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# Acute kidney injury in patients with cerebrovascular stroke and its relationship to short-term mortality

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**ABSTRACT**

The adverse outcome after cerebrovascular stroke (CVS) is determined not only by the neurological deficits but also by medical comorbidities including kidney dysfunction. We studied the frequency of acute kidney injury (AKI) with CVS and its relationship to short-term mortality. This study included 80 patients with stroke (mean age: 62.5 ± 6.2 years). Stroke severity was determined using Scandinavian Stroke Scale (SSS). Serum creatinine (SCr), creatinine clearance (CrCl) and kidney injury molecule-1 (KIM-1) concentrations were the measured markers of AKI. Follow-up was done for 3-months or till death. Cox proportional hazards model was used to evaluate contributors to mortality. Compared to reference group, patients had higher SCr ($p < 0.05$) and KIM-1 ($p < 0.001$) and lower CrCl ($p < 0.01$). The majority of patients (86.25%) had normal SCr, while 57.5% had lower CrCl (<70 ml/min) and 92.5% had higher KIM-1 (>0.75 ng/ml). Mortality rate was 35%. Compared to survivors, patients who died had lower SSS, higher SCr and KIM-1 and lower CrCl (all $p < 0.001$). Higher SCr [Hazard ratio (HR), 1.65; 95% CI, 1.41 to 1.93], KIM-1 [HR, 1.63; 95%CI, 1.21 to 2.19] and lower CrCl [HR, 1.34; 95% CI, 1.09 to 1.65] significantly predicted worse short-term survival. We conclude that AKI is a common complication of CVS. Increase in SCr, KIM-1 and decrease in CrCl concentrations are associated with worse short-term outcome with stroke.

**Keywords:** Cerebrovascular stroke, acute kidney injury, kidney injury molecule-1, mortality.

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## INTRODUCTION

Cerebrovascular stroke (CVS) is a major cause of disability and poor quality of life. The high rates of disability and mortality due to CVS are determined not only by the neurological deficits but also by the associated medical comorbidities as cardiovascular disease, hypertension, diabetes and renal dysfunction (de Haan et al., 1995; M'Buyamba-Kabangu et al., 1995; MacWalter et al., 2002; Tsagalis et al., 2009; Theofanidis, 2015).

Acute kidney injury (AKI) is characterized by abrupt deterioration in kidney function which clinically manifesting as a reversible acute increase in nitrogen waste products, measured by blood urea nitrogen (BUN) and serum creatinine (SCr) levels with or without reduced urine output over the course of hours to weeks (Schrier et al., 2004). AKI is a common comorbid condition in the community with different medical events which include cardiovascular disease (Smith et al., 2003), diabetes mellitus (Kelly et al., 2009; Vaidya et al., 2011; Fu et al., 2012), hypertension (Perneger et al., 1993) and cerebrovascular stroke (MacWalter et al., 2002; Tsagalis et al., 2009; Zacharia et al., 2009; Kobayashi et al., 2010; Rayes et al., 2011) and intensive care unit (Hoste and Schurgers, 2008). AKI has an estimated incidence of 2 to 3 cases per 1,000 persons. Seven percent of hospitalized patients and about two-thirds of patients in intensive care units can develop AKI (Liano and Pascual, 1996; Hoste and Schurgers, 2008). Although, AKI is common and imposes a heavy burden of illness (morbidity and mortality), however, it is amenable to prevention, early

detection and treatment.

In 2012, AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) (KDIGO AKI Work Group 2012) as any of the followings: increase in SCr by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 h; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or decrease in urine volume to <0.5 ml/kg/h for 6 h. However, in current clinical practice, diagnosis and classification of AKI is based on elevations in serial SCr, BUN, creatinine clearance (CrCl) and raised ratio of urea to Cr. SCr and BUN are insensitive and nonspecific markers for AKI. Increase in the SCr occurs few days after AKI. SCr and BUN primarily reflect changes in glomerular filtration and to a lesser extent tubular secretion thus are not true injury markers (Schrier et al., 2004). In the last decade, new serum or plasma and urine renal markers have been identified. They are true markers of kidney injury, help to distinguish between various types of kidney insults, establish the duration and severity of injury, predict the clinical outcome and help to monitor response to treatment (Soni et al., 2009). Urinary AKI markers are classified as enzymes released from damaged tubular cells, low-molecular-weight proteins and proteins produced in the kidney and associated with the development of AKI and structural and functional proteins of renal tubules (Urbschat et al., 2011). Kidney injury molecule-1 (KIM-1) has been qualified by the Food and Drug Administration and European Medicines Agency as a highly sensitive and specific urinary biomarker to diagnose (at the earliest stages), differentiate, and monitor kidney injury from variety of acute and chronic kidney diseases. It is also useful in assessment of severity of and predicting compromised outcome or mortality due to AKI (van Timmeren et al., 2006; Liangos et al., 2007; Han et al., 2008; Vaidya et al., 2011) and for monitoring response to therapy (Waanders et al., 2009). KIM-1 is a marker for renal proximal tubular damage (van Timmeren et al., 2006). Tubular injury is the hallmark of proteinuric (van Timmeren et al., 2006), toxic (Dieterle and Marrer, 2008) and ischemic kidney diseases (Vaidya et al., 2011). KIM-1 is very low or is not detectable in healthy individuals and higher concentrations become detectable within few hours of ischemic acute tubular necrosis (Huang and Don-Wauchope, 2011). KIM-1 is a type I cell membrane glycoprotein and its structure has adhesion molecule properties. KIM-1 functional role is to confer on epithelial cells the ability to recognize and phagocytose dead cells that are present in the post-ischemic kidney and contribute to the obstruction of the tubule lumen that characterizes AKI (Bailly et al., 2002).

## Aim of the study

Limited studies were done to investigate AKI with acute CVS and its relationship to early, short-term and long-term mortality. These studies rely on measurements of SCr and CrCl which are markers of glomerular filtration rate but they are less sensitive for detection of early kidney injury. This prospective study aims to determine the frequency of AKI in patients with CVS and its relationship to short-term mortality (3-months). This is the first study which investigates AKI in patients with acute stroke using KIM-1, a true and sensitive marker of acute ischemic tubular kidney injury. Early detection of AKI in the community of patients with CVS may provide valuable information related to the disease and vascular risk burdens, early intervention and preventive strategies as will be discussed latter.

## PATIENTS AND METHODS

### Study design

This is a prospective study which included 80 consecutive hospitalized patients with acute CVS.

### Patients

Patients were recruited (over a period of 3 months) from the hospitalized patients admitted to the departments of Neurology and Psychiatry, Assiut and Al-Azhar University Hospitals, Assiut, Egypt within one week of stroke onset. Stroke was defined as acute onset of focal neurological deficits attributable to cerebrovascular disease and documented by computerized tomography (CT) or magnetic resonance imaging (MRI). Inclusion criteria for patients were: 1) first-ever CVS, 2) age ranged from 40 to 65 years, 3) patients with ischemic or hemorrhagic strokes were included, and 4) patients admitted to the hospital within one week of stroke onset. Patients were regularly followed up monthly for 3 months or till death through the out-patient Neurology clinic of the University Hospitals to control for the therapeutic measures and secondary prevention.

Informed consent to participate in the study was obtained from patients or their relatives. The local ethical committee of Assiut and Al-Azhar University Hospitals approved the study. Excluded from the study were patients with: 1) persistent disturbed level of consciousness; 2) brain ischemia due to cardio-respiratory arrest; 3) pre-existing chronic renal failure; 4) emergent cardiac disease or undergoing cardiothoracic surgery; 5) exposure to intravascular contrast-media, nephrotoxic medications as aminoglycosides, and amphotericin, drug overdose or drug poisoning; 6) trauma; 7) sepsis; 8) heart failure; 9) glomerulonephritis from any cause e.g. infection, vasculitis, etc; 10) critical care; and 11) urinary tract obstruction.

### Assessment procedures

#### *Demographic and clinical characteristics*

Baseline medical and neurological assessments were done. Demographic data included: age, sex, and history of stroke vascular risk factors (e.g. smoking, hypertension, diabetes mellitus, hypercholesterolemia, cardiac disease and transient ischemic attacks). Drug history included history of use of over-the-counter (OTC) formulations and herbal remedies or recreational drugs. The social history included history of exposure to tropical diseases. Physical examination included evaluation of fluid status, signs for acute and chronic heart failure, and infection. Urine analysis and microscopic examination as well as urinary chemistries may be helpful in determining the underlying cause of AKI. Imaging tests,

especially abdominal ultrasound, are important components of the evaluation for patients with AKI and for exclusion of urinary outlet obstruction.

The degrees of patients' motor and functional disabilities were determined using Scandinavian Stroke Scale (SSS) (Barber et al., 2004). The SSS is a validated neurological stroke scale that evaluates stroke severity on a score from 0 to 58 with lower scores indicating more severe strokes. SSS takes <10 min to administer.

### *Neuroimaging characteristics*

A non-contrast CT brain scan (GE BrightSpeed Elite 16 Slice CT-Japan) examination was done for all patients while MRI-brain (Philips 1.5T Achieva MRI, Netherland) was done in selected patients (as when CT revealed no abnormalities). The following radiological data were collected: presence of hemorrhage, infarct subtypes. The infarct size was defined as: a) large if the infarction involved more than half of a cerebral hemisphere; b) small if the infarction involved >15 mm in diameter but less than one half of a cerebral hemisphere; and c) lacunar if the infarction was <15 mm in diameter. Lacunar infarcts are localized to the territories of deep perforating arteries.

### *Carotid color duplex examination*

Examination of the intima-media thickness of the carotid arteries (CA-IMT) was manually performed using a 5MHZ linear transducer of a color duplex flow imaging system (Acuson 128 XP, Acuson Corporation, Mountain View, CA, USA), which operates in several modes: real time B, color Doppler and spectral Doppler modes. We investigated the degree of stenosis in the common carotid artery (CCA). Significant stenosis of the cervical arteries, defined as a narrowing of ≥30% of the lumen (Widder et al., 1990).

### *Ultrasonography (US) of the kidney*

US was done using a real time ultrasound equipment capable of B-mode imaging, pulsed wave duplex scanning, color Doppler flow imaging and power Doppler imaging (GE, LOGIQ 3 Color Doppler Machine, Korea) using a convex-array probe (3.5 MHz).

### *Laboratory measurements*

Laboratory measurements included: serum creatinine (SCr), electrolytes, complete blood count and differential, blood sugar (fasting and post-prandial), liver function, lipogram [serum total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c)] and urine analysis. Serum levels of TC, TG, HDL-c and LDL-c were measured by enzymatic colorimetric method using the auto analyzer Hitachi 911 (Boehinger, Mannheim, USA). Serum creatinine (SCr) and urinary creatinine concentrations were analyzed using Roche/Hitachi 911 systems chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Urine was collected for 24 h for estimation of creatinine clearance (CrCl). Urine samples were freshly collected and centrifuged at 1000 *g* for 5 min to remove particulate matter and the supernatants were stored at -20°C. The biomarkers were normalized to the urinary creatinine concentration. CrCl (ml/min) was calculated using the Cockroft and Gault (1976) formula: CrCl = (140−age) × weight (kg)/(serum creatinine × 72[×0.85 for women]). We considered the cutoff normal higher limit value of SCr is 124 µmol/L and the cutoff normal lower limit value of CrCl is 70 ml/min. Urinary kidney injury molecule-1 (KIM-1) protein was measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Uscn Life Science Inc.) (Han et al., 2008). We considered the cutoff normal higher limit value of KIM-1 is 0.75 ng/ml. Laboratory results of patients were compared with values of reference group from our laboratory (matched for age and sex).

### Statistical analysis

Calculations were done with the statistical package SPSS for windows, version 12.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared with the $\chi^2$ test, and continuous variables were compared with the unpaired *t* test or Mann-Whitney *U* test as indicated. Continuous data were presented as means ± SD and categorical data as percentages. To evaluate which factors contribute to 3-months mortality, we used a univariate Cox proportional hazards model. Factors that were found to contribute to the outcome in the univariate analyses at $p < 0.1$ were included in the multivariate model. In the multivariate analyses, statistical significance was reached at $p < 0.05$. Associations are presented as hazards ratio (HR) with their corresponding 95%, confidence interval (CI).

## RESULTS

This study included 80 patients with acute stroke (male = 44; female = 36), with mean age 62.5 ± 6.2 years. The majority of patients had ischemic stroke (72.5%) while 27.5% had hemorrhagic stroke. Among patients with ischemic stroke, 57.5% had large sized infarctions. Smoking, hypertension, diabetes, ischemic heart disease, hypercholesterolemia/dyslipidemia and carotid stenosis were the associated vascular risk factors. The mean value for stroke severity on admission as assessed by SSS was 42.43 ± 10.93. Table 1 showed the demographic, clinical and laboratory characteristics of the studied groups. Compared to values from the reference group, patients with stroke had lower urinary volume/24 hours (range = 380.00 to 4200.00 ml, mean = 1841.43 ± 682.00 ml versus 2580.64 ± 465.56 ml for the reference group; $p < 0.05$), higher SCr (range = 18.00 to 363.00 µmol/L, mean = 101.56 ± 54.36 µmol/L versus 64.82 ± 24.68 µmol/L for the reference group; $p < 0.01$), lower CrCl (range = 5.60 to 241.00 ml/min, mean = 62.75 ± 33.43 ml/min versus 85.09 ± 20.33 ml/min for the reference group; $p < 0.01$) and high KIM-1 (range = 0.10 to 10.50 ng/ml, mean = 4.47 ± 1.61 ng/ml versus 0.63 ± 0.12 ng/ml for the reference group; $p < 0.001$). Only eleven (13.75%) patients had SCr above 124 µmol/L (range: 139 to 363 µmol/L) while the majority (n = 69 or 86.25%) had SCr below 124 µmol/L (range: 31 to 100 µmol/L). Forty six (57.5%) patients had CrCl below 70 ml/min (range: 5.6 to 68.9 ml/min) while 34 (42.5%) had CrCl above 70 ml/min (range: 76 to 229.2 ml/min). Six (7.5%) patients had KIM-1 value of 0.1 ng/ml while 74 (92.5%) had KIM-1 more than 0.75 ng/ml (range: 1.2 to 9.0 ng/ml). Mortality rate within the 3-months follow-up period was 35% (ischemic stroke = 10 or 35.71%; hemorrhagic stroke = 18 or 64.29%). Compared to survivors, patients who died during the 3-months of follow-up were older, had prolonged hospital stay, higher

**Table 1.** Demographic, clinical and laboratory characteristics of the studied groups.

| Parameter | Patients (n = 80) |
|---|---|
| Age (years) | 42 – 65 (58.84 ± 3.49) |
| Males/females | 44/36 |
| Duration of hospital stay (days) | 3 - 10 (7.50 ± 2.82) |
| | |
| Type of stroke: | |
| Ischemic | 58 (72.5%) |
| Hemorrhagic | 22 (27.5%) |
| | |
| Size of infarction: | |
| Large size of infarction | 46 (57.5%) |
| Small size infarctions | 9 (11.25%) |
| Lacunar infarctions | 3 (3.75%) |
| | |
| Risk factors: | |
| Smoking | 44 (55%) |
| Hypertension | 36 (45%) |
| Diabetes mellitus | 45 (56.25%) |
| Ischemic heart disease | 58 (72.50%) |
| Hypercholesterolemia/dyslipidemia | 35 (43.75%) |
| | |
| Carotid stenosis (≥30%) | 28 (35%) |
| Scandinavian Stroke Scale (SSS) | 42.43 ± 10.93 |
| | |
| Laboratory results: | |
| Urinary volume/24 h (ml) | 380.00 - 4200.00 (1841.43 ± 682.00) |
| Serum creatinine (µmol/L) | 18.00 – 363.00 (101.56 ± 54.36) |
| Creatinine clearance (ml/min) | 5.60 – 241.00 (62.75 ± 33.43) |
| KIM-1 (ng/ml) | 0.10 - 10.50 (4.47 ± 1.61) |

Data are expressed as range, mean ± SD and number (%).

frequency of hemorrhagic stroke or large sized infarctions and vascular risk factors, lower SSS and significant higher levels of SCr and KIM-1 and lower urine volumes and CrCl (all $p < 0.001$) (Table 2). Significant correlations were reported between KIM-1 and SCr (r = 0.432, $p$ = 0.032) and CrCl (r = -0.356, $p$ = 0.046). Using Cox proportional-hazards model, stroke survivors had lower SCr and KIM-1 and higher CrCl. Higher SCr [Hazard ratio (HR), 1.65; 95% confidence interval (CI) 1.41 to 1.93], higher KIM-1 [HR, 1.63; 95% CI, 1.21 to 2.19] and lower CrCl [HR, 1.34; 95% CI, 1.09 to 1.65] were significantly predicted worse short-term survival after adjustment for confounders (age, SSS, smoking, hypertension, diabetes and ischemic heart disease).

## DISCUSSION

The results of this prospective study indicate that: 1) AKI is a common complication after acute CVS. Both ischemic tubular (as evidenced by higher concentrations of KIM-1) and glomerular (as evidenced by higher concentrations of SCr and lower CrCl) injuries are associated with CVS; 2) Not only motor and functional disabilities after CVS can adversely influence the short-term survival but also AKI is a significant predictor of mortality after adjusting other confounders; 3) This study highlighted that the increase in comorbidities may explain in part the increased overall mortality in patients who develop AKI in the acute phase of stroke; and 4) Although, the results showed that KIM-1 is not superior to SCr or CrCl in the prediction of short-term mortality in stroke patients, however, KIM-1 seems to be more sensitive (92.5%) for detection of early kidney injury compared to CrCl (57.5%) or SCr (13.75%).

First, the results of this study indicate that AKI is very common with acute CVS. The majority of patients had higher levels of KIM-1 (92.5%), a marker of tubular injury and lower CrCl (57.5%), a marker of glomerular filtration dysfunction. AKI has been previously reported in patients with different types of CVS including subarachnoid hemorrhage, intracerebral hemorrhage and cerebral

**Table 2.** Comparative results of the demographic, clinical and laboratory characteristics between survivors and case fatality after 3-months follow-up.

| Parameter | Survivors (n = 52) | Case fatality (n = 28) |
|---|---|---|
| Age (years) | 56.68 ± 4.06 | 62.42 ± 2.80*§ |
| Males/females | 23/29 | 21/7 |
| Duration of hospital stay (days) | 3.32 ± 1.06 | 8.75 ± 1.55** |
| | | |
| Type of stroke: | | |
| Ischemic | 48 (92.31%) | 10 (35.71%***) |
| Hemorrhagic | 4 (7.69%) | 18 (64.29%****) |
| | | |
| Size of infarction: | | |
| Large size of infarction | 22 (42.31%) | 24 (85.71%***) |
| Small size infarctions | 7 (13.46%) | 2 (7.14%***) |
| Lacunar infarctions | 3 (5.77%) | 0 |
| | | |
| Risk factors: | | |
| Smoking | 23 (44.23%) | 21 (75%***) |
| Hypertension | 18 (34.62%) | 20 (71.43%***) |
| Diabetes mellitus | 21 (40.38%) | 24 (87.51%***) |
| Ischemic heart disease | 30 (57.69%) | 28 (100%***) |
| Hypercholesterolemia/dyslipidemia | 17 (32.69%) | 18 (64.29%***) |
| | | |
| Carotid stenosis (≥30%) | 12 (23.07%) | 16 (57.14%***) |
| Scandinavian Stroke Scale (SSS) | 42.43 ± 10.93 | 22.26 ± 6.83*** |
| | | |
| Laboratory results: | | |
| Urinary volume/24 h (ml) | 2642.64 ± 654.55 | 796.23 ± 230.00***§§§ |
| Serum creatinine (µmol/L) | 72.46 ± 26.84 | 142.56 ± 34.80***§§§ |
| Creatinine clearance (ml/min) | 79.98 ± 24.15§ | 34.70 ± 10.06***§§§ |
| KIM-1 (ng/ml) | 2.80 ± 0.23§§ | 6.43 ± 0.82***§§§ |

Data are expressed as range, mean ± SD and number (%). Significance (*survivors versus case fatality; §patients versus reference group) *§$p < 0.05$, **§§$p < 0.01$, ***§§§$p < 0.001$, ****§§§§$p < 0.0001$.

infarctions (M'Buyamba-Kabangu et al., 1995; MacWalter et al., 2002; Tsagalis et al., 2009; Zacharia et al., 2009; Kobayashi et al., 2010; Rayes et al., 2011). However, we reported higher frequencies because all previous studies assessed SCr and CrCl which are insensitive for detection of early kidney injury but we used KIM-1 in addition to SCr and CrCl which is a sensitive and a specific marker for detection of early ischemic AKI (Van Timmeren et al., 2006; Liangos et al., 2007; Dieterle and Marrer 2008; Han et al., 2008; Soni et al., 2009; Waanders et al., 2009; Huang and Don-Wauchope, 2011; Vaidya et al., 2011; Urbschat et al., 2011).

The exact mechanism(s) underlying AKI with stroke is unknown and has to be explored. In general, the association between two disease states could be due to: 1) chance association; 2) bidirectional causal association, that is, one disorder causes the other; 3) a shared risk factor for the two disease states, or 4) a common biology underlying both conditions. There is growing evidence in medical literature of the role of cardio- and cerebrovascular diseases in renal dysfunction in view of the similarities between vascular beds of the kidney, heart and brain. Renal dysfunction may indicate a higher comorbidity burden, especially in atherosclerotic risk factors and diseases (Kannel, 1992). It seems that the degree of renal dysfunction present in stroke patients may simply be a marker of end-organ damage from long standing arterial stiffness of small and large arteries due to atherosclerosis and its associated vascular risk factors (e.g. aging, smoking, hypertension, diabetes mellitus and cardiovascular diseases) (McCullough and Ahmad, 2011) or independent of other risk factors for atherosclerosis. Age is a risk factor for AKI. Experimental and human studies showed that aged kidney is more susceptible to ischemic injury than young animals (Zager and Alpers, 1989; Chen et al., 2007). Aging causes renal microvascular disease, reductions in renal blood flow, altered glomerular structure and function (decreased number, increased size, and tubulointerstitial fibrosis) (Fillit and Rowe, 1992), decline of the cellular antioxidant

defense in the tubular cells (Akcetin et al., 2000; de Cavanagh et al., 2004). Smoking is a risk factor for AKI. It has been reported that chronic nicotine exposure increases the extent of renal injury induced by warm ischemia-reperfusion as evidenced by morphological changes, increase in markers of oxidative stress, increase in plasma creatinine level and KIM-1 expression and may facilitates progression of AKI to chronic kidney injury (Arany et al., 2011). Essential hypertension is a risk factor for AKI. It has been reported that in the absence of clinically detected parenchymal renal disease, essential hypertension induces early renal damage than non-hypertensive subjects (Perneger et al., 1993). Diabetes mellitus is a risk factor for AKI. Tubular dysfunction is common in early course of diabetic nephropathy (Fu et al., 2012). In patients with type 1 diabetes with normoalbuminuria, KIM-1 levels were reported to increase and higher levels were observed in patients with microalbuminuria but decreased with the regression of microalbuminuria (Vaidya et al., 2011). It was also observed that KIM-1 expression was increased with glomerular injury in proteinuric kidney disease in diabetic animals (Zhao et al., 2011). Also chronic kidney disease with diabetes increases the risk of AKI. It was observed that after months of a single episode of acute ischemia to the diabetic kidney, a rapid progression of nephropathy occur with impaired function, severe renal inflammation, microvascular dysfunction, fibrosis and apoptotic cell death and post-ischemic inflammatory syndrome accelerates diabetic chronic kidney disease (Kelly et al., 2009). All types of cardiovascular disease including stroke have been found to be associated with renal function impairment (Sarnak et al., 2003). KIM-1 was found to be elevated in symptomatic heart failure in patients with apparently normal kidney function indicating tubular injury in chronic heart failure (Zanchetti et al., 2001). Several reports have found that chronic kidney disease is an independent risk factor for cerebrovascular stroke and cerebrovascular disease conversely predicts the outcome of kidney function (Kobayashi et al., 2010). Studies showed that silent brain infarctions were important independent prognostic factor for the progression of kidney disease in patients with chronic kidney disease. The severity of stroke could reflect the degree of injury in renal small vessels (Kobayashi et al., 2010).

Second, the results of this study indicate that AKI is an independent predictor of short-term mortality after acute stroke. In accordance, Friedman (1991) found that among stroke survivors, SCr independently predicted mortality even after adjustment for confounders. M'Buyamba-Kabangu et al. (1995) in their study which designed to assess the relationship between hypertension and fatality rates and its determinants in black patients with recent stroke reported higher levels of urea in patients who died compared to survivors. MacWalter et al. (2002) reported that after acute stroke, patients with high mortality risk had reduced admission CrCl, raised SCr and urea concentrations (even within conventional reference levels), and raised ratio of urea to creatinine. Tsagalis et al. (2009) reported that AKI was an independent predictor of 10-years mortality ($p < 0.01$) after stroke and for the occurrence of new composite cardiovascular events ($P < 0.05$) after adjustment for available confounding variables. Decrease in CrCl was found to be associated with significantly worse 3-month outcomes in patients with aneurysmal subarachnoid hemorrhage (Zacharia et al., 2009).

Third, this study highlights that the increase in comorbidities may explain in part the increased overall mortality in patients who develop AKI in the acute phase of stroke. We observed that patients who died during follow-up were older, had prolonged hospital stay, higher frequency of hemorrhagic stroke or large sized infarctions and vascular risk factors and lower SSS. Previous studies reported that stroke outcome in the first 30 days has been found to be largely determined by the level of consciousness and type and severity of stroke. Also age (Alonso Martinez et al., 1995), neurological score on admission, and comorbidities as diabetes mellitus (Sacco et al., 1994), hypertension (Dennis et al., 1993; Sacco et al., 1994) and cardiovascular diseases (Zacharia et al., 2009) independently predicted adverse outcomes and elevated mortality in stroke patients in short- and long-term follow-up.

Fourth, although, KIM-1 is not superior to SCr or CrCl in the prediction of short-term mortality in stroke patients, however, KIM-1 seems to be more superior in detection of early kidney injury compared to CrCl or SCr. To our knowledge, this is the first study in which KIM-1 was used to assess kidney injury with CVS.

### Limitations of the study

Despite the importance of our results, we recognize that there are some limitations as follow: 1) renal function was only assessed during hospitalization (within the 2$^{nd}$ or 3$^{rd}$ day after admission). We did not have data concerning renal function in the follow up or whether AKI is reversible; 2) it is possible that the increase in KIM-1 or decrease in CrCl simply reflect dehydration, electrolyte imbalance or acid-base disturbances and thus monitoring of patients, adequate hydration by intravenous fluid replacement therapy and early nasogastric feeding, correction of electrolyte imbalance are able to correct or reverse AKI. It is also be possible that kidney injury associated with acute CVS is an indication of a concomitant injury in other organ systems.

## CONCLUSIONS AND RECOMMENDATIONS

This study indicates that AKI is a common complication of

CVS. We suggested that the increase in short-term mortality after acute CVS is not only determined by the comorbid vascular risk factors but also a small increase in SCr or decrease in CrCl even within the reference levels (markers of glomerular filtration) and increase in KIM-1 (a marker of tubular injury) are associated with worse short-term outcomes with stoke. We suggest that management of blood pressure and diabetes mellitus, and avoidance of potential nephrotoxic insults could potentially prevent the development of AKI. The use of angiotensin-converting enzyme inhibitors in high-cardiovascular-risk patients to lower blood pressure is important in secondary prevention. Also vasodilators and antioxidants can effectively improve renal perfusion and restore renal function and renal microvascular disease (Futrakul and Futrakul, 2008).

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