Survival of Patients on Hemodialysis and Predictors of Mortality
A Single-Centre Analysis of Time-Dependent Factors

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Introduction. This study aimed to evaluate the outcome and predictors of survival in hemodialysis patients of Hasheminejad Kidney Center where a comprehensive dialysis care program has been placed since 2004.

Materials and Methods. Data of 560 hemodialysis patients were used to evaluate 9-year survival rates and predictors of mortality. Cox regression models included comorbidities as well as averaged and 6-month-averaged time-dependent values of laboratory findings as independent factors.

Results. Survival rates were 91.9%, 66.0%, 46.3%, and 28.5%, at 1, 3, 5, and 9 years, respectively, in all patients and 90.8%, 61.6%, 42.1%, and 28.0% in 395 incident patients starting hemodialysis after 2004. Adjusted survival models demonstrated age, male sex, diabetes mellitus, cardiovascular disease, and high-risk vascular access as baseline predictors of mortality, as well as averaged low hemoglobin level (hazard ratio [HR], 1.98; 95% confidence interval [CI], 1.36 to 2.90) and a single-pool KT/V < 1.2 (HR, 2.28; 95% CI, 1.60 to 3.26). The averaged high-density lipoprotein cholesterol (HR, 0.67; 95% CI, 0.55 to 0.81) and serum creatinine (HR, 0.71; 95% CI, 0.64 to 0.79) levels demonstrated protective effects. The adjusted time-dependent model further revealed the significant association of hypocalcemia (HR, 1.63; 95% CI, 1.13 to 2.34), hypercalcemia (HR, 1.50; 95% CI, 1.02 to 2.21), and hyperphosphatemia (HR, 1.68; 95% CI, 1.20 to 2.37) with death.

Conclusions. Our patients have relatively comparable survival rates with high-profile dialysis centers. Aiming to better achieve the recommended targets, especially hemoglobin and nutritional and bone metabolism factors, should be considered for optimal dialysis outcomes.

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INTRODUCTION

Variations of dialysis patient survival between countries reveal achievement of better survival rates by some, such as Japan and European countries.[1,2] In the United States, despite the observed decrease in dialysis death rate between 2004 and 2008 compared to a decade earlier, only 50% of dialysis patients and 82% of those who received preemptive transplant were still alive after 3 years of the start of renal replacement therapy.[3] In Europe, figures are better, with the expected remaining life years being about 10.7 years for patients starting dialysis between the ages 40 and 44 years and adjusted 5-year survival rate of 54%.[4] These differences, which could also be noted between different centers within the same country, are shown to be driven

by the factors dependent on the patterns of medical care and dialysis practice, as well as patient's demographic, clinical, and genetic characteristics. The main determinants of the risk of mortality in hemodialysis patients are age at the start of dialysis, diabetes mellitus (DM) as the underlying cause of end-stage renal disease, and low residual renal function, as well as facility-level factors such as center size.[5,6,7] There are also risk factors, such as cardiovascular disease, malnutrition, dialysis inadequacy, and serum electrolyte imbalances, which are preventable or correctable, and thus the center of focus of best practice guidelines.[5,8,9,10,11] Identifying and planning strategies to reduce these risk factors are essential to achieve better survival outcomes.

There are very few studies in Iran documenting dialysis practice and survival data. In this study, we aimed to provide the long-term survival rates of our hemodialysis center and examine the leading risk factors for mortality. Many dialysis care-related factors associated with mortality are time-dependent and their alterations show a stronger association with mortality than their averaged values of the entire period of being on renal replacement therapy.[9,12] We implemented a time-dependent prognostic model in order to take into account alterations in laboratory measurements and thus better understand their association with mortality.

MATERIALS AND METHODS

Study Population

Since March 2004, we have collected long-term hemodialysis data at Hasheminejad Kidney Center using a software program specifically designed and developed for dialysis units (Hemodialysis Data Processor Software). Data of the patients under hemodialysis from March 2004 to November 2013 were extracted and refined for this retrospective study of patient survival.

Baseline Demographic and Clinical and Laboratory Data

Baseline data included age on admission to our dialysis unit, sex, marital status, employment status, smoking habit, walking disability, underlying causes of end-stage renal disease, type of vascular access, and medical history of DM, hypertension, and cardiovascular disease. Patients who needed assistance for walking or were not able to walk were considered disabled as opposed to those who could walk without assistance. High-risk patients were defined as those with any of the followings: DM, central nervous system diseases, malignancy, walking disability, or an age of 65 years and older. High-risk vascular access was defined as any vascular access during the 3 months after admission other than arteriovenous fistula (AVF).

Laboratory Data

Laboratory data included repeated measurements of blood hemoglobin, single-pool KT/V, and plasma levels of calcium, phosphate, intact parathyroid hormone (PTH), potassium, cholesterol, triglyceride, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), serum iron, ferritin, total iron binding capacity, blood urea nitrogen, creatinine, potassium, albumin, and protein (total amount of two classes of albumin and globulin). The summary estimates of the repeated measurements were calculated as the average value during the study follow-up and also the average values calculated for each 6-month interval since the start date of the follow-up (time-dependent values). The calculated average values of the following laboratory data were further categorized according to their reference ranges, as high and low values: hemoglobin (10 g/dL to 12 g/dL); calcium (8.4 mg/dL to 9.5 mg/dL); phosphate (3.5 mg/dL to 5.5 mg/dL); intact PTH (150 pg/mL to 300 pg/mL); potassium (3.5 mEq/L to 5 mEq/L); low-density lipoprotein cholesterol (70 mg/dL to 130 mg/dL); protein (5.5 g/dL to 8 g/dL); and single-pool KT/V ($\geq$ 1.2). The remaining laboratory measurements (HDLC, triglyceride, ferritin, and creatinine; all reported as mg/dL) were treated as continuous variables. Variables highly correlated with the above laboratory parameters or with similar clinical value, including blood urea nitrogen, total cholesterol, albumin, serum iron and total iron binding capacity were not included in the analysis. Serum sodium was not included in the study because of the high number of variables.

Statistical Analysis

Descriptive data were summarized as proportion or mean ± standard deviation. The study follow-up period was from March 21st, 2004 to November 17th, 2013. The Kaplan-Meier method was used

to create survival curves and survival rates were reported for the patients who initiated hemodialysis at this center during the study follow-up period and all of the patients who started on hemodialysis before or after the start of the study (incident and prevalent patients). For the prevalent patients, the follow-up start dates were set to the study start date. Events were considered censored for cases of transfer to other centers, change of dialysis modality, kidney transplantation, or recovery of kidney function.

The Cox proportional hazard models were used to evaluate the factors predicting mortality. Repeated laboratory measurements were examined in the models, as well as 6 baseline factors including age, sex, walking disability, high-risk vascular access, and medical history of DM and cardiovascular disease. Two sets of analyses were done for repeated measurements using either the averaged values or the time-dependent values, as described above. Missing data were less than10% for any of the patients. For each of the analyses of the averaged and time-dependent values, 3 sets of models were examined: (1) unadjusted cox regression model for each baseline variable, and repeated laboratory values and time averaged values; (2) Cox regression models for repeated laboratory values and time averaged values, each adjusted for baseline variables only; and (3) fully adjusted models including all repeated and time averaged measurements and baseline values.

All statistical analyses were done using the SAS, version 9.2 (SAS Institute, Inc., Cary, NC). *P* values less than 0.05 were considered significant.

RESULTS

Baseline and clinical data of 565 patients were reviewed. Five patients were excluded from the analyses due to data quality issues and analyses were done on 560 prevalent and incident hemodialysis patients (Table 1). The median follow-up period of the patients was 25 months (1 to 116 months). At the end of study, 221 (39.5%) of patients had died (Table 2). Mortality rate was 34.4% for incident dialysis patients and 51.5% for prevent dialysis patients. Survival rates were 91.9%, 66.0%, 46.3%, 35.6%, and 28.5%, at 1, 3, 5, 7, and 9 years, respectively, in all 560 patients and 90.8%, 61.6%, 42.1%, 28.0%, and 28.0% in 395 incident patients (Figure 1).

Table 1. Patients' Characteristics*

Characteristic	Value
Age, y	
Mean value	54.8 ± 17.7 (11 to 89)
≥ 65 years old	197 (35.2)
Male sex	323 (57.7)
Marital status	
Single, divorced, or widowed	118 (21.1)
Married, living with partner	442 (78.9)
Employed	192 (35.0)
Smoker	102 (18.2)
Dialysis hours per session	
< 4 hours	7 (1.3)
4	534 (95.4)
> 4	19 (3.4)
Dialysis session per week	
2	34 (5.9)
3	526 (93.9)
Walking ability	
Walks without help	429 (76.6)
Walks with help	60 (10.7)
Uses wheelchair or crutches	67 (12.0)
Unable to walk	4 (0.7)
Cause of end-stage renal disease	
Diabetes mellitus	201 (35.9)
Glomerulonephritis	27 (4.8)
Hypertension	69 (12.3)
Obstructive uropathy	4 (0.7)
Others	43 (7.7)
Polycystic kidney disease	28 (5.0)
Reflux nephropathy	9 (1.6)
Stone	11 (2.0)
Unknown	168 (30.0)
Other comorbidities	
Cardiovascular disease	167 (29.8)
Cerebrovascular disease	7 (1.3)
Malignancy	1 (0.2)
Vascular access (within 3 months of admission)	
Arteriovenous fistula	397 (74.2)
Arteriovenous native graft	7 (1.3)
Arteriovenous synthetic graft	10 (1.9)
Permanent central vein catheter	2 (0.4)
Temporary central vein catheter	117 (21.9)
High-risk group	364 (64.9)
Single-pool KT/V	
Mean value	1.30 ± 0.25
≥ 1.2	382 (68.1)

*Values in parentheses are percent for frequencies and range for mean value.

Mortality risk increased by 3% with each year increase in age at admission (95% confidence interval [CI], 2% to 4%; $P < .001$). Survival rates were lower in patients with an age of 65 years and older (hazard ratio [HR], 2.33; 95% CI, 1.78

Table 2. Patients' Outcomes

Outcome	Value
Median time on dialysis, mo	26.0 (1 to 398)
Median study follow-up, mo	25.0 (1 to 116)
Last status	
Dead	221 (39.5)
Alive	185 (33.0)
Transplanted	90 (16.1)
Transferred	54 (9.6)
Changed dialysis modality	7 (1.3)
Recovered	3 (0.5)
Cause of death	
Cardiovascular	98 (45.4)
Cerebrovascular	27 (12.5)
Gastrointestinal	4 (1.9)
Infectious	30 (13.9)
Neoplastic	13 (6.0)
Other	3 (1.4)
Pulmonary	6 (2.8)
Trauma or accident	1 (0.5)
Not identified	34 (15.7)

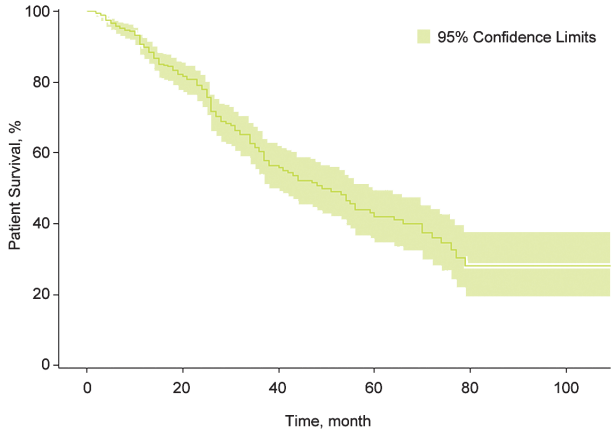

Figure 1. Survival curves for all and incident patients, calculated since the start of the follow-up (March 2004).

to 3.05; $P < .001$), DM (HR, 1.83; 95% CI, 1.39 to 2.40; $P < .001$), cardiovascular disease (HR, 1.93; 95% CI, 1.47 to 2.54; $P < .001$), walking disability (HR, 2.62; 95% CI, 1.99 to 3.46; $P < .001$), and high-risk vascular access on admission (HR, 1.41; 95% CI, 1.02 to 1.95; $P = .04$). Overall, survival rates were significantly lower in the high-risk group (HR, 2.94; 95% CI, 2.14 to 4.04; $P < .001$; Figure 2). Survival rates were not associated with male sex in unadjusted analysis (HR, 1.27, 95% CI, 0.97 to 1.66; $P = .09$).

Tables 3, to 5 summarize the association of laboratory measurements treated as averaged and time-dependent values (unadjusted, each adjusted for baseline variables, and fully adjusted, respectively). Unadjusted Cox regression analysis showed that low hemoglobin levels were associated with mortality, and when adjusted for baseline variables, and fully adjusted, it maintained to be a significant risk factor (Tables 4 and 5). Low phosphorus levels were significantly associated with mortality in the unadjusted models and model adjusted for baseline variables, but in the fully adjusted model, a marginal effect on mortality was observed only with the time-dependent variables. Low calcium and high phosphorus levels were significantly associated with mortality only as time-dependent variables in the adjusted model, and a high calcium level remained a significant risk factor as a time-dependent value. Low serum intact PTH level was a risk factor for mortality in the unadjusted model, had marginal significance in the adjusted model, and lost significance after full adjustment. The protective effect of each unit increase in HDLC was observed in all 3 models, while this protective effect was only found with the time-dependent serum triglyceride values. The time-dependent low LDLC level was a significant predictor of mortality, in the unadjusted model and the model adjusted for baseline variables, but not in the fully adjusted one. Low level of serum protein was a risk factor when included in the unadjusted models as an averaged value, but lost it significance in the adjusted models. The protective effect of high protein level was demonstrated by the time-dependent analyses, in unadjusted and adjusted models. Low single-pool KT/V was a risk factor for mortality in all 3 models. Higher serum creatinine levels significantly decreased mortality in all 3 models; however, the protective effect of higher potassium was diminished after full adjustment. In the fully adjusted models, male sex became a significant predictor of mortality (Table 6).

DISCUSSION

In this single-center study of 560 hemodialysis patients, we presented the results of patient survival and risk factors of mortality over 9 years.

Adjusted rates of all-cause mortality are 6.5 to 7.4 times greater for dialysis patients than for the general population.[5] With improving dialysis techniques and patient care, mortality rates have declined by nearly 26% since 1985 and by 21%

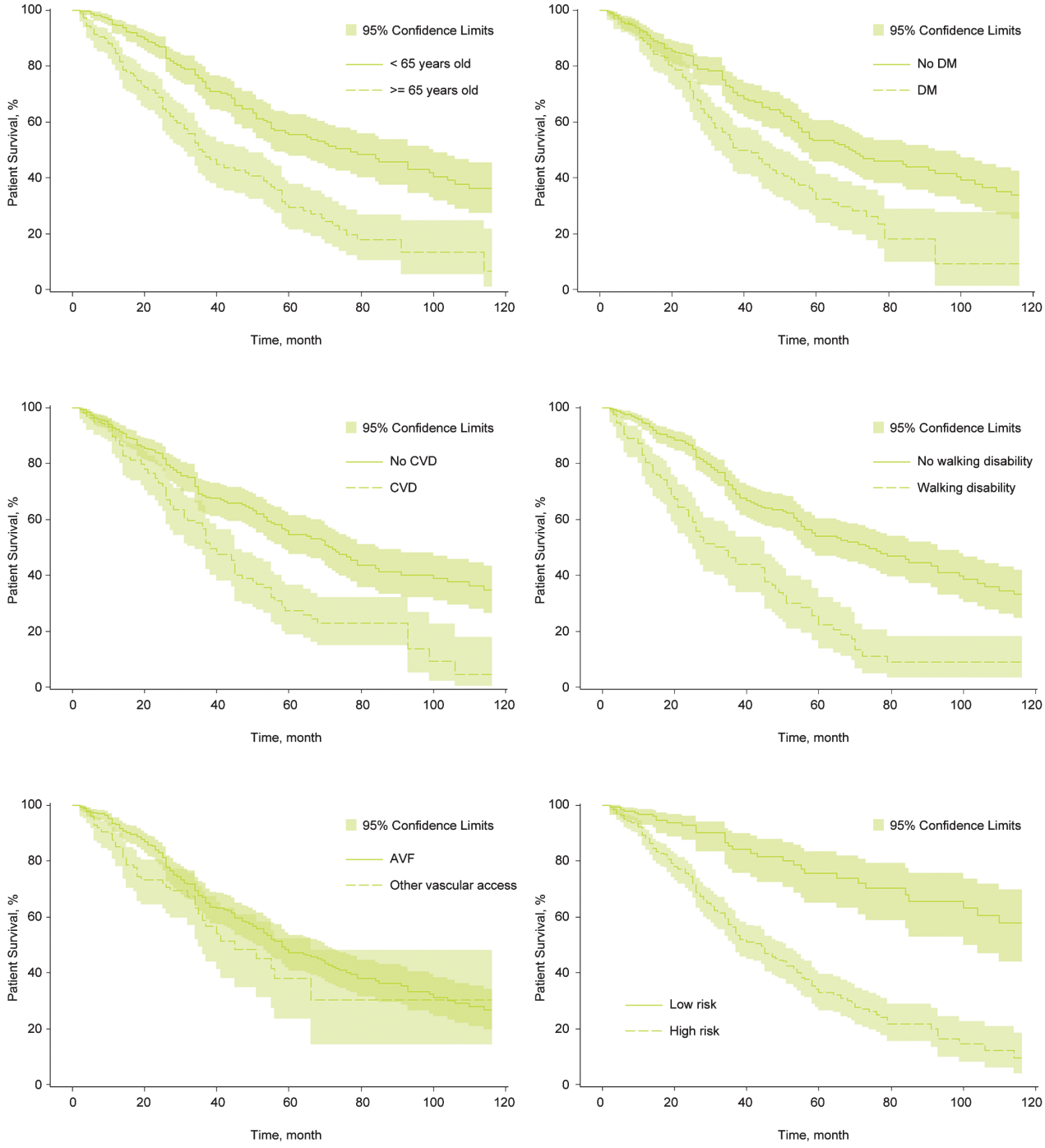

Figure 2. Survival curves by baseline factors significantly associated with mortality, for all studied patients, calculated since the start of the follow-up (March 2004). DM indicates diabetes mellitus; CVD, cardiovascular disease; and AVF, arteriovenous fistula. High-risk patients were defined as those with any of the following: DM, central nervous system diseases, malignancy, walking disability, or an age of 65 years and older.

since 2000.[5] However, in the United States, only 76% of hemodialysis patients who started dialysis in 2007 survived up to 1 year, 54% up to 3 years, and 40% up to 5 years.[3] The European and Japanese registries have shown lower mortality rates compared to the United States data.[13] The largest multicenter study from Khouzestan province, Iran, showed that 1-, 5-, 10-, and 15-year survival rates of hemodialysis patients were 83%, 25.2%, 3.8%, and 1.0%, respectively.[14] Our survival rates

Table 3. Unadjusted Cox Regression Analysis of the Association of Laboratory Studies With Mortality of Hemodialysis Patients Using Averaged Values Versus Using Time-dependent Values (Average Values of Each 6-Month Interval) in the Model*

	Models with Averaged Values		Models with Time-dependent Values	
Parameter	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Hemoglobin				
Low	1.61 (1.20 to 2.16)	.001	1.64 (1.23 to 2.19)	< .001
High	0.93 (0.56 to 1.54)	.76	0.89 (0.58 to 1.36)	.59
Serum ferritin				
Low	1.15 (0.73 to 1.80)	.56	0.63 (0.40 to 1.00)	.049
High	0.93 (0.69 to 1.24)	.62	1.04 (0.77 to 1.40)	.82
Serum calcium				
Low	1.08 (0.74 to 1.58)	.70	1.24 (0.90 to 1.71)	.19
High	1.54 (1.09 to 2.18)	.02	1.28 (0.91 to 1.80)	.16
Serum phosphate				
Low	7.39 (3.95 to 13.84)	< .001	4.17 (2.76 to 6.32)	< .001
High	0.84 (0.64 to 1.11)	.23	1.05 (0.78 to 1.40)	.76
Serum intact PTH				
Low	1.53 (1.09 to 2.15)	.02	1.48 (1.05 to 2.11)	.03
High	0.84 (0.61 to 1.17)	.30	0.91 (0.63 to 1.32)	.62
Serum potassium				
Low	6.18 (0.84 to 45.37)	.07	2.20 (0.29 to 16.54)	.44
High	0.63 (0.48 to 0.83)	.001	0.54 (0.41 to 0.70)	< .001
Serum protein				
Low	4.21 (1.03 to 17.16)	.045	1.34 (0.50 to 3.64)	.56
High	0.68 (0.42 to 1.09)	.11	0.64 (0.43 to 0.94)	.02
LDLC				
Low	0.97 (0.68 to 1.40)	.88	1.36 (1.00 to 1.85)	.049
High	1.82 (1.11 to 2.97)	.02	1.45 (0.94 to 2.24)	.10
HDLC†	0.75 (0.63 to 0.89)	< .001	0.84 (0.74 to 0.95)	.007
Serum triglyceride†	0.99 (0.97 to 1.01)	.19	0.98 (0.96 to 0.99)	.006
Serum creatinine	0.73 (0.68 to 0.78)	< .001	0.75 (0.70 to 0.80)	< .001
Single-pool KT/V				
Low	2.13 (1.59 to 2.84)	< .001	1.27 (0.95 to 1.70)	.11

*Values are categorized for all parameters (except for HDLC, triglyceride, and creatinine) and compared to the reference categories (the middle range for all except single-pool KT/V, which is compared to high values). HR indicates hazard ratio; CI, confidence interval; PTH, parathyroid hormone; LDLC, low-density lipoprotein cholesterol; and HDLC, high-density lipoprotein cholesterol.
†By 10-unit increments

for incident hemodialysis patients were 90.8%, 61.6%, and 42.1% at 1, 3, and 5 years, respectively, which indicates much better survival rates than Khouzestan province report and US registries and close to those from European and Japanese registries.[3,14,13] This is probably because we reported a single-center outcome, which is expected to be better than large registries, due to higher standards of dialysis quality as compared to registries that include several dialysis units with variable size and quality of care.

As shown in this study, older age, male sex, DM, and cardiovascular disease are of the most important baseline predictors of mortality in hemodialysis patients. Not surprisingly, adjusted rates of mortality rise by age, in the prevalent ESRD population aging 65 years and older, and tend to be higher in men than in women.[7,4] In the 2010 annual report of the European Renal Association-European Dialysis and Transplantation Association, the adjusted 5-year survival probability of the incident dialysis patients older than 75 years was 19.9% compared to 77.2% in patient younger than 20 years.[4] In addition to the lower life expectancy in the elderly, many age-associated factors, such as malnutrition, inflammation, and heart failure, seem to affect lower survival in older dialysis patients, but survival models cannot be adjusted for all of them.[15,16]

The underlying cause of ESRD affects patient mortality, with chronic glomerulonephritis having the best and DM having the worst prognosis among other causes of ESRD.[5] We found that DM increased the risk of death by 40%. Schroijen and

Table 4. Cox Regression Analysis of the Association of Laboratory Studies With Mortality of Hemodialysis Patients, Adjusted for Baseline Factors, Using Averaged Values Versus Using Time-dependent Values (Average Values of Each 6-Month Interval) in the Model*

	Models with Averaged Values		Models with Time-dependent Values	
Parameter	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Hemoglobin				
Low	2.59 (1.90 to 3.55)	< .001	2.16 (1.60 to 2.91)	< .001
High	1.15 (0.69 to 1.93)	.59	0.95 (0.62 to 1.45)	.82
Serum ferritin				
Low	1.23 (0.78 to 1.95)	.37	0.71 (0.45 to 1.12)	.14
High	0.90 (0.67 to 1.22)	.51	1.01 (0.75 to 1.37)	.92
Serum calcium				
Low	1.24 (0.84 to 1.83)	.29	1.53 (1.10 to 2.13)	.01
High	1.58 (1.10 to 2.25)	.01	1.35 (0.95 to 1.92)	.09
Serum phosphate				
Low	4.60 (2.35 to 9.00)	< .001	3.16 (2.06 to 4.85)	< .001
High	1.20 (0.89 to 1.61)	.23	1.38 (1.02 to 1.86)	.03
Serum intact PTH				
Low	1.35 (0.95 to 1.93)	.09	1.40 (0.98 to 1.99)	.06
High	1.07 (0.77 to 1.51)	.68	1.07 (0.74 to 1.56)	.71
Serum potassium				
Low	4.35 (0.58 to 32.57)	.15	1.29 (0.17 to 9.58)	.80
High	0.77 (0.58 to 1.03)	.07	0.64 (0.48 to 0.84)	.001
Serum protein				
Low	3.71 (0.89 to 15.42)	.07	1.42 (0.52 to 3.87)	.49
High	0.75 (0.47 to 1.22)	.25	0.65 (0.44 to 0.97)	.03
LDLC				
Low	1.08 (0.75 to 1.56)	.68	1.38 (1.01 to 1.88)	.04
High	1.53 (0.93 to 2.54)	.10	1.46 (0.94 to 2.27)	.10
HDLC†	0.74 (0.62 to 0.88)	< .001	0.82 (0.72 to 0.94)	.003
Serum triglyceride†	0.99 (0.97 to 1.02)	.59	0.98 (0.96 to 1.00)	.04
Serum creatinine	0.77 (0.71 to 0.84)	< .001	0.79 (0.73 to 0.84)	< .001
Single-pool KT/V				
Low	2.14 (1.58 to 2.89)	< .001	1.26 (0.93 to 1.69)	.13

*Each parameter is 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 HDLC, triglyceride, and creatinine) and compared to the reference categories (the middle range for all except single-pool KT/V, which is compared to high values). HR indicates hazard ratio; CI, confidence interval; PTH, parathyroid hormone; LDLC, low-density lipoprotein cholesterol; and HDLC, high-density lipoprotein cholesterol.
†By 10-unit increments

colleagues showed a higher mortality in dialysis patients with DM either as the underlying disease or as comorbidity.[17] The same group later showed that dialysis patients with DM as an underlying disease had a higher mortality compared to those with DM as a comorbid disease, suggesting that survival in diabetic dialysis patients is affected by the time of DM onset and thus the extent to which DM has induced organ damage.[18]

We documented a better survival in patients who had an AVF within the first 3 months of initiation of hemodialysis (74% of our patients), with a 40% to 60% higher mortality risk with non-AVF access types. Arteriovenous grafts and central vein catheters have been shown to be associated with increased cardiovascular and infection-related death compared to AVF.[19,20] Interestingly, even a change from arteriovenous access to a catheter was associated with an antecedent decrease in serum albumin level, weight loss, and higher risk of non-access-related hospitalization.[21] Also patients using tunneled central vein catheters sometime during the follow-up and prior to death have 6.9-fold higher odds of death from sepsis compared with those using only AVF or arteriovenous grafts.[20] Our data on vascular access was limited to the time of dialysis initiation with a 3-month assessment period, and looking at the changes of the vascular access type during the follow-up period would have provided us with a better estimate of the

Table 5. Fully Adjusted Cox Regression Analysis of All Factors Associated With Mortality of Hemodialysis Patients, Using Averaged Laboratory Values Versus Using Time-Dependent Values (Average Values of Each 6-Month Interval) in the Model*

	Model with Averaged Values		Model with Time-dependent Values	
Parameter	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Hemoglobin				
Low	1.98 (1.36 to 2.90)	< .001	1.65 (1.18 to 2.32)	.004
High	1.33 (0.74 to 2.39)	.35	1.04 (0.67 to 1.62)	.87
Serum ferritin				
Low	0.87 (0.50 to 1.49)	.61	0.75 (0.45 to 1.23)	.25
High	0.77 (0.44 to 1.37)	.38	1.01 (0.73 to 1.38)	.98
Serum calcium				
Low	1.33 (0.83 to 2.13)	.24	1.63 (1.13 to 2.34)	.008
High	1.39 (0.92 to 2.12)	.12	1.50 (1.02 to 2.21)	.04
Serum phosphate				
Low	1.99 (0.57 to 6.95)	.28	1.70 (0.98 to 2.93)	.06
High	1.36 (0.93 to 1.98)	.11	1.68 (1.20 to 2.37)	.003
Serum intact PTH				
Low	1.21 (0.79 to 1.85)	.38	1.38 (0.94 to 2.03)	.10
High	1.02 (0.70 to 1.49)	.92	1.10 (0.74 to 1.63)	.64
Serum potassium				
Low†	…	…	…	…
High	1.12 (0.79 to 1.61)	.53	0.78 (0.57 to 1.06)	.11
Serum protein				
Low	0.67 (0.08 to 5.43)	.71	0.62 (0.19 to 2.01)	.42
High	0.73 (0.43 to 1.23)	.24	0.67 (0.44 to 1.02)	.06
LDLC				
Low	0.97 (0.64 to 1.46)	.87	1.21 (0.87 to 1.69)	.25
High	0.93 (0.48 to 1.80)	.84	1.42 (0.87 to 2.30)	.16
HDLC‡	0.67 (0.55 to 0.81)	< .001	0.77 (0.67 to 0.89)	< .001
Serum triglyceride‡	0.98 (0.96 to 1.00)	.10	0.98 (0.96 to 1.00)	.06
Serum creatinine	0.71 (0.64 to 0.79)	< .001	0.77 (0.70 to 0.84)	< .001
Single-pool KT/V				
Low	2.28 (1.60 to 3.26)	< .001	1.42 (1.03 to 1.96)	.03

*The fully adjusted model included all of the repeated measure laboratory and dialysis adequacy parameters as well as baseline factors (see Table 6). Values are categorized for all parameters (except for HDLC, triglyceride, and creatinine) and compared to the reference categories (the middle range for all except single-pool KT/V, which is compared to high values). HR indicates hazard ratio; CI, confidence interval; PTH, parathyroid hormone; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; CVD, cardiovascular access; and VA, vascular access.
†Results for low potassium values were not interpretable because of low volume.
‡By 10-unit increments

Table 6. Baseline Factors in the Fully Adjusted Cox Regression Analysis of Mortality for Hemodialysis Patients*

	Model with Averaged Laboratory Values		Model with Time-dependent Laboratory Values	
Baseline Parameter	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	1.02 (1.00 - 1.03)	.01	1.02 (1.00 - 1.03)	.008
Male sex	1.48 (1.04 - 2.11)	.03	1.42 (1.02 - 1.97)	.04
Diabetes mellitus	1.42 (1.01 - 2.00)	.045	1.39 (1.01 - 1.92)	.045
Walking disability	1.30 (0.91 - 1.86)	.15	1.23 (0.88 - 1.72)	.22
Cardiovascular disease	1.50 (1.09 - 2.06)	.01	1.61 (1.18 - 2.20)	.003
High-risk vascular access	1.40 (0.95 - 2.07)	.09	1.61 (1.10 - 2.34)	.01

*These baseline factors were included in the models with all laboratory values demonstrated in Table 5.

impact of vascular access on mortality.

We found that the walking disability on admission affected patient survival in unadjusted analyses. In addition to the poor initial physical function of the patients, this association may also be explained by their long-term likelihood of limited physical activity after starting dialysis. A correlation has been found between decreased physical activity

over time and dialysis patient mortality.[22,23] A simple observation of physical ability of dialysis patients, at the start of and throughout the dialysis period, in order to make timely intervention, may improve their survival on dialysis.

Similar to what is shown in the abovementioned studies about DM, vascular access, and physical function, weight of many risk factors vary in different phases of the disease depending on their time of presence or their level or severity.[24] Conventionally, studies of prognostic factors in dialysis patients incorporate fixed-in-time effects of all explanatory variables, regardless of their changes over time. Regression models usually use the baseline and mean (average over time) laboratory values. This approach disregards the temporal information on the disease course and may lead to a bias in results caused by fixed values.[25] Time-dependent analysis of prognostic data is increasingly used in clinical research in order to incorporate the dynamic effect of time-varying factors. We built time-dependent Cox regression models to better understand the proportional effect of laboratory factors that may vary with time and evaluate the short-term effects of abnormal values that would otherwise be masked by the summarized data.[26,27,24]

Our study supported the effect of dialysis efficacy on patient survival with all models, but more prominently in the model with averaged single-pool KT/V; mortality risk increased more than twice with low single-pool KT/V. The first observational studies showed a clear relationship between low dialysis efficacy and patient survival and the high mortality in US dialysis patients seemed to result from the progressive decline in dialysis dose in this country.[28,29] On the other hand, in the Tassin experience, excellent 20-year survival rates were associated with a mean single-pool KT/V of 1.67, together with a high incidence of full rehabilitation, almost excellent blood pressure control, and no antihypertensive medications.[10] The HEMO study could not show any advantage of a higher-dose or a high-flux membrane hemodialysis.[30] However, in a marginal structural model of survival analysis on 68110 patients that accounted for time-varying confounding and exposure, a single-pool KT/V less than 1.2 was associated with a higher risk of mortality, compared to a single-pool KT/V of 1.2 to 1.4, and higher single-pool KT/V levels were associated with incremental increase in survival.[31] While time-averaged analysis suggest that a low average KT/V is linked with poor outcomes, time-dependent models also add to our knowledge that a decrease in KT/V below the recommended level will put the patient's life at risk.

Hemoglobin level is another important predictor of mortality in ESRD patients, which was also documented in our study with both averaged and time-dependent hemoglobin levels [32] The Normal Hematocrit Trial was one of the first randomized controlled trials which shed doubt on the recommendation of complete correction of anemia by erythropoietin.[33] In a large observational study on 58058 patients, greater survival was associated with a time-dependent (13-week averaged) hemoglobin between 12 g/dL and 13 g/dL and treatment with erythropoiesis-stimulating agents, while declining hemoglobin over time was associated with poorer survival.[34] In the TREAT trial, increased the risk of stroke was reported in patients with hemoglobin levels targeted to 13 g/dL.[35] On the other hand, falling hemoglobin and requiring higher erythropoiesis-stimulating agent doses were associated with decreased survival.[36] Our study showed increased mortality in patients with both averaged and time-dependent hemoglobin levels less than 10 g/dL. However, we failed to show the detrimental effect of high hemoglobin levels.The fact that higher levels of hemoglobin were not commonly seen in our patients can explain the insignificant results.

Disorders of mineral metabolism have been suggested as important predictors of mortality of hemodialysis patients.[37] Analysis of data from 107.200 hemodialysis patients showed that high time-averaged calcium levels were associated with higher risk of death, while the association for low calcium level was dependent on its interactions with other factors such as phosphorus and PTH levels.[38] The Dialysis Outcomes and Practice Patterns Study's survival models with both baseline and time-dependent values identified categories with the lowest mortality risk for calcium (8.6 mg/dL to 10.0 mg/dL), phosphorus (3.6 mg/dL to 5.0 mg/dL), and PTH (101 pg/mL to 300 pg/mL).[12] However, only models including time-dependent values were able to identify significant mortality risks with low calcium, phosphate, or PTH levels.[12] In our cohort, the effect of abnormal calcium and

phosphorus levels were better documented in the fully adjusted model taking into account the interaction between these electrolytes as well as PTH. However, this effect was seen only with time-dependent values. The overall average of calcium and phosphate over the long-term period of being on dialysis may not reflect the variation of these factors over time, while the time-dependent analysis showed the complete picture consistent with the large studies of the field.

Factors such as serum creatinine, serum albumin and protein, and lipid profile are known predictors of nutritional status of ESRD patients, and their low serum values are associated with mortality.[39,40,41,9] As previously shown, serum creatinine has a good correlation with lean body mass and the protective effect of serum creatinine may be due to better maintenance of body mass and good nutrition.[39,9] Time-dependent analysis showed that increases in body mass index and increases in serum albumin were associated with reduced short-term risk of mortality, emphasizing the immediate effect of nutritional status of the patients survival.[9] We demonstrated a strong protective effect of creatinine level associated with survival in all adjusted and unadjusted models, which probably masked similar effects of serum levels of other nutrition indicators in the fully adjusted models. In the time-dependent model, however, we could still see the marginally significant protective effect of high triglyceride and protein levels.

Serum potassium has an important role in mortality of hemodialysis patients. In a study on 81013 hemodialysis patients, serum potassium between 4.6 mEq/L to 5.3 mEq/L was associated with the greatest survival, whereas values lower than 4.0 mEq/L or 5.6 mEq/L and greater were associated with increased mortality, and the death risk of serum potassium of 5.6 mEq/L and greater remained consistent after adjustments.[38] We found an unexpectedly protective effect of high predialysis potassium levels on mortality in unadjusted Cox regression analysis, which was diminished in the fully adjusted model. We speculate that the protective effect of potassium may have been a confounding factor related to good nutrition, which was diminished by controlling for creatinine and lipid profile in the adjusted models. Hyperkalemia in ESRD patients should be interpreted with cautious taking into account the nutritional status of the patients. Because of low volumes, we were not able to do further analysis on potassium levels in subgroups by nutritional indicators.

CONCLUSIONS

This 9-year follow-up study of our hemodialysis program was indicative of survival rates relatively comparable to acceptable rates at the international level. We identified most of the classic hemodialysis mortality risk factors in our cohort such as DM, cardiovascular disease, hemoglobin, dialysis adequacy, and bone metabolism and nutrition indicators. The time-dependent survival analysis enabled us to have a better picture of all risk factors, which would be otherwise neglected with conventional survival models.

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CONFLICT OF INTEREST

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