Risk factors and antihypertensive medications for mortality in elderly hospitalized hemodialysis patients: a multicenter retrospective study in China

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Abstract

Background Elderly Hemodialysis patients are increasing yearly. Antihypertensive medications are commonly prescribed to hemodialysis patients but the optimal regimens to prevent morbidity and mortality are unknown. The goal of our study was to compare the association of routinely prescribed antihypertensive regimens with outcomes and analyze the risk factors in elderly hemodialysis patients.

Methods This study was a retrospective cohort study based on data from adult hemodialysis patients (≥ 18 years old) admitted to 15 hospitals in China between 1 January 2009 and 31 December 2011. The characteristics of elderly hemodialysis patients (≥ 60 years old) were analyzed. Antihypertensive drugs into the following regimens: β -blockers, calcium channel blockers, renin-angiotensin system (RAS) blocking drugs and α -blockers. Logistic regression analysis was used to explore the risk factors for death adjusting for clinical and laboratory values and antihypertensive medications.

Results A total of 7135 patients on maintenance hemodialysis including 2738 elderly patients were enrolled in this study. The mean levels of hemoglobin, albumin, blood calcium, phosphorus and parathyroid hormone (PTH) in elderly group were lower than the younger group. We compared the characteristics of 2492 survived elderly maintenance hemodialysis patients and 246 patients who died. Aging (OR = 1.59, 95% CI: 1.13-2.24), central venous catheter (OR = 1.62, 95% CI: 1.53-1.72) and Charlson comorbidities index >3 (OR=1.97, 95% CI: 1.49-2.60) were independently risk factors of mortality in elderly maintenance hemodialysis patients. High levels of hemoglobin (OR=0.76, 95%CI: 0.73-0.79), albumin (OR=0.87, 95%CI: 0.77-0.98), uric acid (OR=0.90, 95%CI: 0.84-0.96) and those taking angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) (OR=0.77, 95%CI: 0.58-0.90) had a lower risk of mortality.

Conclusions Age, Charlson Comorbidities index >3 , anemia and malnutrition, the use of central venous catheters and low serum uric acid level are risk factors for mortality in elderly maintenance hemodialysis patients. Taking ACEI/ARB can reduce the mortality of elderly maintenance hemodialysis patients.

Background

With development of hemodialysis technology and aging of population, patients who need renal replacement therapy are increasing and getting older [1-2]. There are many prognostic factors impacting dialysis patients' mortality, such as: patient-related and therapy-related factors. Age, malnutrition and comorbidities are mainly patient-related factors. Antihypertensive drugs, serum uric acid level and vascular access type are, at least partly, therapy-related factors [3].

Hypertension is common and contributes to adverse outcomes in patients undergoing dialysis. Antihypertensive drugs are prescribed to hemodialysis patients commonly but the contribution to life span are unclear. The benefits of RAS blocking drugs are well-established in the general population, particularly among those with diabetes, congestive heart failure (CHF), or coronary artery disease (CAD). However, conflicting evidence from trials and concerns about hyperkalemia limit RAS blocking drugs use

in hemodialysis patients, relative to other antihypertensive agents, including beta blockers and calcium channel blockers[4-5]. This study was to investigate the association of different kinds of antihypertensive drugs with mortality in Chinese elderly hemodialysis patients.

Methods

Patients

A multicenter, retrospective cohort of maintenance hemodialysis (MHD) patients (aged ≥ 18 years old) in 15 tertiary hospitals in China from 1 January 2009 to 31 December 2011 was recruited. The inclusion criteria were as follows: definite diagnosis of stage of chronic kidney disease 5 stage and undergoing hemodialysis treatment for more than 3 consecutive months. Patients with acute kidney injury, received a kidney transplant or undergone nephrectomy were excluded. The Medical Ethics Committee of the Chinese PLA General Hospital approved the study protocol and waived patient consent.

Demographic and Clinical Data

Finally included in the study were 7135 patients, who were divided into 3 groups according to age: 4397 patients aged less than 60 years; 1808 elderly patients between 60 and 75; and 930 very elderly patients aged over 75. 2738 elderly MHD patients including 2492 survived patients and 246 patients who died. The following information: name, age, gender, hospital number, primary diseases of renal failure, cause of admission, discharge diagnosis, vascular access type and the cause of death were collected from electronic medical records and laboratory databases. Laboratory indicators consisted of albumin, hemoglobin, calcium, phosphorus and PTH levels. Types of vascular access for hemodialysis were divided into two different groups: the CVC group, which included both tunneled and non-tunneled catheters, and the AV group, which included AVF and AVG. The Charlson comorbidity index (CCI) score was calculated for each patients according to their comorbidity profile [6]. We classified antihypertensive drugs into the following regimens: β -blockers, calcium channel blockers, renin-angiotensin system blocking drugs and α -blockers.

Statistical Analysis

SPSS software (version 22.0) was applied to Statistical analysis. Continuous variables were expressed as mean $\pm$ standard deviation. Categorical variables were expressed as n(%). One-way ANOVA or the Kruskal-Wallis test was used for continuous variables. The χ^2 test was used for categorical variables. Logistic regression analysis was used to explore the risk factors for death in the elderly MHD patients. All tests were two-sided tests and a P value < 0.05 was considered statistically significant.

Results

The average age of hospitalized hemodialysis patients was 53.0 ± 17.8 years old, male patients accounted for 51.1% (table 1). The top three primary diseases in elderly dialysis patients were diabetic

nephropathy, hypertension and glomerulonephritis. The top two reasons for the hospitalization of elderly patients were infection and cardiovascular disease (table 2). The central venous catheters was accounted for 27.9%, 67.5% and 75.7% for patients aged < 60, 60-74 and ≥ 75 years respectively ($P < 0.05$). As age increased, the mean value of hemoglobin, albumin, serum calcium, phosphorus and PTH were decreased ($P < 0.05$).

We analysed the characteristics of 2738 elderly MHD patients by comparing 2492 survived patients with 246 patients who died (table 3). Aging (OR = 1.59, 95% CI: 1.13-2.24), central venous catheter (OR = 1.62, 95% CI: 1.53-1.72) and CCI $\times 3$ (OR=1.97, 95% CI: 1.49-2.60) were independently risk factors of mortality in elderly maintenance hemodialysis patients. High levels of hemoglobin (OR=0.76, 95%CI: 0.73-0.79), albumin (OR=0.87, 95%CI: 0.77-0.98), uric acid $\times$ OR=0.90, 95%CI: 0.84-0.96 and those taking ACEI/ARB (OR=0.77, 95%CI: 0.58-0.90) had a lower risk of mortality (table 4).

Discussion

Many elderly hemodialysis patients suffer from various complications and have to be hospitalized, and even require repeated hospitalizations. The high hospitalization rate not only aggravates the financial burden and psychological pressure of elderly hemodialysis patients, but also greatly increases the mortality rate [7]. We found that the proportion of secondary kidney diseases such as diabetes and hypertension in elderly hemodialysis patients was high, which is consistent with the results of other studies [8-9]. The incidence of anemia and hypoalbuminemia was high in elderly hemodialysis patients. A study of 78,420 dialysis patients found that hemodialysis patient's hospitalization risk is increased by 67% for every 1 g/dL decrease in albumin and increased by 9% for each 1 g/dL drop in hemoglobin [10]. Therefore, we must pay great attention to the nutritional problems in elderly hemodialysis patients in order to reduce the hospitalization rate and improve the quality of life.

Elderly hemodialysis patients often suffer from decreased bone synthesis and reabsorption, and PTH secretion is inhibited [11]. They have degenerative function of hormone secretion and activity, decrease expression of anti-aging Klotho gene and uremic toxins [12]. The intake of phosphorus decreases and hypophosphatemia develops, causing a decrease in PTH levels. The specific mechanism of low transport bone disease in elderly hemodialysis patients remains to be further explored [13]. There is a positive correlation between serum PTH levels and serum albumin, creatinine and total cholesterol concentrations in elderly hemodialysis patients [14]. The main therapeutic goal of low-transplant renal bone disease is to reduce calcium ion and vitamin D load, avoid excessive inhibition of PTH, maintain PTH activity and improve the quality of life of hemodialysis patients [15].

Studies have confirmed that hypophosphatemia can increase the all-cause mortality and infection-related mortality of hemodialysis patients compared with the range of serum phosphorus recommended by the kidney disease outcomes quality initiative (KDOQI) [16-18]. Other studies have found that hypophosphatemia increases the mortality of hemodialysis patients over 65 years old [19]. Hypophosphatemia was an independent risk factor for infection, especially in elderly dialysis patients

[20]. Hypocalcemia is an independent predictive risk factor for left ventricular diastolic dysfunction in chronic kidney disease patients.

Elderly hemodialysis patients have a higher mortality rate, and many factors affect their risk of death. Patients with more comorbidities had higher hospitalization costs, lower survival rates, and a higher risk of death. Age, CCI, malnutrition, serum uric acid level, and CVC are known factors associated with the risk of mortality among hemodialysis patients [21-23]. Hur et al discussed that low serum uric acid is associated with higher mortality [24].

The treatment of hypertension in dialysis patients is complex and there is no relevant guide [25-28]. There are mainly four kinds of antihypertensive drugs commonly used in maintenance hemodialysis patients: RAS blockers, calcium ion antagonists, β -blockers and α -blockers.

RAS blockers are mainly divided into angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists. These drugs have great advantages in dialysis patients due to their low dialysis clearance rate, stable hemodynamics, definite antihypertensive effect and cardio-cerebral organ protection [29].

The prevalence of microinflammation in hemodialysis patients is an important predictor of cardiovascular disease and death in MHD patients [30]. ARB drugs can directly participate in the regulation of the body's immune system and significantly reduce the level of serum inflammation indicators in hemodialysis patients [31-32].

Dialysis patients taking RAS blockers had a reduction in all-cause mortality and cardiovascular mortality compared with beta-blockers [29]. ARBs can reduce the overall mortality and cardiovascular mortality of hemodialysis patients, but the use of ACEI did not find its impact on mortality. Combination of ACEI and ARB increases the mortality of hemodialysis patients [33-35]. However, some studies have found that ARB drugs cannot reduce the risk of cardiovascular events and total mortality in long-term dialysis patients compared with other antihypertensive drugs [36-37]. Therefore, large-scale clinical trials are needed to verify the advantages and disadvantages of ACEI/ARB in dialysis patients.

Although the proportion of calcium ion antagonists used in elderly hemodialysis patients is large, the correlation analysis in this study showed no significant effect on the mortality of elderly hemodialysis patients. One study divided 130 dialysis patients into two groups according to whether they used calcium antagonists and found that hemoglobin was low in hemodialysis patients who used calcium antagonists, probably because calcium antagonists attenuate the activity of erythropoietin [38-40].

A 10-year follow-up study of long-term hemodialysis patients receiving various antihypertensive drug treatments found that beta-blockers can significantly reduce all-cause mortality in hemodialysis patients [41]. A recent study found that hemodialysis patients who used a combination of beta-blockers and renin-angiotensin system antagonists had the lowest mortality rates [42].

Although we conducted a large-scale study of the clinical features about the hospitalized elderly hemodialysis patients, there are still some problems and deficiencies: First, this study is a retrospective case data, cross-sectional survey design and there was no follow up and we used logistic regression instead of cox regression. Second, the patient list here is extracted from inpatient data. This makes things very different from an outpatient hemodialysis database study. Inpatients are unwell and hemoglobin, phosphate, calcium, these are naturally deranged while patients are acutely unwell. For example: a lower inpatient hemoglobin would be naturally associated with more acute diseases and possibly longer hospital stay. Third, there was a lack of blood pressure values that could heavily influence clinicians' antihypertensive prescription decisions. In addition, there is still a lack of data on dialysis.

Conclusions

Age, CCI > 3, anemia and malnutrition, use of central venous catheters and low level of serum uric acid are the risk factors for mortality in elderly maintenance hemodialysis patients. Renin-Angiotensin System Blockade might provide a benefit in protecting elderly hemodialysis patients from mortality.

Abbreviations

CVD: cardiovascular disease; CCI: Charlson comorbidities index; CKD: chronic kidney disease; ESRD: end-stage renal disease; MHD: [maintenance hemodialysis](#); PTH: parathyroid hormone; ACEI/ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. RAS: renin-angiotensin system; BMI: body mass index; CHF: congestive heart failure; CAD: coronary artery disease; KDOQI: kidney disease outcomes quality initiative.

Declarations

Ethics approval and consent to participate

The Medical Ethics Committee of the Chinese PLA General Hospital approved the study protocol and waived patient consent.

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable.

Funding

Not applicable.

Authors' contributions

Each author contributed to the design of the study and interpretation of the data. YHS, GYC, YFX, JQL and SL conceived and designed the study. YHS and GYC participated in the literature searches data analysis and interpretation. YHS drafted the manuscript. GYC and XMC revised the final manuscript. All authors read and approved the final manuscript.

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There are no conflicts of interest to declare.

Availability of data and materials

All the data supporting the conclusions of this article are contained within the manuscript. The individual patient-level dataset was not made publically available due to containing potentially identifying patient data; however, the study dataset may be made available from the authors upon request.

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Tables

Table 1. The clinical characteristics of hospitalized elderly maintenance hemodialysis patients

	Total	≤60 years	60-74 years	≥75 years	P value
Patient cases	7135	4397	1808	930	
Age (years)	53.0±17.8	41.3±11.4	68.1±3.7	79.0±4.1	≤0.05
Male	51.1%	54.0%	45.9%	47.6%	≤0.05
Primary disease≤%≤					≤0.05
Chronic glomerular disease	40.2	52.2	18.3	10.5	
Diabetic nephropathy	21.3	17.5	38.3	43.1	
Hypertensive kidney damage	17.3	15.7	18.2	23.3	
Other/Unknown	21.2	14.6	25.2	23.1	
Central venous catheter	34.4%	27.9%	67.5%	75.7%	≤0.05
Albumin (g/L)	36.4±5.6	38.4±4.6	34.4±3.8	32.3±4.2	≤0.05
Hemoglobin (g/L)	96.0±17.9	101.1±15.6	95.4±16.9	82.2±18.3	≤0.05
PTH(pg/mL)	278.1±201.3	321.9±168.3	259.4±114.2	234.2±109.2	≤0.05
Calcium (mmol/L)	2.09±0.63	2.15±0.31	2.05±0.46	1.99±0.33	≤0.05
Phosphorus (mmol/L)	1.99±0.43	2.05±0.78	1.89±0.53	1.65±0.44	≤0.05

Table 2. The reasons for the hospitalization of elderly maintenance hemodialysis patients

Reasons for hospitalization	cases	ratio(%)
Infection	668	24.4
Coronary heart disease	580	21.2
Heart failure	274	10.0
Electrolyte and acid-base balance disorders	178	6.5
Cerebrovascular disease	144	5.3
Dysfunction of hemodialysis access	127	4.6
Hypertension	126	4.6
Arrhythmia	120	4.4
Tumor	112	4.1
Gastrointestinal bleeding	96	3.5
Fracture	90	3.3
Secondary hyperparathyroidism	78	2.8
Serous cavity fluid	23	0.8
Hypotension	21	0.8
Intestinal obstruction	10	0.4
Other and unknown reasons	91	3.3

Table 3. Characteristics of 2738 elderly hospitalized maintenance hemodialysis patients

	Deceased (n=246)	Living (n=2492)	Pvalue
Age	75.02±7.26	71.45±6.27	<0.001
Male	127[51.6%]	1146[46.0%]	0.09
Duration of dialysis(months)	35.3±4.6	32.1±5.2	0.12
Central venous catheter	134[65.7%]	856[54.5%]	<0.01
CCI[3	234[95.1%]	2173[87.2%]	<0.01
Hemoglobin (g/L)	86.33±21.45	92.95±19.34	<0.001
Albumin (g/L)	30.53±8.70	35.3±6.2	<0.001
Calcium (mmol/L)	2.04±0.31	2.10±0.24	0.32
Phosphorus (mmol/L)	1.99±0.76	2.01±0.57	0.55
Uric acid[umol/L]	301.91±215.71	336.19±138.87	<0.001
Triglycerides[mmol/L]	1.32±0.67	1.48±0.71	0.45
Cholesterol[mmol/L]	3.54±1.56	4.08±1.67	<0.05
creatinine[umol/L]	706.23±392.52	722.12±416.73	0.37
PTH[mg/dl]	201.52±240.21	254.13±232.12	0.33
α-Receptor Blockers	26[10.6%]	310[14.2%]	0.39
β-Receptor Blockers	78[31.7%]	657[26.4%]	0.07
Calcium Channel Blocker	160[65%]	1525[61.2%]	0.22
ACEI/ARB	69(28%)	859[34.5%]	0.05

Table 4.Logistic regression analyses for mortality in elderly maintenance hemodialysis patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.26(1.09-1.46)	<0.01	1.59 (1.13-2.24)	<0.01
Male	1.10(0.94-1.28)	0.23	1.02(0.89-1.17)	0.78
Hemodialysis(months)	0.71(0.45-1.13)	0.12	0.86(0.53-1.40)	0.54
Central venous catheter	1.58(1.01-2.48)	<0.05	1.62(1.53-1.72)	<0.05
CCI3	2.04(1.64-2.54)	<0.01	1.97(1.49-2.60)	<0.01
Hemoglobin(g/L)	0.77(0.68-0.87)	<0.001	0.76(0.73-0.79)	<0.001
Albumin(g/L)	0.85(0.78-0.93)	<0.01	0.87(0.77-0.98)	<0.01
Calcium(mmol/L)	0.87(0.63-1.20)	0.40	0.89(0.72-1.10)	0.37
Phosphorus(mmol/L)	0.96(0.43-2.14)	0.92	0.96(0.43-2.14)	0.86
serum uric(umol/L)	0.91(0.86-0.96)	<0.01	0.90(0.84-0.96)	<0.01
triglyceride(mmol/L)	0.90(0.79-1.03)	0.11	0.98(0.81-1.19)	0.84
cholesterol(mmol/L)	0.58(0.49-0.69)	<0.001	0.92(0.81-1.04)	0.20
serum creatinine(umol/L)	0.98(0.89-1.08)	0.68	0.86(0.68-1.09)	0.21
PTH(mg/dl)	1.08(0.73-1.60)	0.70	1.02(0.64-1.63)	0.70
α -blockers	0.84(0.57-1.25)	0.40	0.83(0.54-1.27)	0.39
β -blockers	1.30(0.98-1.72)	0.07	1.27 (0.98-1.63)	0.06
calcium ion antagonists	1.18(0.90-1.55)	0.21	1.16(0.91-1.49)	0.09
ACEI/ARB	0.76 (0.58-0.99)	<0.01	0.77(0.58-0.90)	<0.01