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Low estimated glomerular filtration rate is associated with poor outcomes in patients who suffered a large artery atherosclerosis stroke

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ABSTRACT

Objectives: The relationship between low estimated glomerular filtration rate (eGFR) and the outcome of ischemic stroke remains controversial, despite the close association between kidney dysfunction and atherosclerosis.

Methods: This study conducted subgroup analysis using data from the prospective Taiwan Stroke Registry to investigate the relationship between eGFR at the time of admission and 6-month functional outcomes in patients with the large artery atherosclerotic (LAA) subtype of acute ischemic stroke. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and outcomes were defined as modified Rankin Scale and mortality status at 6 months post stroke.

Results: Of the 8052 patients with the LAA subtype of acute ischemic stroke in this study, 3312 (41.1%) had eGFR <60 mL/min/1.73 m^2. The adjusted odds ratios of worse functional outcomes following a stroke were 1.10 (95% confidence interval [CI], 0.95–1.28), 1.60 (95% CI, 1.22–2.11) and 1.60 (95% CI, 1.10–2.33) in patients with eGFR 30–59, 15–29, and <15 as compared with those with eGFR 60–119 mL/min/1.73 m^2, respectively. Increased risk of mortality was closely and independently related to high NIHSS scores and low eGFR levels. Stroke severity and eGFR were also synergistically related to 6-month mortality, with an

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adjusted hazard ratio of 21.19 (95% CI, 9.69–46.35) in patients with NIHSS >15 and eGFR <15 mL/min/1.73 m^2, compared with those with NIHSS 0–5 and eGFR 60–119 mL/min/1.73 m^2.
Conclusions: Low eGFR was significantly and independently associated with 6-month functional outcomes and mortality in patients with the LAA subtype of acute ischemic stroke. The deleterious relationship between low eGFR levels and mortality following stroke was exacerbated by its synergistic association with stroke severity.

1. Introduction

Stroke is the leading cause of chronic disability and the third leading cause of mortality worldwide [1]. Kidney dysfunction is also being recognized as an important public health concern [2], and patients with dysfunctional kidneys face a higher risk of cardiovascular disease and stroke [3,4]. For example, in a large cohort study in China, 14%–16% of stroke patients were shown to have kidney dysfunction [5]. A previous meta-analysis study further revealed that the relative risk of stroke was 1.43 among patients with an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 [6]. The close association between stroke and kidney dysfunction is partly explained by their common vascular risk factors [7]. In addition, kidney dysfunction has been shown to be an independent risk factor for atherosclerosis in both humans and animals [8,9], and patients with kidney dysfunction are more likely to have unstable atherosclerotic plaques [10]. Thus, kidney dysfunction increases the risk of suffering from the large artery atherosclerosis (LAA) subtype of ischemic stroke [11].

The precise nature of the relationship between low eGFR and ischemic stroke outcomes remains controversial [12–15]. Some researchers have claimed that the functional outcome of ischemic stroke is worse in patients with low eGFR [12,13], while other researchers have been unable to identify such an association [14,15]. These mixed results may be related to heterogeneity of stroke subtypes among study populations. In addition, not only low eGFR but also high eGFR (≥120 ml/min/1.73 m^2) was associated with higher post-stroke mortality [13], but its influence on specific stroke subtypes is still not clear. The known association between kidney dysfunction and atherosclerosis [8,9], as well as between LAA and high stroke mortality [16,17], compelled us to explore the impact that eGFR level has on stroke outcomes, with a particular focus on the LAA subtype. We hypothesized that both low and high eGFR levels have negative impact on the outcome after LAA subtype ischemic stroke. We also evaluated the combined effects of eGFR levels and stroke severity on the risk of mortality.

2. Methods

2.1. Patients

Between May 2006 and April 2009, 42,610 patients with acute stroke were prospectively registered with the Taiwan Stroke Registry (TSR) [18]. The TSR is a nationwide program, which was established to provide a reliable national stroke database. A total of 39 academic and community hospitals participated in the program, and a 4-step quality control regimen was followed to ensure the reliability of data [18]. Patients were registered within 10 days from the onset of stroke, and the stroke was defined according to the World Health Organization as rapid developing focal neurological deficit lasting for longer than 24 h [19]. Study protocol was approved by the ethics committee at each participating hospital, and written informed consent was obtained from all participants. If a subject was incommunicable, we obtained informed consent from his/her family.

To be included in our study, patients should have received a neurological assessment and computerized tomography (CT) and/or magnetic resonance imaging (MRI) to clarify ischemic stroke from hemorrhagic stroke. A total of 31,336 patients with acute ischemic stroke were identified in the TSR database, and they were divided into 5 subtypes according to TOAST criteria (The Trial of Org 10,172 in Acute Stroke Treatment) [20]. Among them, 8215 patients presented the LAA subtype. The LAA subtype was defined by either significant (>50%) stenosis or occlusion of a major cervical or cerebral artery based on carotid duplex sonography, transcranial color-coded sonography, CT/MRI angiography, or conventional angiography. Patients without serum creatinine data at the time of admission were excluded, which resulted in a total of 8052 patients included in the study.

2.2. Data collection

Clinical data were compiled prospectively by TSR-trained neurologists and nurses (Supplementary data). To assess the impact of eGFR on stroke outcomes, we collected data related to the following parts: (1) preadmission demographic profile, previous medical history, and medications taken prior to admission; (2) score on the National Institutes of Health Stroke Scale (NIHSS) at the time of admission, risk factors of stroke, serum creatinine levels, electrocardiogram results, CT/MRI findings, and duplex sonographic results; and (3) mortality and modified Rankin scale (mRS) score 6 months after onset of stroke, which were obtained via phone interview. Those who were followed up for less than 6 months and without event (mortality) were censored. The number of lost to follow-up at 6 months was 2844. Serum creatinine level and other lab data were collected at individual hospitals upon admission.

We calculated eGFR using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, specifically:

$$\mathrm{eGFR} = 141 \times \min(\mathrm{SCr}/k, 1)^{a} \times \max(\mathrm{SCr}/k, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times [1.018 \text{ if Female}] \times [1.1 \text{ in Chinese population}],$$

where SCr is serum creatinine level on admission; k is 0.7 for females and 0.9 is for males; a is −0.329 for females and −0.411 is for males; min indicates the minimum of SCr/k or 1; and max indicates the maximum of SCr/k or 1 [21]. Our classification of kidney dysfunction was in accordance with that of the K/DOQI Clinical Practice Guidelines, in which low eGFR was defined as eGFR <60 mL/min/1.73 m^2 [22], and high eGFR as eGFR ≥120 mL/min/1.73 m^2 [13].

2.3. Statistical analysis

Eligible patients with LAA ischemic stroke were stratified into 5 subgroups according to eGFR level (≥120 mL/min/1.73 m^2, 60–119 mL/min/1.73 m^2, 30–59 mL/min/1.73 m^2, 15–29 mL/min/