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Association between renal dysfunction and 3-year mortality in patients with acute first-ever ischemic stroke

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ABSTRACT

Objective: The influence of renal dysfunction on the clinical presentation and outcomes of patients with acute ischemic stroke is still controversial. We investigate the influence of renal dysfunction on the outcomes of patients with acute first-ever ischemic stroke.
Methods: Nine-hundred thirty-four patients with acute first-ever ischemic stroke were enrolled and followed for 3 years. Renal function was assessed using the equation of the Modification Diet for Renal Disease for estimated glomerular filtration rate (eGFR). Serum creatinine levels were obtained within 3 days of acute stroke onset. Reduced eGFR was defined as eGFR < 60 ml/min/1.73 m^2. Clinical presentation, risk factors for stroke, laboratory data, co-morbidities, and outcomes were recorded.
Results: Total 264 patients (28.3%) had a reduced eGFR. The prevalence of older age, hypertension, and atrial fibrillation was significantly higher in patients with a reduced eGFR. Total anterior circulation syndrome occurred more frequently among patients with a reduced eGFR ($P = 0.010$). Multivariate Cox regression revealed that a reduced eGFR is a significant predictor of 3-year mortality (HR = 1.67, 95% CI = 1.06–2.62, $P = 0.026$).
Conclusion: Reduced eGFR during the acute stroke stage is associated with increased risk of 3-year mortality. Furthermore, risk of acute complications and poor functional outcomes following discharge was significantly higher in patients with a reduced eGFR.

1. Introduction

Stroke is a continuously evolving medical problem, being the third leading cause of death in Taiwan [1,2]. Chronic kidney disease (CKD) is a worldwide public health concern; its prevalence and incidence in Taiwan is among the highest worldwide [3–5]. Patients with CKD have a higher prevalence of cardiovascular and cerebrovascular diseases [6–9]. Recent studies suggested that CKD is associated with increased risk of incident stroke among patients with pre-existing atherothrombotic disease [10–12]. CKD in stroke patients has been suggested to predict mortality. However, other studies found that CKD is not a prognostic factor in acute stroke [12,13]. Most studies enrolled all types of stroke (including hemorrhage) patients, and did not specifically select patients with ischemic stroke. Hojs et al. suggested that renal dysfunction is associated with increased in-hospital mortality in ischemic stroke patients; however, these patients were not followed up for a long time [14]. Additionally, a recent study suggested that CKD is associated with recurrent stroke, cardiovascular events or all-cause mortality in patients with recent small subcortical infarcts, but the patient number is only 192 [15]. Given that the average annual incidence rate of first-ever stroke in Taiwan is 330 per 100,000, and that in all of the first-ever stroke patients, a greater proportion of patients suffer from ischemic stroke (71%) than cerebral hemorrhage (22%) [1,16], research focusing on the influence of CKD in patients with ischemic stroke is warranted.

Therefore, the aims of this study were to investigate: (1) the role of renal dysfunction in patients with acute first-ever stroke on clinical presentations, acute complications, and functional outcomes after discharge; and (2) whether renal dysfunction is an independent predictor of 3-year mortality or recurrent stroke.

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2. Materials and methods

This prospective clinical study followed the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital (CGMH), Taipei, Taiwan.

2.1. Study patients

All patients involved in this study were recruited from the Stroke Unit of the Department of Neurology at CGMH from January 1, 2001 to December 31, 2003. Only patients with first-ever ischemic stroke were enrolled, and individuals with either previous stroke, infarction or hemorrhage, or a diagnosis of uncertain type of stroke were excluded. The clinical diagnosis of acute ischemic stroke was according to the World Health Organization criteria, which was further confirmed by brain computed tomography or magnetic resonance imaging (MRI) scan [17]. Patients with symptoms lasting less than 24 h without evidence of acute cerebral infarction in the MRI were diagnosed as transient ischemic attack (TIA) and were excluded.

Co-morbidities were determined after an in-depth review of the medical records, including history and physical examination, progress notes, discharge summaries, and consultations. Hypertension was defined as known hypertension diagnosed by a clinician, or systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg on two different occasions, with the second measurement taken more than 5 days after the stroke [18–21]. Diabetes mellitus (DM) was diagnosed in patients with previously treated DM or in patients with fasting plasma glucose ≥126 mg/dL, a 2-h value in the oral glucose tolerance test or a random plasma glucose concentration ≥200 mg/dL, in the presence of symptoms. Hyperlipidemia was defined as a fasting blood cholesterol level was ≥200 mg/dL and/or a triglyceride level was ≥200 mg/dL. Atrial fibrillation (AF) was diagnosed if it was present on a standard 12-lead ECG. Coronary artery disease (CAD) was diagnosed if there were past incidences of acute myocardial infarction or angina pectoris. Congestive heart failure (CHF) was present if the patient was previously diagnosed by a cardiologist or the condition was found by physical examination and confirmed by transthoracic cardiac echo study. Cigarette smoking was defined as a current smoker or a smoker with cessation less than 5 years ago.

Renal function on admission was assessed using the abbreviated equation from the Modification Diet for Renal Disease (MDRD) study. The formula is, as follows [22]:

$$\text{Estimated glomerular filtration rate (eGFR) (in ml/ min per 1.73 m}^2\text{)} = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).$$

Since the use of the MDRD formula requires that renal function is in a steady state, patients with acute kidney injury (AKI) were excluded. The absolute or relative change in serum creatinine was used to define AKI on the basis of the definition of Acute Dialysis Quality Initiative Group, where an absolute increase in serum creatinine of either ≥0.3 mg/dL(≥25 μmol/l) or a percentage increase of ≥50% was indicative of AKI [23].

Patients were divided into 2 groups according to the eGFR: normal eGFR group, which comprised of patients with an eGFR ≥60 ml/min/1.73 m^2, and reduced eGFR group, which comprised of patients with an eGFR < 60 ml/min/1.73 m^2 [10,24].

2.2. Definition and clinical subtypes of ischemic stroke

Clinical subtypes of ischemic stroke were rated according to the classification of the Oxfordshire Community Stroke Project (OSCP) classification. The subtypes were partial anterior circulation syndrome, total anterior circulation syndrome (TACS), posterior circulation syndrome, and lacunar syndrome (LACS) [25]. TIA was defined by the new tissue-based definition endorsed by the American Stroke Association [26]. TIA mimics were excluded. Clinical course of acute stroke stage, mean length of acute-ward stay, mortality rates during and following acute ward stay, and frequency of medical complications were monitored. Stroke in evolution refers to a neurologic deficit that progresses (increased severity of the neurological signs) within 7 days after stroke onset [27]. Functional outcomes upon discharge were assessed according to the modified Rankin Scale (mRS) [28,29]. "Functionally dependent" was defined as having an mRS score of 3, 4 or 5.

2.3. Laboratory measurements

All blood samples were obtained upon admission and were centrifuged, and stored at −70 °C until use in assays. Serum albumin, creatinine, cholesterol, triglyceride, sodium, white blood cell counts, and hemoglobin levels were assayed and recorded. All other markers were analyzed by standard automated laboratory methods.

2.4. Follow-up

Patients were followed-up for 3 years after initial assessment. Follow-up consisted of clinical examinations at 1 and 3 months after first stroke and then every 3 months. Clinical examinations during follow-up included history taking, physical and neurological examinations, and mRS score assessment. New major medical problems (e.g. death, recurrent cerebral infarction, cerebral hemorrhage, epilepsy, cancer, cardiovascular diseases, head injury, etc.) were recorded during follow-up. Lipid profile, renal function, liver function and blood sugar were followed every 3–6 months. End points included recurrent ischemic stroke or death. Recurrent stroke was defined as any new focal neurological deficit of sudden onset that lasting at least 24 h for which no other cause could be found other than ischemic stroke. A diagnosis of recurrence was not done where symptoms could be attributed to edema, mass effect, brain shift syndrome or hemorrhagic transformation, and could not be diagnosed within 24 h of the index stroke. Every death occurring during the follow-up was reviewed.

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as a number or percentage for each item. Comparisons among the 2 patient groups were performed by the Chi-square or Student's t tests. Independent associations between the various variables and the probability of having reduced eGFR were analyzed using logistic regression. All variables with a $P < 0.1$ in the univariate logistic regression were then entered into a stepwise, backward multivariate logistic regression. The Cox proportional hazards model was used to determine the significance of each variable in predicting 3-year all-cause mortality. A univariate Cox model, assessing all previously identified variables, was used to measure hazard ratio (HR) for mortality. A backward, stepwise multivariate Cox regression model was also used to identify the risk factors for 3-year mortality. All statistical calculations were performed with SPSS 13.0 for Windows.