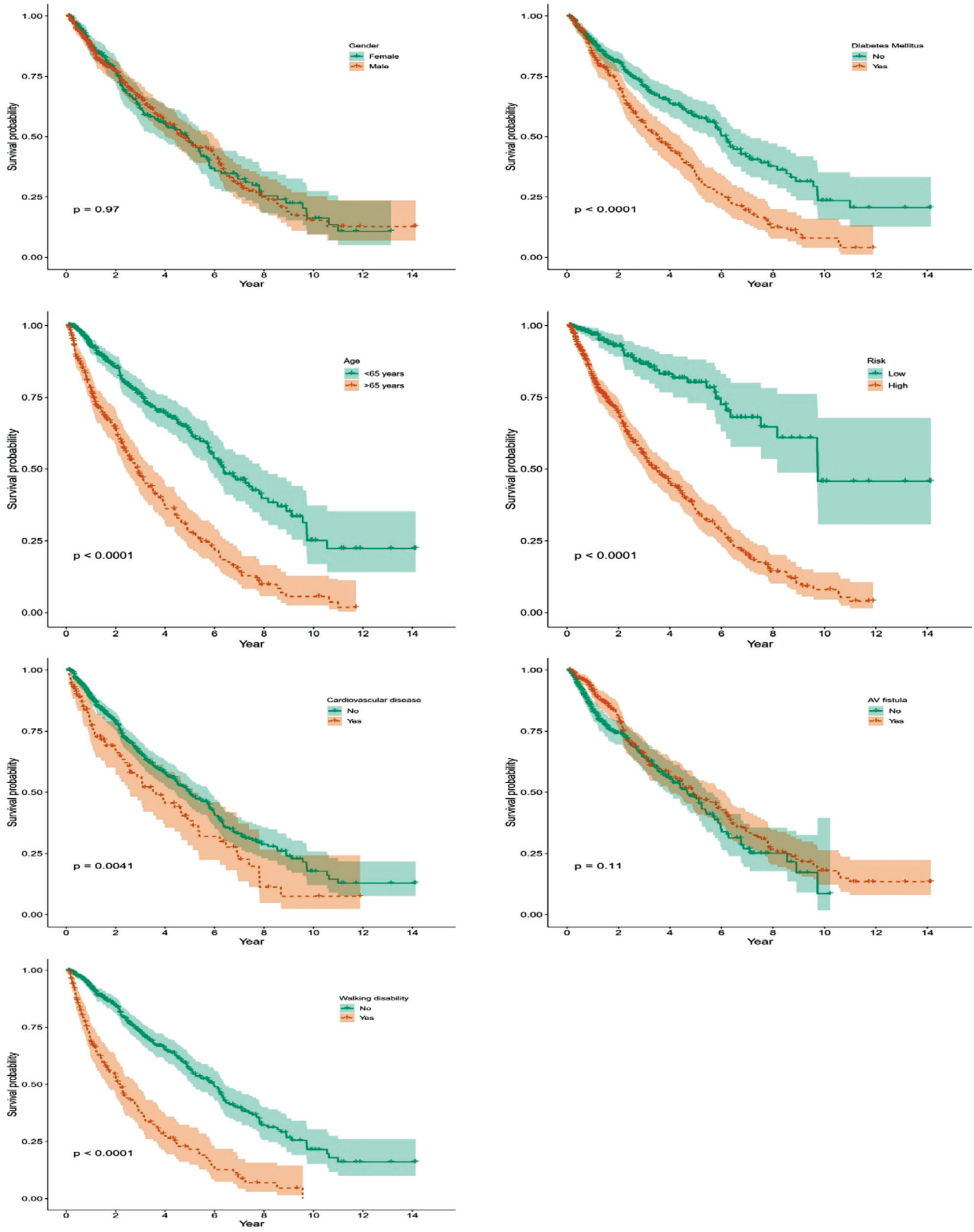

Figure 2. Survival Curves 751 Maintenance Hemodialysis Patients Adjusted for Baseline Demographic and Clinical

Table 3. Unadjusted Cox Regression Analysis of the Association of Laboratory Values with Mortality in 751 Maintenance Hemodialysis Patients, Using Averaged Laboratory Values (with 6-Month Intervals) vs. Time-Dependent Values in the Model*

	Model with Averaged Values		Model with Time-dependent Values	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y	1.039 (1.031 to 1.047)	< .001	1.039 (1.031 to 1.047)	< .001
Gender (Male)	1.004 (0.798 to1.265)	> .05	1.004 (0.798 to1.265)	> .05
Diabetes Mellitus	1.808 (1.442 to 2.268)	< .001	1.808 (1.442 to 2.268)	< .001
Cardiovascular Disease	1.501 (1.135 to 1.986)	< .05	1.399 (1.326 to1.475)	< .001
Walking Disability	3.055 (2.41 to 3.872)	< .001	2.793 (2.66 to 2.932)	< .001
HDL-C, mg/dL	0.985 (0.971 to 0.999)	< .05	0.99 (0.966 to 1.015)	> .05
Triglyceride, mg/dL	0.999 (0.997 to 1)	> .05	1.001 (0.999 to 1.003)	> .05
Creatinine, mg/dL	0.714 (0.676 to 0.755)	< .001	0.79 (0.753 to 0.828)	< .001
Hb < 10, g/dL	2.252 (1.752 to 2.895)	< .001	2.256 (1.743 to 2.92)	< .001
Hb > 12, g/dL	1.16 (0.695 to 1.936)	> .05	1.013 (0.714 to 1.437)	> .05
Ca < 8.4, mg/dL	1.218 (0.908 to 1.634)	> .05	1.139 (0.878 to 1.476)	> .05
Ca > 9.5, mg/dL	1.989 (1.361 to 2.904)	< .001	1.065 (0.768 to 1.477)	> .05
Pi < 3.5, mg/dL	4.879 (2.938 to 8.104)	< .001	1.947 (1.416 to 2.676)	< .001
Pi > 5.5, mg/dL	0.773 (0.608 to 0.982)	< .05	0.964 (0.746 to 1.246)	> .05
iPTH < 150, pg/mL	1.84 (1.385 to 2.444)	< .001	1.55 (0.946 to 2.541)	> .05
iPTH > 300, pg/mL	0.631 (0.471 to 0.845)	< .05	0.82 (0.489 to 1.376)	> .05
K < 3.5, mEq/L	11.531 (3.579 to 37.149)	< .001	4.308 (2.702 to 6.867)	< .001
K > 5, mEq/L	0.523 (0.391 to 0.7)	< .001	0.705 (0.538 to 0.924)	< .05
LDL-C < 70, mg/dL	0.786 (0.598 to1.033)	> .05	0.944 (0.517 to 1.722)	> .05
LDL-C > 130, mg/dL	1.973 (1.136 to 3.428)	< .05	1.064 (0.367 to 3.089)	> .05
Protein < 5.5, g/dL	12.964 (3.97 to 42.338)	< .001	0.842 (0.114 to 6.207)	> .05
Protein > 8, g/dL	1.157 (0.8 to 1.675)	> .05	0.778 (0.36 to 1.681)	> .05
Ferritin < 200, ng/mL	1.633 (0.927 to 2.874)	> .05	0.75 (0.349 to 1.611)	> .05
Ferritin > 500, ng/mL	0.93 (0.699 to 1.237)	> .05	1.159 (0.731 to 1.835)	> .05
Single-pool Kt/V > 1.2	0.642 (0.488 to 0.845)	< 0.05	0.783 (0.726 to 0.844)	< .001

*Values are categorized for all parameters (except for HDL-C, TG, and Cr) and compared to the reference categories (the middle range for all parameters except for Single-pool Kt/V, which was compared to high values).
Abbreviations: HR, hazard ratio; CI, confidence interval; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Pi, serum phosphorus; Ca, serum calcium; Hb, hemoglobin; K, serum potassium.

SpKt/V < 1.2 were significantly associated with mortality (Table 5).

DISCUSSION

The current study was done on 751 incident hemodialysis patients in a 14-year follow-up period. The survival rates for these patients were 88%, 65%, 48%, 16 %, and 12% at 1, 3, 5, 10, and 14 years; respectively. In comparison with the earlier study in our center, carried out in 2013 on 395 incident patients, there was no significant change in the survival rates.[8] The US renal data system report in 2009 showed the 1, 3, 5, and 10-year survival of ESKD patients on maintenance hemodialysis in the United States as 79%, 53%, 35%, and 11.2%; respectively.[10] High quality of dialysis and patients management and the lower sample size of a single center study, may have contributed to better survival rates in our center and other single-center studies compared to registry reports.

However, there are different reports of hemodialysis survival from Iran. In a study conducted in Khuzestan province of Iran, 1, 5, 10, and 15-year survival rates of hemodialysis patients accounted for 83%, 25.2%, 3.8%, and 1.0%, respectively.[11] In another study in Kerman province, Iran, 5-year survival rate of ESKD patients was reported 43.4%.[12] The results of these reports may show the diverse quality of dialysis in different centers of our country and this emphasizes on the need for a stricter surveillance of dialysis quality throughout the country.

In our study, older age, male sex and DM were the most important baseline predictors of mortality and for each year increase of the age at admission, mortality risk rose about 4%. Elderly patients are more commonly afflicted by different comorbidities such as cardiovascular and cerebrovascular disease, malignancies, mental and physical disabilities, and vascular access problems.[13,14,15] Similarly, DOPPS

Table 4. Cox Regression Analysis of the Association of Laboratory Studies with Mortality in 751 Maintenance Hemodialysis Patients Adjusted for Baseline Factors, Using Averaged Laboratory Values (with 6-Month Intervals) vs. Time-Dependent Values in the Model*

	Model with Averaged Values		Model with Time-dependent Values	
	HR (95% CI)	*P*	HR (95% CI)	*P*
HDL-C, mg/dL	0.982 (0.967 to 0.998)	< .05	0.987 (0.961 to 1.013)	> .05
Triglyceride, mg/dL	0.999 (0.998 to 1.001)	> .05	1.002 (1 to 1.004)	> .05
Creatinine, mg/dL	0.756 (0.706 to 0.809)	< .001	0.851 (0.806 to 0.898)	< .001
Hb < 10, g/dL	2.974 (2.283 to 3.874)	< .001	2.468 (1.901 to 3.205)	< .001
Hb > 12, g/dL	0.928 (0.549 to 1.569)	> .05	0.923 (0.65 to 1.312)	> .05
Ca < 8.4, mg/dL	1.674 (1.239 to 2.26)	< .05	1.291 (0.994 to 1.676)	> .05
Ca > 9.5, mg/dL	1.613 (1.089 to 2.387)	< .05	0.976 (0.701 to 1.359)	> .05
Pi < 3.5, mg/dL	2.941 (1.725 to 5.014)	< .001	1.695 (1.229 to 2.338)	< .001
Pi > 5.5, mg/dL	1.213 (0.944 to 1.56)	> .05	1.291 (0.994 to 1.677)	> .05 (0.055)
iPTH < 150, pg/mL	1.689 (1.261 to 2.261)	< .001	1.382 (0.84 to 2.274)	> .05
iPTH > 300, pg/mL	0.986 (0.728 to 1.335)	> .05	1.109 (0.655 to 1.878)	> .05
K < 3.5, mEq/L	7.209 (2.182 to 23.819)	< .001	3.201 (2 to 5.124)	< .001
K > 5, mEq/L	0.697 (0.518 to 0.938)	< .05	0.834 (0.634 to 1.097)	> .05
LDL-C < 70, mg/dL	0.898 (0.68 to 1.186)	> .05	1.139 (0.607 to 2.134)	> .05
LDL-C > 130, mg/dL	1.597 (0.917 to 2.781)	> .05	1.033 (0.349 to 3.06)	> .05
Protein < 5.5, g/dL	12.726 (3.812 to 42.484)	< .001	0.667 (0.088 to 5.057)	> .05
Protein > 8, g/dL	1.196 (0.822 to 1.739)	> .05	0.818 (0.372 to 1.798)	> .05
Ferritin < 200, ng/mL	1.838 (1.037 to 3.259)	< .05	0.77 (0.358 to 1.657)	> .05
Ferritin > 500, ng/mL	0.792 (0.593 to 1.058)	> .05	1.13 (0.711 to 1.795)	> .05
Single-pool Kt/V > 1.2	0.543 (0.405 to 0.728)	< .001	0.773 (0.716 to 0.835)	< .001

*Each parameter was adjusted for baseline factors that include age, sex, walking disability, diabetes mellitus, cardiovascular disease, and high-risk vascular access.
Values are categorized for all parameters (except for HDL-C, triglyceride, and creatinine) and compared to the reference categories (the middle range for all parameters except for SpKT/V, which was compared to high values).
Abbreviations: HR, hazard ratio; CI, confidence interval; PTH, parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

found that the age at admission, is associated with 3-6-fold increased risk of mortality.[16]

Underlying disease of hemodialysis patients like DM can decrease their survival rate.[8] We found that DM tends to increase the risk of death by 73%, which was congruent with previous studies. Schroijen *et al.* demonstrated a significant association between DM, either as a comorbid condition or as an underlying disease and high mortality rate.[17] They later found that due to the variety of organ damages, DM as an underlying disease is more detrimental on survival rate compared to DM as a comorbid condition.[18] In the USRDS report, 5-year survival rate for diabetic patients with ESKD was only 30% after initiation of hemodialysis.[10]

Compared to AVF, central vein catheters are associated with less desirable outcome and tend to increase the risk of mortality.[8,19,20] Allon *et al.*, showed that switching patients from AVF to other access types resulted in development of malnutrition and inflammation.[21] Correspondingly, decreases in serum albumin level, protein catabolic rate and patients' weight was observed.[21] Furthermore, non- AVF access types were associated with infection related and cardiovascular induced hospitalization and death.[19,20,22] However, in our study there was no significant difference between survival rates of patients with AVF and non-AVF access. The previous study in our center reported a higher mortality rate in patients with non-AVF compared to AVF access, which comprised 74% of the sample size.[8]

In agreement with our previous report, walking disability at admission is another important predictor of survival. Probable etiologies are neuromuscular disorders, generalized weakness due to severe anemia, electrolyte imbalance, fatigue, muscle cramps, sleep disturbances, and

Table 5. Fully Adjusted Cox Regression Analysis of all Factors Associated with Mortality of 751 Maintenance Hemodialysis Patients, Using Averaged Laboratory Values (in 6-Month Intervals) vs. Time-Dependent Values in the Model *

	Model with Averaged Values		Model with Time-dependent Values	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y	1.017 (1.006 to 1.028)	< .01	1.033 (1.027 to 1.039)	< .001
Gender (Male)	1.56 (1.14 to 2.135)	< .01	1.396 (1.194 to 1.631)	< .001
Diabetes Mellitus	1.193 (0.903 to 1.578)	> .05	1.729 (1.484 to 2.014)	< .001
Cardiovascular Disease	1.115 (0.784 to 1.584)	> .05	0.838 (0.693 to 1.013)	> .05 (0.068)
Walking Disability	1.446 (1.066 to 1.962)	< .05	2.505 (2.104 to 2.983)	< .001
HDL-C, mg/dL	0.968 (0.952 to 0.985)	< .001	0.987 (0.98 to 0.994)	< .001
Triglyceride, mg/dL	0.999 (0.998 to 1.001)	> .05	1.001 (1 to 1.001)	> .05 (0.063)
Creatinine, mg/dL	0.715 (0.656 to 0.78)	< .001	0.842 (0.811 to 0.874)	< .001
Hb < 10, g/dL	1.95 (1.409 to 2.7)	< .001	1.496 (1.257 to 1.779)	< .001
Hb > 12, g/dL	0.803 (0.447 to 1.443)	> .05	1.126 (0.947 to 1.338)	> .05
Ca < 8.4, mg/dL	1.432 (0.96 to 2.137)	> .05 (0.078)	1.1 (0.923 to 1.309)	> .05
Ca > 9.5, mg/dL	1.093 (0.664 to 1.799)	> .05	1.122 (0.924 to 1.364)	> .05
Pi < 3.5, mg/dL	0.963 (0.362 to 2.559)	> .05	0.901 (0.721 to 1.127)	> .05
Pi > 5.5, mg/dL	1.697 (1.256 to 2.292)	< .01	1.305 (1.104 to 1.542)	< .01
iPTH < 150, pg/mL	1.612 (1.152 to 2.256)	< .01	0.869 (0.725 to 1.041)	> .05
iPTH > 300, pg/mL	0.939 (0.673 to 1.31)	> .05	0.824 (0.687 to 0.987)	< .05
K < 3.5, mEq/L	11.536 (2.154 to 61.792)	> .05	0.922 (0.52 to 1.636)	> .05
K > 5, mEq/L	0.74 (0.526 to 1.041)	> .05	1.12 (0.959 to 1.309)	> .05
LDL-C < 70, mg/dL	0.79 (0.585 to 1.067)	> .05	0.899 (0.772 to 1.045)	> .05
LDL-C > 130, mg/dL	0.901 (0.442 to 1.835)	> .05	1.933 (1.431 to 2.611)	< .001
Protein < 5.5, g/dL	4.463 (1.013 to 19.662)	< .05	1.054 (0.611 to 1.818)	> .05
Protein > 8, g/dL	1.031 (0.682 to 1.559)	> .05	1.142 (0.958 to 1.363)	> .05
Ferritin < 200, ng/mL	1.63 (0.787 to 3.378)	> .05	0.88 (0.68 to 1.139)	> .05
Ferritin > 500, ng/mL	0.784 (0.571 to 1.078)	> .05	0.816 (0.689 to 0.966)	< .05
Single-pool Kt/V > 1.2	0.607 (0.435 to 0.847)	< .01	0.743 (0.635 to 0.87)	< .001

*The fully adjusted model included all of the repeated laboratory measurements, dialysis adequacy parameters, and baseline factors. Values were categorized for all parameters (except for HDLC, triglyceride, and creatinine) and compared to the reference categories (the middle range for all parameters except for Single-pool Kt/V, which was compared to high values).
Abbreviations: HR, hazard ratio; CI, confidence interval; iPTH: intact parathyroid hormone; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol, Pi: Serum phosphorus, Ca: Serum calcium, Hb: Hemoglobin, K: Serum potassium; CVD, cardiovascular access; and VA, vascular access.

psychosomatic disorders.[23,24] Consistently, physical activity is associated with less fatigability, improved quality of life and outcome among hemodialysis patients.[25,265] Hence, to detect and modify this important prognostic factor, a targeted physical examination on admission and planning for improving the patient physical capabilities through physical therapy and other reinforcement methods is recommended.

In our study, an efficacious dialysis, defined as SpKt/V more than 1.2, reduced the mortality risk by about 26% in all three models, as demonstrated in previous studies. The effect of prolongation of hemodialysis time on patient survival is addressed in many studies.[27,28] In DOPPS, the effect of increased treatment time (TT) was also evaluated and they reported an independent, but synergistic effect of TT and Kt/V on ESKD patients' survival.[29]

The severity of anemia and timely treatment can improve survival.[30] However, normalization of hematocrit level with erythropoietin in ESKD patients with coexisting CVD was not associated

with better outcome.[31] Fluctuations in Hemoglobin level occur in ESKD patients, which are mostly due to changes in nutritional status, inflammation, and treatment regimens. This phenomenon happens over time, thus time-dependent correlation between Hemoglobin level and survival can give us better insight.[32] We showed the correlation between low levels of time-dependent Hemoglobin and mortality in all three models. However, the mean value of Hemoglobin was 10.6 mg/dL in our study cohort and only 8.3% of the patients had high Hemoglobin level; thus, the adverse effects of high Hemoglobin could not be observed.

According to our study, high serum ferritin level seemingly serves as a protective factor. Since the level of ferritin and other acute phase reactants are altered due to inflammatory response and nutritional status, this protective effect should be interpreted with caution[33]. Hemodialysis patients have different levels of serum ferritin across countries and ethnic groups.[34] According to DOPPS, significantly higher serum ferritin levels were detected in USA compared to Europe and Japan.[34] Bazeley *et al.* did not find a significant difference between ferritin and other inflammatory markers regarding mortality risk prediction.[35] In the study by Kalantar-Zadeh *et al.*, high ferritin levels seemed to be correlated with higher mortality, but after adjustment for patient characteristics and malnutrition–inflammation complex syndrome the correlation was lost.[36]

The target ranges of minerals to pose the lowest risk of mortality are reported by DOPPS.[37] Hypercalcemia, hyperphosphatemia and hyperparathyroidism might be preceded by coexisting CVD, which affects the outcome.[38,39] A meta-analysis of nine cohort studies, reported a nonlinear correlation between very low and very high serum phosphorus level and all-cause mortality in hemodialysis patients.[40] In our study high phosphorus levels were significantly associated with mortality after full adjustment.

Based on the confounding effect of malnutrition-inflammation complex, and that pro-inflammatory cytokines tend to suppress iPTH secretion in CKD patients, it is hard to conclude a direct relationship between iPTH level and mortality in hemodialysis patients.[41] In the studies done by Palmer *et al.* and Block *et al.*, moderate to severe hyperparathyroidism and serum hyperphosphatemia were associated with high mortality rate among hemodialysis patients.[42,43] In our study an iPTH concentration more than 300 pg/ml was correlated with mortality. Yet in another study done in Iran, serum iPTH levels more than 600 pg/ml was a predictor of mortality.[44] Because of the confounding factors such as Ca and P, the possible relationship between iPTH levels and mortality should be interpreted with caution.[44]

Nutritional status management is a crucial step in the treatment of hemodialysis patients and can affect the outcome. Accordingly, derangements in serum protein, albumin, Cr and cholesterol levels tends to decrease the survival rate by 6% per year.[45] In our study, under-nutrition, as well as over-nutrition, as previously defined by high BMI and increased cholesterol level, and neglected by reverse epidemiology theory, had long-term negative effects on survival.[46,476] Data analysis of hemodialysis patients in the phase 5 of DOPPS showed a significant association between low albumin level (< 3.2 g/dL)and mortality.[48] Likewise, improvements in nutritional status increased survival in short-term.[49]

In line with other studies, our study showed that high Cr level was associated with better survival. Similarly, high HDL-C levels exerted protective effect.[8] Our results demonstrated high LDL-C level was significantly associated with higher mortality rate. However, the "reverse epidemiology" hypothesis and many other studies contend that high cholesterol level is related to low mortality.[47,50,51,52,53] Yet, high LDL-C contributes to atherosclerosis progression, which can potentially lead to cardiovascular mortality, the most common cause of death in hemodialysis patients.[54] Moreover, inflammatory state, malnutrition, and advanced CVD may lower serum cholesterol levels in hemodialysis patients. It is also suggested that advanced CVD may lead to inflammation and malnutrition.[51,54,55] So our finding of a higher mortality rate related to higher LDL-C should be taken into attention and examined against the reverse epidemiology hypothesis with precision.

Further studies are needed to answer this question in detail by investigating the different associations (U or J shaped) between these laboratory markers and survival in hemodialysis patients.

One of the strengths of our study is using the time-dependent values of laboratory measurements,

in addition to the average values, which over a long-term follow-up period, can more accurately reflect the chorological variations of these factors. The time-dependent analysis shows a scenario closer to the complete picture of the patient consistent with the large studies of the field.

CONCLUSIONS

Our findings were in agreement with other international studies regarding the common predictors of mortality in HD patients such as DM, anemia, dialysis adequacy, bone metabolism parameters and nutritional indicators. Survival rates in the current study, conducted on incident patients, are comparable to previous studies as well as our former study on 2013. Since covariates tend to fluctuate over time, we believe that analysis of time-dependent values enabled us to properly detect risk factors with less bias, compared to survival models using only averaged values.

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