PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute kidney injury without need for dialysis, incidence, its impact on long term stroke survival and progression to chronic kidney disease.
AUTHORS	Pande, Shrikant; Roy, Debajyoti; Khine, Aye Aye; Win, May; Lolong, Lorecar; Shan, Ni Thu; Tan, Pei Ting; Tu, Tian Ming

VERSION 1 – REVIEW

REVIEWER	Odutayo, Ayodele Li Ka Shing Knowledge Institute, Applied Health Research Centre
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript entitled "Acute kidney injury without need for dialysis, incidence and its impact on long term stroke survival" by Ponde et al. The authors have conducted a retrospective study of AKI in adults with stroke. While the topic is important, I have the following concerns about the manuscript: MAJOR 1. Abstract (Page 3, Line 26-27): The authors state that "AKI appears to independently affect stroke survival and may also lead to chronic kidney disease". There is no data presented in the abstract to support the conclusion regarding chronic kidney disease. 2. Results: The authors indicate in the methods section that they collected data on demographic, clinical and comorbidity characteristics of the participants. However none of this data is presented in a baseline characteristics table and only age, sex and stroke subtype are reported in the first paragraph of the results. As well, none of these variables are included in their multivariable regression. Indeed, the regression only includes age and AKI. Can the authors kindly provide a baseline characteristics table as well as explain variable selection for their multivariable model 3. Discussion (Page 8, Line 12): The authors present results on the number of participants progressing to CKD and ESRD but none of these findings are reported in the results section. Can the authors kindly rectify. MINOR 1. Abstract (Page 3, Line 21): The spelling of KDIGO is incorrect. 2. Abstract (Page 3, Line 37): The authors state that this could be the first study on long term survival following stroke in relation to AKI. I would disagree with this assertion. Indeed, reference 17 in the authors reference list is a study on AKI outcomes in adults with stroke which focused on 17 year mortality.

REVIEWER	Grosjean, Fabrizio Fondazione IRCCS Policlinico San Matteo, Npehrology,Dialysis-Transplantation
REVIEW RETURNED	07-Jun-2021

GENERAL COMMENTS	Pande et al. in their retrospective study enrolling 616 subjects admitted in rehabilitation facility after stroke (median follow-up of 141 months) show that AKI occurred during and after acute stroke was associated with lower long term survival. Major criticism: - The manuscript lacks of baseline demographic description. The Authors should consider to provide a detailed table (i.e. age; sex; comorbidities as diabetes, previous stroke, chronic ischemic heart disease, chronic heart failure, peripheral artery disease, obesity, atrial fibrillation; NIHSS; baseline blood tests). -The Authors should report severity of AKI describing number of cases by AKI classes -The Authors report mulitvariable cox regression analysis data only in results section , however the manuscript would benefit of clear descriptive multivariate analysis table. Was the analysis adjusted only for age? - I'm not sure that table 1 and 2, Figure 1 to 3 add fundamental informations to the paper. I would cite the results of the univariate analysis in the appropriate section. - I would remove descriptive text paragraph inserted after Table 2 in figure legends section - I believe that the manuscript would improve in quality if the Authors add further data regarding progression of kidney function impairment in patients who experienced AKI. In particular it would be intersting to know the degree of eGFR decline and its association with severity of AKI. I would properly report the data in the results section and not in the discussion as in the actual manuscript version. - CKD is often underdiagnosed. How the Authors were able to identify the presence of pre-existing CKD? Minor criticism: - 5th paragraph in the abstract: "KDIGO" instead of "KEDIGO" - carefully check capital letter /ponctuation (i.e. 5th introduction paragraph) -I would consider to omit the first 3 paragraphs of the method section -Did the Authors mean : …admission blood tests..? (5th sentence in statistical analysis paragraph of methods section) -The Authors should consider for sake of clarity to revise results section as following " 616 patients on 670 admitted in the Rehabilitation Facility met selection criteria…" Avoiding the sentence starting as ".. Of the 670 stroke patients, those with…..were excluded.." because already specified in exclusion criteria. -I suggest to revise Figure 4 in more suitable form (avoid "_" in text, use "non AKI" instead of "normal", remove "K_F_normalVsAKI" text, replace "month_surv" with "Months", use % 0 to 100 instead of decimal to label Y axis, report p significance in graph)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ayodele Odutayo, Li Ka Shing Knowledge Institute, University of Oxford Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences
Comments to the Author:
Thank you for the opportunity to review the manuscript entitled “Acute kidney injury without need for dialysis, incidence and its impact on long term stroke survival” by Pande et al. The authors have conducted a retrospective study of AKI in adults with stroke. While the topic is important, I have the following concerns about the manuscript:

MAJOR
1. Abstract (Page 3, Line 26-27): The authors state that “AKI appears to independently affect stroke survival and may also lead to chronic kidney disease”. There is no data presented in the abstract to support the conclusion regarding chronic kidney disease.

Reply and corrections : This data has been revised and we have included this in the data, separate tables.
AKI does show impact on survival and effects development of CKD in long term. We also compared this with those with normal kidney function at the time of stroke.
However, as the first statistician only analysed multivariable in relation to age, we have repeated the analysis. From the updated analysis, AKI is predictor only in univariate analysis.

2. Results: The authors indicate in the methods section that they collected data on demographic, clinical and comorbidity characteristics of the participants. However, none of this data is presented in a baseline characteristics table and only age, sex and stroke subtype are reported in the first paragraph of the results. As well, none of these variables are included in their multivariable regression. Indeed, the regression only includes age and AKI. Can the authors kindly provide a baseline characteristics table as well as explain variable selection for their multivariable model.
Reply and corrections: we have included all the demographic details and multivariate analysis.
The regression analysis with other significant variables is included.
The AKI although showed significant impact on survival in univariate model.
However, adjusting for other variables, the AKI does not appear to be a significant factor for survival.

3. Discussion (Page 8, Line 12): The authors present results on the number of participants progressing to CKD and ESRD but none of these findings are reported in the results section. Can the authors kindly rectify?

Reply and corrections: we have amended this and included this in the results section.

MINOR
1. Abstract (Page 3, Line 21): The spelling of KDIGO is incorrect.

Reply and corrections: thank you, we have amended this now.

2. Abstract (Page 3, Line 37): The authors state that this could be the first study on long term survival following stroke in relation to AKI. I would disagree with this assertion. Indeed, reference 17 in the authors reference list is a study on AKI outcomes in adults with stroke which focused on 17-year mortality.
Reply and corrections: we agree with you entirely as this is not the first study and indeed prospective any retrospective analysis have been published before.
We have mentioned that this could be the first data locally, from Singapore, reviewing the long-term survival outcomes following stroke in relation to AKI.
We are not implying that this is the first data.

Reviewer: 2
Dr. Fabrizio Grosjean, Fondazione IRCCS Policlinico San Matteo
Comments to the Author:
Pande et al. in their retrospective study enrolling 616 subjects admitted in rehabilitation facility after stroke (median follow-up of 141 months) show that AKI occurred during and after acute stroke was associated with lower long-term survival.
Major criticism:
- The manuscript lacks of baseline demographic description. The Authors should consider to provide a detailed table (i.e., age; sex; comorbidities as diabetes, previous stroke, chronic ischemic heart disease, chronic heart failure, peripheral artery disease, obesity, atrial fibrillation; NIHSS; baseline blood tests).
Reply and corrections: we have included all the demographic details and multivariate analysis. We however do not have certain parameters i.e., data on obesity, NIHSS scores, due to inaccuracies in the documentation for these parameters.
All others, gender, comorbidities, admission bloods, IHD, COPD, PVD, AF, are included. Previous strokes: our data only included those who presented first time stroke.
The regression analysis with other significant variables is included.
The AKI although showed significant impact on survival in univariate model.
However, adjusting for other variables, the AKI does not appear to be a significant factor for survival

The Authors should report severity of AKI describing number of cases by AKI classes
Reply and corrections: we have included this as a separate table indicating severity of AKI.

The Authors report multivariable cox regression analysis data only in results section, however the manuscript would benefit of clear descriptive multivariate analysis table. Was the analysis adjusted only for age?
Reply and corrections: we have included the baseline parameters and tables. However, adjusting for other variables, the AKI does not appear to be a significant factor for survival

- I'm not sure that table 1 and 2, Figure 1 to 3 add fundamental information's to the paper. I would cite the results of the univariate analysis in the appropriate section.
Reply and corrections: we have removed the figures 1 to 3.

- I would remove descriptive text paragraph inserted after Table 2 in figure legends section.
Reply and corrections: thank you, we have deleted this the tables are amended.

- I believe that the manuscript would improve in quality if the Authors add further data regarding progression of kidney function impairment in patients who experienced AKI. In particular it would

be interesting to know the degree of eGFR decline and its association with severity of AKI. I would properly report the data in the results section and not in the discussion as in the actual manuscript version.

Reply and corrections: Once again we wish to thank you for your comments.
We have reviewed the data and categorised the patient's data according to AKI classification based on severity.
We have included this in the results section: AKI severity, progression to CKD and the duration.

- CKD is often underdiagnosed. How the Authors were able to identify the presence of pre-existing CKD?

Reply and corrections: Thank you for the comment. Singapore is a small country with a public healthcare system with excellent database, which is accessible to all medical practitioners. Based on these records, and as mentioned in the methods, we excluded those patients with CKD /ESRF, and those Haemodialysis. We have used KDIGO definition: for diagnosis of AKI.
Staging of AKI was done as per the KDIGO guidelines (grade 1 to 3).
CKD: definition was used as per KDIGO Criteria: abnormal kidney function for 3 months or more.

Of the total 681 patients of which those patients with baseline renal function was available for comparison and 64 patients were labelled CKD, ESRF or those on haemodialysis were excluded for the purpose of this study.
AKI labelled patients included in this study: were those patients with known normal renal function, including serum creatinine, e GFR, 3 months or longer prior to admission and after the AKI diagnosis the renal function (serum creatinine, GFR returned to normal within the admission period or less than 3 months during follow-up period).

Minor criticism:
- 5th paragraph in the abstract: "KDIGO" instead of "KEDIGO"
- carefully check capital letter /punctuation (i.e. 5th introduction paragraph)
Reply and corrections: we have amended this.

-I would consider to omit the first 3 paragraphs of the method section

Reply and corrections: these paragraphs are removed now.

-Did the Authors mean : …admission blood tests..? (5th sentence in statistical analysis paragraph of methods section)
Reply and corrections: we have amended it to blood tests.

-The Authors should consider for sake of clarity to revise results section as following "616 patients on 670 admitted in the Rehabilitation Facility met selection criteria…" Avoiding the sentence starting as ".. Of the 670 stroke patients, those with…..were excluded.." because already specified in exclusion criteria.
Reply and corrections: this is now amended.

-I suggest to revise Figure 4 in more suitable form (avoid "_" in text, use "non AKI" instead of "normal", remove "K_F_normalVsAKI" text, replace "months" with "Months", use % 0 to 100 instead of decimal to label Y axis, report p significance in graph)

Reply and corrections: we have made these changes.