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Title: Acute kidney injury without need for dialysis, incidence and its impact on long term stroke survival.

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Abstract

Introduction: Stroke patients 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.

Design, setting, participants: Retrospective analysis of stroke patients admitted at Rehabilitation facility in Changi General Hospital, Singapore, between June 2008 and May 2017, with median follow up of 141 (120-163) months.

Outcome measures, results: Of the 616 patients, mean age (63.6), 173 (28%) died during follow-up. Raised urea, [2.21 (1.3,3.7, p=0.003], creatinine [1.45 (1.08,1.99), p=0.013] and low e-GFR [2.48 (1.77,3.48), p=<0.001] during stroke affected survival adversely.
Multivariable analysis: AKI, as per KEDIGO criteria, during stroke admission (n=48), [1.79(1.16,2.75), p=<0.001] and all AKI including stroke and during follow-up period (n=74), [1.78(1.29,2.45), p=<0.001] were significantly associated with poor long-term survival.
Conclusion: AKI appears to independently affect stroke survival and may also lead to chronic kidney disease. Proactive and adequate management of hydration status, treatment of sepsis, fluctuations in blood pressure and avoidance of nephrotoxic drugs can prevent AKI. A multidisciplinary care with involvement of renal physician can be considered to improve renal injuries and survival following stroke.

Article summary

Strengths and limitations.

1. All ethnic and socioeconomic groups are represented in the data.
2. This could be the first study on long-term survival outcomes following stroke in relation to AKI.
3. Retrospective observational and single centre study which may lead to potential selection bias and reporting bias.
4. The exact details and causes of AKI are not known.
5. Those patients who could not make it to rehabilitation facility are no represented.

Key words: stroke, acute kidney injury, comorbidities, long-term survival

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 the survival ~~of~~ in these patients (3, 4).

The stroke patients with more severe neurological deficit are at an increased risk for

medical complications like urinary tract and chest infections which in turn are associated with poor functional recovery. (5,6,7)

Dehydration, sepsis and fluctuations in blood pressure following stroke increases the risk of acute kidney injury (AKI) with consequent poor survival. Elderly patients with decreased eGFR are a population at increased risk for AKI. (8, 9, 10)

AKI is also known to progress to chronic kidney disease (CKD) and in those with pre-existing CKD result in further deterioration in renal function. (11, 12) Co-existent diabetes mellitus and poorly controlled hypertension in stroke patients may also contribute to CKD. (13,14)

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

Although AKI is increasingly recognised as significant risk factor, its impact on survival in stroke patients 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 and its impact on long- term survival following strokes (ischaemic and haemorrhagic).

Methods

Patients: This study was conducted in Changi general hospital, Singapore, with all the modern facilities for emergency and specialist care. The acute stroke unit is equipped with facilities for diagnosis and treatment including thrombolysis for strokes.

Management of stroke is streamlined through the Emergency department, Acute stroke unit, Neurosurgical department (as required), followed by transfer to the Rehabilitation services. All the patients admitted with a diagnosis of stroke undergo

the necessary investigations including those required to establish the underlying causes as per a standardised protocol based on established guidelines for stroke. Based on the initial and subsequent clinical conditions and scan findings, the neurosurgical team gets involved in further interventions. All the stroke patients are eventually referred to inpatient rehabilitation services. The neuro-rehabilitation department is equipped with all up-to date facilities. A multidisciplinary team review the patients throughout in-patient and follow up outpatient based on requirement.

This is a retrospective analysis of stroke patients (both infarction and spontaneous intracerebral haemorrhage) who had met the selection criteria of the study and were consecutively admitted to the Neuro-rehabilitation 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 outpatient. 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 (a) incomplete follow-up records including those patients who were repatriated to other countries, (b) patients less than 21 years of age (as per CIRB guideline), (c) transient ischaemic attacks (d) pre-existent CKD, ESRF (end-stage renal failure) or patients on dialysis.

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 > 26.5 mmol/L over baseline within 48 hours as per the 2012 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 (computerised tomography), MRI (magnetic resonance imaging), MRA (magnetic resonance angiography)], ECG (electrocardiography) 12 leads, continuous monitor or Holter, carotid Doppler and echocardiogram. The patients were classified as per Oxfordshire classification (for stroke territory) (19) and TOAST for ischaemic strokes. (20)

The Singhealth Centralized Institutional Review Board 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.

Patient and public Involvement statement: due to 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 21st October 2019. The material was housed in the hospital's medical record database and in the records of the clinician at the neuro-rehabilitation facility. The data collected included demographic details, diagnosis, type of stroke (ischaemic, intracerebral bleed), and CT/MRI findings for stroke territory, admission electrolytes, clotting profiles, premorbid medications, and comorbidities. The treatment modalities included thrombolysis, medical treatments for raised intracranial pressure, neurosurgical interventions.

Statistical analysis: Categorical data are presented as frequency (percentage), and continuous data are presented as mean (standard deviation) for Normally distributed data and geometric mean and range for positively skewed data. Associations between

mortality and demographic factors, clinical features, co-morbidities and admission bloods for the cohort of 616 patients were assessed using Cox proportional hazards regression. Hazard ratios and their associated 95% confidence intervals are presented. A two-tailed p-value of < 0.05 was considered to be statistically significant. The analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp. Armonk, New York).

Results

Patient Characteristics: A total of 616 (females: 36%) patients with mean age of 63.6 years, met the selection criteria. Whilst 443 (70%) of the patients had ischemic strokes, 190 (28%) of them had haemorrhagic strokes. The median follow-up period was 141 (120 to 163) months, and 173 (28%) patients died during this period.

AKI and its effect on survival:

Biochemical parameters at the time of stroke: raised urea, creatinine and were. associated with poor survival. Raised urea [2.21 (1.3,3.7), p= 0.003], raised creatinine: [1.45 (1.08, 1.99); p<0.013] and educed e-GFR [(2.48 (1.77, 3.48), p<0.001)]. (Table 1) (Figures: 1,2,3)

AKI and survival: Of the 670 stroke patients, those with pre-existing CKD, ESRF those on dialysis and with incomplete data were excluded. AKI was noted in 122(19.80 %) of the remaining 616 patients. Of the 122 patients with AKI, 48(39.34%) developed AKI during stroke admission and remaining 74(60.65%) developed AKI during follow up period. (Table 2)

Multivariable analysis:

The multivariate cox regression analysis after adjusting for age showed that AKI was an independent predictor for mortality. Adjusted hazard ratio: AKI. [1.79(1.16,2.75), p=<0.001]. (Table 2)

Discussion:

In our study cohort of 616 patients with stroke, followed up over a median period of 141 (120-163) months and we found AKI in 48 patients during the index admission and a further 74 developed AKI episodes during the subsequent follow-up period. During follow-up, 76 progressed to CKD and 7 developed ESRF. AKI, both at the time of stroke admission and during follow up period was an independent risk factor for poor survival outcome in our study. (Fig. 4)

However 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, contrast induced nephropathy.

Chronic kidney disease and ESRF along with HD are associated with hypertension (HTN) and diabetes mellitus (DM). These patients are susceptible for vascular complications including stroke. The short and long-term survival in this group of people has been extensively studied in the past.

In contrast AKI and its relationship has not been studied enough and only few studies are done to review its impact on stroke patients. However, from available data, AKI has been shown to be a common complication following ischaemic and haemorrhagic stroke (21, 22, 23) and causes increased mortality in ischaemic stroke (22).

Grosjean et.al**,** in their retrospective analysis found higher incidence of AKI post stroke and its association with cardio-embolic and haemorrhagic stroke. AKI was also associated with longer length of stay, higher comorbidity index, and worse disability score. Although the in-patient 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 (FIM), and comorbidity index due to incomplete data. We did not include length of stay as an outcome measure as has been reported earlier (24). The reason for this is, as some of the stroke patients 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 in-patient stay.

AKI and its relationship with cardioembolic strokes has been studied and the increased incidence of AKI in these patients is thought to be result of haemodynamic dysfunction associated with underlying atrial fibrillation (AF). (25) Other factors, which may increase AKI, include, anticoagulants (26) and anaemia (27,28, 29). Meta-analysis of AKI and stroke patients 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 (CCF) (17, 23) and higher national institutes of stroke health scale (NIHSS) scores (17, 22). The study also concluded that AKI was associated with increased cost, length of stay (LOS), and cardiovascular events. (30) Our study group had mean age of 64.2 years, and AKI seem to impact survival even in younger age group of stroke patients. (Fig 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 was documented as first insult. We also note that 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 post stroke survival. However, the impact of the comorbidities associated with stroke i.e., 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 lead 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 is a retrospective analysis, our findings are similar and suggest that AKI is a strong and independent predictor of poor survival following stroke**.**

Snarska et.al. in their study concluded, that haemorrhagic stroke patients with AKI had worse outcomes as compared to 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 protective effect against development of AKI in acute stroke. (32)

Our study also suggested that each subsequent admission for medical or surgical reasons i.e., 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 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 stroke patients with chronic kidney disease, end stage renal failure on haemodialysis, [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 strongly corelated with poorer survival

Acute stroke management which may prevent AKI includes management of hydration status, adequate and timely treatment of sepsis, avoidance of nephrotoxic agents and indwelling catheters.

A multidisciplinary approach for prevention of AKI with renal team may be beneficial. Modifiable risk factors such as DM, HTN need careful management.

We are planning prospective study to validate our findings.

Author contributions: Pande S D, Roy D M: concept, data, literature search and write up. Khine A A, Win M M, Lolong L, Shan N: data collection, methodology. Tin A S, Statistical analysis, tables, graphs, editing.

Competing interest: none of the authors have any conflict of interest to declare.

Funding: No funding was obtained from any source for this study.

Data sharing statement: all data is included in the manuscript, any further data required, we will seek Singhealth IRB approval

Human and Animal Rights: this study does not involve any intervention involving humans or animals. The data collected is retrospective. Singhealth CIRB number: 2015/3112.

Informed consent: Due to the retrospective nature of data collection, Singhealth Centralised IRB approved for waiver of consent.

Acknowledgements: Clinical trials and research unit, Changi general hospital.

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Figure legends:

Figure 1: Survival (K-M) graph: relationship of raised urea at the time of stroke with survival.
Figure 2: Survival (K-M) graph: relationship of raised creatinine at the time of stroke with survival.
Figure 3: Survival (K-M) graph: relationship of e GFR at the time of stroke with survival.
Figure 4: Survival (K-M) graph: relationship of AKI with survival.

Table 1.
Hazard ratios in relation to urea, creatinine, e-GFR.

		Univariate Cox Regression	
		Hazard Ratio (95% CI)	**p-value**
Admission Urea	>=7.7 6% (35)	2.21 (1.3,3.7)	0.003*
	<7.7 94% (581)	1	
Admission Creatinine	>=90 36% (222)	1.45 (1.08,1.99)	0.013*
	<90 64% (394)	1	
Admission eGFR	<60 15% (93)	2.48 (1.77,3.48)	<0.001*
	>=60 85% (522)	1	
	Missing n=1		

Table 2:
Hazard ratios in relation to AKI.

		Univariate Cox Regression	
		Hazard Ratio (95% CI)	**p-value**
1. AKI only those during stroke admission	AKI 9% (48)	2.87 (1.9,4.3)	<0.001*
	Normal 91% (494)	1	
2. AKI: including during the stroke admission and follow-up period.	All AKI 20% (122)	2.33 (1.7,3.2)	<0.001*

	Normal 80% (494)	1	

1. AKI at the time of stroke: The Univariate cox regression showed that Having AKI renal status were significantly associated with mortality.

The multivariate cox regression analysis after adjusting for age showed that both age and AKI renal status were independent predictors for mortality. Adjusted hazard ratios are age [1.08 (1.06,1.09), p=<0.001] and AKI [1.79(1.16,2.75), p=<0.001]

2. AKI during stroke admission and follow-up period: The Univariate cox regression showed that Having All potential AKI renal status were significantly associated with mortality.

The multivariate cox regression analysis after adjusting for age showed that both age and All potential AKI renal status were independent predictors for mortality. Adjusted hazard ratios are age [1.08 (1.06,1.09), p=<0.001] and AKI [1.78(1.29,2.45), p=<0.001].

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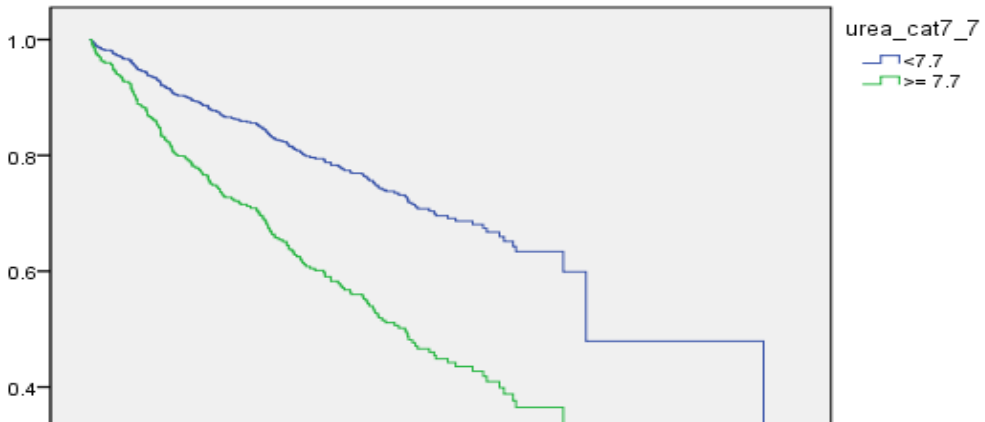

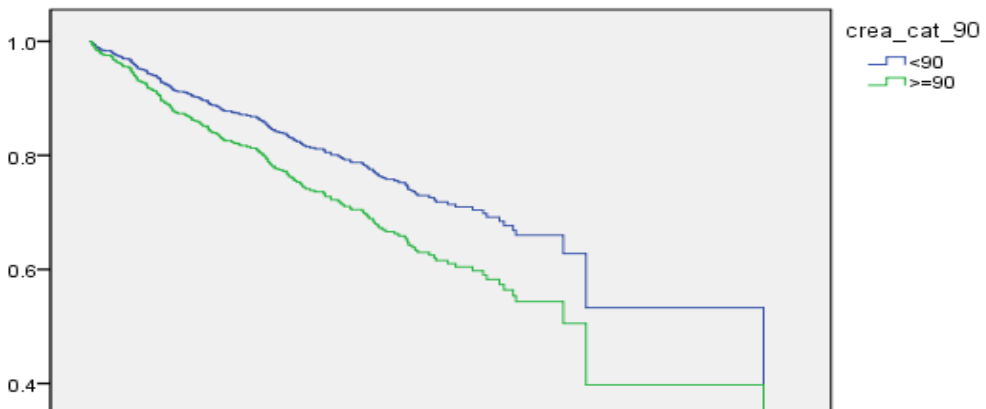

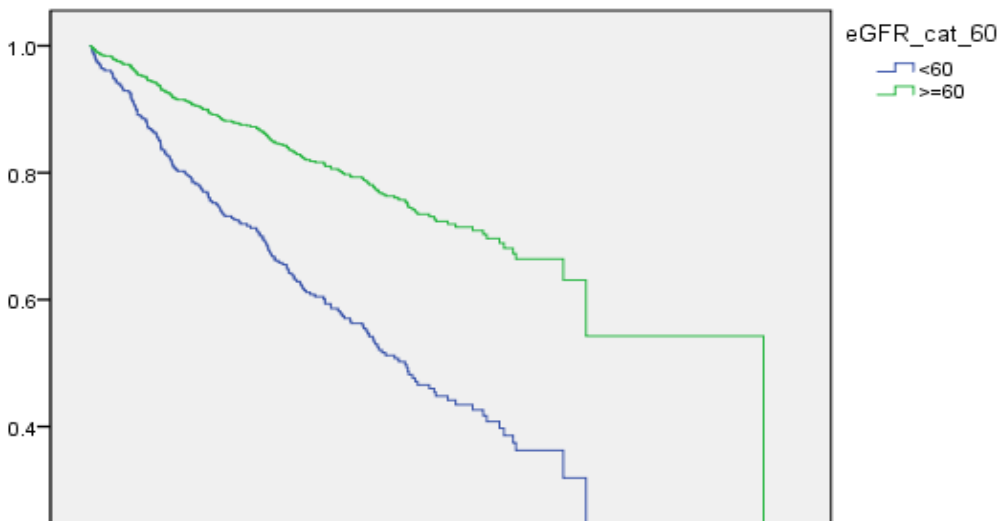

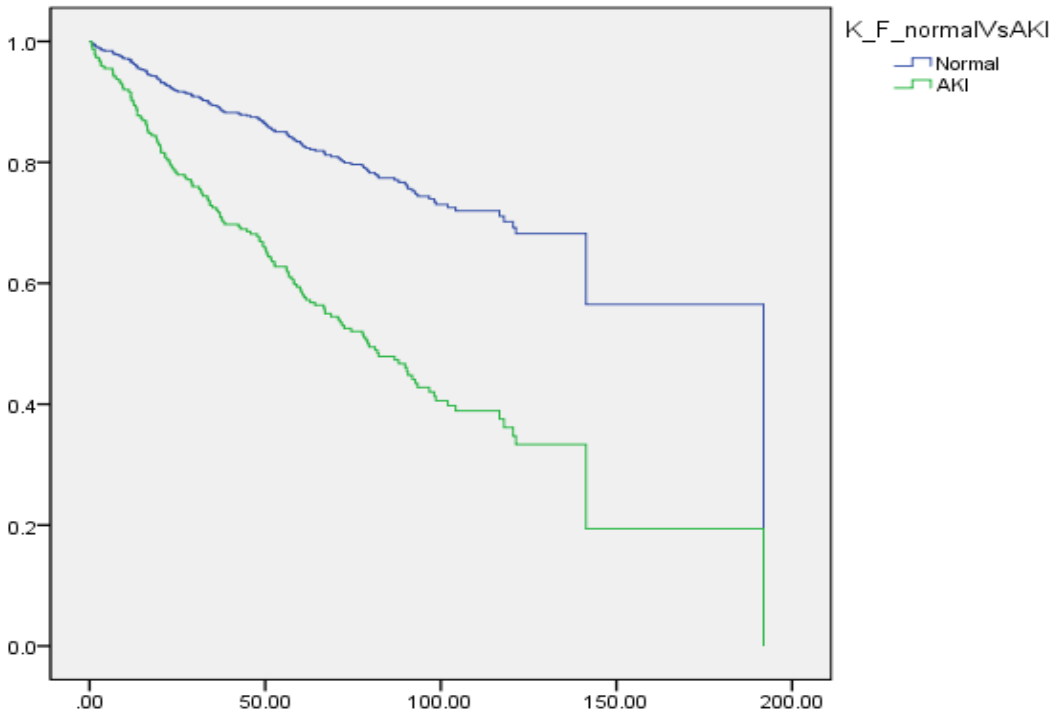

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies1*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			**3**
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, 5, 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4,5,6*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			5,6

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4,5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	TABLE 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6 and Table 1
		(*b*) Report category boundaries when continuous variables were categorized	6 Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			6,7,8,9
Key results	18	Summarise key results with reference to study objectives	6 Table 1,2
Limitations			10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1, 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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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Title: 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: Stroke patients 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.

Design, setting, participants: Retrospective analysis of stroke patients admitted at Rehabilitation facility in Changi General Hospital, Singapore, between June 2008 and May 2017, with median follow up of 141 (120-163) months.

Outcome measures, results: univariate analysis: Total 681 patients, median age (63.6) years, 173 (28%) died during follow-up. Elevated blood urea, [3.02 (2.17, 4.22) P= <0.001], creatinine [1.96 (1.50, 2.57) p=<0.001] during stroke affected survival adversely.

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

Conclusion: we found AKI during stroke admission was associated with increased mortality as compared to 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 chronic kidney disease.

Key words: stroke, acute kidney injury, chronic kidney disease, progression to CKD comorbidities, long-term survival.

Article summary

Strengths and limitations

1. All ethnic and socioeconomic groups are represented in the data.
2. This is the first study from Southeast Asia on long-term survival outcomes following stroke in relation to AKI.
3. The effect of AKI in development of subsequent CKD is described.
4. Retrospective observational and single centre study which may lead to potential selection bias and reporting bias.
5. Due to retrospective nature of the study the causes of the 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 the survival ~~of~~ in these patients (3, 4).

The stroke patients with more severe neurological deficit are at an increased risk for medical complications like urinary tract and chest infections which in turn are

associated with poor functional recovery. (5,6,7)

Dehydration, sepsis, and fluctuations in blood pressure following stroke increases the risk of acute kidney injury (AKI) with consequent poor survival. Elderly patients with decreased eGFR are a population at increased risk for AKI. (8, 9, 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) Co-existent diabetes mellitus and poorly controlled hypertension in stroke patients may also contribute to CKD. (13,14)

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

Although AKI is increasingly recognised as significant risk factor, its impact on survival in stroke patients 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 chronic kidney disease.

Methods

Patients: This is a retrospective analysis of stroke patients (both infarction and spontaneous intracerebral haemorrhage) who had met the selection criteria of the study and were consecutively admitted to the Neuro-rehabilitation 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 outpatient. 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 (a) incomplete follow-up records including those patients who were repatriated to other countries, (b) patients less than 21 years of age (as per CIRB guideline), (c) transient ischaemic attacks (d) pre-existent CKD, ESRF (end-stage renal failure) or patients on haemo-dialysis (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 > 26.5 mmol/L over baseline within 48 hours as per the 2012 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 (computerised tomography), MRI (magnetic resonance imaging), MRA (magnetic resonance angiography)], ECG (electrocardiography) 12 leads, continuous monitor or Holter, carotid Doppler and echocardiogram. The patients were classified as per Oxfordshire classification (for stroke territory) (19) and TOAST for ischaemic strokes. (20)

The Singhealth Centralized Institutional Review Board 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.

Patient and public Involvement statement: due to 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 21st October 2019. The material was housed in the hospital's medical record database and in the records of the clinician at the neuro-rehabilitation facility. The data collected included demographic details, diagnosis, type of stroke (ischaemic, 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, neurosurgical interventions.

Statistical analysis: Categorical data are presented as frequency (percentage), and continuous data are presented as mean (standard deviation) for Normally distributed data and geometric mean and range for positively skewed data. Associations between mortality and demographic factors, clinical features, co-morbidities, and admission blood tests for the cohort of 617 patients were assessed using Cox proportional hazards regression. Hazard ratios and their associated 95% confidence intervals 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 (SPSS) version 22.0 (IBM Corp. Armonk, New York).

Results

Patient Characteristics: A total of 617 (females: 36%) patients with mean age of 63.6 years, met the selection criteria. Whilst 443 (70%) of the patients had ischemic strokes, 190 (28%) of them had haemorrhagic strokes. The median follow-up period was 141 (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 (2.17, 4.22) P= <0.001],

and elevated serum creatinine [HR 1.96 (1.50, 2.57) p=<0.001] at the stroke admission affected survival adversely in long term. (Table 1)

AKI and survival: 617 of the 681 stroke patients 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 long term [2.16 (1.49, 3.13) <0.001]. (Table 2)

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

AKI was noted in further forty-seven patients during 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 hazard ratio: AKI (HR: 1.30 95% CI: 0.79, 2.16, P=0.305). (Table 4)

Discussion:

In our retrospective cohort of 617 patients with stroke, followed up over a median period of 11.75 years: we noted AKI in 12.15% patients during the stroke admission. On follow-up, 28% patients with AKI subsequently progressed to CKD. Of the seventy-five patients with AKI, 49 (65%) were KDIGO grade 1 and 26 (35%) were KDIGO grade 2. None of the patients with AKI required renal replacement therapy.

The AKI patients who progressed to CKD was 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, contrast induced nephropathy.

Chronic kidney disease and ESRF are often associated with hypertension (HTN) and diabetes mellitus (DM). These patients are susceptible for vascular complications including stroke. The short and long-term survival in this group of people have been extensively studied in the past.

In contrast AKI and its relationship has not been studied adequately and only few studies have reviewed its impact on stroke patients. However, from available data, AKI has been shown to be a common complication following ischaemic and haemorrhagic stroke (21, 22, 23) and causes increased mortality in ischaemic stroke (22).

Grosjean et.al**,** in their retrospective analysis found higher incidence of AKI post stroke and its association with cardio-embolic and haemorrhagic stroke. AKI was also associated with longer length of stay, higher comorbidity index, and worse disability score. Although the in-patient 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 (FIM), and comorbidity index due to incomplete data. We did not include length of stay as an outcome measure as has been reported earlier (24). The reason for this is, as some of the stroke patients 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 in-patient stay.

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 (AF). (25) Other factors, which may increase AKI, include, anticoagulants (26) and anaemia (27,28, 29).

Meta-analysis of AKI and stroke patients 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 (CCF) (17, 23) and higher national institutes of stroke health scale (NIHSS) scores (17, 22). The study also concluded that AKI was associated with increased cost, length of stay (LOS), and cardiovascular events. (30) Our study group had mean age of 63.6 years, and AKI impact survival even in younger age group of stroke patients. (Fig 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 was documented as first insult. We also note that 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 post stroke survival. However, the impact of the comorbidities associated with stroke i.e., 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 is 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 haemorrhagic stroke patients with AKI had worse outcomes as compared to 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 protective effect against development of AKI in acute stroke. (32)

Our study also suggested that each subsequent admission for medical or surgical reasons i.e., 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 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 stroke patients with chronic kidney disease, end stage renal failure on haemodialysis, (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 chronic kidney disease

Acute stroke management strategies which may prevent AKI, includes 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 renal team may be beneficial.

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

We are planning prospective study to validate our findings.

Contributorship statement: Pande S D, Roy D, Tu TM: concept, data, literature search and write up. Khine A A, Win M M, Lolong L, Shan N: data collection, methodology. Tan PT: Statistical analysis, tables, graphs, editing.

Competing interest: none of the authors have any conflict of interest to declare.

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Data sharing statement: no additional data is available.

All the data that us publicly available and used in the writing of this article in the text and the reference list is generated by me (Pande S.D).

Human and Animal Rights: this study does not involve any intervention involving humans or animals. The data collected is retrospective. Singhealth CIRB number: 2015/3112.

Informed consent: Due to the retrospective nature of data collection, Singhealth Centralised IRB approved for waiver of consent.

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Word count: 2003.

Figure legend: Kaplan-Meier survival graph showing in group with AKI on admission vs. those without.

Ethics statement: due to the retrospective nature of data collection, the Singhealth CIRB (2015/3112) has given waiver of consent as the data is anonymised and no intervention is planned.

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Table 1: Univariate of chrematistics associated with progression to mortality (n=681)

	N	Univariate HR (95% CI]	P value
Age (year)	681	1.08 (1.07, 1.09)	<0.001
Gender			
Male	423	Reference	0.124
Female	258	1.24 (0.94, 1.63)	
Ethnicity			
Chinese	447	Reference	
Indian	55	0.90 (0.51, 1.59)	0.710
Malay	152	1.32 (0.97, 1.80)	0.075
Others	27	0.66 (0.29, 1.50)	0.323
Stroke: haemorrhagic vs ischemic			
Haemorrhagic	191	Reference	0.055
Ischemic stroke	490	1.36 (0.99, 1.88)	
Cardioembolic stroke			
No	288	Reference	
Moderate risk	73	2.58 (1.65, 4.02)	<0.001
High risk	185	3.75 (2.69, 5.21)	<0.001
Artery size			
Small	187	Reference	0.018
Large	296	1.50 (1.07, 2.09)	

Stroke classification			
LACS	323	Reference	
TACS	30	2.36 (1.33, 4.16)	0.003
PACS	187	1.57 (1.13, 2.17)	0.007
POCS	131	1.55 (1.08, 2.21)	0.016
Undefined	10	2.00 (0.73, 5.47)	0.175
Significance infection, Hep B, HIV			
No	668	Reference	0.465
Yes	13	0.65 (0.21, 2.04)	
Cirrhosis			
No	669	Reference	0.088
Yes	12	2.03 (0.90, 4.58)	
Malignancy			
No	622	Reference	<0.001
Yes	59	2.06 (1.42, 2.98)	
Fracture neck of femur			
No	659	Reference	0.590
Yes	22	0.80 (0.35, 1.80)	
Atrial fibrillation			
No	506	Reference	<0.001
Yes	175	2.39 (1.82, 3.15)	
Recurrent cerebrovascular accidents: during follow-up			
No	613	Reference	0.858
Yes	68	1.04 (0.68, 1.59)	
Peripheral vascular disease			
No	600	Reference	0.004
Yes	81	1.68 (1.18, 2.39)	
Chronic obstructive pulmonary disease			
No	667	Reference	0.029
Yes	14	2.10 (1.08, 4.10)	
Ischemic heart disease			
No	465	Reference	<0.001
Yes	216	1.65 (1.26, 2.16)	
Hypertension			
No	168	Reference	0.012
Yes	513	1.55 (1.10, 2.18)	
Diabetes mellitus			
No	412	Reference	0.025
Yes	269	1.36 (1.04, 1.78)	
Known history of hyperlipidaemia			
No	383	Reference	<0.001
Yes	298	1.71 (1.31, 2.24)	
High total cholesterol: during stroke admission			
No	324	Reference	<0.001
Yes	326	0.54 (0.40, 0.71)	
Total cholesterol to LDL ratio			
No	303	Reference	<0.001
Yes	336	0.61 (0.46, 0.80)	
Low sodium			

No Yes	579 102	Reference 1.90 (1.38, 2.62)	<0.001
Patient with neurosurgical intervention for stroke. No Yes	626 55	Reference 0.51 (0.27, 0.96)	0.036
High potassium No Yes	554 127	Reference 0.68 (0.46, 0.99)	0.044
High glucose	681	1.03 (1.005, 1.05)	0.018
Haemoglobin	681	0.77 (0.72, 0.83)	<0.001
White blood cell count	681	0.94 (0.90, 0.99)	0.009
Platelet count	680	0.99 (0.99, 1.00)	0.093
Raised blood urea No Yes	602 78	Reference 3.02 (2.17, 4.22)	<0.001
Raised serum creatinine No Yes	408 273	Reference 1.96 (1.50, 2.57)	<0.001
Thrombolysis with r TPA for ischemic strokes only No Yes	533 148	Reference 0.55 (0.26, 1.17)	0.123
Raised intracranial pressure and treatment received during stroke. No Yes	643 38	Reference 0.72 (0.50, 1.03)	0.069

Table 2: Univariate of relationship of AKI to long term stroke mortality.

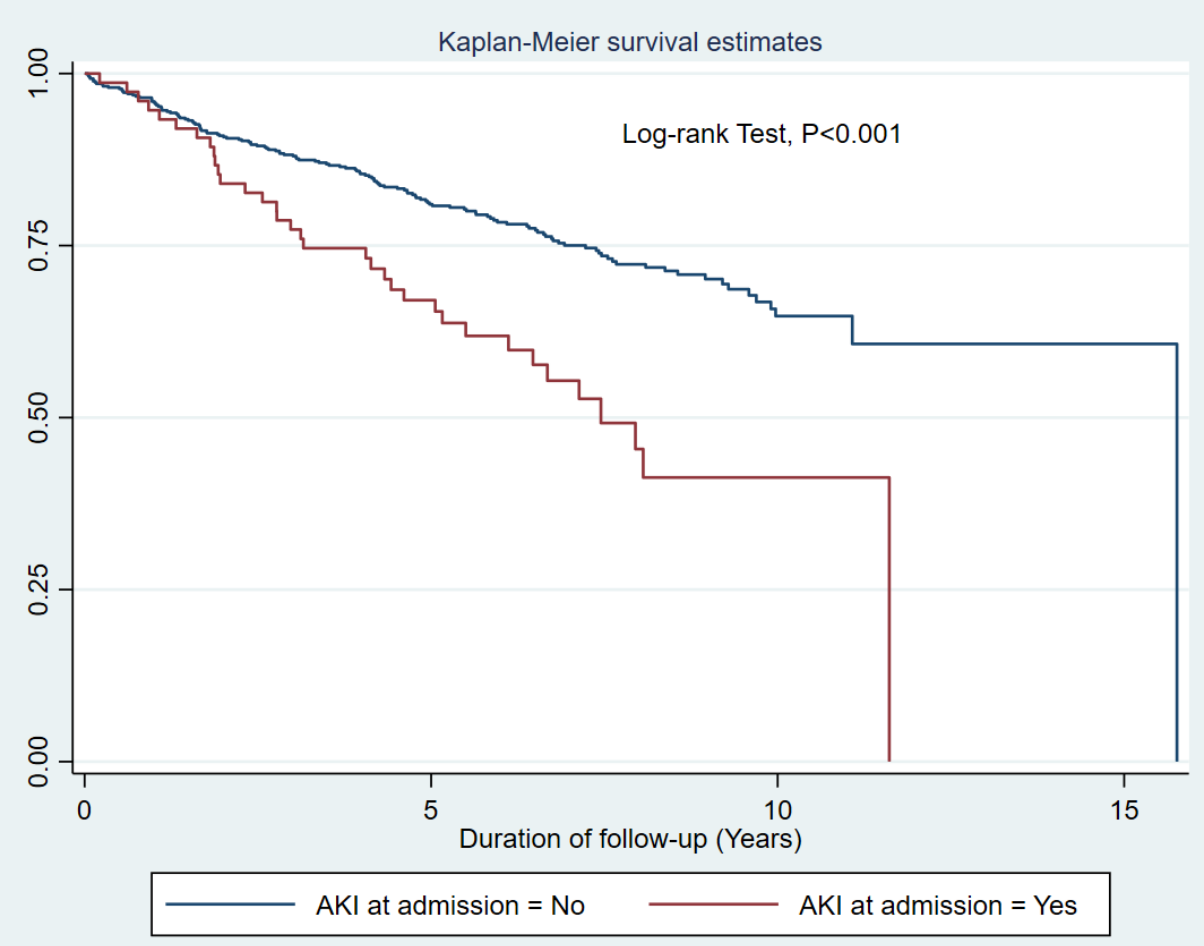
Acute kidney injury at stroke admission	N	HR (95% CI)	P value
No	542	Reference	<0.001
Yes	75	2.16 (1.49, 3.13)	

Table 3: Association of AKI grading and progression to chronic kidney disease (CKD).

Acute kidney injury at stroke.	Total	Grade I	Grade II/III	P value
Acute kidney injury at stroke	54 (72.0)	49 (70.0)	5 (100.0)	0.183
Acute kidney injury at stroke progressing to CKD	21 (28.0)	21 (30.0)	0 (0.0)	

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

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



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies1*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			**3**
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, 5, 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4,5,6*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			5,6

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4,5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	TABLE 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6 and Table 1
		(*b*) Report category boundaries when continuous variables were categorized	6 Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			6,7,8,9
Key results	18	Summarise key results with reference to study objectives	6 Table 1,2
Limitations			10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1, 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.