

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prediction of Outcomes after Acute Kidney Injury in Hospitalized Patients : Protocol for a Systematic Review
AUTHORS	Arora, Tanima; Martin, Melissa; Grimshaw, Alyssa; Mansour, Sherry; Wilson, Francis

VERSION 1 – REVIEW

REVIEWER	Liming Li School of Public Health, Peking University.
REVIEW RETURNED	13-Jul-2020

GENERAL COMMENTS	<ol style="list-style-type: none"> 1. For the assessment of risk of bias, what will be the purpose of NOS scale since PROBAST will be used? Will ROB tool for RCTs also be used? 2. Dialysis and mortality were not clearly included in the keyword for search. 3. It has been strengthened that this SR will help utilize healthcare resources, however, calibration of prediction models was not adequately addressed in current methodology. 4. Can the authors explain what are retrospective RCTs? 5. As for exclusion criteria, I don't think it was reasonable to exclude studies describing models using novel biomarkers or studies describing treatment-related outcomes. 6. To be accurate, the use of "AKI outcomes" should be avoided and replaced by "outcomes after AKI" or "outcomes of AKI".
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REVIEWER	Luke Hodgson Western Sussex Hospitals NHS Foundation Trust, University of Surrey
REVIEW RETURNED	26-Jul-2020

GENERAL COMMENTS	This is a well written protocol.
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REVIEWER	Wouter De Corte az groeninge hospital, Kortrijk, Belgium
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	<p>First, I would like to thank the editor and the authors giving me the opportunity reviewing this manuscript. This study protocol addresses an interesting topic: prediction of outcome after AKI using ML techniques. I have only minor remarks:</p> <ul style="list-style-type: none"> - page 4, line 11 typo <p>Methods and analysis: exclusion of RCT with at least 100 subjects. Why this "cut-off"?</p> <p>p10: "Keywords in search": There needs to be a balance in</p>
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	<p>searching between making the search comprehensive enough to encompass everything on the topic and precise enough to only capture specifically relevant topics. The presented search seems quite "broad". As a consequence the authors may retrieve more non-relevant articles. Maybe the search can be made more precise using specific outcome measures?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Liming Li

Institution and Country: School of Public Health, Peking University, China

Please state any competing interests or state 'None declared': None declared.

Thank you very much for your helpful comments and feedback on our review paper. We really appreciate your suggestions and have tried to incorporate and address most of the points you raised. Transcribed below are your comments, followed by our team's response in red text and, where necessary, a text box with a screenshot of modifications made to the manuscript.

1. For the assessment of risk of bias, what will be the purpose of NOS scale since PROBAST will be used? Will ROB tool for RCTs also be used?

The Newcastle Ottawa scale has been removed. PROBAST- a tool to assess the risk of bias and applicability of Prediction Model Studies will be the main risk of bias tool used for this review. This tool is applicable to different types of studies, including cohort, case control and randomized control trials.

Risk of Bias and Quality Assessment

Assessment of risk of bias will be done using the risk assessment tool below:

PROBAST: Prediction model risk of bias assessment tool assesses the risk of bias in diagnostic and prognostic prediction model studies taking into consideration 4 domains (participants, predictors, outcome, analysis). It assess both risk of bias and concerns regarding applicability of studies that developed or validated multivariable prediction models for diagnosis or prediction.¹⁷

2. Dialysis and mortality were not clearly included in the keyword for search.

Please see attached search appendix. Dialysis and mortality keywords were searched in lines 14 and 15.

3. It has been strengthened that this SR will help utilize healthcare resources, however, calibration of prediction models was not adequately addressed in current methodology.

Thank you for your comments and suggestions. We plan to address the calibration and discrimination of predictive models in our results, and will be capturing this data. This data report will be included in the “limitations” section of the study. We have elaborated upon this section in the manuscript. In the text box below, please find edits made to the manuscript to reflect these edits.

1. *What models exist to predict outcomes after AKI and how well do they perform? A Data Report will be constructed showcasing the different models that have been used to predict outcomes of interest after AKI, alongside the strength of the model.*

2. *What are the most commonly used features in models predicting outcomes after AKI? Data will be collected and reported to highlight the main features used to establish predictive models.*

3. *What are some of the major limitations and challenges in predictive modeling for outcomes after AKI? Limitations will focus on strength of models, and whether discrimination and calibration has been referenced to and/or described and a report will be made on the Area under Receiver Operating Curve (AUROC) for each model. Limitations will also focus on validation of studies and report whether the individual study was internally validated, externally validated or not validated.*

4. Can the authors explain what are retrospective RCTs?

By retrospective RCT we are referring to the retrospective analysis of randomized control trials.

5. As for exclusion criteria, I don't think it was reasonable to exclude studies describing models using novel biomarkers or studies describing treatment-related outcomes.

Our systematic review of literature on predictive models used to predict outcomes after Acute Kidney Injury (AKI) was planned with the intent of reviewing literature on all prognostic models that exist in regard to outcomes after AKI. Specifically, our focus is on the use of refined machine learning methods to predict outcomes.

We excluded models using biomarkers from this study as we believe the use of biomarkers to predict clinical outcomes is a separate prediction entity in itself, whereby the clinician is required to place the order to collect blood and/or urine and detect biomarkers. Instead, our review focuses on identifying models that have the potential to be built into the electronic health record system and require minimum input from the physician. We hope that identifying such models, and reporting on their strength and efficacy, will benefit healthcare as these may be incorporated into the daily workflow of the attending physician.

In regard to treatment related outcomes, again our focus is primarily on the prediction of outcomes after acute kidney injury, specifically the outcomes of resolution, progression to RRT and mortality. A review of prognostic models used to predict these outcomes has not been published as of yet, and thus we feel information on this specific area is crucial to share with the scientific and medical community.

6. To be accurate, the use of "AKI outcomes" should be avoided and replaced by "outcomes after AKI" or "outcomes of AKI".

Thank you for this suggestion. I have modified the text and replaced all “AKI outcomes” with “outcomes of AKI”. Please see text box below for example of change :

<p>models in the recent years, inefficient statistical methods, small sample size, missing data and lack of validation are some common faults that have limited their use¹¹.</p> <p>Clinical implications of an accurate prediction model for <u>outcomes after AKI</u></p> <p>Models that predict outcomes are particularly useful when advising patient families</p>	<div style="border-left: 1px solid red; padding-left: 5px;"> <p>Arora, Tanima Deleted: post-</p> <p>Arora, Tanima Deleted: outcomes</p> </div>
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Reviewer: 2

Reviewer Name: Luke Hodgson

Institution and Country: Western Sussex Hospitals NHS Foundation Trust, University of Surrey, UK

Please state any competing interests or state 'None declared': None declared

This is a well written protocol.

Thank you very much for your kind words and support.

Reviewer: 3

Reviewer Name: Wouter De Corte

Institution and Country: az groeninge hospital, Kortrijk, Belgium

Please state any competing interests or state 'None declared': none declared

Thank you very much for your helpful comments and feedback on our review paper. We really appreciate your suggestions and have tried to incorporate and address most of the points you raised. Transcribed below are your comments, followed by our team's response in red text.

First, I would like to thank the editor and the authors giving me the opportunity reviewing this manuscript. This study protocol addresses an interesting topic: prediction of outcome after AKI using ML techniques. I have only minor remarks:

- page 4, line 11 typo Thank you. This typo has been fixed.

Methods and analysis: exclusion of RCT with at least 100 subjects. Why this "cut-off"? Our group selected a "cut off" of at least 100 subjects for each study we include in this systematic review to ensure that the study was statistically significant and would be generalizable to the population. Smaller studies tend to run a higher risk of model overfitting, thus we decided that a minimum of 100 subjects should be present in the study. This has been reflected in the manuscript as follows :

<p><i>Criteria for considering studies in this review</i></p> <ol style="list-style-type: none"> 1. <u>Study Design</u> : Original data from retrospective and prospective randomized controlled trials and observational cohort studies with at least 100 subjects <u>(to minimize the risk of model overfitting and increase generalizability of the study)</u>. 2. <u>Population</u> : Studies that enroll adult (age greater than or equal to 18 years) hospitalized patients who have a diagnosis of AKI (based on KDIGO criteria, or others).

p10: "Keywords in search": There needs to be a balance in searching between making the search comprehensive enough to encompass everything on the topic and precise enough to only capture specifically relevant topics. The presented search seems quite "broad". As a consequence the authors may retrieve more non-relevant articles. Maybe the search can be made more precise using specific outcome measures?

Please see the search appendix. Systematic review searches should be exhaustive and comprehensive to ensure no relevant article is missed. This balance was reached by developing relevant terms using controlled vocabulary and keywords for every database. The modification made in the manuscript is as below :

Keywords in Search

The search includes controlled vocabulary and keywords for acute kidney injury, prediction or artificial intelligence, and death or dialysis (please reference AKI search appendix for more details).

VERSION 2 – REVIEW

REVIEWER	Wouter De Corte az groeninge Kortrijk
REVIEW RETURNED	02-Dec-2020
GENERAL COMMENTS	The authors addressed the remarks made by the reviewer in an appropriate way.