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.3,4 AKI is case of decreasing kidney function from hours to days according to RIFLE criteria.5,6 Atherosclerosis, arterial hypertension, and diabetes mellitus whereas risk factors of cerebrovascular accident are common predisposing condition to create AKI.7
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. 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.

**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.

**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.](image-url)
### Table 1: Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study, Publication year</th>
<th>Country</th>
<th>Study Design</th>
<th>Overall Study Population</th>
<th>Demographic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covic A et al(^1)</td>
<td>Romania</td>
<td>Cohort</td>
<td>1090 patients</td>
<td>Age, gender, glomerular filtration rate, blood pressure, past medical history, drug history</td>
</tr>
<tr>
<td>Kamouchi M et al(^2)</td>
<td>Japan</td>
<td>Cohort</td>
<td>5689 patients</td>
<td>Age, gender, past medical history, blood pressure, complication, stroke therapy, functional outcome</td>
</tr>
<tr>
<td>Khatri M et al(^3)</td>
<td>United States of America</td>
<td>Cohort</td>
<td>1357 patients</td>
<td>Race, smoking, type of stroke, past medical history, mortality</td>
</tr>
<tr>
<td>Tsagalis G et al(^4)</td>
<td>Greece</td>
<td>Cohort</td>
<td>2155 patients</td>
<td>Age, gender, past medical history, blood pressure, types of stroke, glomerular filtration rate, haematocrit, creatinine, blood glucose</td>
</tr>
<tr>
<td>Sae G et al(^5)</td>
<td>United States of America</td>
<td>Cohort</td>
<td>614,454 patients</td>
<td>Age, gender, complications, in hospital procedures, hospital bed size, hospital teaching status, hospital charges, functional outcome</td>
</tr>
</tbody>
</table>

### Table 2: Risk of bias.

<table>
<thead>
<tr>
<th></th>
<th>Covic A et al(^1)</th>
<th>Kamouchi M et al(^2)</th>
<th>Khatri M et al(^3)</th>
<th>Tsagalis G et al(^4)</th>
<th>Sae G et al(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)?</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other bias?</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Not clear</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study of Subgroup</th>
<th>Acute kidney injury +</th>
<th>Acute kidney injury-</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Covic A et al(^1)</td>
<td>68</td>
<td>158</td>
<td>119</td>
</tr>
<tr>
<td>Kamouchi M et al(^2)</td>
<td>37</td>
<td>128</td>
<td>282</td>
</tr>
<tr>
<td>Khatri M et al(^3)</td>
<td>92</td>
<td>243</td>
<td>246</td>
</tr>
<tr>
<td>Sae G et al(^5)</td>
<td>11982</td>
<td>140294</td>
<td>29712</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>140823</td>
<td>148767</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>121179</td>
<td>30359</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Study of subgroup</th>
<th>Ischemic CVA</th>
<th>Intracerebral hemorrhage</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Covic A et al(^1)</td>
<td>123</td>
<td>932</td>
<td>35</td>
</tr>
<tr>
<td>Khatri M et al(^3)</td>
<td>72</td>
<td>528</td>
<td>171</td>
</tr>
<tr>
<td>Tsagalis G et al(^4)</td>
<td>286</td>
<td>1011</td>
<td>49</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2471</td>
<td>1169</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>481</td>
<td>255</td>
<td></td>
</tr>
</tbody>
</table>

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)
sodium
constantly
still
accident
accident
order
DISCUSSION
3)
3
CVA
Studies
Mortality
Figure
patients
studies
no
incidence
patients
(Table
meta
evidence
with
significant
that
reported
CI,
and
random
effect
model,
AKI,
compared
those
who
did
or
multivariate
models.13
Study
did
address
whether
the
association
between
AKI
and
ischaemic
stroke
mortality
is
causal,
while
they
attempted
to
adjust
for
several
risk
factors
that
have
been
shown
to
contribute
in-hospital
mortality.
Khatiri
et
al,
also
explained
physiologically
derangement
associated
with
AKI
including
increased
inflammation
and
oxidative
stress.
Khatiri
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

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
occurred
2.2% of
the
patients
with
ischaemic
stroke.
Kamouchi
et
al,
study
showed
patients
with
CVA
5.7-fold
ten
tend
to
have
AKI
comorbidity.12

Khatiri
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
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AKI
and
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stroke
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but
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cardiovascular
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hemorrhagic
study,
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the
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was
1.05.14

Saeed
et
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a
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of
samples
compared
to
other
studies.15
Saeed
et
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about
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AKI
can
occurred
in
the
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of
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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.
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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Conflict of interest: None declared
Ethical approval: Not required

REFERENCES


