Abnormal admission kidney function predicts higher mortality in stroke patients

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ABSTRACT

Objectives: To investigate the impact of abnormal kidney function on stroke outcome.

Methods: This was a retrospective cohort of stroke patients admitted to King Abdulaziz University Hospital in Kingdom of Saudi Arabia between 2010 and 2014. Serum creatinine and urine protein were collected at admission. We defined proteinuria as urine protein dipstick ≥ 1. Estimated glomerular filtration (eGFR) rate was calculated by Modification of Diet in Renal Disease Study equation in mL/min/1.73m². Abnormal kidney disease was defined as Creatinine > 126 mg/dl or eGFR < 60. Clinical characteristics and outcomes including one-year mortality and 30-day readmission were compared between patients with versus (vs.) without abnormal kidney function and/or proteinuria.

Results: Out of 548 patients, 507 had creatinine measurement at admission and 193 patients had abnormal kidney function. These patients tended to be older (median age 67 years vs. 60.5 for those with normal kidney function), men (66.7% vs. 54.3%), and hypertensive (96% vs. 88%). Diabetes prevalence did not differ between the 2 groups. Proteinuria was not associated with future mortality. Abnormal kidney function was a significant predictor of post-stroke one-year mortality (adjusted OR = 2.5, 95% CI = 1.4 to 4.6; p-value = 0.003).

Conclusion: Abnormal kidney function doubled the risk of one-year mortality post stroke in our cohort. High-risk groups, including older hypertensive men, could be targeted for aggressive moni-toring and early treatment of risk factors.

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Stroke is a leading cause of mortality and morbidity worldwide. There are many modifiable and non-modifiable stroke risk factors including hypertension, diabetes, hyperlipidemia, and ethnicity. Many of these risk factors are shared between stroke and other diseases like coronary artery disease, chronic kidney disease, and peripheral artery disease. Chronic kidney disease (CKD) affects 10-15% of the general population. However, it is not regarded as one of the traditional stroke risk factors. Yet, both stroke and CKD have similar risk factors and the interaction between the 2 conditions could impact the outcome of the other. The presence of abnormal kidney function could have implications for stroke prognosis. The presence of atherosclerosis together with the activated reninangiotensin system will eventually lead to vascular manifestations including stroke. In addition, several CKD-associated mechanisms may contribute to platelet dysfunction, coagulation disorders, endothelial dysfunction, inflammation and increased risk of atrial fibrillation: one of the most common stroke mechanisms. Moreover, the limited use of oral anticoagulants and other antithrombotic treatments in CKD patients will lead to poor stroke outcome in these patients with an increased mortality risk at 1- and 10-years.

Given the reported high prevalence of vascular risk factors in Saudi population, the prevalence of CKD in stroke patients is expected to be high. However, the degree of this association and whether it would still carry poor outcome compared to the published literature is not known. This study aims to investigate the association and impact of abnormal baseline kidney function on the outcome of stroke in these patients.

**Methods.** This was a retrospective cohort of all stroke patients admitted to King Abdulaziz University Hospital with ischemic or hemorrhagic stroke from January 2010 to December 2014. Patients with primary diagnosis of stroke were identified using International Classification of Diseases codes (ICD-9 or ICD-10).

Adults of 18 years or more with the diagnosis of stroke were included while pediatric patients were excluded. The medical records were reviewed, and information were extracted regarding clinical data, and length of stay in hospital (LOS), medications and discharge destination. The frequency of readmission within 30 days were also collected. Mortality data were collected from the electronic medical records up to one year following discharge.

We collected data on levels of serum creatinine (Cr) at the time of admission. In addition, we defined the presence of proteinuria based on admission urine protein dipstick of +1 or more. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation. We defined abnormal kidney function as Cr level>126 mg/dl or eGFR<60 mL/min/1.73m². We categorized patients with abnormal kidney function according to the stages of CKD using the Kidney Disease Outcomes Quality Initiative (KDOQI) CKD classification.

Variables were summarized as appropriate; reporting the mean/median for continuous variables, and the proportions for categorical variables. Clinical characteristics and outcomes were compared between patients with vs. without abnormal kidney function using Student T test or Chi Square test for continuous or categorical variables, respectively. To identify the association between abnormal kidney function and one-year stroke mortality, a logistic regression model was fit to test univariable and multivariable predictors including age, sex, presence of hypertension, diabetes, stroke subtype, length of hospital stay, and 30-day readmission; in addition to CKD. All tests were carried out using STATA software package with a p-value of 0.05 for significance level.

**Results.** Out of 548 stroke patients, 507 had admission Cr measurements. The mean Cr level was 121.4 mg/dl (median 91, range 30 to 663). 193 patients had abnormal kidney function. Compared to patients with normal creatinine, those patients were older (mean age 67 years vs. 60.5 for those with normal function), mostly men (66.7 vs 54.3%), and had higher prevalence of hypertension (96% vs. 88%) but there was no difference in diabetes prevalence between the 2 groups (65.8% vs. 63%).

Out of 286 patients who had a urinalysis carried out, 148 (51.8%) had proteinuria. Their median age was 66 years, and women represented 39.9%. The proportion of those with HTN was 92.5%, and the median eGFR was 56.8. The median admission HBA1c was 8.4% and Cr was 111.5 mg/dl.

Table 1 shows patients classified into CKD stages. Patients in the advanced CKD stages were older and predominantly men. There was a higher prevalence
of proteinuria with the more advanced CKD stages although this difference was not significant. The HbA1c levels had an inverted U shaped distribution with higher readings in stages 3 and 4 compared to stages 1, 2, and 5.

Mortality at one-year among patients with abnormal kidney function was more than double those with normal function. It was highest among patient with CKD stage 5 compared to stage 4 and 3 respectively. There was no difference in the 30-day readmission rate between the groups (Table 2). Patients with proteinuria had a median LOS of 14.7 days, 30-day readmission rate of 41.3%, and one-year mortality of 34.5%.

Abnormal kidney function was a significant predictor of post-stroke one-year mortality (OR 2.5, CI=95% 1.4 to 4.6) as was age, length of hospital-stay, and 30-day readmission. The presence of proteinuria was not associated with higher risk of one-year mortality.

**Discussion.** In this study, we identified that abnormal baseline kidney function was an independent predictor of stroke mortality at one-year in our cohort. Patients with CKD were older men with hypertension.

Other studies have reported similar results as ours. Synhæve et al. showed that patients with low eGFR had 70% mortality at 15-year compared to 24% among those with normal eGFR. Others reported that patient with CKD stage 5 had the highest 30-days post stroke mortality compared to other CKD stages. Another study reported that following a stroke, both short term (30 days) and long-term mortality rates are significantly higher in those with renal dysfunction.

The impact of CKD on stroke mortality may have several mechanisms. Both the brain and the kidneys are low-resistance-end arterial organs that allow for high-volume perfusion con-tinuously and passively throughout systole and diastole. Moreover, Hypertension, which is more prevalent in patients with CKD, also plays a major role in the increased risk of stroke and stroke mortality. Nitric oxide (NO), which regulates the cerebral microcirculation, may be deficient in patients with kidney disease. It is also a major contributor to post stroke angiogenesis and collateralization, which in turn are predictors for stroke outcomes.

The significance of proteinuria in this setting is not certain. Similar to our results, Xiao et al. did not show any evidence that proteinuria is associated with increased future mortality. However, a meta-analysis showed that the risk of stroke is increased by 71-92% in patients with proteinuria/albuminuria. The lack of association between proteinuria and stroke mortality in our cohort could be explained by the fact that proteinuria is an indicator of early renal damage. Those with a more severe kidney injury would have elevated Cr and thus classified into advanced CKD stages. Another potential explanation is our qualitative definition of proteinuria. The impact of CKD on stroke mortality may be deficient in patients with kidney disease. It is also a major contributor to post stroke angiogenesis and collateralization, which in turn are predictors for stroke outcomes.

The lack of association between proteinuria and stroke mortality in our cohort led to some missing data of baseline and outcome parameters, including the causes leading to one-year mortality.

**Table 1** Baseline clinical characteristics of patients in each chronic kidney disease stage.

| Clinical characteristics | Cr† | Age‡ | Females§ | Hypertension¶ | Diabetes‖ | HbA1C¶¶ | LOS§§ | eGFR†† | Proteinuria†‡‡ |
|-------------------------|-----|------|----------|--------------|-----------|---------|--------|-------|-------------|
| CKD Stage 1 and 2       | <126| 60.5 years | (45.7) | (88) | (63) | 7.5 | 9 | 84 | (43.5) |
| CKD Stage 3 (n=134)     | 126.5| 65 years | (39.6) | (94.8) | (70.9) | 7.9 | 11.9 | 47.7 | (53) |
| CKD Stage 4 (n=35)      | 239 | 68 years | (45.7) | (94.1) | (67.7) | 8.3 | 12.8 | 23.8 | (76.9) |
| CKD Stage 5 (n=24)      | 478 | 66 years | (50) | (95.9) | (66.7) | 6.3 | 8.5 | 10.4 | (87.5) |

*Median, p-value for differences between the chronic kidney disease stages, †p=0.0001, ¶p=0.8335, ††p=0.030, ‡‡p=0.5342, §§p=0.1755, ¶¶p=0.560, ¶¶¶p=0.0011, CKD - Chronic kidney disease, Cr - serum creatinine level in mg/dl, eGFR - Estimated glomerular filtration rate, HbA1C - hemoglobin A1c (glycated hemoglobin), LOS - Length of stay.

**Table 2** Outcome data according to CKD stages and stroke outcome.

| CKD stages | 30-day readmission (%) | 1-year mortality (%) |
|------------|------------------------|----------------------|
| CKD Stage 1 and 2 | (23.5) | (21.5) |
| CKD Stage 3 (n=134) | (28.5) | (32.1) |
| CKD Stage 4 (n=35) | (21.9) | (42.9) |
| CKD Stage 5 (n=24) | (30.4) | (50) |

CKD - Chronic kidney disease.
In summary, we identified that abnormal baseline kidney function doubled the risk of one-year mortality in our cohort. Future studies should seek ways to mitigate these poor outcomes including identification of early markers of impaired kidney function that could also serve as an indicator of cerebrovascular damage. High-risk groups, including older hypertensive men, could be the target of aggressive monitoring and control of their vascular risk factors and kidney function.

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