Acute kidney injury without need for dialysis, incidence, its impact on long-term stroke survival and progression to chronic kidney disease

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ABSTRACT

Introduction Patients who had a stroke are at increased risk of sepsis, dehydration and fluctuations in blood pressure, which may result in acute kidney injury (AKI). The impact of AKI on long-term stroke survival has not been studied well.

Objective We aimed to identify incidence of AKI during acute stroke, follow-up period and its impact on long-term survival and development of chronic kidney disease (CKD).

Design, setting and participants Retrospective analysis of patients who had a stroke admitted at the rehabilitation facility in Changi General Hospital, Singapore, between June 2008 and May 2017, with median follow-up of 141 (95% CI 120 to 163) months.

Outcome measures and results of univariate analysis Total 681 patients, median age 63.6 years, 173 (28%) died during follow-up. Elevated blood urea (3.02, 95% CI 2.17 to 4.22; p<0.001) and creatinine (1.96, 95% CI 1.50 to 2.57; p<0.001) during stroke affected survival adversely.

Excluding patients with CKD, we analysed the remaining 617 patients. AKI was noted in 75 (12.15%) patients during the index admission, and it affected survival adversely (2.16, 95% CI 1.49 to 3.13; p<0.001). Of the patients with AKI, 21 of 75 (28%) progressed to CKD over a median follow-up of 40.7 months.

Conclusions We found AKI during stroke admission was associated with increased mortality as compared with those without AKI on univariate analysis. AKI without need of renal replacement therapy was also associated with progression to CKD in this cohort. This suggests that patients with AKI need to have their renal function monitored longitudinally for development of CKD.

INTRODUCTION

Stroke results in significant disabilities, long-term complications and requirement for long-term follow-up. Stroke is a major cause of mortality,1 and survival has been studied within various subgroups of strokes.2 The comorbidities independently have been shown to affect survival in these patients.3–4

Patients who had a stroke with more severe neurological deficit are at an increased risk of medical complications like urinary tract and chest infections, which in turn are associated with poor functional recovery.5–7

Dehydration, sepsis and fluctuations in blood pressure following stroke increases the risk of acute kidney injury (AKI) with consequently poor survival. Elderly patients with decreased estimated glomerular filtration rate (eGFR) are a population at increased risk of AKI.8–10

AKI is also known to progress to chronic kidney disease (CKD) and in those with preexisting CKD results in further deterioration in renal function.11 12 Coexistent diabetes mellitus (DM) and poorly controlled hypertension (HTN) in patients who had a stroke may also contribute to CKD.13 14

AKI not only is associated with increased mortality but also contributes to prolonged length of stay (LOS) and increased financial burden to the healthcare system.15 16

Although AKI is increasingly recognised as a significant risk factor, its impact on survival in patients who had a stroke and relationship with subsequent progression to CKD have not been studied adequately. Literature search revealed limited studies done on this subject, including only one prospective study.17

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ All ethnic and socioeconomic groups are represented in the data.
⇒ This is the first study from Southeast Asia on long-term survival outcomes following stroke in relation to acute kidney injury (AKI).
⇒ The effect of AKI in the development of subsequent CKD is described.
⇒ Retrospective observational and single-centre study which may lead to potential selection bias and reporting bias.
⇒ Due to the retrospective nature of the study, we can not comment on the causes of AKI.
In the present study, we aimed to identify the incidence of AKI, its impact on long-term survival following strokes (ischaemic and haemorrhagic) and development of CKD.

METHODS

Patients
This is a retrospective analysis of patients who had a stroke (both infarction and spontaneous intracerebral haemorrhage) who had met the selection criteria of the study and were consecutively admitted to the neurorehabilitation facility at the Changi General Hospital from June 2008 to May 2017. The follow-up period ranged from 6 to 163 months. All the patients included in the current study were discharged from the rehabilitation facility and were followed up regularly as outpatients. The subsequent records of hospital admissions and follow-up changes in the general physical and neurological status and treatment regimens were available electronically and in paper format for all patients.

The exclusion criteria were (1) incomplete follow-up records including those patients who were repatriated to other countries, (2) patients less than 21 years of age (as per CIRB guideline), (3) transient ischaemic attacks, (4) pre-existent CKD, end-stage renal failure (ESRF) or patients on haemodialysis (HD).

Acute kidney injury
Only those patients whose baseline creatinine at least 3 months prior to admission was available were included. AKI was defined as an increase of >26.5 mmol/L over baseline within 48 hours as per the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Those with AKI which progressed to CKD during follow-up were documented.

Stroke and its subtypes were diagnosed by a stroke physician on admission based on clinical examination, brain imaging (CT, MRI and magnetic resonance angiography), ECG 12 leads, continuous monitor or Holter, carotid Doppler and echocardiogram. The patients were classified as per Oxfordshire classification (for stroke territory) and Trial of Org10172 in Acute Stroke Treatment (TOAST) for ischaemic strokes.

Patient and public involvement statement
Due to the retrospective nature of the study, this is not applicable.

Sampling procedure
All the electronic and paper medical records of the patients from the time stroke was diagnosed, follow-up visits and additional admissions were reviewed until May 2017. Last follow-up date of demise and renal function was 21 October 2019. The material was housed in the hospital's medical record database and in the records of the clinician at the neurorehabilitation facility. The data collected included demographic details, diagnosis, type of stroke (ischaemic and intracerebral bleed), and CT/MRI findings for stroke territory, admission electrolytes, lipid panel, full blood count, clotting profiles, premorbid medications and comorbidities. The treatment modalities included thrombolysis, medical treatments for raised intracranial pressure and neurosurgical interventions.

Statistical analysis
Categorical data are presented as frequency (percentage), and continuous data are presented as mean (SD) for normally distributed data and geometric mean and range for positively skewed data. Associations between mortality and demographic factors, clinical features, comorbidities and admission blood tests for the cohort of 617 patients were assessed using Cox proportional hazards regression. HRs and their associated 95% CIs are presented.

A two-tailed p value of <0.05 was statistically significant. The analysis was performed using the Statistical Package for the Social Sciences V.22.0.

RESULTS

Patient characteristics
A total of 617 (women: 36%) patients with a mean age of 63.6 years met the selection criteria. While 443 (70%) of the patients had ischaemic strokes, 190 (28%) of them had haemorrhagic strokes. The median follow-up period was 141 (95% CI 120 to 163) months, and 173 (28%) patients died during this period.

Univariate analysis: impaired urea, creatinine and its effect on survival
This included all 681 patients; raised blood urea (HR 3.02, 95% CI 2.17 to 4.22; p≤0.001) and elevated serum creatinine (HR 1.96, 95% CI 1.50 to 2.57; p≤0.001) at the stroke admission affected survival adversely in the long term (table 1).

AKI and survival
Of the 681 stroke patients, 617 met the selection criteria. AKI was noted in 75 (12.15%) patients during stroke admission. The univariate analysis of these patients showed that AKI was associated with poorer survival in the long term (2.16, 95% CI 1.49 to 3.13; p<0.001) (table 2).

AKI grading was documented 95% CIs are presented. A two-tailed p value <0.05 was statistically significant. The analysis was performed using the Statistical Package for the Social Sciences V.22.0.

Multivariable analysis
The multivariate cox regression analysis after adjustment for age and other comorbidities did not show AKI as an independent predictor for mortality (adjusted HR for AKI 1.30, 95% CI 0.79 to 2.16; p=0.305) (table 4).
Table 1 Univariate analysis of characteristics associated with progression to mortality (n=681)

| Characteristic                                      | N   | Univariate HR (95% CI) | P value |
|-----------------------------------------------------|-----|------------------------|---------|
| Age (year)                                          | 681 | 1.08 (1.07 to 1.09)    | <0.001  |
| Gender                                              |     |                        |         |
| Male                                                | 423 | Reference              |         |
| Female                                              | 258 | 1.24 (0.94 to 1.63)    | 0.124   |
| Ethnicity                                           |     |                        |         |
| Chinese                                             | 447 | Reference              |         |
| Indian                                              | 55  | 0.90 (0.51 to 1.59)    | 0.710   |
| Malay                                               | 152 | 1.32 (0.97 to 1.80)    | 0.075   |
| Others                                              | 27  | 0.66 (0.29 to 1.50)    | 0.323   |
| Stroke: haemorrhagic versus ischaemic                |     |                        |         |
| Haemorrhagic                                        | 191 | Reference              |         |
| Ischaemic stroke                                    | 490 | 1.36 (0.99 to 1.88)    | 0.055   |
| Cardioembolic stroke                                |     |                        |         |
| No                                                  | 288 | Reference              |         |
| Moderate risk                                       | 73  | 2.58 (1.65 to 4.02)    | <0.001  |
| High risk                                           | 185 | 3.75 (2.69 to 5.21)    | <0.001  |
| Artery size                                         |     |                        |         |
| Small                                               | 187 | Reference              | 0.018   |
| Large                                               | 296 | 1.50 (1.07 to 2.09)    |         |
| Stroke classification                               |     |                        |         |
| LACS                                                | 323 | Reference              |         |
| TACS                                                | 30  | 2.36 (1.33 to 4.16)    | 0.003   |
| PACS                                                | 187 | 1.57 (1.13 to 2.17)    | 0.007   |
| POCS                                                | 131 | 1.55 (1.08 to 2.21)    | 0.016   |
| Undefined                                           | 10  | 2.00 (0.73 to 5.47)    | 0.175   |
| Significance infection, Hep B, HIV                  |     |                        |         |
| No                                                  | 668 | Reference              |         |
| Yes                                                 | 13  | 0.65 (0.21 to 2.04)    | 0.465   |
| Cirrhosis                                           |     |                        |         |
| No                                                  | 669 | Reference              |         |
| Yes                                                 | 12  | 2.03 (0.90 to 4.58)    | 0.088   |
| Malignancy                                          |     |                        |         |
| No                                                  | 622 | Reference              |         |
| Yes                                                 | 59  | 2.06 (1.42 to 2.98)    | <0.001  |
| Fracture neck of femur                              |     |                        |         |
| No                                                  | 659 | Reference              |         |
| Yes                                                 | 22  | 0.80 (0.35 to 1.80)    | 0.590   |
| Atrial fibrillation                                 |     |                        |         |
| No                                                  | 506 | Reference              |         |
| Yes                                                 | 175 | 2.39 (1.82 to 3.15)    | <0.001  |
| Recurrent cerebrovascular accidents: during follow-up|     |                        |         |
| No                                                  | 613 | Reference              |         |
| Yes                                                 | 68  | 1.04 (0.68 to 1.59)    | 0.858   |
| Peripheral vascular disease                         |     |                        |         |
| No                                                  | 600 | Reference              |         |
| Yes                                                 | 81  | 1.68 (1.18 to 2.39)    | 0.004   |
| Chronic obstructive pulmonary disease               |     |                        |         |
| No                                                  | 667 | Reference              |         |
| Yes                                                 | 14  | 2.10 (1.08 to 4.10)    | 0.029   |
| Ischaemic heart disease                             |     |                        |         |
| No                                                  | 465 | Reference              | <0.001  |
| Yes                                                 | 216 | 1.65 (1.26 to 2.16)    |         |

Continued

Table 1 Continued

| Characteristic                                      | N   | Univariate HR (95% CI) | P value |
|-----------------------------------------------------|-----|------------------------|---------|
| Hypertension                                        |     |                        |         |
| No                                                  | 168 | Reference              |         |
| Yes                                                 | 513 | 1.55 (1.10 to 2.18)    | 0.012   |
| Diabetes mellitus                                   |     |                        |         |
| No                                                  | 412 | Reference              |         |
| Yes                                                 | 269 | 1.36 (1.04 to 1.78)    | 0.025   |
| Known history of hyperlipidaemia                    |     |                        |         |
| No                                                  | 383 | Reference              |         |
| Yes                                                 | 298 | 1.71 (1.31 to 2.24)    | <0.001  |
| Total cholesterol: LDL ratio                        |     |                        |         |
| No                                                  | 324 | Reference              |         |
| Yes                                                 | 326 | 0.54 (0.40 to 0.71)    | <0.001  |
| Low sodium                                          |     |                        |         |
| No                                                  | 579 | Reference              |         |
| Yes                                                 | 102 | 1.90 (1.38 to 2.62)    | <0.001  |
| Patient with neurosurgical intervention for stroke  |     |                        |         |
| No                                                  | 626 | Reference              |         |
| Yes                                                 | 55  | 0.51 (0.27 to 0.96)    | 0.036   |
| High potassium                                      |     |                        |         |
| No                                                  | 554 | Reference              |         |
| Yes                                                 | 127 | 0.68 (0.46 to 0.99)    | 0.044   |
| High glucose                                        |     |                        |         |
| No                                                  | 681 | Reference              | 0.018   |
| Yes                                                 | 681 | 1.03 (1.005 to 1.05)   |         |
| Haemoglobin                                         |     |                        |         |
| No                                                  | 681 | Reference              | <0.001  |
| Yes                                                 | 681 | 0.77 (0.72 to 0.83)    |         |
| White blood cell count                              |     |                        |         |
| No                                                  | 681 | Reference              | 0.009   |
| Yes                                                 | 681 | 0.94 (0.90 to 0.99)    |         |
| Platelet count                                      |     |                        |         |
| No                                                  | 680 | Reference              | 0.093   |
| Yes                                                 | 680 | 0.99 (0.99 to 1.00)    |         |
| Raised blood urea                                   |     |                        |         |
| No                                                  | 602 | Reference              | <0.001  |
| Yes                                                 | 78  | 3.02 (2.17 to 4.22)    |         |
| Raised serum creatinine                            |     |                        |         |
| No                                                  | 408 | Reference              | <0.001  |
| Yes                                                 | 273 | 1.96 (1.50 to 2.57)    |         |
| Thrombolysis with rTPA for ischaemic strokes only   |     |                        |         |
| No                                                  | 533 | Reference              | 0.123   |
| Yes                                                 | 148 | 0.55 (0.26 to 1.17)    |         |
| Raised intracranial pressure and treatment received during stroke |     |                        |         |
| No                                                  | 643 | Reference              | 0.069   |
| Yes                                                 | 38  | 0.72 (0.50 to 1.03)    |         |

DISCUSSION

In our retrospective cohort of 617 patients who had a stroke and followed up over a median period of 11.75 years, we noted AKI in 12.15% of the patients during the stroke admission. On follow-up, 28% of the patients with AKI subsequently progressed to CKD. Of the seventy-five patients with AKI, 49 (65%) were KDIGO grade 1 and 26
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Table 2  Univariate of relationship of AKI to long-term stroke mortality

| AKI at stroke admission | N   | HR (95% CI)       | P value |
|-------------------------|-----|-------------------|---------|
| No                      | 542 | Reference         | <0.001  |
| Yes                     | 75  | 2.16 (1.49 to 3.13) |         |

AKI, acute kidney injury.

(35%) were KDIGO grade 2. None of the patients with AKI required renal replacement therapy.

Patients with AKI who progressed to CKD were over a median duration of 40.7 months.

Due to retrospective nature of data collection, we are unable to comment on the underlying causes of AKI, which could be multifactorial, including infections, dehydration, nephrotoxic medications and contrast-induced nephropathy.

CKD and ESRF are often associated with HTN and DM. These patients are susceptible to vascular complications including stroke. The short-term and long-term survival in this group of people have been extensively studied in the past.

In contrast, AKI and its relationship have not been studied adequately, and only a few studies have reviewed its impact on patients who had a stroke. However, from available data, AKI has been shown to be a common complication following ischaemic and haemorrhagic strokes and causes increased mortality in ischaemic stroke.

Grosjean et al in their retrospective analysis found a higher incidence of AKI post stroke and its association with cardioembolic and haemorrhagic strokes and causes increased mortality in ischaemic stroke.

In contrast, AKI and its relationship have not been studied adequately, and only a few studies have reviewed its impact on patients who had a stroke. However, from available data, AKI has been shown to be a common complication following ischaemic and haemorrhagic strokes and causes increased mortality in ischaemic stroke.

Grosjean et al in their retrospective analysis found a higher incidence of AKI post stroke and its association with cardioembolic and haemorrhagic strokes. AKI was also associated with longer LOS, higher comorbidity index and worse disability score. Although the inpatient mortality was worse, the authors found that long-term survival over 19.2 months was not affected.

We are unable to draw conclusions on disability scores (functional independence measure (FIM)) and comorbidity index due to incomplete data. We did not include LOS as an outcome measure as has been reported earlier. The reason for this is that some of the patients who had a stroke are discharged to community hospital for further rehabilitation and others to nursing homes due to severity of stroke. As a result, it does not accurately reflect the inpatient stay.

Table 3  Association of AKI grading and progression to CKD

| AKI at stroke | Total | Grade I | Grade II/III | P value |
|---------------|-------|---------|--------------|---------|
| AKI at stroke | 54 (72.0) | 49 (70.0) | 5 (100.0) | 0.183 |
| AKI at stroke progressing to CKD | 21 (28.0) | 21 (30.0) | 0 (0.0) | |

AKI, acute kidney injury; CKD, chronic kidney disease.

Table 4  Multivariable analysis of factors associated with long-term stroke mortality

| Age (year) | Multivariate HR (95% CI) | P value |
|------------|--------------------------|---------|
| No         | 1.07 (1.05 to 1.09)      | <0.001  |
| Yes        | 1.30 (0.79 to 2.16)      | 0.305   |

Malignancy

| No         | 1.64 (1.07 to 2.52)      | 0.024   |
| Yes        | Reference                |         |

Atrial fibrillation

| No         | 1.23 (0.86 to 1.75)      | 0.255   |
| Yes        | Reference                |         |

Peripheral vascular disease

| No         | 1.26 (0.81 to 1.94)      | 0.304   |
| Yes        | Reference                |         |

Chronic obstructive airway disease

| No         | 1.43 (0.69 to 2.95)      | 0.332   |
| Yes        | Reference                |         |

Ischaemic heart disease

| No         | 1.28 (0.91 to 1.80)      | 0.159   |
| Yes        | Reference                |         |

Hypertension

| No         | 1.46 (0.80 to 1.75)      | 0.040   |
| Yes        | Reference                |         |

Diabetes mellitus

| No         | 0.96 (0.65 to 1.43)      | 0.854   |
| Yes        | Reference                |         |

History of hyperlipidaemia

| No         | 0.95 (0.68 to 1.33)      | 0.776   |
| Yes        | Reference                |         |

High cholesterol at stroke admission

| No         | 0.62 (0.44 to 0.87)      | 0.006   |
| Yes        | Reference                |         |

Low sodium

| No         | 1.39 (0.92 to 2.11)      | 0.118   |
| Yes        | Reference                |         |

Patient with neurosurgical intervention for stroke

| No         | 1.09 (0.52 to 2.31)      | 0.816   |
| Yes        | Reference                |         |

High glucose

| No         | 1.03 (0.99 to 1.07)      | 0.185   |
| Yes        | Reference                |         |

Hb

| No         | 0.97 (0.88 to 1.06)      | 0.475   |
| Yes        | Reference                |         |

High creatinine

| No         | 1.13 (0.75 to 1.71)      | 0.568   |
| Yes        | Reference                |         |

AKI, acute kidney injury.

AKI and its relationship with cardioembolic strokes have been studied, and the increased incidence of AKI in these patients is thought to be result of haemodynamic dysfunction associated with underlying atrial fibrillation.
admission, ischaemic heart disease (IHD), conge-
sis AKI was associated with increased cost, LOS and
Health Stroke Scale scores. The study also concluded
IHD, need further investigation in relation to AKI.

bidities associated with stroke, that is, AF, DM, HTN and
on poststroke sur-
tive kidney repair but persist in maladaptive repair that led

mitochondrial dysfunction, cell death and inflammation
explained from preclinical studies which suggest that
mechanism of AKI and long-term renal impairment
was explained from preclinical studies which suggest that
mitochondrial dysfunction, cell death and inflammation
as ‘pathogenic mechanisms which can resolve with adap-
tive kidney repair but persist in maladaptive repair that led
to progressive chronic disease.’ Literature search shows
only one prospective study by Tsagalis et al in patients
following stroke, where the authors studied AKI in 2155
subjects. They concluded that AKI is a powerful indicator
of 10-year mortality and cardiovascular events. Although
our data are a retrospective analysis, our findings on

univariate analysis suggest that AKI has impact on poor
survival following stroke.

Snarska et al in their study concluded that patients who
had haemorrhagic stroke with AKI had worse outcomes
as compared with those who had ischaemic stroke. The
authors also concluded to monitor renal function, hydra-
tion and avoidance of nephrotoxic drugs as preventive
strategy.

Currently, there are no pharmacological agents for
prevention of AKI. Edaravone, which is used for acute
ischaemic strokes, has been studied from the Fukuoka
Registry cohort. The authors observed that it has a protec-
tive effect against development of AKI in acute stroke.

Our study also suggested that each subsequent ad-
mision for medical or surgical reasons, that is, sepsis, surgery
followed by intensive care stay leads to additional insults
to kidney. Each insult to kidney leads to further deteriora-
tion of renal function with the end result being CKD and
ESRF. During these episodes of acute illness and hospi-
talisations, maintaining renal perfusion with close moni-
toring may help to prevent long-term renal damage.

In our previously published study of patients who had
a stroke with CKD and end-stage renal failure on HD, we
concluded that apart from increased morbidity and
recurrent hospitalisations, this group of patients had
severely reduced life expectancy.

CONCLUSIONS

In our study, we found AKI is common both during acute
admission for stroke as well as subsequent follow-up
period. Despite not requiring dialysis, these AKI episodes
were associated with poorer survival and subsequent
development of CKD.

Patients with AKI during stroke admission need to have
their renal function assessed periodically for development
of CKD. Acute stroke management strategies which
may prevent AKI include careful assessment of hydration
status, adequate and timely treatment of sepsis, avoidance
of nephrotoxic agents and indwelling catheters.

A multidisciplinary approach for prevention of AKI
with the renal team may be beneficial.

Modifiable risk factors such as DM and HTN need
careful management.

We are planning to conduct a prospective study to vali-
date our findings.

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