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Association of Dose and Frequency on the Survival of Patients on Maintenance of Hemodialysis in China: A Kaplan-Meier and Cox-Proportional Hazard Model Analysis

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Background: Dialysis frequency and dose are controversial prognostic factors of hemodialysis morbidity and mortality. The aim of this study was to find out the effect of frequency and dosage of dialysis on mortality and survival in a group of Chinese hemodialysis patients.


Material/Methods: In total, 183 patients seen from February 2008 to January 2018, who were on maintenance hemodialysis for at least 3 months, were included in the study cohort. An anonymized database of age, gender, diabetic status, comorbidities, date of initiation of dialysis, hematological characters, biochemical variables, and status of survived or died was established from DICOM (Digital Imaging and Communications in Medicine) files of patients. Kaplan-Meier and Cox-proportional hazard model was used for calculation of survival over time at 95% confidence level.

Results: Overall, the 10-year survival rate was 27%. Kaplan-Meier analysis showed patient survival as 94% at one-year, 59% at 5-years, and 27% at 10-years. Hemoglobin, serum albumin, calcium, potassium, phosphorous, calcium-phosphorous-products, and hemodialysis frequency and the dose had a significant effect on survival. Cox regression proportional hazard model showed that patients with serum albumin level of >4 g/dL were better associated with survival. Patients who underwent twice-weekly hemodialysis had 4.26 times less chance of survival as compared to patients with thrice-weekly hemodialysis. A higher dialysis dose of >1.2 spKt/V offered better survival as compared to a lower dose of <1.2 spKt/V.

Conclusions: Hypoalbuminemia, hemodialysis time, and hemodialysis frequency were significantly associated with mortality.

MeSH Keywords: **Glomerular Filtration Rate • Hemodialysis Units, Hospital • Hypoalbuminemia • Kaplan-Meier Estimate • Kidney Failure, Chronic • Morbidity**

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Background

In recent decades, end-stage renal disease (ESRD) has become a major health concern with an alarming increase in incidence as well as prevalence. The number of ESRD patients continues to increase rapidly with an estimated annual growth rate of nearly 7%, that in turn poses an enormous financial burden on society. Worldwide, a large number of patients with ESRD undergo dialysis treatment (either hemodialysis or peritoneal dialysis) and kidney transplantation [1]. In China, the most populous country of Asia comprising 20% of worlds' population, the estimated prevalence of dialysis patients in 2012 was 215 per million population [2]. Hemodialysis remains the predominant choice of renal replacement therapy over the options of peritoneal dialysis and kidney transplantation [3].

Even with major research efforts to identify better management of dialysis patients, morbidity and mortality continued to increase in ESRD patients. In addition to higher mortality and morbidity, there are several other factors that have been shown to influence patient outcomes for ESRD patients [4]. Although all prognostic factors predictive of survival and better quality of life in hemodialysis patients are not yet known, there are a number of factors that have a well-known and widely accepted influence on survival among hemodialysis patients. Such factors include advanced age, malnutrition, difficult vascular access, the presence of cardiovascular disease, comorbidities such as diabetes mellitus and hypertension, and their associated complications [5]. The higher prevalence of such factors explains higher mortality among hemodialysis patients. According to the Chinese Renal Data System, glomerular disease followed by diabetic nephropathy and hypertension constitute the major causes of ESRD among hemodialysis patients. The increased incidence of hypertension, obesity, and type 2 diabetes mellitus, along with advanced age, further increases the risk of ESRD in China, thus demanding more economic and disease management facilities [2].

Apart from these well-known and widely accepted prognostic factors for survival in hemodialysis patients, there are some controversial factors that may also influenced morbidity and mortality among hemodialysis patients. One such globally accepted controversial prognostic factor is dialysis frequency [6] and its dose [7]. The gold standard of dialysis treatment in terms of dialysis frequency, duration, and dose of dialysis is yet to be determined. Recently, many research studies have suggested that higher morbidity accompanied by frequent heart complications, malnutrition, depression, and other bone-related disorders are partly caused by inadequate dialysis dose and frequency [8]. Dialysis dose and frequency directly affects the quality of life and leads to diminished longevity. In order to improve overall mortality rates and achieve an acceptable survival prognosis for hemodialysis patients, we conducted a

Cox-proportional hazard model analysis to find out the association of dialysis dose and frequency as prognostic factors in assessing survival of hemodialysis patients.

The objective of this observational study was to find out the effect of hypoalbuminemia, hemodialysis time and frequency, and gender on mortality and survival among Chinese hemodialysis patients.

Material and Methods

Ethical consideration and consent to participate

An exception for this study was granted from the World Health Organization trial registry by Renmin Hospital of Wuhan University, China and Southwest Hospital, Third Military Medical University, China. However, the study was registered in the research registry (www.researchregistry.com), UID No.: researchregistry3667, dated January 15, 2008. The protocol (OS/RH/HU/15/08 dated December 15, 2007) of the study was approved by Renmin Hospital of Wuhan University, China and Southwest Hospital, Third Military Medical University, China. The study adhered to the law of PR China, STROBE guidelines, and 2013 Declarations of Helsinki. Written consent was obtained from all patients or their guardian by signing a pre-designed patient consent Performa regarding the study and publication of it in all formats (hard and/or electronic) irrespective to time and language.

Inclusion criteria

The current study analyzed an incident cohort of ESRD patients of Renmin Hospital of Wuhan University, China and Southwest Hospital, Third Military Medical University, China from February 2008 to January 2018. Incident patients who were on maintenance hemodialysis for at least 3 months were included in the study cohort. Patients included in the study were diagnosed with ESRD if they suffer an irreversible decline in glomerular filtration rate for more than 3 months as calculated by Cockcroft-Gault renal function estimating formula [9]. Moreover, patients who had underlying kidney disease diagnosed on the basis of clinical and laboratory parameters, such as the volume of daily diuresis less than 250 mL, were also included in the study. In total, 37 children (age <18 years) and 150 adults (age ≥18 years) were included in the analysis.

Exclusion criteria

Participants were not considered eligible for enrollment if they suffered from acute renal failure, were transferred from any other modality of renal replacement therapy to hemodialysis or if they died or ceased hemodialysis (for any reason) before 3 months. Patients who ever received nocturnal

hemodialysis, home hemodialysis, or peritoneal dialysis during follow-up were excluded from the analysis. Patients who were transferred to the other dialysis center during the 10-year study period were also excluded from the analysis because the data collected from the other dialysis centers were difficult to obtain and did not provide complete information related to the study hypothesis.

Methods of data collection

An anonymized database was established with the intent of prospective data collection of all the patients included in the study cohort from DICOM (Digital Imaging and Communications in Medicine) files of patients. Briefly, the database captured demographic variables such as age, gender, diabetic status, comorbidities, date of initiation of dialysis as well as hematological and biochemical variables and status during follow-up (i.e., survived or died). Patients were censored if they died during the follow-up period or were lost to follow-up due to change of dialysis modality (transplantation, conversion to peritoneal dialysis) or other reasons.

Details of hemodialysis

All patients were dialyzed using standard bicarbonate hemodialysis for 4 hours twice- or thrice-weekly. Polyethylene glycol substituted cellulose delivered dialysis dose was measured by spKt/V with maximum dialysis dose of 1.6 spKt/V and a minimum targeted dose of ≥ 1.2 spKt/V. According to the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines, dialysis dose > 1.2 spKt/V is considered as the minimum dialysis dose [10]. Therefore, a cutoff value of 1.2 spKt/V of dialysis dose was used for hemodialysis to study the effect of dialysis dose in relation to survival. Dialysate flow rate was controlled at 500 mL/min while blood flow rate was targeted according to individual patient requirements.

Statistical analysis

Mean \pm standard deviation and number (percentages) were used for initial summarization of data. Continuous variables were analyzed using independent *t*-test, while categorical variables were studied using chi square or Fisher exact test [11]. Univariate and multivariate logistic regression analysis was performed to identify independent factors that had an impact on mortality [12]. Results of the study were pooled if clinical heterogeneity of patient outcomes, interventions, and populations was minimal [6]. As the primary endpoint of analysis was death, Kaplan-Meier and Cox-proportional hazard model were used for calculation of survival over time [12]. A confidence interval of 95% ($P < 0.05$) was considered statistically significant. SPSS Statistics (IBM Inc., USA) was used for statistical analysis. Intention-to-treat analysis method was performed.

Results

Eight hundred and two patients receiving maintenance hemodialysis for a minimum of 3 months from February 2008 to January 2018 were recruited for the current study. Out of these patients, 183 patients met inclusion criteria and were included in the study. STROBE flow chart of a multicentric cohort study is reported in Figure 1.

The demographic and clinical characteristics of the study population are summarized in Table 1. The majority of the study population were male (58%); the mean age was 51.3 ± 13.5 years. Seventy-one patients (39%) were diabetics.

The details of the underlying kidney diseases among the study patients is shown in Figure 2. Among the underlying kidney diseases, diabetic nephropathy was the most common (41.7%) while lupus nephritis was the least common (2%) cause of kidney disease.

Overall, the 10-year survival rate in the study group was 27%. Survival of the whole cohort by Kaplan-Meier analysis showed patient survival as 94% at one year, 59% at 5 years and 27% at 10 years. The hemodialysis characteristics and laboratory values of patients are shown in Table 2. Nearly 69% of patients were on a twice-weekly hemodialysis schedule while the remaining 31% were hemodialyzed thrice weekly. At baseline, 3%, 87%, and 10% of patients were dialyzed using a central permanent catheter, arteriovenous fistulae (AVFs), or arteriovenous grafts (AVGs) respectively. All the variables associated with mortality were assessed by cross-tabulation.

Among laboratory values, there was a significant difference in the mean values of survivors and non-survivors with respect to hemoglobin, serum albumin, calcium, potassium, phosphorous, and CPP (calcium phosphorous product). Hemodialysis frequency and dose were the only characteristics that showed significant differences in both groups. All the statistically significant variables (significant phi and Cramer's V coefficient) were then subjected to univariate analysis. Significant variables ($P < 0.1$) in univariate analysis were further subjected to multivariate analysis (Table 3).

The variables that showed significant *P* value (< 0.05) in multivariate analysis were then finally subjected to Cox regression proportional hazard model (Table 4). Among the variables included for assessing survival functions using the Cox model, serum albumin delivered dialysis dose and frequency of hemodialysis were found to be statistically significantly affecting survival. Patients with serum albumin level of > 4 g/dL were better associated with survival (HR 1.17, $P = 0.001$). Similarly, those who underwent twice-weekly hemodialysis had 4.26 times less chance of survival as compared to patients with

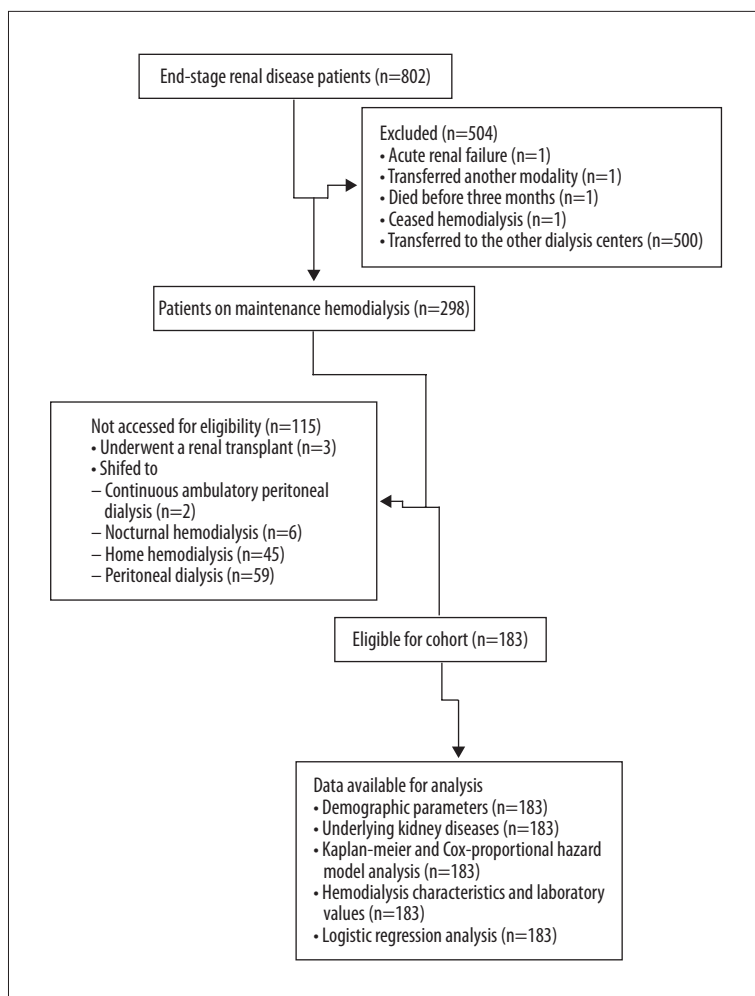


Figure 1. STROBE flow chart of a multicentric cohort study. Intention-to-treat analysis.

thrice-weekly hemodialysis ($P=0.043$). Lastly, a higher dialysis dose of >1.2 spKt/V offered better survival as compared to a lower dose of <1.2 spKt/V ($P=2.03$).

The most common cause of overall mortality was observed to be sepsis (39%) followed by ischemic heart disease (Figure 3).

Discussion

The current study reports on the prospective long-term follow-up of a large cohort of incident hemodialysis patients in a hemodialysis centers in Renmin Hospital of Wuhan University, China and Southwest Hospital, Third Military Medical University, China. The main findings of the study were that at the end of 10-years follow-up, 133 out of 183 patients died with an estimated mortality rate of 72.7%. The overall mortality rate reported in the study was considerably higher but compared favorably with the United States renal data system (USRDS) [13]. Another reason for overall high mortality in our study was the long follow-up period in the study. To the best of our knowledge, there

have been few studies conducted where the study examined the effect of dialysis efficiency in an incident cohort of hemodialysis patients with long-term follow-up [14–16]. The overall 10-year mortality rate in available studies was 75% [16] that coincides with the mortality rate reported in our analysis. The analysis of our study data showed that serum albumin level, hemodialysis frequency, and hemodialysis dose as measured by spKt/V were independently associated with increased survival.

In our study there was no significant differences in the delivered dialysis dose between males and females. Although in the univariate analysis, females had a greater risk of death with an odds ratio of 2.88, however, in the multivariate analysis this difference was insignificant. Similar findings were seen in a study in which females are found to have a greater risk of death [17] with an adjusted risk odds ratio of 3.9, and this difference remained significant in a multivariate analysis [18]. This is in contrast with findings that demonstrated no significant difference for survival between dialyzing women and men [19,20]. The results of our observational study revealed discrimination in the dialysis of men and women.

Table 1. Demographic profile of study participants.

Characteristics	Variables	Overall patients (n = 183)
Age (years, mean ±SD)		51.37±13.5
Gender	Male	106 (58)
	Female	77 (42)
Anthropometric characteristics (mean ±SD)	Weight (kg)	67.3±9.6
	Height (cm)	159.45±17.5
	BMI (kg/m ²)	24.2±2.7
Marital status	Married	161 (88)
	Single	22 (12)
Race	Chinese	164 (90)
	Indians	11 (6)
	Others	8 (4)
Smoking status	Current smoker	124 (68)
	Ex-smoker	13 (7)
	Non-smoker	46 (25)
Employment status	Employed	142 (78)
	Unemployed	20 (11)
	Student	7 (4)
	House wife	14 (7)
Blood pressure (mean ±SD)	Systolic blood pressure (mmHg)	142.12±17.31
	Diastolic blood pressure (mmHg)	86±11.32
Co-morbidities	Diabetes	71 (39)
	Hypertension	53 (29)
	Ischemic heart disease	60 (33)
	Peripheral vascular disease	40 (22)
	Cerebrovascular accident	18 (10)
	Myocardial infarction	20 (11)
	Chronic obstructive pulmonary disease	11 (6)
	Hypothyroidism	5 (3)
	Hyperlipidemia	15 (8)
	Hepatitis B	5 (3)
	Hepatitis C	11 (6)
Pericarditis	7 (4)	
	Cardiac arrhythmia	13 (7)

Categorical data were represented as a number (percentage), continuous data were represented as mean ±SD.

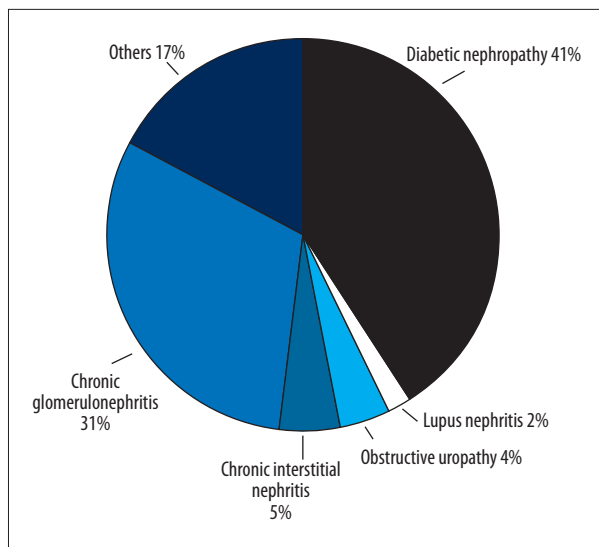


Figure 2. Underlying kidney disease among study participants.

According to one dialysis study, an inadequate hemodialysis dose was associated with mortality and treatment failure [21]. Similarly, our study showed increasing hemodialysis dose >1.2 spKt/V resulted in better survival regardless of age and gender. These findings were contrary to the findings of the HEMO study, which is the largest trial of hemodialysis patients. Results of the HEMO trial showed that increasing dialysis dose did not improve clinical outcome in hemodialysis patients but rather it increased the relative risk of death especially with higher dose i.e., >1.6 spKt/V. These differences in study results can be explained by different study population, methodological differences, and longer follow-up time (3 years versus 10 years). Furthermore, it is worth noting that the HEMO study excluded patients with low serum albumin while the study did not exclude such patients specifically [22].

A crossover pilot trial reported that frequent hemodialysis improved blood pressure control, but also time and financial

Table 2. Laboratory values and hemodialysis characteristics.

Measures		Overall n=183	Death n=133	Survived n=50	*p-Value	
Laboratory values (mean ±SD)	Serum albumin (g/dl)	3.8±1.8	3.2±1.1	3.7±2.3	0.021	
	Cholesterol (mg/dl)	173.2±4.2	162.1±7.6	169.2±3.4	0.634	
	BUN (mg/dl)	Pre-dialysis	69.3±8.1	71.7±4.2	64.5±3.3	0.071
		Post dialysis	37.2±4.8	44.3±2.3	33.6±1.8	0.101
	Bilirubin (mg/dl)	0.48±0.07	0.59±0.5	0.51±0.08	0.092	
	Hemoglobin (g/dl)	9.2±3.4	8.7±2.2	9.7±1.7	0.012	
	Serum Calcium (mg/dl)	9.1±4.2	10.8±2.8	9.3±1.1	0.046	
	Serum Potassium (mEq/L)	5.1±2.1	4.8±2.6	5.8±1.7	0.028	
	Serum Phosphorous (g/dl)	4.9±1.7	4.4±2.1	5.1±1.6	0.041	
	CPP (mg ² /dl ²)	42±17	46.3±6.2	42.4±4.1	0.038	
Hemodialysis characteristics	Hemodialysis frequency	twice	126 (69)	102 (77)	24 (48)	0.089
		thrice	57 (31)	31 (23)	26 (52)	
	Dialysis dose (spKt/V)	1.26±1.1	0.88±0.25	1.72±0.24	0.003	
	Blood flow rate (mL/min)	219.5±10.1	221.5±12.6	217.6±29.4	0.578	
	Dialysate flow rate (mL/min)	500	500	500	>0.99	
	Interdialytic weight gain (kg)	2.32±0.98	2.52±0.94	2.12±1.03	0.245	
	Vascular access	AVF	159 (87)	116 (87)	43 (86)	0.99
		AVG	19 (10)	13 (10)	6 (12)	0.654
Permanent catheter		5 (3)	4 (3)	1 (2)	0.845	

BUN – blood urea nitrogen; CPP – calcium phosphorous product; AVF – arteriovenous fistula; AVG – arteriovenous graft. Categorical data were represented as a number (percentage), continuous data were represented as mean ±SD. * Chi-Square test for categorical data, independent student t-test for continuous data Association.

Table 3. Logistic regression analysis for prediction of factors affecting mortality.

Variables	Univariate analysis			Multivariate analysis		
	p-Value*	OR	95% CI for OR	p-Value*	OR	95% CI for OR
Age (years)	0.071	1.1	0.9–1.35	0.456	1.4	1.12–2.04
Female gender	0.032	2.88	1.02–13.15	0.025	4.23	2.56–8.96
BMI (<20 kg/m ²)	0.312	1.78	0.45–5.16	–	–	–
Hemoglobin (<11.5 g/dl)	0.043	1.74	0.13–25.02	0.723	1.96	1.23–5.67
Serum K (<4 mEq/L)	0.093	1.33	1.02–7.96	0.041	7.45	2.14–45.46
Serum K (>5.5 mEq/L)	0.541	1.81	0.56–7.12	–	–	–
Serum P (<5 mg/dl)	0.0621	1.39	0.43–8.12	0.712	0.41	0.045–11.56
Serum P (>5 mg/dl)	0.827	0.64	0.21–3.12	–	–	–
Serum calcium (<8 mg/dl)	0.061	0.87	1.01–2.56	0.412	3.22	0.78–8.95
Serum calcium (>9.6 mg/dl)	0.201	1.24	0.25–5.63	–	–	–
CPP (mg ² /dl ²) (<45)	0.054	1.72	0.32–8.65	0.601	0.72	0.05–4.67
CPP (mg ² /dl ²) (>55)	0.671	0.77	0.15–4.14	–	–	–
Serum albumin (<4 g/dl)	0.031	2.01	0.12–17.6	0.051	7.34	2.67–24.56
IHD	0.041	1.67	1.12–8.92	0.416	2.11	1.55–9.78
Diabetes mellitus (Fasting plasma glucose level ≥7.0 mmol/l (126 mg/dl))	0.048	1.34	0.94–1.43	0.456	0.95	0.05–3.21
Hyperlipidemia (LDL >130 mg/dL)	0.172	0.78	0.15–3.48	–	–	–
Hypertension (≥140 mmHg systolic, ≥90 mmHg diastolic BP)	0.231	1.10	1.04–7.8	–	–	–
Peripheral vascular disease	0.412	0.67	0.34–5.34	–	–	–
Dialysis dose (<1.2 spKt/V)	0.022	1.4	0.21–5.32	0.051	4.43	2.78–16.34
Dialysis dose (>1.2 spKt/V)	0.318	0.1	0.03–1.65	–	–	–
Twice weekly HD	0.031	2.21	0.56–7.12	0.031	0.45	0.16–2.98
Nephropathy	0.09	1.11	0.9–1.25	0.52	1.5	1.11–2.13
Nephritis	0.098	1.12	0.9–1.26	0.61	1.6	1.11–2.12
Uropathy	0.097	1.13	0.9–1.27	0.63	1.7	1.11–2.11

HD – hemodialysis; P – phosphorous; BMI – body mass index; IHD – ischemic heart disease; CPP – calcium phosphate product; CI – confidence of interval; BP – blood pressure.

burden [23]. Similar results were seen in our study, where patients who were on twice-weekly hemodialysis sessions were significantly associated with mortality ($P=0.03$, OR 0.45). With respect to the results of hemodialysis characteristics, the trial revealed that more frequent hemodialysis improved overall survival.

Malnutrition is another well-known risk factor for adverse outcomes and mortality in hemodialysis patients. Studies have

demonstrated an increased mortality with hypoalbuminemia [18,24,25]. A plasma albumin concentration of less than 4 g/dl is independently associated with mortality. Our study also revealed similar results, that patients with lower albumin level <4 g/dl had statistically significant increased mortality. Since hypoalbuminemia is associated with malnutrition, effective strategies to prevent malnutrition and infectious complications may ultimately increase survival outcomes in hemodialysis patients.

Table 4. Assessment of survival predictors by using Cox regression proportional hazard function.

Risk factors	p-Value	Exp (B) or Hazard ratio (HR)
Female gender (1)	0.261	0.72
Serum K	0.334	0.45
Serum albumin (>4 g/dl)	0.001	1.17
Dialysis dose (spKt/V >1.2)	0.01	2.03
Twice weekly HD	0.043	4.26

p<0.05 were considered significant.

The majority of deaths in our study were due to sepsis followed by ischemic heart disease leading to 67.5% of total deaths. These findings are consistent with the findings of the United States Renal Data System (USRDS) [13]. Out of 67.5% of reported deaths, 38% of the deaths were due to sepsis alone, the majority of which were vascular access related infections. Withdrawal from dialysis is another important cause of mortality among hemodialysis patients. In our study, 4% of deaths were due to withdrawal from dialysis, which was less than rates reported by USRDS in which withdrawal from dialysis was the third most common cause of death [13]. Our study showed that neither the type of kidney disease nor the comorbid diseases affected survival. This was in agreement with another reported study [18].

There were several limitations to our study. For example, the study failed to evaluate the effect of blood urea nitrogen on ischemic heart disease. The long time required for the study may have introduced patient variabilities. The study was most reliable with regards to the DICOM data for patients; at the time of drafting and editing the report, several patients died or were transferred to the other care center.

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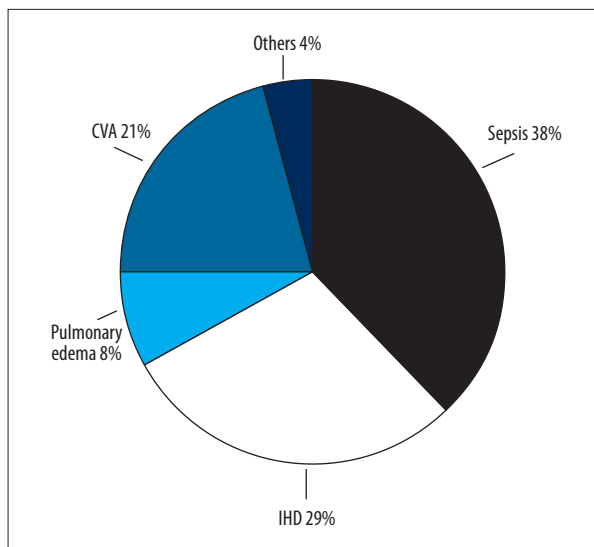


Figure 3. Causes of overall mortality in among study participants.

Conclusions

The current study attempted to rule out factors that affect mortality and survival outcomes in hemodialysis patients. The study indicated that hypoalbuminemia, hemodialysis time, and frequency were significantly associated with mortality. The dialysis time and frequency are beneficial to patient survival. However, large randomized clinical trials are needed to confirm these findings in larger settings, as all hemodialysis patients are not able to tolerate enhanced dialysis delivery. The observational study suggests the potential clinic benefits for routine practice in dialysis center for the future.

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Conflict of interest

None.

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