Predictors of Clinical Outcomes in Hemodialysis Patients
A Multicenter Observational Study

Tayebeh Soleymanian,[1] Hossein Niyazi,[2]
Shaghayegh Noorbakhsh Jafari Dehkordi,[2] Shokoufeh Savaj,[3]
Hassan Argani,[4] Iraj Najafi[1]

[1]Nephrology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Nephrology Research Center, Shariati Hospital, Tehran University of Medical Sciences-International Branch, Tehran, Iran
[3]Firouzgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[4]Urology and Nephrology Research Center, Modares Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Introduction. Cardiovascular and noncardiovascular mortality and morbidity rates of hemodialysis patients are high despite improvement in dialysis delivery.
Materials and Methods. Hemodialysis patients (n = 532) from 9 hemodialysis facilities were enrolled in this cohort study in September 2012. Causes of death, hospitalization, and hemodialysis exit were recorded during a 28-month follow-up period. A Cox proportional hazard model was used to predict death adjusting for case-mix variables, nutrition variables, bone mineral variables, Kt/V, vascular access, and Charlson comorbidities index.
Results. Patients were 56.0 ± 15.4 years old (57% men). A total of 161 patients (30%) died (17 per 100 patient years), and the most common causes of death were cardiovascular diseases (42%) and infections (25%). Transplantation rate was 7 per 100 patient years and hospitalization frequency was 0.76 per patient year. Based on the multivariable Cox proportional hazard model, the mortality hazard ratio was 1.03 (95% confidence interval [CI], 1.01 to 1.05; $P = .007$) for age (years), 0.21 (95% CI, 0.11 to 0.40; $P < .001$) for serum albumin (g/dL), 1.21 (95% CI, 1.03 to 1.42; $P = .02$) for serum phosphorus (mg/dL), 1.001 (95% CI, 1.0005 to 1.002; $P = .001$) for serum intact parathyroid hormone (pg/mL), 1.58 (95% CI, 1.01 to 2.51; $P = .047$) for hemodialysis catheter (compared to arteriovenous fistula), and 1.75 (95% CI, 1.59 to 1.94; $P < .001$) for the Charlson score.
Conclusions. Nutritional factors, comorbidities, vascular access, and abnormal mineral metabolism are the main determinants of mortality and morbidity in hemodialysis patients.

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INTRODUCTION

Hemodialysis patients struggle with significantly higher rates of inflammation, malnutrition, hospitalization, and mortality compared with the general population.[1,2] Vascular calcification, atherosclerosis, and volume overload contribute to increased cardiovascular disease and mortality in dialysis patients.[3-6] However, studies have indicated that noncardiovascular mortality, mainly infections, is increased to the same extent as cardiovascular mortality (8-fold) in comparison with the general population.[7,8] Underlying chronic inflammatory processes owing to uremia, malnutrition, oxidative stress, and dialysis-related infections, as well as decreased immune response, lead to higher rates of sepsis, malignancy, and their mortalities in dialysis patients.[9-15]

The main aim of this study was to define

predictors of mortality in a cohort of hemodialysis patients from 9 facilities. We also determined the rate and causes of mortality and hospitalization in these patients.

MATERIALS AND METHODS

In this study 532 maintenance hemodialysis patients were recruited from 9 facilities in September 2012. The enrolled facilities, which signed to collaborate with this study, were from 3 different regions of Tehran, Iran: 2 facilities with 167 patients from north of Tehran, 5 facilities with 217 participants from center of Tehran, and 2 facilities with 148 patients from south of Tehran. All patients had to be at least 18 years old while receiving outpatient hemodialysis for at least 2 weeks (7.5% of patients were on dialysis for less than 3 months).

A comprehensive data collection form comprising all demographic, clinical, and laboratory information was designed, the components of which were birth date, sex, marital status, literacy, job, smoking, cause of end-stage renal disease, dry weight, height, pre- and postdialysis blood pressure, previous parathyroidectomy, renal replacement therapy history, kidney transplant candidacy, access-related questions, Charlson comorbidities, ischemic heart disease (IHD), quality of life assessment (Short Form-36), characteristics of hemodialysis treatment, delivered Kt/V, medications, and 30 laboratory elements (all drawn predialysis and also postdialysis blood urea nitrogen [BUN]). In all facilities, complete blood count; pre- and postdialysis BUN; fasting blood glucose; and serum levels of creatinine, sodium, potassium, calcium, phosphorus, and alkaline phosphatase were being checked monthly. Serum levels of albumin, lipid profile, iron, total iron binding capacity, ferritin, intact parathyroid hormone (PTH), alanine aminotransferase, aspartate aminotransferase, C-reactive protein, and uric acid were measured quarterly, while viral markers were tested every 6 months. At least 2 to 3 of the last constitutive laboratory data were recorded in the form and their mean value was applied for analysis.

Patients were followed up to February 2015. The last follow-up time was the last visit or whenever the patients left hemodialysis because of renal recovery, transfer to peritoneal dialysis, or undergoing transplantation (1 month after peritoneal dialysis transfer or transplantation). Patients who were transferred to a different facility were followed there. The study was approved by the specialized review boards and ethic committees. Informed patient consent was obtained.

The Charlson comorbidity index (CCI)[16] was calculated for each patients according to their comorbidity profile. Because all patients had kidney disease, we omitted its score from the CCI. Patients were considered to have IHD if they underwent coronary artery bypass surgery or percutaneous coronary intervention, or if they were on medical therapy because of a diagnosis of IHD made by coronary angiography, dobutamine stress echocardiography, or stress myocardial perfusion imaging.

Data was extracted from the administrative forms and medical records by well-trained medical students in collaboration with dialysis unit staff (and relevant nephrologists if needed). Information obtained during the follow-up period included causes of hospitalization and date and cause of exit from hemodialysis therapy because of recovery of kidney function, kidney transplantation, peritoneal dialysis transfer, and death.

Demographic characteristics and laboratory data of the patients were summarized using percentage of the total, means ± standard deviation, or medians (interquarter range), as appropriate. Mean values of the last 2 to 3 laboratory results for each patient were used in the analyses. Categorical variables were compared using the chi-square or the Fisher exact tests, and continuous variables were compared using the *t* test or the Mann-Whitney U test, as appropriate. Cox proportional hazard models were used for reporting the hazard ratio (HR) associated with death, while controlling for the relevant covariates. The follow-up time for each patient was the time of event (death) or censoring (recovery, peritoneal dialysis, transplantation, or last visit), whichever developed first. Death in the 1st month of transfer to peritoneal dialysis or transplantation was included.

Unadjusted and incremental levels of multivariable adjustment were used as case-mix variables (age, sex, and hemodialysis vintage), nutrition variables (serum albumin, creatinine, pre-dialysis BUN, hemoglobin, total iron binding capacity, and body mass index), bone mineral

variables (calcium, phosphorus, and intact PTH), single-pool Kt/V, vascular access, and diabetes mellitus or CCI (except kidney disease). We added diabetes mellitus or CCI to the final model to appreciate the effect of various comorbidities on adjustment of different variables. The data analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, IL, USA). Significance level was considered as a *P* less than .05.

RESULTS

Patients

The mean age of patients was 56.0 ± 15.4 years, and 302 (57%) of them were men. The mean duration of dialysis was 44.6 ± 49.1 months (median, 25 months; interquartile range, 55 months). Diabetes mellitus (41%), glomerular disease (15.5%), urologic problems (9.5%), autosomal dominant polycystic kidney disease (3%), other hereditary disorders (2.5%), and unknown or other causes including hypertension (28.5%) were the common causes of end-stage renal disease in our patients. Ischemic heart disease had involved 43% of the patients. Fifty patients (9.5%) had kidney transplant failure and 7 patients (1.5%) were transferred from peritoneal dialysis. The prevalence of hepatitis C was 3.9% (n = 20). Myocardial infarction (9.8%), congestive heart failure (25.5%), cerebrovascular disease (11.7%), peripheral vascular disease (23.7%), chronic obstructive pulmonary disease (6.6%), malignancy (5.2%), peptic ulcer disease (3.8%), connective tissue disease (3%), liver cirrhosis (1.5%), and dementia (1.3%) were the common comorbidities.

Patients were followed up for a median of 28 months (range, 0.5 to 30 months; 948 patient years).

Table 1. Demographic, Clinical, and Laboratory Data of Hemodialysis Patients*

Characteristics	All Patients (n = 532)	Survived (n = 371)	Died (n = 161)	*P*
Male sex	302 (56.8)	218 (58.8)	84 (52.2)	.16
Age, y	56.0 ± 15.4	53.8 ± 15.3	63.7 ± 13.2	< .001
Weight, kg	66.5 ± 14.3	66.8 ± 14.1	65.5 ± 14.9	.34
Body mass index, kg/m^2	24.4 ± 4.6	24.4 ± 4.3	24.4 ± 5.2	.94
Diabetes mellitus	219 (41.0)	128 (34.5)	91 (56.5)	< .001
Hemodialysis vintage, mo	25 (11 to 66)	25 (11 to 68)	24 (9 to 64)	.34
Renal replacement therapy vintage, mo	30 (12 to 72)	34 (12 to 80)	24 (9.5 to 66)	.02
Charlson comorbidity score (except kidney disease)	2 (0 to 3)	1 (0 to 2)	4 (3 to 5)	< .001
Hospitalization, patient year	0.76 (0 to 1.54)	0.40 (0 to 0.82)	2.18 (1.33 to 3.64)	< .001
Ischemic heart diseases				
None	304 (57.1)	261 (70.4)	43 (26.7)	
Medical therapy	139 (26.1)	55 (14.8)	84 (52.2)	
Stent	28 (5.3)	21 (5.7)	7 (4.3)	
Coronary artery bypass grafting	61 (11.5)	34 (9.2)	27 (16.8)	< .001
Hemodialysis vascular access				
Arteriovenous fistula	384 (72)	285 (76.8)	99 (61.5)	
Arteriovenous graft	37 (7.0)	23 (6.2)	14 (8.7)	
Catheter	111 (21)	63 (17.0)	48 (29.8)	0.001
Laboratory data (serum)				
Albumin, g/dL	3.90 ± 0.35	3.99 ± 0.32	3.71 ± 0.36	< .001
Hemoglobin, g/dL	10.6 ± 1.5	10.6 ± 1.5	10.4 ± 1.5	.22
Glucose, mg/dL	136 ± 73	131 ± 72	147 ± 76	.03
Triglyceride, mg/dL	151 ± 79	155 ± 81	141 ± 73	.06
Cholesterol, mg/dL	150 ± 36	149 ± 34	150 ± 41	.89
Creatinine, mg/dL	8.6 ± 2.8	9.1 ± 2.9	7.7 ± 2.3	< .001
Predialysis blood urea nitrogen, mg/dL	56.4 ± 13.5	57.2 ± 13.6	54.5 ± 12.9	.047
Single-pool Kt/V	1.31 ± 0.21	1.32 ± 0.21	1.28 ± 0.20	.12
Potassium, mEq/L	5.2 ± 0.7	5.2 ± 0.6	5.1 ± 0.6	.20
Calcium, mg/dL	8.9 ± 0.8	8.9 ± 0.7	8.8 ± 0.7	.34
Phosphorus, mg/dL	5.5 ± 1.3	5.5 ± 1.2	5.5 ± 1.3	.37
Intact parathyroid hormone, pg/mL	320 (158 to 572)	329 (165 to 557)	301 (147 to 602)	.37

*Values are mean standard deviation or median (range) for continuous variables and frequency (percentage) for categorical variables.

During the follow-up period, 294 (55%) were still on hemodialysis, 67 (13%) were transplanted, 7 (1.5%) were transferred to peritoneal dialysis, 3 (0.5%) had renal recovery, and 161 (30%) died. Transplantation rate was 7 per 100 patient years. Rate of transplantation for patients on hemodialysis less than 3 months was 18 per 100 patient years. Patients' characteristic s and outcomes are shown in Table 1.

Mortality

During the follow-up period (948 patient years) a total of 161 (30%) deaths happened (17 per 100 patient years). The most common causes of death were cardiovascular disease in 42%, infections in 25%, malignancy in 7%, and cachexia in 6% (Table 2). Cardiovascular mortality had an indirect impact on mortality of at least another 28% of the participants. Cardiovascular mortality included myocardial infarction, congestive heart failure, cerebrovascular accident, and cardiac arrest.

Nonsurvived patients compared to survived ones were significantly more likely to have diabetic mellitus (56.5% versus 34.5%, $P < .001$), had a higher prevalence of ischemic heart disease (72.0% versus 29.5%, $P < .001$), were older (63.7 ± 13.2 versus 53.8 ± 15.3 years, $P < .001$), had higher catheter access (29.8% versus 17.0%, $P = .001$), higher CCI scores (3.83 ± 1.80 versus 1.19 ± 1.20, $P < .001$), and had lower levels of serum albumin (3.71 ± 0.36 g/dL versus 3.99 ± 0.32 g/dL, $P < .001$), serum creatinine (7.71 ± 2.28 mg/dL versus 9.10 ± 2.87 mg/dL, $P < .001$), and predialysis BUN (54.5 ± 12.9 mg/dL versus 57.2 ± 13.6 mg/dL, $P = .047$). There was a trend for lower Kt/V in nonsurvived patients (1.28 ± 0.20 versus 1.32 ± 0.21, $P = .12$).

Table 2. Causes of Mortality in 161 Hemodialysis Patients

Death Causes	Number (%)
Coronary artery disease	56 (34.8)
Cerebrovascular accident	11 (6.8)
Cachexia and cardiovascular disease	8 (5)
Access problems and cardiovascular disease	5 (3.1)
Fracture complications and cardiovascular disease	8 (5)
Gastrointestinal bleeding and cardiovascular disease	1 (0.6)
Catheter infection and cardiovascular disease	17 (10.6)
Diabetic foot infection and cardiovascular disease	10 (6.2)
Other infections and cardiovascular disease	4 (2.5)
Catheter infection	3 (1.9)
Other infections	5 (3.1)
Cachexia and infection	2 (1.2)
Arteriovenous graft problems (rupture and surgery)	2 (1.2)
Cirrhosis complications	6 (3.8)
Chronic obstructive pulmonary disease	4 (2.5)
Malignancy	11 (6.8)
Kidney transplantation (first month)	3 (1.9)
Acute abdomen and infection	2 (1.2)
Dialysis side effect (air emboli)	1 (0.6)
Trauma	1 (0.6)
Unknown	1 (0.6)

We used Cox regression proportional hazard analysis to ascertain variables that were predictive of mortality. Age, diabetes mellitus, IHD, CCI, catheter access, dialysis vintage, and serum values of albumin, creatinine, and predialysis BUN were significantly predictors of mortality in univariable analysis. In incremental models multivariable analysis, in which respectively demographic, nutritional, bone mineral, Kt/V, vascular access, and CCI variables were incorporated, we found that age, serum albumin, intact PTH, catheter access, and CCI were independent predictors of mortality, respectively. With adding CCI to the model, serum phosphorus and female sex became significant predictors of mortality as well, and the significance value of intact PTH was increased. If instead of CCI, the diabetes mellitus was included in the model, it became a significant independent predictor of death, and in addition to increasing significant value of intact PTH, a trend toward predictability of serum phosphorus and body mass index was generated. When we figured IHD to the model as the solely comorbid condition, it still maintained its own significant value; however, the significant level of age was decreased (Table 3).

Hospitalization

A total of 719 admissions happened with a 948 patient years' follow-up. Annual admission frequency was 0.76 per patient year. Cardiovascular problems accounted for 31% of admission causes (0.23 per patient year), infections for 32% (0.24 per patient year), access insertion-repair for 24% (0.18 per patient year), and other problems for 13%. Ten percent of admissions were because of catheter infection (0.07 per patient year); 8.5%, diabetic foot infection; and 6.5%, pneumonia. Fractures constituted 3.5% of the admissions.

Table 3. Hazard Ratio of Mortality for Risk Factors in Unadjusted and Adjusted Models in Maintenance Hemodialysis Patients*

Characteristics	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y	1.04 (1.02 to 1.05)	< .001	1.03 (1.01 to 1.04)	.001	1.03 (1.01 to 1.05)	.007
Female sex	1.18 (0.86 to 1.60)	.3	1.18 (0.78 to 1.77)	.43	1.51 (0.97 to 2.34)	.06
Dialysis vintage, mo	0.996 (0.992 to 0.999)	.03	…	…	…	…
Body mass index, kg/m^2	0.99 (0.96 to 1.03)	.73	0.96 (0.91 to 1.001)	.09	0.97 (0.93 to 1.01)	.26
Diabetes mellitus	1.99 (1.46 to 2.72)	< .001	1.90 (1.25 to 2.89)	.003	…	…
Charlson comorbidity score†	1.62 (1.52 to 1.72)	< .001			1.75 (1.59 to 1.94)	< .001
Vascular access (referent: arteriovenous fistula)						
Arteriovenous graft	1.45 (0.83 to 2.54)	.19	1.38 (0.71 to 2.69)	.34	1.17 (0.61 to 2.26)	.65
Catheter	2.17 (1.51 to 3.11)	< .001	1.58 (1.01 to 2.49)	.048	1.58 (1.01 to 2.51)	.047
Serum albumin, g/dL	0.14 (0.09 to 0.22)	< .001	0.15 (0.08 to 0.29)	< .001	0.21 (0.11 to 0.40)	< .001
Hemoglobin, g/dL	0.93 (0.84 to 1.02)	.13	…	…	…	…
Predialysis blood urea nitrogen, mg/dL	0.98 (0.97 to 0.99)	.03	…	…	…	…
Serum creatinine, mg/dL	0.85 (0.79 to 0.91)	< .001	…	…	…	…
Serum transferrin, µg/dL	1.00 (0.99 to 1.003)	.82	…	…	…	…
Serum calcium, mg/dL	0.94 (0.76 to 1.16)	.56	…	…	…	…
Serum phosphorus, mg/dL	0.95 (0.83 to 1.08)	.41	1.14 (0.96 to 1.34)	.13	1.21 (1.03 to 1.42)	.02
Serum parathyroid hormone, × 100 pg/mL	1.00 (0.99 to 1.00)	.62	1.10 (1.00 to 1.10)	.05	1.10 (1.05 to 1.20)	.001
Single-pool Kt/V, 0.1 unit	0.44 (0.18 to 1.05)	.06	…	…	…	…

*Adjusted model 1 includes all variables and diabetes mellitus, while model 2 includes Charlson comorbidity score instead of diabetes mellitus.
HR indicates hazard ratio and CI indicates confidence interval.
†Kidney disease is excluded.

DISCUSSION

Despite improvement in care of dialysis patients, patient survival remains a crucial issue. However, mortality rate of dialysis patients have declined in recent years indicating favorable results with improvement in dialysis therapy.[17] The present study determined detailed information about hemodialysis practices and outcomes in our hemodialysis patients. Its facilities assignment from different regions of Tehran empowered assessment of outcomes and its predictors based on detailed information for a representative of hemodialysis patients.

Overall, our patients were younger, with higher serum albumin and phosphorus levels, and lower dialysis adequacy, compared with the hemodialysis patients of developed countries (United States, Europe, and Japan).[18] It might be assumed that high transplantation rate in our patients would leave older patients on hemodialysis; however, while 13% of our patients left dialysis for kidney transplantation, 9.5% of participants had been transferred to dialysis owing to transplant failure.

There is a large variation in mortality of dialysis patients in various countries. This could be explained by differences in baseline comorbid conditions including diabetes mellitus and cardiovascular disease as important prognostic variables, age, catheter vascular access, and unaccounted demographic factors.[19,20]

In the present study, mortality rate was 17 per 100 patient years. This mortality rate seems to be acceptable given that our transplantation rate is rather high (7 and 18 per 100 patient years for patients longer and shorter than 3 months on hemodialysis, respectively); therefore, leaving more unhealthy patients with further comorbidities on dialysis. However, our patients were much younger than other reports although overall life expectancy for our general population is less as well. Furthermore, the higher serum albumin and phosphorus values point out superior nutrition of our patients, recognizing that low serum albumin is a much stronger independent predictor of higher mortality than high serum phosphorus.

Catheter access is one of main prognostic factors due to higher infection rate and perhaps delivering less effective dialysis. There is enormous variation in catheter percentage from the least in Japan (0.1%) to the most in Canada (49.1%).[19] Proportion of catheter use in our patients was rather high (18.5%; the Kidney Disease Outcomes Quality

Initiative recommendation is less than 10%) and catheter infection accounted for 12.5% of deaths. In agreement with other reports, the median of our patients' CCI scores was 2 (not counting kidney disease).[21]

Other studies have revealed a strong association between catheter use, hyperphosphatemia, and hyperparathyroidism with mortality as well.[22-25] Unlike most studies concerning equal or higher mortality rates in men,[26,27] our results revealed a significant association between female sex and mortality after full adjustment for all covariates. Interestingly, in agreement with some studies,[28,29] we did not observe adjusted survival benefit with higher hemoglobin values or greater Kt/V.

In the present study, the percentage of death causes was similar to other studies. The most common causes of death were respectively cardiovascular disease (42%), infections (25%), malignancy (7%), and cachexia (6%). There were some overlaps between cardiovascular and noncardiovascular causes of mortality in our patients, and cardiovascular mortality had an indirect impact on mortality of at least another 28% of the participants. Based on other reports, sepsis particularly could induce aggravation of underlying heart failure leading to death.[12]

In reports from the United States, Europe, and Japan, the leading cause of death was cardiovascular (20% to 40%) followed by infection (10% to 20%) and malignancy (5% to 10%).[7,8,30,31] Withdrawal from dialysis or suicide is relatively common in the United States and Europe.[32-34] Intriguingly, we did not have any report of withdrawal or suicide as a cause of death, perhaps because of better family support or unawareness of patients to their disease course. It is delineated that variability in mortality rates over dialysis population worldwide is partially consistent with the variability in background atherosclerotic cardiovascular mortality rates in the relevant general population (with different genetic and environmental factors).[35]

We used the Cox proportional hazard model in order to define the predictors of mortality. In incremental multivariable analysis, the predictive power of each variable is revised because of adjustment for other predictor variables. Serum albumin was constantly a strong predictor of death. The next powerful factor associated with mortality was CCI score. Other significant independent variables were age, catheter access, serum intact PTH, and serum phosphorus. There was a trend for higher mortality among women. Notably, female sex and serum phosphorus only became significant predictors after adjustment for underlying comorbidities. Therefore, given that adjustment for comorbidities determines some prognostic factors, it should be considered in constructing case mix.[36] Likewise, after adjustment for other variables, particularly comorbidities, Kt/V became a weak predictor of mortality, indicating patients with more comorbidities were most likely to have less dialysis adequacy perhaps owing to the use of catheter access and less tolerance to complete dialysis time with adequate blood flow rate.

Furthermore, the risk of mortality increased 1.9-folds for diabetic patients when we added diabetes mellitus instead of CCI to the model, and the predictor variables except sex, and to some extent, serum phosphorus had no reversal. This implies that diabetes mellitus is quite common and it covers the most prevailing variables of comorbidities like myocardial infarction, heart failure, cerebrovascular accident, and peripheral vascular disease. Moreover, after counting IHD as the exclusive comorbidity, the risk of mortality in patients with IHD was 4.3-folds, while the significance value of age was declining simultaneously. It illustrates that age captures the effect of the IHD fairly because older patients die mainly due to coronary artery disease.

Admission of the dialysis patients for both complications of dialysis or treatment of comorbid conditions imposes an immense burden on health finance.[37] There are considerable differences in hospitalization rate over countries.[26] Prevalence of catheter usage and type of access care, number of underlying comorbidities, and treatment policies affect the hospitalization rate and length of admissions.[26] For instance, some facilities manage the catheter infection as outpatient therapy when it does not have clear indications (like sepsis or heart failure) for admission.

In the present study, hospitalization frequency was 0.76 per patient year. Infection, cardiovascular, and access problems were the common causes of admissions. In a European countries report, hospitalization rates for cardiovascular disease and vascular access-related infection respectively ranged from 0.19 to 0.43 and 0.01 to 0.08 per patient

years.[26] These numbers for our study were 0.23 and 0.07 per patient years, respectively.

Of the strengths of present study was the enrollment of reasonable representative sample of hemodialysis population from different regions of Tehran. Although compared to some other studies the sample size is small, we covered detailed comorbidities, nutritional markers, laboratory data, dialysis adequacy, and vascular access. Limitations of our study are observational study, using both prevalent and incident (7.5% of patients) population, not considering the residual kidney function, and perhaps persistence of other residual confounders. Other limitation is that we did not use time-dependent results of the variables, and some variables will be changed along the time course. However, we utilized the average of at least 2 or 3 laboratory data at study entry.

CONCLUSIONS

Our hemodialysis patients were younger with better nutritional status, but with higher serum phosphorus levels and lower Kt/V, compared to average levels in developed countries. Mortality and hospitalization rates are within the range of other countries. Serum albumin, comorbidities, abnormal bone minerals, and vascular access are among the most significant determinants of mortality in maintenance hemodialysis patients.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Department of Nephrology, Shariati Hospital, North Kargar St, Tehran, Postal Code: 1411713135, Iran
Tel : +98 21 8490 2469
Fax: +98 21 8802 6010
E-mail: soleymanian@tums.ac.ir

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