

Risk factors for mortality at beginning of maintenance hemodialysis

Shao-Bin Yu¹, Huai-Hong Yuan², Stephen Salerno³, Shen-Ju Gou¹, Wen-Wen Chen¹, Hong-Liu Yang¹, Yi Li³, Ping Fu¹

¹Kidney Research Institute, Division of Nephrology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China;

²Department of Nephrology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China;

³Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA.

Hemodialysis (HD) is a crucial renal replacement therapy for patients with end-stage renal disease. Despite improvements in dialysis technology, mortality for maintenance HD (MHD) patients remains high. To improve the quality of life among MHD patients, it is necessary to examine the risk factors associated with mortality. In this study, we retrospectively analyzed patients' conditions at the beginning of dialysis and assessed the risk factors for mortality in MHD patients treated at the Center for Hemodialysis in West China Hospital, Sichuan University, China. The aim of this study was to identify significant risk factors to guide the treatment of MHD patients and targeted early preventions to improve prognosis.

This was a single-center, retrospective study at the HD center between July 2013 and July 2018. The protocol was approved by the Medical Ethics Committee of the West China Hospital, Sichuan University. Patients were eligible for inclusion if (1) they underwent regular HD at the center for more than 3 months; (2) the applied treatment plan included HD with a standard bicarbonate dialysate formulation (three sessions a week, 4 h each session); and (3) enoxaparin calcium was provided to the patient as an anti-coagulant at a dose of 60 to 80 IU/kg. Patients were excluded from the study if they (1) were less than 18 years old; (2) received simultaneous peritoneal dialysis with HD; (3) had missing medical data; or (4) had a heart valve disease or a myocardial infarction. Baseline data, including demographic data, primary diseases, complications, and laboratory tests, were collected when a patient started HD. All patients were followed up until death, withdrawal from HD, transfer to another dialysis center, or the end of the study (April 2019).

Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated as the mean \pm standard deviation for continu-

ous variables and frequencies (percentages) for categorical variables. Univariate models were first fit to explore the unadjusted relationships between mortality and each of the predictors. These associations were then compared to models that adjusted for age. The survival of patients with different pneumonia statuses was compared via Kaplan-Meier curves. The log-rank test was performed to determine whether survival differed significantly between MHD patients with and without pneumonia. A multivariate Cox model was then fit on all the predictors to assess the adjusted associations of these predictors with mortality. Potential risk factors for MHD patient hospitalization were then examined using multivariate stepwise logistic regression. Hospitalization was defined as 1 if the patient was hospitalized and 0 if not.

A total of 311 eligible patients were included, 33 (11%) of whom died across the duration of the study. Baseline characteristics for the patients are given in Supplementary Table 1, <http://links.lww.com/CM9/A187>. As shown in the table, males accounted for 57% of the study sample. The mean age was 53 years, with 77% of patients using an arteriovenous fistula as their vascular access point, 75% of patients having diabetes, and 15% of patients having pneumonia. The average duration of dialysis was 43 months. The average hemoglobin level was 90.042 ± 20.989 g/L, urea was 24.360 ± 11.457 mmol/L, cholesterol was 3.886 ± 1.060 mmol/L, and albumin was 39.440 ± 6.082 g/L.

Among the 33 MHD patients who died, cardiovascular disease (CVD) was the primary cause of death (18 cases, 55%), followed by pneumonia (five cases, 15%). Multiple organ failure and gastrointestinal bleeding each accounted for four deaths (12%), and two patients (6%) died of tumor-related complications.

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Shao-Bin Yu and Huai-Hong Yuan contributed equally to the work.

Correspondence to: Dr. Fu Ping, Kidney Research Institute, Division of Nephrology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: fupinghx@163.com

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Table 1: Unadjusted HR, aHR, and 95% CI from Cox proportional hazards models on 311 MHD patients.

Predictors	Model 1			aHR	Model 2			aHR	Model 3		
	HR	95% CI	P		95% CI	P	95% CI		P		
Age	1.048	(1.023, 1.074)	<0.001	–	–	–	1.028	(1.000, 1.056)	0.048*		
Duration of dialysis	0.846	(0.808, 0.885)	<0.001	0.853	(0.817, 0.890)	<0.001	0.831	(0.788, 0.876)	<0.001*		
Vascular access	0.254	(0.124, 0.520)	<0.001	0.300	(0.144, 0.626)	0.001	0.634	(0.286, 1.405)	0.262		
Diabetes	3.167	(1.595, 6.289)	0.001	1.638	(0.725, 3.701)	0.235	1.442	(0.614, 3.388)	0.401		
Pneumonia	3.775	(1.901, 7.498)	<0.001	2.959	(1.468, 5.966)	0.002	3.179	(1.454, 6.953)	0.004*		
Calcification	0.893	(0.527, 2.084)	0.893	0.534	(0.253, 1.128)	0.100	0.460	(0.190, 1.117)	0.086		
Albumin	0.916	(0.874, 0.961)	<0.001	0.842	(0.803, 0.882)	<0.001	0.937	(0.889, 0.987)	0.015*		
Urea	0.961	(0.923, 1.000)	0.049	0.979	(0.932, 1.029)	0.406	1.002	(0.968, 1.036)	0.925		
Cholesterol	1.308	(1.040, 1.646)	0.022	0.746	(0.506, 1.099)	0.138	1.440	(1.077, 1.925)	0.014*		

Model 1 presents univariate analysis results in which each variable is independently fit in a Cox model. Model 2 presents the results where each Cox model is adjusted for age and the predictor of interest. Model 3 presents the fully adjusted multivariate Cox model results. Significant fully adjusted hazard ratios are marked with an *. HR: Hazard ratios; aHR: Adjusted hazard ratios; CI: Confidence intervals; MHD: Maintenance hemodialysis.

Supplementary Figure 1, <http://links.lww.com/CM9/A189> presents the Kaplan-Meier curves for survival stratified by pneumonia comorbidity status. Although the plot shows differences in survival time, median survival was not reached in either group. The log-rank test suggests that there were significant differences in survival depending on pneumonia status ($P < 0.001$), such that patients with pneumonia had shorter survival times than patients without pneumonia.

The unadjusted and adjusted Cox model results are given in Table 1. All predictors were found to be highly significant except for calcification. After adjusting for age, the hazard ratios (HRs) for diabetes, urea, and cholesterol were found to be greatly attenuated such that these predictors were no longer statistically significant. This suggests that age confounded the relationship between these predictors and mortality. The fully adjusted model results suggest that only age, pneumonia status, and cholesterol level were significant risk factors for mortality. Compared with patients without pneumonia, patients with pneumonia had 3.179 times the hazard of death (adjusted HR [aHR] 3.179, 95% confidence interval [CI]: 1.454–6.953). Additionally, being 1 year older was associated with a 2.8% greater hazard of death (aHR 1.028, 95% CI: 1.000–1.056), and every 1 mmol/L higher cholesterol level was associated with a 44% greater hazard of death (aHR 1.440, 95% CI: 1.077–1.925). The duration of dialysis and increased albumin levels were shown to have slightly protective associations (aHR: 0.831, 95% CI: 0.788–0.876 and aHR: 0.937, 95% CI: 0.889–0.987, respectively).

Multivariate stepwise logistic regression was then carried out to analyze the risk factors for HD patient hospitalization. The results indicated that there were increased odds of hospitalization associated with being 1 year older (OR 1.041, 95% CI 1.019–1.063). In addition, the odds of hospitalization were 3.128 times higher for patients with pneumonia than for patients without pneumonia (OR 3.128, 95% CI: 1.718–5.696) [Supplementary Table 2, <http://links.lww.com/CM9/A188>].

The results of our study demonstrated that cardiovascular and cerebrovascular diseases accounted for 55% of

all patient deaths, followed by pneumonia (15%). This study further demonstrated that age, pneumonia status, and cholesterol level were significant risk factors for mortality in MHD patients, while age and pneumonia status were associated with increased odds of hospitalization. Hatakeyama *et al*^[1] showed that MHD patient survival was related to age. The median survival time of patients younger than 50 years old was 20 years, while for patients 60 to 79 years old, survival was reduced to 7.7 years, and for those older than 80 years of age, median survival was only 2.6 years. As age increases, the risk of cardiovascular and cerebrovascular diseases also increases in MHD patients. This phenomenon may be related to the complexity of underlying diseases, as well as the ageing of organs in elderly dialysis patients. However, some studies have revealed that 40% of young dialysis patients also die from CVDs,^[2] suggesting that in patients with MHD, CVD should be assessed more thoroughly.

Elevated cholesterol increases the risk of death in patients with MHD. Our study also found that cholesterol is a mortality risk factor in MHD patients. A similar study showed that the use of statins in patients with chronic kidney disease (CKD) and dyslipidemia before HD could reduce all-cause mortality and the risk of dialysis in these patients. These findings suggested that treating high cholesterol may reduce MHD patient mortality.

Protein malnutrition commonly exists among patients with MHD and is caused by long-term dialysis, disordered digestive function, and the release of inflammatory mediators. Thus, protein energy expenditure is also a predictor of mortality in CKD patients. Consistent with a report by Ebrahimi *et al*,^[3] our results suggested that albumin is a risk factor for death in MHD patients. Similar studies showed that MHD patient mortality increased as the serum levels of albumin decreased.^[4] When malnutrition exceeded a certain capacity in HD patients, combined with the presence of inflammation, the patients' mortality rates peaked. As an important indicator for malnutrition, for every 1 g/L reduction in albumin level, the relative risk for MHD patient mortality increased by 40%.

Infection is another common cause of MHD patient hospitalization and the leading cause of death in dialysis patients. According to data obtained from the United States Renal Data System (USRDS), 27.9% of MHD patients are diagnosed with pneumonia during the first year of HD. The incidence of pneumonia increases the rate of hospitalization, as reported in our previous study.^[5] Complications such as pneumonia in MHD patients can not only increase the occurrence of anemia, which further promotes cardiovascular events, but can also induce the release of inflammatory mediators and promote the development of atherosclerosis. Pneumonia can also cause congestion in the alveolae and decrease the ability to perform microbial removal, thereby inducing cardiac insufficiency. Therefore, the management of hospitalized MHD patients with pneumonia should be intensified.

Although we used multiple methods to ensure quality, our study still has several limitations. First, the sample size was small, and the data were limited to investigating disease-specific mortality, although we tried to obtain all available information from the included patients. Second, the factors associated with all-cause mortality are complicated, and we may have failed to consider all possible related factors. Due to the limited data available from medical records, we focused on the most significant factors that can inform clinical practice. Finally, we only included patients in one Tertiary A hospital, which may have introduced selection bias. The association between the risk factors and mortality, such as dialysis duration, needs to be interpreted with caution. Further prospective trials are warranted to address these important questions based on our results.

In summary, more attention should be paid to elderly patients with MHD. The prognosis of MHD patients can be improved by increasing albumin levels, lowering cholesterol, and reducing the incidence of pneumonia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due

efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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