Chronic Kidney Disease, All-Cause Mortality and Cardiovascular Mortality Among Chinese Patients with Established Cardiovascular Disease

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Aim: This study was conducted to investigate the role of chronic kidney disease (CKD) in 1-year all-cause mortality and cardiovascular mortality among Chinese patients who were at least 50 years old and had a history of coronary artery disease (CAD), stroke, or peripheral vascular disease (PAD), or with two or more cardiovascular risks.

Methods: Of 3,732 hospitalized patients enrolled, 3,423 patients (91.7%) with complete data were eligible for 1-year follow-up. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m².

Results: 1,166 (34.1%) were diagnosed with CKD. Most cases were unrecognized. Patients having an eGFR of <30 mL/min/1.73 m² were less likely to be prescribed beta-blockers, statins, or aspirin (all p<0.001). A powerful relationship was observed between the severity of renal dysfunction and all causes of death or cardiovascular death. Adjusted for other covariates, the hazard ratio (HR) for all causes of death and for cardiovascular death among patients with an eGFR of 30−45 mL/min/1.73 m² was 1.70 (95% CI, 1.18−2.45) and 1.85 (95% CI, 1.12−3.01) as compared with 2.93 (95% CI, 1.96−4.38) and 3.47 (95% CI, 1.91−6.31) for patients with an eGFR of <30 mL/min/1.73 m².

Conclusions: One third of Chinese patients at high risk for atherosclerotic events were diagnosed with CKD. Most of these cases were unrecognized and undertreated. An eGFR of <45 mL/min/1.73 m² was an independent predictor of all causes of death and of cardiovascular death.


Key words: Chronic kidney disease, Cardiovascular disease, All-cause mortality, Cardiovascular mortality
risk factor for death or CVD outcomes\textsuperscript{2, 8-18}. Therefore, there is an urgent need to develop and implement strategies aimed at slowing the progression of CKD and preventing the development or worsening of CVD. The most promising strategies will most likely use a multidisciplinary approach to deliver multiple interventions, which should include high risk screening programs for early detection, and patient education. However, despite the high prevalence of chronic kidney disease in those with atherosclerosis, disease management is not optimized for such patients\textsuperscript{19-21}. 

Therefore, we hereby initiated a multicenter prospective study to establish the role of CKD in 1-year all-cause mortality and cardiovascular mortality among patients who had evidence of vascular disease or with two or more cardiovascular risks. Additionally, we wanted to evaluate medical treatments for CKD in China.

**Methods**

**Study Subjects**

This investigation is based on a large-scale epidemiological study in China with cross-sectional and longitudinal parts. The details of the registry and early findings have been described elsewhere\textsuperscript{22}. 

From Oct. 2004 to Jan. 2005, 3732 hospitalized Chinese patients from eight University Hospitals in Beijing and Shanghai, who were at least 50 years old and had a history of coronary artery disease (CAD), stroke, or peripheral artery disease (PAD), or with two or more cardiovascular risk factors were sequentially enrolled in the study. All subjects were inpatients from various departments and were admitted to hospital because of CAD, stroke, PAD, hypertension, hyperlipidemia, or diabetes. Patients with any of the following were excluded: New York Heart Association (NYHA) class III-IV congestive heart failure, pregnancy or current lactation, mental disorder, serious diabetes and resultant complications (e.g., ketoacidosis or hypertensive crisis), or secondary hypertension. Patients who had already received a kidney transplant or who were receiving maintenance dialysis at admission were also excluded. The local ethics committee approved the study and all participants gave written informed consent.

**Definition**

Patients were defined as having CAD if they had a history of myocardial infarction (MI), angina, revascularization by percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Strokes were confirmed from medical records according to the criteria of the National Survey of Stroke\textsuperscript{23}. PAD was defined as an ankle brachial index (ABI) of ≤0.9, or peripheral revascularization or amputation because of PAD.

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or if the patient was currently being treated for hypertension. Diabetes mellitus (DM) was defined as an established fasting glucose concentration ≥7.0 mmol/L, or if the patient was using insulin or oral medications for diabetes. Smoking habits were recorded and those who smoked at least 10 cigarettes/day were considered smokers. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were determined using standard laboratory techniques. Lipid disorder was defined as a TC level >5.7 mmol/L, a LDL-C level >3.6 mmol/L, or treatment with antihyperlipidemic agents.

**Estimated Glomerular Filtration Rate (GFR)**

Renal function was assessed using eGFR. Blood was collected by venipuncture after an overnight fast of at least 10 hrs. The serum creatinine (Scr) concentration was measured by the Jaffe method. eGFR was calculated using a new equation, developed by altering the Modification of Diet in Renal Disease (MDRD) equation, based on data from Chinese CKD patients\textsuperscript{24}.

\[
eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times \text{Scr (mg/dL)}^{-1.234} \times \text{age (year)}^{-0.179} \times \begin{cases} 1.159 \text{ (female)} \end{cases}
\]

We used a modified National Kidney Foundation classification of chronic kidney disease\textsuperscript{25}, which classifies eGFR in the following ranges: at least 60 mL/min/1.73 m\textsuperscript{2}, 45 to 59 mL/min/1.73 m\textsuperscript{2} (stage 3a), 30 to 44 mL/min/1.73 m\textsuperscript{2} (stage 3b), and <30 mL/min/1.73 m\textsuperscript{2} (stage 4 and stage 5). eGFR values <60 mL/min/1.73 m\textsuperscript{2} were considered abnormal and indicative of reduced kidney function and CKD. Unrecognized CKD was defined post hoc when the diagnosis of renal insufficiency (RI) (eGFR <60 mL/min/1.73 m\textsuperscript{2}) was missing from the diagnosis list on the data form.

**Outcomes**

Outcomes of interest included all causes of death and cardiovascular death. Cardiovascular death is defined as death due to CAD or stroke. After a follow-up period of 13.6 months ending in April 2006, death was identified from hospital records or by contacting the participants’ families. Causes of death were investigated using medical records and informant interviews.
Statistical Analysis

Means, standard deviations and percentages were used to describe the baseline characteristics. Continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables are expressed as frequencies and percentages. For descriptive purposes, eGFR is presented as a categorical variable, but was also treated as a continuous measure in statistical tests. Baseline characteristics were analyzed with the use of a one-way ANOVA for continuous variables and Chi-square test for categorical variables. To examine the relationship between eGFR and cause of death or cardiovascular death, a multivariate Cox regression analysis was conducted with patients having a normal eGFR (≥60 mL/min/1.73 m²) as the reference group. Statistical significance was considered as a 2-tailed probability of less than 0.05. All statistical analyses were performed with SPSS (Statistics Package for Social Science) version 11.5.

Results

During a mean follow-up time of 13.6 ± 1.5 months, 309 participants (8.3%) were lost because of changes of telephone number or family address. Among the missing participants were 13, 29, 55 and 212 patients with eGFR ≤30, 30–45, and ≥60 mL/min/1.73 m², respectively. Baseline characteristics were comparable between those followed completely and those lost to follow-up. There were 3,423 participants with complete data for up to 1 year of follow-up.

The population sample included 1,639 (47.9%) women with a mean (SD) age of 69.2 (9.4) years. Overall, 1,911 (55.8%) patients had CAD, 925 (27.0%) had PAD, 1,164 (34%) had stroke, 734 (21.4%) had multiple risk factors and 1,066 (31.2%) had two or three diseases.

Baseline characteristics of the study population according to the severity of renal insufficiency are presented in Table 1. A total of 2,257 (65.9%) patients had a normal eGFR of ≥60 mL/min/1.73 m², 680 (19.9%) patients had an eGFR of 45–59 mL/min/1.73 m², 300 (8.8%) patients had an eGFR of 30–44 mL/min/1.73 m² and 186 (5.4%) patients had an eGFR of <30 mL/min/1.73 m². A total of 1,166 (34.1%) patients had calculated eGFR values <60 mL/min/1.73 m². CKD was unrecognized by hospital physicians in 949 (81.4%, 95% confidence interval [CI], 79–84%) patients with an eGFR <60 mL/min/1.73 m². Specifically, a diagnosis of CKD was absent in 82.0% of patients with an eGFR of 30–45 mL/min/1.73 m² and in 38.7% of patients with a eGFR of <30 mL/min/1.73 m².

Mean age as well as systolic and pulse pressure all increased with progressively lower eGFR values. The proportion of the sample population with hypertension, and a history of CKD and PAD was also higher with decreasing eGFR values (p<0.01). As shown in Table 1, patients having an eGFR of <30 mL/min/1.73 m² were less likely to be prescribed beta-blockers, statins, or aspirin (all p<0.001).

Follow-up revealed that 294 patients had died (8.6%). Cardiovascular death occurred in 121 (41.2%) of the cases.

For all patients, a continuous inverse relationship was evident between the severity of renal dysfunction and mortality as well as cardiovascular death. After adjustments for age and sex, a Cox regression model showed that a 10 mL/min/1.73 m² decrease in eGFR conferred an increased risk of all causes of death (HR 1.12, 95% CI, 1.05–1.19, p<0.001) and cardiovascular death (HR 1.12, 95% CI, 1.03–1.22, p=0.009) at one year.

In the age- and gender-adjusted analysis (Table 2), the hazard ratio (HR) for all causes of death and cardiovascular death for patients with an eGFR of 30–45 mL/min/1.73 m² and patients with an eGFR of <30 mL/min/1.73 m² was highly statistically significant. The HR for patients with an eGFR of 45–59 mL/min/1.73 m² was not significant. Adjusted for age, sex, hypertension, dyslipidemia, current or former smoker, diabetes mellitus, CAD, peripheral artery disease, and stroke, the hazard ratio (HR) for all causes of death and cardiovascular death for patients with an eGFR of 30–45 mL/min/1.73 m² was 1.70 (95% CI, 1.18–2.45) and 1.85 (95% CI, 1.12–3.01) as compared with 2.93 (95% CI, 1.96–4.38) and 3.47 (95% CI, 1.91–6.31) for patients with an eGFR of <30 mL/min/1.73 m².

Discussion

In a representative population of Chinese patients with CVD, we demonstrated that among patients over 50 years of age with a history of CAD, stroke, or PAD, or with two or more cardiovascular risks, there was greater than 33% prevalence of stage three CKD or worse according to the National Kidney Foundation guidelines. There was an increasing tendency in the prevalence of hypertension, diabetes, PAD and prior MI with eGFR decreasing at baseline (Table 1). However, even after controlling for all significant explanatory variables, an eGFR of ≤45 mL/min/1.73 m² was significantly correlated with all causes of mortality and cardiovascular mortality in this population.

The MDRD equation is recommended for esti-
Table 1. Baseline Characteristics, Cardiac Medication, All-cause Death, and Cardiovascular Death of Patients Stratified by eGFR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>eGFR (mL/min/1.73 m²)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 30 (n = 186)</td>
<td>30–45 (n = 300)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>70.6 ± 9.3</td>
<td>73.3 ± 8.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>119 (64.0)</td>
<td>212 (70.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 ± 4.0</td>
<td>24.4 ± 3.8</td>
</tr>
<tr>
<td>HT (%)</td>
<td>161 (86.6)</td>
<td>247 (82.3)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>57 (30.6)</td>
<td>103 (34.3)</td>
</tr>
<tr>
<td>Current or former smoker (%)</td>
<td>82 (44.1)</td>
<td>151 (50.3)</td>
</tr>
<tr>
<td>DM (%)</td>
<td>94 (50.5)</td>
<td>136 (45.3)</td>
</tr>
<tr>
<td>CAD</td>
<td>85 (45.7)</td>
<td>176 (58.7)</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>30 (16.1)</td>
<td>64 (21.3)</td>
</tr>
<tr>
<td>Prior angina pectoris (%)</td>
<td>78 (41.9)</td>
<td>164 (54.7)</td>
</tr>
<tr>
<td>PCI</td>
<td>15 (8.1)</td>
<td>31 (10.3)</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (2.2)</td>
<td>12 (4.0)</td>
</tr>
<tr>
<td>Peripheral artery disease, (%)</td>
<td>83 (44.6)</td>
<td>121 (39.7)</td>
</tr>
<tr>
<td>stroke</td>
<td>64 (34.4)</td>
<td>119 (39.7)</td>
</tr>
<tr>
<td>Unrecognized CKD</td>
<td>72 (38.7)</td>
<td>246 (82.0)</td>
</tr>
<tr>
<td>Recognized CKD or history of CKD</td>
<td>114 (61.3)</td>
<td>54 (18.0)</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>4.2 ± 2.7</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>eGFR</td>
<td>16.3 ± 8.8</td>
<td>38.6 ± 4.3</td>
</tr>
</tbody>
</table>

Cardiac Medication

| Aspirin                        | 107 (57.5)     | 215 (71.7)     | 508 (74.7)     | 1,425 (63.1)   | <0.0001 |
| Beta-blockers                  | 59 (31.7)      | 135 (45.0)     | 310 (45.6)     | 806 (35.7)     | <0.0001 |
| ACE inhibitors or ARBs         | 103 (55.4)     | 196 (65.3)     | 433 (63.7)     | 1,146 (50.8)   | <0.0001 |
| Statins                        | 50 (26.9)      | 133 (44.3)     | 294 (43.2)     | 783 (34.7)     | <0.0001 |
| CCB                            | 104 (55.9)     | 119 (39.7)     | 255 (37.5)     | 816 (36.2)     | <0.0001 |
| Diuretics                      | 74 (39.8)      | 138 (46.0)     | 204 (30.0)     | 557 (24.7)     | <0.0001 |

Outcome

| All cause death                | 39 (21.0)      | 47 (15.7)      | 60 (8.8)       | 148 (6.6)      | <0.0001 |
| Cardiovascular death           | 14 (7.5)       | 19 (6.3)       | 28 (4.1)       | 60 (2.6)       | <0.0001 |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCB = calcium channel blocker; DM = Diabetes mellitus; eGFR = estimated glomerular filtration rate; HT = hypertension; MI = myocardial infarction; PCI = percutaneous coronary intervention

Table 2. All-cause Mortality and Cardiovascular Mortality by eGFR

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Age- and Gender-Adjusted HR (95% CI)</th>
<th>Fully Adjusted Model* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>≤ 30</td>
<td>3.10 (2.08–4.75)</td>
<td>3.76 (1.62–5.65)</td>
</tr>
<tr>
<td>30–45</td>
<td>2.17 (1.13–2.54)</td>
<td>1.95 (1.02–2.94)</td>
</tr>
<tr>
<td>45–60</td>
<td>0.99 (0.72–1.39)</td>
<td>1.07 (0.65–1.79)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
</tbody>
</table>

*Adjusted for covariates, including age, sex, hypertension, dyslipidemia, current or former smoker, diabetes mellitus, CAD, peripheral artery disease, and stroke. \( p < 0.05 \)

Estimating GFR in adults\(^3\,\,25\). However, ethnicity effects occur when using this equation\(^26\). Furthermore, the Chinese population was not included in the development of the MDRD equation. A new equation for estimating GFR, which was developed by modifying the MDRD equation based on data from Chinese
CKD patients, offered significant advantages in different CKD stages when applied to the Chinese population\(^4\). By using this equation, the prevalence of reduced renal function in the present study was estimated to be ~33\%, which was equivalent to that reported by Glynn for patients with CVD in the community\(^5\), by Anavekar for patients enrolled in the VALIANT trial\(^6\), and by Liu for Chinese patients with CAD in the China Heart Survey\(^2\).

The American Heart Association (AHA) suggests that a value of GFR < 60 mL/min/1.73 m\(^2\) should be regarded as abnormal in adult patients with CVD\(^7\). However, the studies which have evaluated eGFR and the risk of outcomes in the general population have come to different conclusions\(^8\) and studies to determine the risk in patients at a high risk for atherosclerotic events, especially in the Chinese population\(^9\), are very limited. Go et al.\(^8\) examined the relationship of GFR and adverse cardiovascular events in >1.1 million adults. With the best cohort (GFR > 60 mL/min/1.73 m\(^2\)) as the point of reference, they found that the risks of adverse events were evident at an eGFR < 60 mL/min/1.73 m\(^2\) and substantially increased with an eGFR < 45 mL/min/1.73 m\(^2\). The reason why our study did not show an increased risk associated with an eGFR of 45–60 mL/min/1.73 m\(^2\) may be due to a relatively small sample size or short-term follow-up. However, the findings of Go et al.\(^8\) and our study suggest that the system could be further refined, since all persons with stage three CKD (GFR, 30 to 59 mL/min/1.73 m\(^2\)) may not be at an equal risk for outcome.

The proportion of patients with CKD who receive appropriate risk-factor modification and intervention is lower than in the general population, a concept termed “therapeutic nihilism”\(^10\). Many databases and registries have shown that this parallels worsening renal function. In our study, patients in the lowest tier of renal function were the least likely to receive risk-modifying cardiovascular medications, such as aspirin, beta-blockers and statins. Even the use of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which can reduce the risk for adverse cardiovascular and renal outcomes, was not satisfying. It is reasonable to think that Chinese patients with CKD suffer from a paradox of high risk for heart disease and a reduced use of standard therapies for treatment and prevention of heart disease.

The patients for this study came from the Departments of Cardiology, Endocrinology, Neurology, and Geriatrics. The physician awareness rate for CKD was only 18.6\% in our study, and the awareness rate among metropolitan Chinese adults was only 7.2\%\(^11\). Given the vast number of under-diagnosed and undertreated patients with CKD in non-nephrology departments, educational efforts focusing on risk factor assessment and management decision-making for patients with CKD are needed to raise awareness in Chinese physicians.

As with any study, ours has certain limitations. First, serum creatinine levels were measured in different hospitals, therefore they were not directly calibrated to values from the MDRD core laboratory. Second, it is well recognized that albuminuria is a powerful independent risk factor for both the progression of kidney disease, as well as the development of CVD. Unfortunately, albuminuria is not consistently performed in these hospitals; therefore we could not adjust for albuminuria. Third, when used in a Chinese population, the MDRD equation underestimated eGFR in cases of near-normal eGFR\(^12\), thereby affecting the strength of the study.

We believe that our study has useful features and raises important questions. The patients in our study are typical among those receiving clinical care. The inclusion of large numbers of subjects with a spectrum of CVD also enabled us to make a more detailed evaluation of the effect of the overlap of CVD and eGFR on outcomes. Our study reinforces the importance of detection of CKD to identify high risk patients in the atherosclerotic population.

**Grant Support**

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