Chronic kidney disease is prevalent in Chinese patients admitted with verified cerebrovascular lesions and predicts short-term prognosis

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Abstract

Objective. Recent studies have identified chronic kidney disease (CKD) as an important risk factor for vascular pathies. While the link between CKD and cardiovascular events is well established, the link with cerebrovascular lesions (CVL) has been less well described.

Methods. We studied the prevalence and prognostic importance of CKD in 1014 incident Chinese patients admitted with verified computerized tomography (CT) or magnetic resonance imaging (MRI) CVL (within the last 7 days). Laboratory data included the urinary microalbumin-to-creatinine ratio, routine urinalysis, fasting plasma glucose, serum creatinine, uric acid and other measures. Estimated glomerular filtration rate was calculated (using the modification of diet in renal disease formula) and CKD stages were classified according to kidney disease outcome quality initiative (K/DOQI) guidelines. Patients were followed for 30 days and any neurological sequelae were recorded.

Results. A total of 1014 patients were enrolled (455 females, aged 68.56 ± 12.17 years). Among these, 708 had ischemic stroke, 197 hemorrhagic stroke and 109 had transient cerebral ischemic attack. Microalbuminuria was detected in 11.2% of patients, while 24.8% had proteinuria. Of all patients, 6.90% had Stage 1, 14.69% Stage 2, 21.60% Stage 3, 2.56% Stage 4 and 1.97% had Stage 5, giving a total prevalence of CKD at 47.7%. In logistic regression, proteinuria (odds ratio = 1.69), hyperglycemia (odds ratio = 1.67) and anemia (odds ratio = 1.37) were independent predictors for risk of sequelae at 30 days for both ischemic and non-ischemic CVL.

Conclusion. We report a high prevalence of CKD among Chinese patients with incident CVL. Proteinuria, hyperglycemia and anemia were prognostic factors in these patients.

Keywords: cerebrovascular lesion; chronic kidney disease (CKD); GFR; proteinuria; risk factor

Introduction

Cerebrovascular lesions (CVL) are a primary cause of adult disability and are one of the most common causes of death worldwide. In Asia, CVLs have become the major cause of death and cause higher morbidity and mortality than all other diseases in China. The Sino MONICA project [1] showed that average incidences of hemorrhagic and ischemic stroke were 65.0 and 111.0/100 000, respectively. In the largest single-cohort study to date (>40 000 patients), Collins et al. [2] reported that short-term, intermediate and long-term mortality rates were 7.4, 11.4 and 19.1%, respectively, for ischemic stroke and 18.8, 24.6 and 31.8% for hemorrhagic stroke. Due to the high mortality and morbidity associated with CVLs, this condition has been receiving increasing attention.

CVL and kidney damage are closely related, and this is partly because CVL is one of the most common complications of end-stage renal disease (ESRD). CVL is also the major cause of death among ESRD patients. The US Renal Data System [3] study showed in 1995 that 4.0, 9.3 and 10.0% of the ESRD patients diagnosed with primary kidney disease, diabetic nephropathy and hypertensive nephropathy, respectively, also developed CVL. In 2006, the respective percentages of those developing CVL had risen to 4.6, 11.3 and 11.2%. Kidney function has also been related to survival rates of CVL. Mac Walter et al. [4] performed a follow-up of 2042 acute stroke participants for 7 years and found that stroke patients with reduced calculated creatinine clearance and raised serum creatinine upon admission had a higher mortality risk.

Recent surveys of chronic kidney disease (CKD) have focused on community populations or patients admitted to nephrology departments. However, few studies have reported on the prevalence of CKD in patients with CVL. Patients with CVL have a high risk for developing CKD,
which underlines the importance and necessity of screening for CKD in this population. We studied correlations between CVL and CKD in five teaching hospitals in Shanghai in order to further understand interactions between these diseases.

Materials and methods

Study population and protocol design

We carried out a multi-center cross-sectional study in patients hospitalized for CVL from June 2007 to February 2008 in the Neurology departments of five teaching hospitals in Shanghai. The most important inclusion criteria were that all patients had stroke or transient cerebral ischemic attack (TIA) diagnosed by brain CT and/or CTA and/or MRI and/or MRA.

Clinical variables

Details of patient disabilities at discharge were recorded. Other relevant clinical data, including electrocardiogram (ECG), chest X-ray and UCG, were also collected. Laboratory data on admission were gathered and included serum creatinine, plasma glucose, routine urine analysis, urine microalbumin-to-creatinine ratio (ACR), serum uric acid, serum lipids and hemoglobin. All serum creatinine samples were tested in a central laboratory at the Shanghai Ruijin Hospital affiliated with Jiao Tong University School of Medicine. All ACR samples were tested by the same method. Urinary albumin was detected by rate nephelometry and urinary creatinine was measured by the basic picric acid method. Estimated glomerular filtration rate (eGFR) was evaluated by the modification of diet in renal disease formula (MDRD) and patients were classified into CKD stages according to K/DOQI guidelines. The MDRD–GFR equation is: eGFR (mL/min/1.73 m²) = 170 × Scr−0.999 × age−0.177 × (0.762 if female) × BUN−0.178 × Alb0.318. All patients were asked to complete a questionnaire that consisted of age, gender, clinical data, including electrocardiogram (ECG), chest X-ray and UCG, were also collected. Laboratory data on admission were gathered and included serum creatinine, plasma glucose, routine urine analysis, urine microalbumin-to-creatinine ratio (ACR), serum uric acid, serum lipids and hemoglobin. All serum creatinine samples were tested in a central laboratory at the Shanghai Ruijin Hospital affiliated with Jiao Tong University School of Medicine. All ACR samples were tested by the same method. Urinary albumin was detected by rate nephelometry and urinary creatinine was measured by the basic picric acid method. Estimated glomerular filtration rate (eGFR) was evaluated by the modification of diet in renal disease formula (MDRD) and patients were classified into CKD stages according to K/DOQI guidelines. The MDRD–GFR equation is: eGFR (mL/min/1.73 m²) = 170 × Scr−0.999 × age−0.177 × (0.762 if female) × BUN−0.178 × Alb0.318. All patients were asked to complete a questionnaire that consisted of age, gender, primary disease and medical history (including hypertension, diabetes, cardiovascular disease, renal disease and hyperlipidemia). ACR between 10 and 25 mg/mmol was defined as microalbuminuria (MAU) and ACR >25 mg/mmol was defined as proteinuria.

Definition and evaluation of risk factors

Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg or history of hypertension. Blood pressures were measured according to the guideline of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) [5].

Hyperglycemia was defined as the use of insulin or oral hypoglycemic medications or a fasting glucose level ≥7 mmol/L or 2 h plasma glucose ≥11.1 mmol/L [6].

Hyperlipidemia was defined as a history of hypercholesterolemia and hypertriglyceridemia or use of medication for hyperlipidemia or a serum cholesterol level >5.70 mmol/L or serum triglyceride level >1.72 mmol/L [7].

Anemia was defined as a history of anemia or use of medication for anemia or hemoglobin <130 g/L for men and <120 g/L for women [8].

Hyperuricemia was defined as a history of hyperuricemia or gout or use of anti-hyperuricemic medicines or a serum uric acid level >420 µmol/L for men and >350 µmol/L for women [9].

Cardiovascular disease (CVD) included a history of both recognized and silent myocardial infarction or undergoing angioplasty and coronary bypass procedures, angina or congestive heart failure or pathologic abnormality on ECG.

Outcomes

Patients were followed up for 30 days after stroke attack. We defined cases according to their short-term prognosis: a no sequelae (non-paralysis) group and a sequelae group (paralysis or death).

Statistical analysis

Statistical analysis was performed by SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Data are presented as means ± standard deviations, medians (for continuous variables) or proportions (for categorical variables). All patients were stratified into two groups (CKD and non-CKD) on the basis of MDRD–GFR and urinary tests. Differences in distributions of the variables between the two groups were analyzed by t-tests and chi-square tests (for the continuous variables). We also fitted a binary logistic regression model to set outcomes at 1 if CKD was present to identify significant risk factors. The original model included age, gender, hypertension, diabetes, CVD, hypercholesterolemia, anemia, hyperglycemia, hyperuricemia and proteinuria. The significance level was set at 0.05.

Results

Demographic characteristics

A total of 1014 patients met the inclusion criteria and were enrolled in the study. They had a mean age of 68.6 ± 12.2 years old (range 14–87 years). Five hundred and fifty-nine (55.1%) were males and 455 (44.9%) were females. Among these, 708 patients had ischemic stroke, 197 patients had hemorrhagic stroke and 109 patients had TIA (Table 1).

Urinary tests

Patients (1004/1014, 99%) were given routine urine tests and/or ACR tests. Of these, 24.8% (249/1004) had dominant proteinuria, while 11.2% (83/739) patients had MAU (ACR 10–25 mg/mmol). In all, the prevalence of dominant proteinuria was greater than that of MAU.

Ischemic stroke patients (701/708, 99%) were given routine urine tests and/or ACR tests. Among these patients, 24.7% (173/701) had dominant proteinuria, while 10.9% (57/523) had MAU.

Hemorrhagic stroke patients (195/197, 99%) were given routine urine tests and/or ACR tests, 33.3% (65/195) had dominant dominant proteinuria, while 16.4% (32/197) had MAU.

TIA patients (108/109, 99.1%) were given routine urine tests and/or ACR test. 10.2% (11/108) of these patients had dominant proteinuria, while 4.9% (4/82) had MAU.

The prevalence of proteinuria differed among these three subtypes of patients with CVL, and the highest prevalence was in the hemorrhagic stroke group. The difference between the hemorrhagic and ischemic stroke groups was significant (P < 0.05).

Kidney function

The average level of serum creatinine was 97.58 ± 72.44 µmol/L (range 25–869 µmol/L). Average eGFR was 75.35 ± 26.44 mL/min/1.73 m² (range 4.2–237 mL/min) (Table 1). Patients of 26.1% (265/1014) had eGFR <60 mL/min. Table 2 shows that the prevalence of CKD in the entire population was 47.7%. After all patients were classified, 47.6% (337/708) of those with ischemic stroke, 55.3% (109/197) with hemorrhagic stroke and 34.9% (38/109) with TIA had CKD.

Risk factors of short-term prognosis of patients with CVL

The major complications in our study patients were hypertension (88.2%), CVD (70.3%), hyperglycemia (37.5%), hyperlipidemia (44.8%), anemia (26.3%), previous CVL (27.9%) and hyperuricemia (18.7%) (Table 1).

We compared these variables in 1014 incident CVL patients between those with (n = 484) or without (n = 530)
CKD determined by K/DOQI stage. The original model included age, gender, hypertension, diabetes, CVD, hypercholesterolemia, anemia, hyperglycemia, hyperuricemia and proteinuria and other factors. A logistic regression model was used to predict the absence of CKD, CKD Stages 1–2 or CKD Stages 3–5 in the 1014 incident patients with CVL. The factors that predicted CKD included age ($P = 0.000$), male sex ($P = 0.000$), hyperglycemia ($P = 0.01$), hypertension ($P = 0.04$) and CVD ($P = 0.007$) (Table 3).

We excluded TIA patients because their condition and prognosis were relatively better than the other patient groups. The remaining 905 subjects (including 708 ischemic stroke patients and 197 hemorrhagic stroke patients) were entered into further analysis and included 506 males and 399 females with an average age of 68.8 $\pm$ 12.0 years. These patients were classified into two groups according to their short-term prognosis: a no sequelae (non-paralysis) group (568 patients) and a sequelae (paralysis or death) group (337 patients).

A logistic regression model (Table 4) was used to show independent predictors of 30-day sequelae in these 905 patients. The prevalence of proteinuria, hypertension, hyperglycemia, anemia and hyperlipidemia was higher in patients with paralysis or death than in patients with non-paralysis. Proteinuria (OR = 1.69), hyperglycemia (OR = 1.67) and anemia (OR = 1.37) were significantly associated with short prognosis in patients with CVL ($P < 0.05$).

### Discussion

This study showed that 47.7% of patients with CVL also had CKD. Proteinuria, microscopic hematuria and decreases in eGFR were markers of kidney damage. This is the first and one of the largest studies of Chinese CKD inpatients with CVL. In these patients, serum creatinine was the most common marker of kidney function. Because creatinine is produced by muscle and its plasma concentration is proportional to muscle mass, formulae such as the Cockcroft–Gault equation and the MDRD equation attempt to correct factors affecting muscle mass, such as age, body size, gender and race. However, these equations have rarely been used in populations similar to that in the present study. At present, there are no equations that have been specifically designed for elderly patients or for patients with CVL. In our study, the MDRD formula was used to evaluate kidney function in our patients.

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<th>Table 1. Clinical and biochemical characteristics of 1014 patients with CVL ($N = 1014$)</th>
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<td>Variable</td>
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<td>CVD</td>
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<td>hyperglycemia</td>
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<td>Previous CVL</td>
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<td>Proteinuria</td>
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<th>Table 2. The prevalence of CKD according to K/DOQI staging in 1014 incident patients with verified CVL</th>
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<th>Table 3. Comparison of selected variables in 1014 incident patients having CVL with ($n = 484$) or without ($n = 530$) CKD according to K/DOQI stage</th>
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<td>Age ($&gt;65$ years) (%)</td>
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having CVL. We found that 26.1% of patients with CVL had eGFR <60 mL/min/1.73 m². Although our patients were recruited from different hospitals, all serum creatinine measurements were made at our center and all eGFRs were calculated using this measurement. CKD among patients with CVL has been little studied. The REGARDS study [10], performed in the USA, included 20 667 participants averaging 66.2 ± 9.0 years and showed a high prevalence of CVL. Their study estimated eGFR by the four-variable MDRD formula and found that 43.3% had an eGFR of <60 mL/min/1.73 m². In our study, 47.7% of patients with CVL also had CKD. In addition, we also used eGFR and abnormal urinalysis (proteinuria and hematuria) to define CKD. The prevalence of CKD in patients with CVL in our study was higher than that in the REGARDS study and also higher than in the coronary heart disease (CHD) [11] population, which was 24.8%. The prevalence of CKD in our study was higher than in the elderly population (≥60 years old) (38.3%), diabetes patients (40.2%) and in hypertension patients (24.6%) from the National Health and Nutrition Examination Surveys [12] study. In our population, the use of the MDRD-GFR equation together with urinoscopy provided a good screen for CKD.

Uronoscopy has been widely used as a non-invasive test for early screening of kidney injury. MAU is a sensitive marker of vascular endothelium function and is also a risk factor for stroke. A Spanish study that enrolled 200 patients (51.5% men, age 72.5 ± 8.5 years) having ischemic stroke within the first 24 h of evolution found that albuminuria (ACR ≥ 30 mg/g) was at 24.5% [13]. In our study, MAU was detected in 11.2% of patients, while proteinuria was found in 24.8% of patients. While studying the prevalence of MAU in the general population, and especially in non-diabetic and non-hypertensive subjects (n = 40856), Hillege et al. [14] found that 7.2% of patients had MAU and 0.2% had proteinuria. The China Heart Survey [11] reported that 22.3 and 8.4% of the participants had MAU and albuminuria, respectively, in Chinese adults (n = 3513) with coronary heart disease. The AusDiab [15] and MAP studies [16] reported that 23.2 and 39.8% of diabetes patients, respectively, had MAU. An examination of ACR in non-insulin dependent diabetes mellitus (NIDDM) patients (n = 214) in the department of Endocrinology at our hospital [17] showed that 23.4% had MAU and 8.8% had proteinuria. Agrawal et al. [18] studied 11 343 non-diabetic hypertensive patients and showed that MAU was present in 32% of men and 28% of women (P < 0.05). Compared with other populations, the prevalence of proteinuria in patients with CVL was much higher than the general population but was similar to that in CVD and diabetes patients. The prevalence of MAU in patients with CVL was lower than in CVD and DM patients, but the prevalence of proteinuria was clearly greater than in these two populations. Thus, in the general population, in the CVD population and in DM patients, proteinuria primarily consists of MAU. The prevalence of proteinuria was high and the proteinuria status of patients with CVL was different from other high-risk populations, which was mainly a dominant proteinuria. The assessment of different CVL subtypes showed that the prevalence of hemorrhagic stroke was higher than ischemic stroke. These findings suggest that the occurrence of proteinuria is related to the severity of CVL.

Sacco et al. [19] studied 30-day prognosis in acute stroke patients and found that age, level of consciousness and stroke type were the determinants of recurrence and mortality after ischemic stroke. They also showed [19, 20] that diabetes or hyperglycemia, CVD and hypertension were significant predictors of long-term mortality. Recently, decreases in eGFR were demonstrated to be prognostic in stroke patients. A study by MacWalter et al. [4] showed that stroke patients with eGFR <38.8 mL/min had poorer outcomes than the control group. Covie et al. [21] suggested that the short-term evolution following stroke is sometimes associated with acute kidney injury (AKI) as a possible complication. Baseline kidney function has emerged as a significant independent marker for short-term survival after an acute stroke and as a risk factor for subsequent AKI. Several studies have demonstrated that CKD is an independent predictor for prognosis in stroke patients.

MacWalter et al. [4] enrolled 2042 unselected consecutive stroke patients, even after adjustment for confounders (age, neurological score, ischemic heart disease, hypertension, smoking and diuretic use), patients with reduced admission calculated creatinine clearance, elevated serum...
creatinine and urea concentrations, elevated ratio of urea to creatinine and higher mortality risk.

In a study performed in Finland, investigators [22] examined a 7-year follow-up of NIDDM (n = 1056) subjects in 1996 and found that dominant proteinuria significantly predicted stroke and other atherosclerotic vascular diseases regardless of other cardiovascular risk factors, including mortality. The higher level of proteinuria was associated with a higher risk for stroke (P < 0.001). The Honolulu Heart Program [23] performed a prospective observational study of 6252 Japanese American men aged from 45 to 68 years over a 27 year period and demonstrated that proteinuria detected by urine dipstick screening predicted increased risk for incident stroke and CHD. Our present findings suggest that the severity of stroke is likely associated with the occurrence of proteinuria. In fact, we found that proteinuria (OR = 1.69) was one of the major high-risk factors for short prognosis in patients with CVL (P = 0.0005). Albuminuria is an important risk factor for vascular complications and for poor prognosis. Therefore, patients with CVL should be screened for MAU in addition to routine urine tests to detect possible renal dysfunction. Hyperglycemia (OR = 1.67) and anemia (OR = 1.37) were also significantly associated with short-term prognosis in patients with CVL. Future work is needed to improve the detection of CKD in this population.

In summary, the prevalence of CKD in our population was 47.7%. It is therefore important to test for CKD among patients with CVL. Proteinuria was also common in our population and was more severe than in other populations. Because proteinuria is an important risk factor for the short prognosis of CVL, a screening for proteinuria that includes evaluation of proteinuria is an important risk factor for the short prognosis and was more severe than in other populations. Because proteinuria was detected by urine dipstick screening predicted increased risk for incident stroke and CHD. Our present findings suggest that the severity of stroke is likely associated with the occurrence of proteinuria. In fact, we found that proteinuria (OR = 1.69) was one of the major high-risk factors for short prognosis in patients with CVL (P = 0.0005). Albuminuria is an important risk factor for vascular complications and for poor prognosis. Therefore, patients with CVL should be screened for MAU in addition to routine urine tests to detect possible renal dysfunction. Hyperglycemia (OR = 1.67) and anemia (OR = 1.37) were also significantly associated with short-term prognosis in patients with CVL. Future work is needed to improve the detection of CKD in this population.

Conflict of interest statement. None declared.

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