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Original Research Article

Ischemic cerebrovascular accident and its secondary renal impairment

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ABSTRACT

Background: Renal impairment is one of the most frequent but anticipated potential complications. The objective of this meta-analysis was to evaluate the renal impairment following ischemic cerebrovascular accident (CVA) patients worldwide.
Methods: Authors were using meta-analysis. Studies were obtained from several databases like Pubmed, Cochrane, Karger and JNS. Keywords were "renal" or "kidney" and "stroke" and "ischemic". Included studies were full-text observational study or randomized control trial (RCT). Subjects in study were newly diagnosed acute kidney disease (AKI) after ischemic CVA, with age range 18-100 years old. From 425 studies, total 5 studies were eligible for this study.
Results: From those 5 studies, it is shown that the pooled risk ratio (RR) for mortality ischemic CVA with AKI was 2.56. AKI appeared insignificantly in both ischemic CVA and intracerebral haemorrhage (ICH) (RR 0.75; p=0.01). The pooled risk ratio had wide heterogeneity (I2 = 0.95) so random effect model was used.
Conclusions: Renal impairment and its mortality appeared more frequent in ischemic CVA with AKI. It still needs more multicentre and long-term period researches in the future to get better understanding AKI in ischemic CVA.

Keywords: Complications, Ischemic cerebrovascular accident, Mortality, Renal impairment

INTRODUCTION

Ischemic cerebrovascular accident (CVA) or stroke is still a major cause of disability in the world. Ischemic CVA has a percentage of 80-85% of stroke types in the world.[1] Stroke prevalence is still high, especially in developing countries like Indonesia. More than 2,000,000 people were diagnosed with stroke in Indonesia in 2013.[2] In Indonesia, the group diagnosed with stroke by health workers increased with age, highest at age ≥75 years, namely men as much as 43.1% and women as many as 67.0%.[2]

CVA happened because interrupted vascular following through the brain due to obstruction or hemorrhagic condition which led to hypoxia state of cerebrum ended up with clinical manifestation usually acute neurological deficits last for long time even creating sequel. CVA is always give complex and serious morbidity and even mortality to the patient either ischemic and hemorrhagic.[2]

Renal impairment is one of the most frequent but anticipated potential complications in patients with cerebrovascular accident.[3] The amount of acute kidney injury (AKI) after CVA is still lack of data, however it is known to be associated with substantial increase in hospital mortality.[4,5] AKI is case of decreasing kidney function from hours to days according to RIFLE criteria.[6,7] Atherosclerosis, arterial hypertension, and diebetes mellitus whereas risk factors of cerebrovascular accident are common predisposing condition to create AKI.[8]

Regarding the data spreaded, there were still minimal observation and the accumulative reports of CVA progress to AKI. Therefore, the objective of this meta-analysis was to evaluate the renal impairment following ischemic cerebrovascular accident (CVA) patients worldwide in order to comprehensively acknowledge prevalence of AKI following stroke and the clinical consequences on morbidity and mortality. A secondary objective was to evaluate the effect of AKI on stroke mortality in ischaemic and hemmorhagic patients.

METHODS

The authors conducted the study using PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) as a guideline for writing.[9] Authors collected related studies from several online databases such as Pubmed, Cochrane, Karger and JNS in May - July 2018 and retrieved published studies in Bahasa Indonesia or English without limitation in publication year. The keywords used were "renal" or "kidney" and "stroke" and "ischemic". The stage was carried out independently and structured by both authors (KRP and AFP).

Inclusion and exclusion criteria were compiled to prevent inconsistencies in research and to address potential study-level bias. The inclusion criteria used were as follows:

Inclusion criteria

- Article written in Bahasa Indonesia or English that discussed AKI incidence and its mortality in CVA.
- Full-text observational (i.e., cohort and retrospective) study or randomized control trial (RCT) study.
- Subjects in study were proved having ischemic CVA and confirmed with computerized tomography (CT) scan.
- Patients with newly diagnosed AKI (according to criteria of each study) after ischemic CVA.
- Subjects with age range 18-100 years old.

Exclusion criteria

- Studies with subjects whose kidney disorder before CVA.
- Experimental study.

Outcome

The primary outcome of the intervention was the mortality in ischemic CVA with AKI and without AKI. The secondary outcome was AKI incidence following ischemic CVA and intracerebral hemorrhage. All outcomes were expressed as risk ratio (RR).

Data extraction

Data extraction was done independently by all authors with the same portion. Differences in opinion were determined by joint discussions to reach agreement. All articles were filtered out of any duplication. Studies that have been collected were reviewed in full text using inclusion and exclusion criteria.

Statistical analysis

The data that has been obtained from the screening results was based on the study criteria, processed using software application (Review Manager version 5.3). Forest plots were used as outputs of research results to describe the pooled risk ratio (RR). Authors use random-effect models (REM) if heterogeneity was obtained in the study, whereas a fixed-effect model (FEM) was used if homogeneity was obtained in the study. Authors checked the bias to prevent inconsistencies in studies by using Cochrane-risk-of-bias tool.[10]

RESULTS

Study selection and risk of bias

A flow diagram of study selection is shown in Figure 1. After initially identifying 425 articles, 212 were excluded and the full texts of 213 were reviewed. Subsequently, 186 studies were excluded, and 27 studies underwent full-text assessment based on inclusion and exclusion criteria as mentioned before. Finally, 5 studies were included in this meta-analysis study (Table 1).

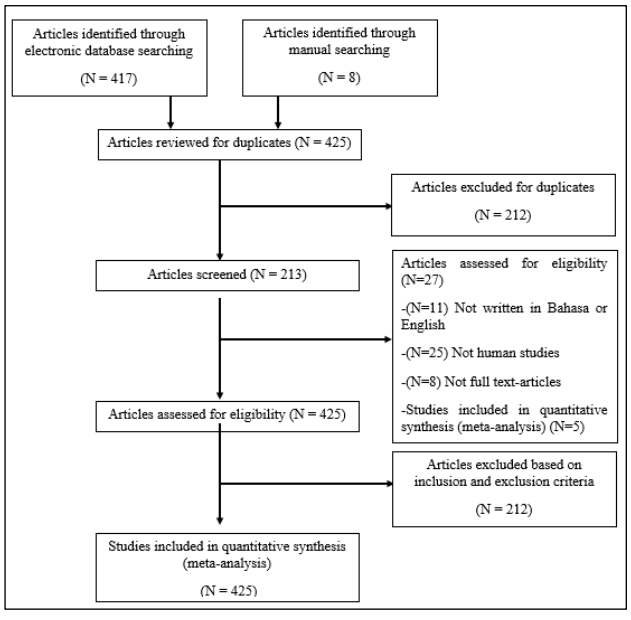

Figure 1: Study flow chart.

Random sequence generation and allocation concealment are not well produced. Blinding of participants and personnel (performance and detection bias) and other sources of bias are also not clearly presented in each study. But each study has a good attrition and reporting bias, so that the overall study can be done based on the criteria in this study (Table 2).

Table 1: Characteristics of the included studies.

Study, Publication year	Country	Study Design	Overall Study Population	Demographic Data
Covic A et al[11]	Romania	Cohort	1090 patients	Age, gender, glomerular filtration rate, blood pressure, past medical history, drug history
Kamouchi M et al[12]	Japan	Cohort	5689 patients	Age, gender, past medical history, blood pressure, complication, stroke therapy, functional outcome
Khatri M et al[13]	United States of America	Cohort	1357 patients	Race, smoking, type of stroke, past medical history, mortality
Tsagalis G et al[14]	Greece	Cohort	2155 patients	Age, gender, past medical history, blood pressure, types of stroke, glomerular filtration rate, haematocrit, creatinine, blood glucose
Saee G et al[15]	United States of America	Cohort	614,454 patients	Age, gender, complications, in hospital procedures, hospital bed size, hospital teaching status, hospital charges, functional outcome

Table 2: Risk of bias.

	Covic A et al[11]	Kamouchi M et al[12]	Khatri M et al[13]	Tsagalis G et al[14]	Saee G et al[15]
Random Sequence Generation?	No	No	No	No	No
Allocation concealment?	No	No	No	No	No
Blinding (performance bias and detection bias)?	Not clear	Not clear	Not clear	Not clear	Not clear
Incomplete outcome data (attrition bias)?	Yes	Yes	Yes	Yes	Yes
Selective reporting (reporting bias)?	Yes	Yes	Yes	Yes	Yes
Other bias?	Not clear	Not clear	Not clear	Not clear	Not clear

Table 3: Analysis of mortality in ischemic CVA patients with AKI compared to those without AKI.

Study of Subgroup	Acute kidney injury +		Acute kidney injury-			Risk ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Covic A et al[11]	68	158	119	932	24.7%	3.37 (2.64, 4.31)
Kamouchi M et al[12]	37	128	282	5561	24.3%	5.70 (4.25, 7.65)
Khatri M et al[13]	92	243	246	1114	25.1%	1.71 (1.41, 2.08)
Saee G et al[15]	11982	140294	29712	474160	25.8%	1.36 (1.34, 1.39)
Total (95% CI)		140823		481767	100%	2.56 (1.42, 4.61)
Total events	121179		30359			
Heterogeneity. $Tau^2 = 0.35$; $Chi^2 = 146.43$, df = 3 ($P < 0.00001$); $I^2 = 98\%$						
Test for overall effect: Z = 3.13 (P = 0.002)						

Table 4: Analysis of AKI incidence in ischemic CVA and intracerebral hemorrhage.

Study of subgroup	Ischemic CVA		Intracerebral hemorrhage			Risk ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Covic A et al[11]	123	932	35	158	30.6%	0.60 (0.43, 0.83)
Khatri M et al[13]	72	528	171	829	34.9%	0.66 (0.51, 0.85)
Tsagalis G et al[14]	286	1011	49	182	34.6%	1.05 (0.81, 1.36)
Total (95% CI)		2471		1169	100%	0.75 (0.53, 1.06)
Total events	481		255			
Heterogeneity. $Tau^2 = 0.07$; $Chi^2 = 9.20$, df = 2 ($P = 0.01$); $I^2 = 78\%$						
Test for overall effect: Z = 1.61 (P = 0.11)						

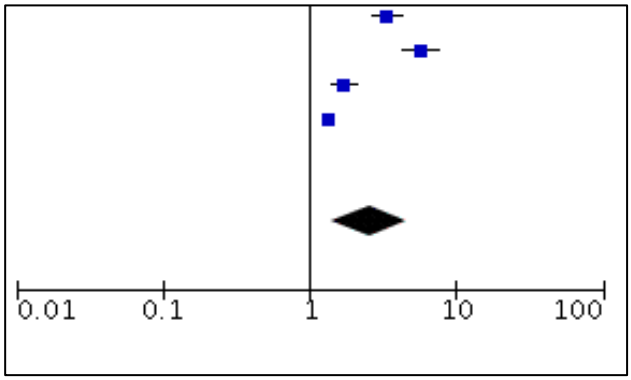

Figure 2: Funnel plot of mortality in ischemic CVA patients with AKI compared to those without AKI.

Mortality relation with AKI incidence in ischemic CVA

Studies that reported effect size on mortality (n=4) we found evidence that the incidence of AKI in ischemic CVA patients significantly increases mortality (95% CI, p <0.05) with risk ratio 2.76 for random effect model (I2 = 98%) (Table 3 and Figure 2).

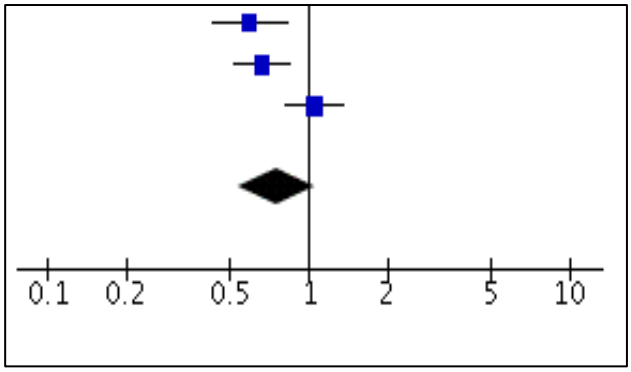

Figure 3: Analysis of AKI incidence in ischemic CVA and intracerebral hemorrhage.

AKI incidence in ischemic CVA and ICH

3 studies were included in AKI incidence analysis, there was no significant incidence between ischemic CVA and ICH (95% CI, p >0.05). The RR is 0.75 in random effect model with heterogeneity (I2 = 78%) (Table 4 and Figure 3).

DISCUSSION

In this meta-analysis study, there are 4 studies included in terms of inclusion criteria. Each of study using criteria in order to recognize AKI, such as AKIN criteria, RIFLE criteria, and creatinine serum level in cerebrovascular accident patients. The mechanism cerebrovascular accident in minimizing or inducing acute kidney injury is still partially understood. However, physiologically body constantly excrete sodium after brain cells death due to sodium waste mechanism of the brain, which called sodium-wasting mechanism of brain.[8] Authors made this paper by following the guideline from PRISMA and Cochrane.[9,10]

Higgins et al, said AKI occurrence was not a rare finding in stroke patients. In one year over 1000 patients cohort, the prevalence of AKI was 14.5% and the incidence of AKI-stroke mortality was high approximately 14% for ischaemic and 36% for hemorrhagic.[10] Risk ratio of this study was 3.37 higher in CVA patients with AKI. Covic et al, also studied comparison between ischaemic and hemorrhagic CVA but the risk ratio was 0.60.[11]

Kamouchi, et al, showed AKI is an independent predictor for short and long-term morbidity and mortality in critically ill patients.[12] AKI occured 2.2% of the patients with ischaemic stroke. Kamouchi et al, study showed patients with CVA 5.7-fold higher tend to have AKI comorbidity.[12]

Khatri et al, studied AKI was a common complication of stroke and that in-hospital death was more than 3-fold higher in patients with ischaemic stroke who had AKI compared to those who did not in univariate or even multivariate models.[13] Study did not address whether the association between AKI and ischaemic stroke mortality is causal, while they attempted to adjust for several risk factors that have been showed to contribute in-hospital mortality. Khatri et al, also explained physiologically derangement associated with AKI including increased inflammation and oxidative stress. Khatri et al, said ischaemic stroke subtype particularly considering that cardioembolic strokes have been associated with higher mortality and perhaps may also be linked with AKI.[13] This study was also comparing patients with AKI in ischaemic and hemorrhagic, however the RR was 0.66.[13]

Tsagalis et al, showed moderate reduction in renal function appeared to be an independent clinically relevant risk factors not only for the overall mortality but also cardiovascular events.[14] This study showed comparison between ischaemic and hemorrhagic study, but the RR was 1.05.[14]

Saeed et al, had a lot of samples compared to other studies.[15] Saeed et al, explained about their study that AKI can occurred in the setting of ICH because various responses; such as volume depletion, rapid blood pressure reduction, contrast exposure, mannitol administration, and atheroembolic diseases. Approximately 6.8% with ICH had AKI in the samples, and study showed higher odds of moderate to severe disability and in-hospital mortality were also seen in ICH patients with AKI.[15] However, this study only sees in patients without comparing ischaemic and hemorrhagic CVA.

All studies agreed to suggest estimated GFR to be useful to identify patients with high risk of death in patients with either ischaemic and hemorrhagic CVA.[11-15] Under this analysis, we take a pooled RR for 4 studies comparing

AKI complication in patients with CVA either ischaemic or hemorrhagic, and the RR was 2.56, meant to be patients with CVA are 2.56 more prone to have AKI in the future. Therefore, researcher tried to analyze the difference between ischaemic and hemorrhagic CVA, however the pooled RR was only 0.75 which it was not able to differentiate the incidence in both CVA subtype.

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