Analysis of Factors Associated with Death in Maintenance Hemodialysis Patients: A Multicenter Study in China

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Abstract

Background: Patients on hemodialysis have a high-mortality risk. This study analyzed factors associated with death in patients on maintenance hemodialysis (MHD). While some studies used baseline data of MHD patients, this study used the most recent data obtained from patients just prior to either a primary endpoint or the end of the study period to find the characteristics of patients preceding death.
Methods: Participants were selected from 16 blood purification centers in China from January 2012 to December 2014. Patients' data were collected retrospectively. Based on survival status, the participants were divided into two groups: survival group and the death group. Logistic regression analysis was performed to determine factors associated with all-cause mortality.
Results: In total, 4104 patients (57.58% male, median age 59 years) were included. Compared with the survival group, the death group had more men and more patients with diabetic nephropathy (DN) and hypertensive nephropathy. The patients preceding death also had lower levels of diastolic blood pressure, hemoglobin, serum albumin, serum calcium, serum phosphate, Kt/V, and higher age. Multivariate analysis revealed that male sex (odd ratio [*OR*]: 1.437, 95% confidence interval [*CI*]: 1.094–1.886), age (*OR*: 1.046, 95% *CI*: 1.036–1.057), and presence of DN (*OR*: 1.837, 95% *CI*: 1.322–2.552) were the risk factors associated with mortality. High serum calcium (*OR*: 0.585, 95% *CI*: 0.346–0.989), hemoglobin (*OR*: 0.974, 95% *CI*: 0.967–0.981), albumin (*OR*: 0.939, 95% *CI*: 0.915–0.963) levels, and dialysis with noncuffed catheter (*OR*: 0.165, 95% *CI*: 0.070–0.386) were protective factors based on a multivariate analysis.
Conclusions: Hemodialysis patients preceding death had lower hemoglobin, albumin, and serum calcium levels. Multivariate analysis showed that male sex, age, DN, low hemoglobin, low albumin, and low serum calcium were associated with death in hemodialysis patients.

Key words: Hemodialysis; Mortality; Risk Factors

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Introduction

A survey in China showed that the number of patients with chronic kidney disease, which gradually leads to end-stage renal disease (ESRD), was approximately 119.5 million.[1] According to the Chinese National Renal Data System (CNRDS), the prevalence of hemodialysis was increasing in 2011–2015. On December 31, 2015, 385,000 hemodialysis cases in the Chinese mainland were reported.[2]

Patients on hemodialysis have higher mortality risks compared with the general population.[3,4] The United States Renal Data System (USRDS) reported that the mortality rate in 2013 of hemodialysis patients was 172/1000 patient-years.[3] Moreover, dialysis patients' risk for fatal hospitalization increased three-fold compared with that of the reference population.[4]

Identifying the factors associated with death in maintenance hemodialysis (MHD) patients is vital. Some studies used baseline data of MHD patients to analyze their survival; however, laboratory data characteristics were variable. Some studies report that hemodialysis patients who are expected to die have certain clinical and biochemical characteristics.[5-7] However, little is known on the state of dialysis patients preceding death, especially in our country. Hence, our study used the most recent data obtained from patients just prior to either a primary endpoint or the end of the study period. This study aimed to determine the characteristics of dying patients and the factors associated with death in MHD patients.

Methods

Study population

This study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital. Patients under MHD therapy in 16 blood purification centers from 12 provinces in China from January 2012 to December 2014 were selected. Inclusion criteria were as follows: age ≥20 years, receiving MHD therapy for at least 3 months, and with laboratory data, including blood pressure, Kt/V, hemoglobin, serum albumin, serum calcium, and serum phosphate.

Based on survival status, the participants were divided into two groups: the survival group (still alive on December 31, 2014) and the death group (died of any cause within the study period). Patients who were lost to follow-up for any reason began peritoneal dialysis, or received kidney transplant before December 31, 2014, were included in the survival group.

Data collection

Data, including sex, age, primary cause of ESRD, dialysis duration, death cause, type of vascular access, dialysis time every week, and laboratory results, were collected retrospectively. Information on the type of vascular access and laboratory results was obtained from the latest hemodialysis records before the primary study endpoints of patient death, lost to follow-up, or the end of the study period. All laboratory data were collected before dialysis.

The primary cause of ESRD was categorized as primary glomerulonephritis (PGN), diabetic nephropathy (DN), hypertensive nephropathy (HTN), and other/unknown. Death causes were classified as cardiovascular events, cerebrovascular events, infection, sudden death of unknown reason, bleeding, cancer, and other/unknown. Dialysis duration was defined as the number of months between their first renal replacement therapy and a primary endpoint or completion of the study. Types of vascular access were arteriovenous fistula (AVF), tunneled cuffed catheter (TCC), noncuffed catheter (NCC), arteriovenous graft, and other/unknown.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or median (interquartile range) for continuous variables according to their distribution and as percentages for categorical variables. Between-group comparison was performed using the Student's *t*-test or Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables.

Univariate analysis was performed for all variables. Variables that affected all-cause mortality ($P < 0.05$) in the univariate analysis were included in the multivariate logistic regression analysis model to determine factors associated with all-cause mortality. A $P < 0.05$ was considered statistically significant. All analyses were performed with Statistical Package for the Social Sciences software (Version 21.0, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Data from 4104 ESRD patients from 16 centers were obtained (57.58% male; age 59 [23] years), among whom 620 patients were dead. The study profile is shown in Figure 1. Table 1 shows that among the 4104 patients, patients with PGN were the most common (n = 1902, 46.35%), followed by those with DN (n = 788, 19.20%) and HTN (n = 460, 11.21%). The majority of the patients had AVF (n = 3259, 79.41%).

The most common cause of death was cardiovascular events (n = 235, 37.90%), followed by cerebrovascular events (n = 126, 20.32%), infection (n = 73, 11.77%), sudden death of unknown reason (n = 36, 5.81%), bleeding (n = 35, 5.65%), cancer (n = 17, 2.74%), and other/unknown (n = 98, 15.81%).

Comparison of two groups

The studied group was divided into two groups based on their outcome: the death group (n = 620) and

the survival group (n = 3484). Table 1 presents the characteristics and comparisons of the two groups. The death group had 61.90% males, while the survival group had 46.31% males (P = 0.013). The death group had a significantly higher median age than the survival group (68 [19] years vs. 58 [23] years). The median dialysis duration (35 [44] months vs. 34 [55] months) was not significantly different between the two groups.

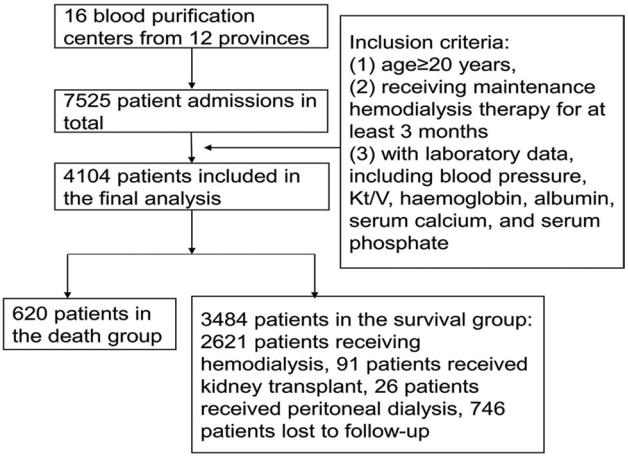

Figure 1: Flow chart of the study.

However, the death group had less patients with 3–12 months of dialysis duration (15.97% vs. 21.33%) but more patients with 25–60 months of dialysis duration (39.19% vs. 30.86%).

The percentage of patients with PGN as the primary cause of ESRD in the death group was lower than that in the survival group (31.13% vs. 49.05%, respectively), while the percentage of patients with DN (35.81% vs. 16.25%) or HTN (15.16% vs. 10.51%) was significantly higher in the death group.

Compared with the survival group, the death group had a lower diastolic blood pressure, hemoglobin, serum albumin, serum calcium, serum phosphate, and Kt/V.

Factors associated with all-cause mortality

Univariate analysis identified several factors associated with mortality, including sex, age, cause of ESRD, type of vascular access, dialysis time every week, diastolic blood pressure, hemoglobin, serum albumin, serum calcium, serum phosphate, and Kt/V [Table 2]. Subsequently, two multivariate analysis models were built: one model consisted of all significant factors in the univariate analysis, while the other excluded laboratory examination. In the nonlaboratory examination model, sex,

Table 1: Characteristics of the studied cohort and comparison of the two groups

Characteristics	All (n = 4104)	Death group (n = 620)	Survival group (n = 3484)	P
Male	2363 (57.58)	385 (61.90)	1978 (46.31)	0.013
Age (years)	59 (23)	68 (19)	58 (23)	<0.001
Dialysis duration (months)	34 (54)	35 (44)	34 (55)	0.934
3–12	842 (20.52)	99 (15.97)	743 (21.33)	<0.001
13–24	727 (17.71)	122 (19.68)	605 (17.37)	
25–60	1318 (32.12)	243 (39.19)	1075 (30.86)	
61–120	862 (21.00)	122 (19.68)	740 (21.24)	
≥121	355 (8.65)	34 (5.48)	321 (9.21)	
Cause of ESRD				
PGN	1902 (46.35)	193 (31.13)	1709 (49.05)	<0.001
DN	788 (19.20)	222 (35.81)	566 (16.25)	
HTN	460 (11.21)	94 (15.16)	366 (10.51)	
Other/unknown	954 (23.25)	111 (17.90)	843 (24.20)	
Type of vascular access				
AVF	3259 (79.41)	492 (79.35)	2767 (79.42)	<0.001
TCC	345 (8.41)	98 (15.81)	247 (7.09)	
NCC	338 (8.24)	18 (2.9)	320 (9.18)	
AVG	26 (0.63)	5 (0.81)	21 (0.60)	
Other/unknown	136 (3.31)	7 (1.13)	129 (3.70)	
Dialysis time every week (h)	12 (2)	12 (4)	11 (2)	0.744
Systolic blood pressure (mm Hg)	145 (20)	145 (30)	145 (19)	0.572
Diastolic blood pressure (mm Hg)	81 (14)	80 (19)	81 (13)	<0.001
Hemoglobin (g/L)	107 (22)	103 (25)	108 (21)	<0.001
Serum albumin (g/L)	38.8 (6.9)	36.3 (8.7)	39.3 (6.2)	<0.001
Serum calcium (mmol/L)	2.23 (0.25)	2.18 (0.30)	2.23 (0.24)	<0.001
Serum phosphate (mmol/L)	1.83 (0.60)	1.70 (0.76)	1.83 (0.57)	<0.001
Kt/V	1.32 (0.33)	1.30 (0.33)	1.33 (0.33)	0.001

Values are presented as median (IQR) or n (%). PGN: Primary glomerulonephritis; DN: Diabetic nephropathy; HTN: Hypertensive nephropathy; AVF: Arteriovenous fistula; TCC: Tunnelled cuffed catheter; NCC: Noncuffed catheter; AVG: Arteriovenous graft; ESRD: End-stage renal disease; IQR: Interquartile range.

Table 2: Univariate analysis of factors associated with all-cause mortality (n = 4104)

Variables	*OR* (95% *CI*)	*P*
Male	1.247 (1.047–1.487)	0.014
Age (per 1 year increase)	1.045 (1.039–1.052)	<0.001
Dialysis duration (3–12 months as referent)		
3–12		<0.001
13–24	1.513 (1.137–2.015)	0.005
25–60	1.696 (1.319–2.182)	<0.001
61–120	1.237 (0.931–1.644)	0.142
≥121	0.795 (0.527–1.199)	0.274
Cause of ESRD (PGN as referent)		
PGN		<0.001
DN	3.473 (2.801–4.306)	<0.001
HTN	2.274 (1.734–2.983)	<0.001
Other/unknown	1.166 (0.910–1.494)	0.224
Type of vascular access (AVF as referent)		
AVF		<0.001
TCC	2.231 (1.733–2.873)	<0.001
NCC	0.316 (0.195–0.513)	<0.001
AVG	1.339 (0.503–3.568)	0.559
Other/unknown	0.305 (0.142–0.657)	0.002
Dialysis time every week	0.953 (0.912–0.996)	0.033
Systolic blood pressure	0.998 (0.993–1.002)	0.300
Diastolic blood pressure	0.985 (0.978–0.991)	<0.001
Hemoglobin	0.980 (0.976–0.985)	<0.001
Serum albumin	0.919 (0.903–0.935)	<0.001
Serum calcium	0.314 (0.221–0.447)	<0.001
Serum phosphate	0.644 (0.549–0.755)	<0.001
Kt/V	0.631 (0.469–0.849)	0.002

PGN: Primary glomerulonephritis; DN: Diabetic nephropathy; HTN: Hypertensive nephropathy; AVF: Arteriovenous fistula; TCC: Tunnelled cuffed catheter; NCC: Noncuffed catheter; AVG: Arteriovenous graft; ESRD: End-stage renal disease; *OR*: Odds ratio; *CI*: Confidence interval.

age, dialysis duration, cause of ESRD, type of vascular access, and dialysis time every week were included. The multivariate logistic regression analysis results are shown in Table 3. Male sex (odd ratio [*OR*] 1.302; 95% confidence interval [*CI*]: 1.080–1.571), age (*OR* 1.042; 95% *CI*: 1.035–1.049), DN (*OR* 2.472; 95% *CI*: 1.969–3.105), HTN (*OR* 1.629; 95% *CI*: 1.224–2.169), and dialysis with TCC (*OR* 1.640; 95% *CI*: 1.244–2.161) were independent risk factors for mortality. Dialysis with NCC (*OR* 0.320; 95% *CI*: 0.192–0.532) seemed to be associated with better outcome.

Table 4 shows the multivariate analyses of factors associated with all-cause mortality adjusted for laboratory examination. These results show that, after adjustment for laboratory variables, male sex, age, and DN were still significantly associated with higher mortality, while dialysis with NCC was associated with lower mortality. Moreover, we observed that high hemoglobin (*OR* 0.974; 95% *CI*: 0.967–0.981), serum albumin (*OR* 0.939; 95% *CI*: 0.915–0.963), and serum calcium (*OR* 0.585; 95% *CI*: 0.346–0.989) levels were protective factors associated with mortality.

Discussion

There exists abundant literature on the risk factors for death in MHD patients, which are based on the baseline data obtained from those patients. However, little is known about the clinical and laboratory parameters associated with the status of MHD patients preceding death, especially in our country. In this study, we used the latest records, i.e., before patient outcome identification or end of the study period, to find the characteristics and factors associated with death in MHD patients. The results showed that the death group had more men and more patients with DN and HTN. Moreover, patients in the group also had higher age and lower levels of diastolic blood pressure, hemoglobin, albumin, serum calcium, serum phosphate, and kt/v compared with survival group. Multivariate analysis showed that male sex, age, DN, and low hemoglobin, albumin, and serum calcium levels were associated with death in hemodialysis patients.

The logistic regression analysis showed that lower hemoglobin and serum albumin were associated with death. The low levels of albumin and hemoglobin might be the result of both inflammatory and nutritional components.[8] Nevertheless, they could also lead to undesirable outcomes. Low hemoglobin level and erythropoiesis-stimulating agents could lead to cardiovascular events, fatigue, and even mortality,[9-12] while low serum albumin level in dialysis patients was also known to be associated with malnutrition, inflammation, and all-cause and cardiovascular mortality.[13-17] The result was partly in accordance with the studies that have reported that MHD patients experienced a decrease in serum albumin level in their final stages of life.[5,6]

Numerous reports have demonstrated that a high level of serum calcium and phosphate could cause vascular calcification and even mortality.[18-20] However, our data showed that serum calcium and phosphate levels of patients in the death group were significantly lower than those of patients in the survival group. Moreover, the logistic regression analysis revealed that lower serum calcium was associated with death. Low serum calcium level could be associated with the hypoalbuminemic status, which might partly explain the results in our study. K/DOQI and KDIGO guidelines state that, because serum calcium is partly bound to serum albumin, total serum calcium decreases 0.8 mg/dl (0.2 mmol/L) for every 1 g decrease in serum albumin below 4 g/dl (40 g/L).[21,22] Furthermore, the time before death course is frequently characterized by a loss of regulatory functions in numerous subsystems of dialysis patients; hence, their system cannot react properly to perturbations.[7] We also speculate that the poor diet of patients in their final stages of life might be a cause of the low serum levels of calcium and phosphate. However, we could only provide the results and suggest

Table 3: Multivariate analyses of factors associated with all-cause mortality unadjusted for laboratory examination (n = 4104)

Variables	*OR* (95% *CI*)	*P*
Male	1.302 (1.080–1.571)	0.006
Age (per 1 year increase)	1.042 (1.035–1.049)	<0.001
Dialysis duration (3–12 months as referent)		
3–12		0.011
13–24	1.221 (0.898–1.660)	0.202
25–60	1.257 (0.956–1.653)	0.102
61–120	0.915 (0.672–1.247)	0.575
≥121	0.718 (0.464–1.111)	0.137
Cause of ESRD (PGN as referent)		
PGN		<0.001
DN	2.472 (1.969–3.105)	<0.001
HTN	1.629 (1.224–2.169)	0.001
Other/unknown	0.959 (0.741–1.242)	0.752
Type of vascular access (AVF as referent)		
AVF		<0.001
TCC	1.640 (1.244–2.161)	<0.001
NCC	0.320 (0.192–0.532)	<0.001
AVG	1.118 (0.394–3.172)	0.834
Other/unknown	0.299 (0.136–0.657)	0.003
Dialysis time every week	0.959 (0.915–1.004)	0.075

PGN: Primary glomerulonephritis; DN: Diabetic nephropathy; HTN: Hypertensive nephropathy; AVF: Arteriovenous fistula; TCC: Tunnelled cuffed catheter; NCC: Noncuffed catheter; AVG: Arteriovenous graft; ESRD: End-stage renal disease; *OR*: Odds ratio; *CI*: Confidence interval.

the phenomena without being able to reason them. Further deep studies are needed to explain these mechanisms and their interactions.

In our study, male was an independent risk factor for mortality, and this study showed that more men than women were undergoing hemodialysis treatment, which is consistent with our national hemodialysis registry data and the USRDS.[2,3] In our results, male sex was associated with a 1.437 times risk of death, which is also seen in other studies.[23,24] The reason remains unclear and currently a topic of research. Furthermore, the Dialysis Outcomes and Practice Patterns Study (DOPPS) analyzed 206,374 patients receiving hemodialysis in 12 countries and found that the survival advantage of women over men in the general population was markedly diminished in hemodialysis patients.[23] The DOPPS study also found that the male-to-female mortality rate ratio in the general population varied from 1.5 to 2.6 for age groups under 75 years, while that in hemodialysis patients was close to 1.[23] In the general population, women have longer life expectancy than men, which could be related to a lower prevalence of cardiovascular risk factors and events in women.[25-27] In hemodialysis patients, men were younger, were less frequently obese, received kidney transplant more frequently, and were less frequently depressed.[23] These factors may partly explain the survival advantage of females in the general population and the lack of that survival advantage in females requiring hemodialysis.

According to the CNRDS, glomerulonephritis (54.2%) was the most frequent disease among Chinese hemodialysis patients in 2015, followed by DN (17.0%) and HTN (9.9%).[2] In our study, the leading cause of ESRD in the survival group was similar to that in the Annual Data Report of CNRDS. However, in the death group, DN (n = 222, 35.81%) accounted for a larger proportion of deaths compared with GN (n = 193, 31.13%). The death group also had a higher proportion of HTN patients than that in the report of CNRDS. Logistic regression analysis also showed that the risks of death in patients with DN or HTN were 2.472 times and 1.629 times higher, respectively, than those of patients with PGN before adjusting for laboratory examination. After adjusting for laboratory examination, DN remained risk factors for death. As reported, the incidence of hypertension, coronary heart disease, and cerebral thrombus in DN patients is higher than those in non-DN patients.[28] The absolute cardiovascular disease (CVD) risk in diabetic patients is two-fold greater than that in persons without diabetes.[29] Conditions associated with diabetes mellitus type 2, such as insulin resistance, hyperinsulinemia, and hyperglycemia, may lead to inflammation, dyslipidemia, endothelial dysfunction, and oxidative stress, which could predispose patients to atherosclerosis and CVD.[30-32]

Our results also showed that NCC was apparently a protective factor in dialysis patients. Patients often used catheters when they initiated hemodialysis; thus, the percentage of NCC use was higher at 3–12 months than at 1 year after dialysis initiation.[2,3] In our study, compared with the death group, more patients in the survival group had a dialysis duration of 3–12 months. Therefore, we hypothesize that this may explain the apparent advantage of NCC.

In this study, we used logistic regression rather than the Cox's proportional hazard model. We began the follow-up on January 1, 2012, rather than the time when patients began their first hemodialysis. The survival time in this study should be calculated from the study entry date (January 1, 2012) to the date of death, lost to follow-up, or the end of the study (December 31, 2014). However, patients who started dialysis before the entry date had survived for a period of time, which should be included in their real survival time. Those might affect the Cox's proportional hazard model analysis to some extent. Thus, we choose the logistic regression to avoid some bias.

This study has some limitations. First, the laboratory data were obtained from the latest records before patient outcome identification. We revealed the characteristics of dying MHD patients. However, patients before death were usually accompanied by complex illness states. We did not study the dynamic changes in these parameters of MHD patients. Thus, longitudinal studies are necessary in the future. Second, there were no lipid profile, uric acid, and body mass

Table 4: Multivariate analyses of factors associated with all-cause mortality adjusted for laboratory examination (n = 4104)

Variables	*OR* (95% *CI*)	*P*
Male	1.437 (1.094–1.886)	0.009
Age (per 1 year increase)	1.046 (1.036–1.057)	<0.001
Dialysis duration (3–12 months as referent)		
3–12		0.599
13–24	1.260 (0.802–1.978)	0.316
25–60	1.398 (0.926–2.108)	0.111
61–120	1.248 (0.785–1.984)	0.349
≥121	1.141 (0.609–2.139)	0.680
Cause of ESRD (PGN as referent)		
PGN		0.001
DN	1.837 (1.322–2.552)	<0.001
HTN	1.522 (0.996–2.325)	0.052
Other/unknown	0.977 (0.689–1.385)	0.896
Type of vascular access (AVF as referent)		
AVF		<0.001
TCC	1.398 (0.933–2.094)	0.104
NCC	0.165 (0.070–0.386)	<0.001
AVG	1.537 (0.340–6.594)	0.577
Other/unknown	1.057 (0.292–3.818)	0.933
Dialysis time every week	0.987 (0.927–1.050)	0.676
Diastolic blood pressure	1.005 (0.995–1.015)	0.333
Hemoglobin	0.974 (0.967–0.981)	<0.001
Serum albumin	0.939 (0.915–0.963)	<0.001
Serum calcium	0.585 (0.346–0.989)	0.045
Serum phosphate	0.902 (0.729–1.117)	0.345
Kt/V	0.800 (0.536–1.194)	0.275

PGN: Primary glomerulonephritis; DN: Diabetic nephropathy; HTN: Hypertensive nephropathy; AVF: Arteriovenous fistula; TCC: Tunnelled cuffed catheter; NCC: Noncuffed catheter; AVG: Arteriovenous graft; *OR*: Odds ratio; *CI*: Confidence interval.

index (BMI) data in the analysis, which might be associated with death in MHD patients. Considering that not all the patients underwent the lipid profile or uric acid examination in this study, we did not include these factors into analysis. Moreover, some hospitals did not record patients' height or BMI in the hemodialysis record. We, therefore, thought that the BMI data might not be accurate enough and did not include it. Third, as the data were collected retrospectively, information bias to some extent existed. Finally, the centers in our study were from top-level hospitals. Medical resources possibly differ in middle- or lower-grade hospitals. Hence, our data do not reflect the overall MHD patients' status in our country.

In conclusion, this study revealed the characteristics of MHD patients prior to death and the factors associated with death in MHD patients. Hemodialysis patients preceding death had lower hemoglobin, albumin, and serum calcium levels but higher age. Multivariate analysis showed that male sex, age, DN, low hemoglobin, albumin, and serum calcium levels were associated with death in hemodialysis patients.

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Conflicts of interest

There are no conflicts of interest.

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