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CLINICAL STUDY

Analysis of Early Kidney Damage in Hospitalized Patients with Chronic Kidney Disease: A Multicenter Study

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Abstract

Background: To identify the risk factors for early kidney damage in hospitalized Chinese patients with chronic kidney disease (CKD). *Methods*: A total of 12 multicenter cross-sectional studies were conducted between January 2005 and January 2006 in Chinese CKD patients with estimated glomerular filtration rate (eGFR) equal to or more than 30 mL/min/1.73 m^2 in Shanghai. CKD was defined according to the K/DOQI guideline. GFR was estimated by the simplified modification of diet in renal disease equation. The demographic, clinical, and laboratory data were collected through a questionnaire and analyzed among eligible patients stratified by three different CKD groups (CKD stages 1, 2, and 3). The relevant clinical and laboratory risk factors for early kidney damage with a GFR $<$ 90 mL/min/1.73 m^2 were determined by logistic regression. *Results*: A total of 822 CKD patients were enrolled in this study. There were significant differences in age and gender among patients with CKD stages 1, 2, and 3. The prevalence of hypertension, cardiovascular disease, cerebral vascular disease, anemia, and hyperuricemia increases when the eGFR declines. Logistic analysis showed that age, hypertension, anemia, and hyperuricemia were independently associated with early kidney damage. *Conclusions*: In CKD patients, we have identified only age, hypertension, anemia, and hyperuricemia as the risk factors for early kidney damage. Risk factors should be managed to prevent accelerated kidney damage in CKD patients.

Keywords: CKD, kidney damage, inpatients

INTRODUCTION

Increasing numbers of patients are nowadays affected by chronic kidney disease (CKD). Recent studies have pointed out that CKD might affect up to 10% of the population worldwide.[1] In China, the prevalence of CKD is about 11–13%, which also suggests a high prevalence of the disease.[2–4] The progression of CKD will ultimately result in end-stage renal disease (ESRD), which is related to high mortality and large amounts of medical expenditures.[5] In this sense, early detection and management of CKD would be beneficial to reduce its burden on the global health-care resources as well as to improve prognosis. Studying disease-related risk factors is an effective strategy to manage CKD; however, recent studies on CKD-related risk factors were mostly performed in ESRD patients, which might not

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fully reflect the situation in those with early stages of kidney damage.[6] In this study, we investigate CKD-related risk factors in patients with early stage kidney damage so as to facilitate the early detection and management of the disease.

METHODS

Study Population and Screening Protocol

From January 2005 to January 2006, CKD inpatients with CKD stages 1–3 from renal departments of 12 hospitals were enrolled in this study. The study was approved by the ethical committees of all the participating hospitals. Informed consent was given by every patient prior to data collection. All patients completed a questionnaire including age, gender, race/nationality, marital status, smoking, alcohol consumption, and medical history [hypertension, diabetes, cardiovascular disease (CVD), cerebral vascular disease, renal disease, hyperlipidemia, and cancer]. Data on physical examination findings and laboratory results were also collected and analyzed.

Definition and Assessment

CKD was defined according to the criteria of K/DOQI.[7] The estimated glomerular filtration rate (eGFR) was assessed by a simplified modification of diet in renal disease (MDRD) equation.[8] Serum creatinine was measured by means of Jaffè kinetic method using the Beckman LX20 autoanalyzer (Beckman Coulter, Brea, CA, USA). Patients with diabetic history or with a fasting glucose >7 mmol/L or 2 h postprandial blood glucose ≥11.1 mmol/L were diagnosed as diabetic.[9] Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or history of hypertension. Blood pressures were measured according to the guidelines presented in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure (JNC 7).[10] Baseline blood pressure was measured by a trained observer using a standard mercury sphygmomanometer on the right arm of the patients in a sitting position after 15 min of rest. Three readings were taken to obtain the final measure of the blood pressure, and the mean of the three readings was calculated. CVD was defined as a history of both recognized and silent myocardial infarction or undergoing angioplasty and coronary bypass procedures, angina, transient ischemic attack (TIA) or congestive heart failure, or pathologic abnormality on EKG. Cerebral vascular disease included a history of stroke or bleeding in brain or TIA or an abnormality found by radiological brain examination. Hypercholesterolemia and hypertriglyceridemia were defined as a history of serum cholesterol >6.21 mmol/L or serum triglyceride >2.26 mmol/L, respectively.[11] Anemia was defined as a history of anemia or hemoglobulin <120 g/L for men and <110 g/L for women.[12] Hyperuricemia was defined as a history of gout or serum uric acid level >420 μmol/L for men and >360 μmol/L for women.[13] Body mass index (BMI) was calculated using the equation [weight (kg)]/[height (m)]^2. Obesity was defined as BMI >28.[14]

Statistical Analysis

Double data entry and management were performed on Epidata software, version 3.1 (Epidata Association, Odense, Denmark). Statistical analysis was performed by SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Data were summarized by mean ± SD (for continuous variables) and proportions (for categorical variables). All CKD patients were stratified into three groups (CKD stages 1, 2, and 3) on the basis of MDRD-GFR. The differences of the distributions of all the variables among the groups were tested by analysis of variance model (for the continuous variable age) and chi-square tests (for the others). We also fitted a logistic regression model to identify the significant risk factors. The candidate variables included age, gender, obesity, smoking, alcohol consumption, hypertension, diabetes, CVD, cerebral vascular disease, hypercholesterolemia, anemia, hyperuricemia, and proteinuria. A p-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the Patients

A total of 822 patients were enrolled in this study, among whom 463 (56.3%) were male and 359 (43.7%) female. The mean age was 49.8 ± 17.8 years (range 14–87 years). Among the patients, 422 (51.3%) had primary glomerulonephritis, 137 (16.7%) had renal vascular diseases, 145 (17.6%) had secondary glomerulonephritis, 52 (6.3%) had renal tubulointerstitial diseases, 32 (3.9%) had other types of renal diseases including chronic infectious, congenital, or cystic renal diseases, and the remaining 34 (4.1%) had kidney damage of unknown causes. The number of patients with CKD stages 1–3 was 268, 192, and 362, respectively. Details are summarized in Table 1.

Characteristics of Risk Factors Associated with Early Kidney Damage

Table 2 shows the characteristics of risk factors associated with kidney damage. In our study, gender and age were closely associated with the severity of kidney damage, and older male patients were found to have lower levels of eGFR. The mean age and percentage of male patients were significantly different among the three groups ($p < 0.001$ and $p = 0.037$, respectively).

There were also significant differences regarding percentage of hypertension, diabetes, CVD, and cerebral vascular disease among the three groups ($p < 0.001$, $p = 0.003$, $p < 0.001$, and $p = 0.001$,

Table 1. Clinical characteristics of 822 participants grouped by CKD stages.

	CKD 1	CKD 2	CKD 3
Number of patients (*n*)	268	192	362
Serum creatinine ratio (μmol/L)	67.8 ± 11.6	97.3 ± 16.9	152.3 ± 46.5
eGFR (mL/min/1.73 m^2)	118.5 ± 25.3	74.7 ± 8.8	44.8 ± 8.8
Diagnosis			
Primary glomerulonephritis, *n* (%)	171 (63.8)	98 (51.0)	153 (42.3)
Renal vascular diseases, *n* (%)	17 (6.3)	31 (16.1)	89 (24.6)
Secondary glomerulopathy, *n* (%)	50 (18.7)	40 (20.8)	55 (15.2)
Diabetic nephropathy, *n* (%)	10 (3.7)	30 (15.6)	37 (10.2)
Other renal diseases, *n* (%)	22 (8.2)	18 (9.4)	44 (12.2)
Unidentified, *n* (%)	8 (3.0)	5 (2.6)	21 (5.8)

Note: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2. The characteristics of risk factors for kidney damage.

	CKD 1	CKD 2	CKD 3	*p*-Value
Number of patients (*n*)	268	192	362	
Age (years)	38.3 ± 15.6	50.8 ± 15.2	57.7 ± 15.9	<0.001
Males, *n* (%)	134 (50)	112 (58.3)	217 (59.9)	0.037
Obesity (BMI > 28), *n* (%)	28 (10.4)	33 (17.2)	52 (14.4)	0.106
Smoking, *n* (%)	51 (19.0)	54 (28.1)	118 (32.6)	0.001
Alcohol consumption, *n* (%)	36 (13.4)	37 (19.3)	65 (18.0)	0.186
Hypertension, *n* (%)	79 (29.5)	118 (61.5)	289 (79.8)	<0.001
Diabetes, *n* (%)	36 (13.4)	47 (24.5)	83 (22.9)	0.003
CVD, *n* (%)	26 (9.7)	49 (25.5)	158 (43.6)	<0.001
Cerebral vascular diseases, *n* (%)	7 (2.6)	17 (8.9)	38 (10.5)	0.001
Anemia, *n* (%)	39 (14.6)	31 (16.1)	113 (31.2)	<0.001
Hyperuricemia, *n* (%)	36 (13.4)	58 (30.2)	210 (58.0)	<0.001
Hypercholesterolemia, *n* (%)	63 (23.5)	51 (26.6)	78 (21.5)	0.413
Hypertriglyceridemia, *n* (%)	111 (41.4)	93 (48.4)	173 (47.8)	0.203
Proteinuria, *n* (%)	229 (85.4)	162 (84.4)	273 (75.4)	0.002
Hematuria, *n* (%)	156 (58.2)	82 (42.7)	90 (24.9)	<0.001

Note: BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease.

respectively). The percentage of patients with hypertension increased whereas the percentage of patients with eGFR decreased. Similar results were also found in patients with CVD, cerebral vascular disease, or diabetes among the three groups. However, no significant differences were observed regarding percentage of obesity, hypercholesterolemia, or hypertriglyceridemia among the three groups ($p > 0.05$).

In our study, we found that patients with CKD stages 2 and 3 had higher percentage of smoking history than those with CKD stage 1 ($p = 0.001$). However, there was no significant difference regarding alcohol consumption within the three groups ($p > 0.05$). There were significant differences regarding percentage of patients with proteinuria or hematuria among the three groups ($p = 0.002$, $p < 0.001$, respectively).

Analysis of Risk Factors Associated with Early Kidney Damage

A logistic regression analysis was used to investigate the risk factors associated with early kidney damage. Age, hypertension, anemia, and hyperuricemia were found to be significantly associated with the early impairment of kidney function ($p < 0.05$); details are summarized in Table 3.

DISCUSSION

Primary glomerulonephritis was the most common cause of CKD in our patients, which accounted for almost half of the patients. In the study by Zhou and colleagues,[15] primary glomerulonephritis was also the major cause of renal diseases in their patients. Though the number of patients with diabetic nephropathy and hypertensive nephropathy rose rapidly, primary glomerulonephritis is still the most common cause of ESRD in the Chinese population.[16] Therefore, studies focusing on primary glomerulonephritis might still be necessary for the management and control of the disease in China.

This study demonstrated that age, hypertension, anemia, and hyperuricemia were the risk factors for early kidney damage. In this sense, further analysis of risk factors may facilitate early detection and management of the disease.

Studies show that hyperuricemia is closely associated with hypertension and coronary heart disease, as well as increased cardiovascular mortality.[17,18] Hyperuricemia is also an important risk factor associated with CKD, especially in patients with early stages of CKD. In the study by Weiner et al.,[19] hyperuricemia was the risk factor for new-onset kidney disease. In

Table 3. Logistic regression analysis.

Variable	eGFR > 90 ($n = 268$)	eGFR < 90 ($n = 554$)	Regression coefficient	95% CI	p-Value
Hyperuricemia	36 (13.4%)	268 (48.4%)	6.090	1.35–2.26	<0.001
Hypertension	79 (29.5%)	407 (73.5%)	3.084	0.73–1.52	<0.001
Age	38.3 ± 15.6	55.3 ± 16.0	1.057	0.04–0.07	<0.001
Anemia	39 (14.6%)	144 (26.0%)	1.848	0.12–1.11	0.015
CVD	26 (9.7%)	207 (37.4%)	1.699	−0.01–1.07	0.054
Cerebral vascular diseases	7 (2.6%)	55 (9.9%)	1.352	−0.60–1.21	0.514
Smoking	51 (19.0%)	172 (31.0%)	1.671	−0.03–1.05	0.063
Proteinuria	229 (85.4%)	435 (78.5%)	1.121	−0.41–0.64	0.667
Male	134 (50.0%)	329 (59.4%)	0.742	−0.74–0.14	0.188
Obesity (BMI > 28)	28 (10.4%)	85 (15.3%)	0.847	−0.73–0.40	0.562
Hypercholesterolemia	63 (23.5%)	129 (23.3%)	0.946	−0.50–0.39	0.805
Diabetes	36 (13.4%)	130 (23.5%)	0.594	−1.06–0.01	0.057
Alcohol consumption	36 (13.4%)	102 (18.4%)	0.605	−1.09–0.08	0.091

Note: BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; eGFR, estimated glomerular filtration rate.

our previous study, we demonstrated that hyperuricemia was one clinical variable closely associated with CKD.[3] As CKD could cause elevated levels of uric acid whereas hyperuricemia could also contribute to the progression of CKD, the role of hyperuricemia in CKD is still uncertain. However, we found that the prevalence of hyperuricemia significantly increased in the early stages of CKD, which was 30.2% in patients with CKD stage 2 and 58% in patients with CKD stage 3, whereas it was 13.4% in patients with CKD stage 1. Our results suggested that hyperuricemia might be an important indicator to predict kidney damage. Similar results were also found in Japan and Thailand.[20,21] Hence, the level of serum uric acid in CKD patients, especially in those with eGFR <90 mL/min/1.73 m^2, should be appropriately monitored during the management of CKD.

CVD and cerebrovascular diseases are risk factors associated with early renal injury in patients with CKD in our study. In the Cardiovascular Health Study, early renal insufficiency was associated with a doubling of total mortality of cardiovascular death, stroke, and heart failure.[22] The Atherosclerosis Risk in Communities (ARIC) study showed that the adjusted cardiovascular hazard ratio for those with a creatinine clearance <60 mL/min was 1.38 compared with a creatinine clearance >90 mL/min in the general population.[22] Reports published elsewhere have suggested that CVD and cerebrovascular diseases are closely related to CKD. The prognosis was also closely associated with severity of kidney damage in patients with CVD or cerebrovascular disease.[23–25]

Hypertension is a well-known risk factor for the development and progression of CKD.[26] Data from the United States demonstrated that hypertension was independently associated with increased risk of developing new CKD.[27,28] In our study, the prevalence of hypertension in patients with normal renal function was similar to that in the general Chinese population. Data from the national hypertension survey in China in 2002 documented that 27.9% of Chinese adults had hypertension[29]; however, it doubled when eGFR < 90 mL/min/1.73 m^2 and kept increasing while eGFR decreased. Our present study found that hypertension was an independent risk factor for early kidney damage in the hospitalized CKD population, and similar results have also been found by Zhang and colleagues.[30]

Anemia is another well-known risk factor for ESRD. It increases the mortality in CKD patients. Both anemia and decreased GFR had a negative impact on prognosis of patients with stroke and coronary diseases.[31,32] The prevalence of anemia in our study was 14.6% in patients with CKD 1, 16.1% in patients with CKD 2, and 31.2% in patients with CKD 3. Similar data were also found from the ARIC study, which showed that the prevalence of anemia in CKD patients with eGFR between 15 and 59 mL/min was significantly higher than that in patients with eGFR > 90 mL/min.[33]

Smoking is a risk factor for CKD and is associated with the development and progression of CKD according to the literature.[27,34] Haroun et al.[27] showed that smoking was associated with high risk for developing CKD in the population. Furthermore, Shankar et al.[34] found a higher odds ratio of CKD associated with increasing pack-years of smoking. These data indicate that smoking cessation will be beneficial for the CKD patients.

In conclusion, this study demonstrated that age, hypertension, anemia, and hyperuricemia are independent risk factors associated with early kidney damage. Special attention should be paid to those factors so as to detect and manage the disease early.

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