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

Shrikant D Pande ,[1] Debajyoti Roy,[2] Aye Aye Khine,[1] May M Win,[1] Lorecar Lolong,[1] Ni Thu Shan,[1] Pei Ting Tan,[3] Tian Ming Tu[4]

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[1]Rehabilitation Medicine, Changi General Hospital, Singapore
[2]Department of Renal Medicine, Changi General Hospital, Singapore
[3]Health Services Research, Changi General Hospital, Singapore
[4]Department of Neurology, National Neuroscience Institute, Neurology, Tan Tock Seng Hospital, Singapore

Correspondence to
Dr Shrikant D Pande;
shrikantpande@yahoo.co.uk

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.

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.

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 pre-existing 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]

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.[18] 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)[19] and Trial of Org10172 in Acute Stroke Treatment (TOAST) for ischaemic strokes.[20]

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).

Of the patients with AKI during the index admission for stroke, 21 of 75 (28%) progressed to CKD over the median follow-up of 40.7 months. AKI grading was documented as per KDIGO classification (table 3).

AKI was noted in a further 47 patients during the stroke follow-up period.

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 chrematistics associated with progression to mortality (n=681)

	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	
Large	296	1.50 (1.07 to 2.09)	0.018
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)	
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
High total cholesterol: during stroke admission			
No	324	Reference	
Yes	326	0.54 (0.40 to 0.71)	<0.001
Total cholesterol: LDL ratio			
No	303	Reference	
Yes	336	0.61 (0.46 to 0.80)	<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	681	1.03 (1.005 to 1.05)	0.018
Haemoglobin	681	0.77 (0.72 to 0.83)	<0.001
White blood cell count	681	0.94 (0.90 to 0.99)	0.009
Platelet count	680	0.99 (0.99 to 1.00)	0.093
Raised blood urea			
No	602	Reference	
Yes	78	3.02 (2.17 to 4.22)	<0.001
Raised serum creatinine			
No	408	Reference	
Yes	273	1.96 (1.50 to 2.57)	<0.001
Thrombolysis with rTPA for ischaemic strokes only			
No	533	Reference	
Yes	148	0.55 (0.26 to 1.17)	0.123
Raised intracranial pressure and treatment received during stroke			
No	643	Reference	
Yes	38	0.72 (0.50 to 1.03)	0.069

LACS, lacunar syndrome; LDL, low-density lipoprotein; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; rTPA, recombinant tissue plasminogen activator; TACS, total anterior circulation syndrome.

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

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[21–23] and causes increased mortality in ischaemic stroke.[22]

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.[24]

We are unable 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.[24] 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

	Multivariate HR (95% CI)	P value
Age (year)	1.07 (1.05 to 1.09)	<0.001
AKI admission		
No	Reference	
Yes	1.30 (0.79 to 2.16)	0.305
Malignancy		
No	Reference	
Yes	1.64 (1.07 to 2.52)	0.024
Atrial fibrillation		
No	Reference	
Yes	1.23 (0.86 to 1.75)	0.255
Peripheral vascular disease		
No	Reference	
Yes	1.26 (0.81 to 1.94)	0.304
Chronic obstructive airway disease		
No	Reference	
Yes	1.43 (0.69 to 2.95)	0.332
Ischaemic heart disease		
No	Reference	
Yes	1.28 (0.91 to 1.80)	0.159
Hypertension		
No	Reference	
Yes	1.18 (0.80 to 1.75)	0.406
Diabetes mellitus		
No	Reference	
Yes	0.96 (0.65 to 1.43)	0.854
History of hyperlipidaemia		
No	Reference	
Yes	0.95 (0.68 to 1.33)	0.776
High cholesterol at stroke admission		
No	Reference	
Yes	0.62 (0.44 to 0.87)	0.006
Low sodium		
No	Reference	
Yes	1.39 (0.92 to 2.11)	0.118
Patient with neurosurgical intervention for stroke		
No	Reference	
Yes	1.09 (0.52 to 2.31)	0.816
High glucose	1.03 (0.99 to 1.07)	0.185
Hb	0.97 (0.88 to 1.06)	0.475
High creatinine		
No	Reference	
Yes	1.13 (0.75 to 1.71)	0.568

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

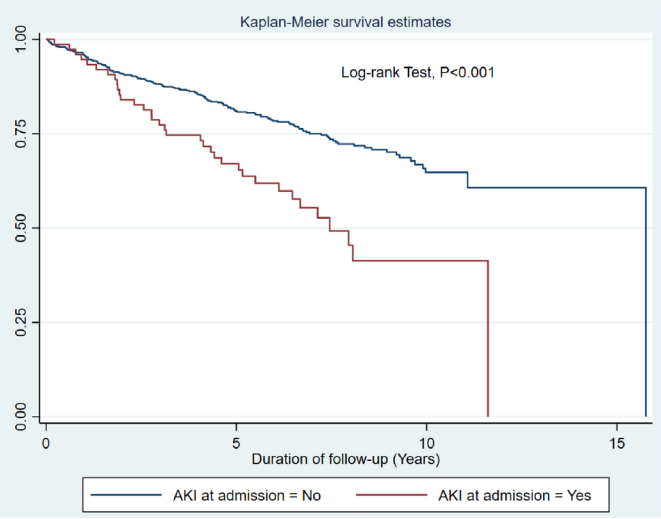

Figure 1 Kaplan-Meier survival graph showing group with AKI on admission versus those without. AKI, acute kidney injury.

(AF).[25] Other factors which may increase AKI include anticoagulants[26] and anaemia.[27–29]

Meta-analysis of patients with AKI and patients who had a stroke concluded that AKI is associated with increased mortality, but the incidence of AKI after stroke is variable.[30] This analysis also shows that AKI after stroke was associated with advanced age,[23] poor renal function on admission,[17 22 23] ischaemic heart disease (IHD),[23] congestive cardiac failure[17 23] and higher National Institutes of Health Stroke Scale scores.[17 22] The study also concluded that AKI was associated with increased cost, LOS and cardiovascular events.[30] Our study group had a mean age of 63.6 years, and AKI impact survival even in the younger age group of patients who had a stroke (figure 1).

In our study, we excluded the patients with known CKD and ESRF and reviewed patients whose renal function was normal prior to or at the time stroke and the AKI were documented as first insult. We also note that a significant number of patients who developed AKI following stroke progressed to CKD. This indicates that even with a premorbid normal renal function, AKI leads to significant impairment of renal function and has a long-term effect on poststroke survival. However, the impact of the comorbidities associated with stroke, that is, AF, DM, HTN and IHD, need further investigation in relation to AKI.

The 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 adaptive kidney repair but persist in maladaptive repair that led to progressive chronic disease.'[12] 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.[17] 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.[31] The authors also concluded to monitor renal function, hydration 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 protective effect against development of AKI in acute stroke.[32]

Our study also suggested that each subsequent admission 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 deterioration of renal function with the end result being CKD and ESRF. During these episodes of acute illness and hospitalisations, maintaining renal perfusion with close monitoring 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,[33] 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 validate our findings.

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Contributors SDP, DR and TMT: concept, data, literature search and write-up. AAK, MMW, LL and NTS: data collection and methodology. PTT: statistical analysis, tables, graphs and editing. SDP accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish. SDP is acting as guarantor.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval The Singhealth Centralised Institutional Review Board (CIRB) approved this study (2015/3112). Informed consent from the patients was waived due to the retrospective nature of the study. All methods were performed in accordance with Singhealth CIRB guidelines approved for data collection and storage.

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Data availability statement All data relevant to the study are included in the article. No additional data is available.

ORCID iD

Shrikant D Pande http://orcid.org/0000-0003-2614-2931

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