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Prediction models for acute kidney injury in critical ill patients: a protocol for systematic review and critical appraisal

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Abstract

Introduction

Acute kidney injury (AKI) has high morbidity and mortality in intensive care units (ICUs), which can lead to chronic kidney disease (CKD), more costs and longer hospital stay. Early identification of AKI is crucial for clinical intervention. Though various risk prediction models have been developed to identify AKI, the overall predictive performance varies widely across studies. Due to the different disease scenarios and the small number of externally validated cohorts in different prediction models, the stability and applicability of these models for AKI in critically ill patients are controversial. The purpose of this systematic review is to map and assess prediction models for AKI in critical ill patients based on a comprehensive literature review.

Methods and analysis

A systematic review with meta-analysis is designed and will be conducted according to the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS). Three databases including Pubmed, Cochrane Library and EMBASE from inception through October 2020 will be searched to identify all studies describing development and/or external validation of original multivariable models for predicting AKI in critical ill patients. Random-effects meta-analyses for external validation studies will be performed to estimate the performance of each model. The restricted maximum likelihood (REML)

estimation and the Hartung-Knapp-Sidik-Jonkman (HKSJ) method under a random-effects model will be applied to estimate the summary C statistic and 95% CI. 95% prediction interval (PI) integrating the heterogeneity will also be calculated to pool C-statistics to predict a possible range of C-statistics of future validation studies. Two investigators will extract data independently using the CHARMS checklist. Study quality or risk of bias will be assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST).

Ethics and dissemination

Ethical approval and patient informed consent are not required because all information will be abstracted from published literatures. We plan to share our results with clinicians and publish them in a general or critical care medicine peer- reviewed journal. We also plan to present our results at critical care international conferences.

OSF registration number 10.17605/OSF.IO/X25AT

Key words

Prediction model; acute kidney injury (AKI); critical ill; systematic review; cohort study

Strengths and limitations of this study

- This study will provide an overall mapping of the available studies on prediction models for acute kidney injury (AKI) in critical ill patients.
- This study will be carried out and reported according to the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS).
- Prediction models for AKI in critical ill patients will be evaluated using the PROBAST tool.
- Meta-analysis of C statistics will be conducted for prediction models that are externally validated in different individual populations.
- Several potential sources of heterogeneity including the differences in clinical scenarios, patients' characteristics, cohort regions or races and statistical methods will need further investigation.

Introduction

Acute kidney injury (AKI) is a common condition among hospitalized critical patients, especially in intensive care units (ICUs), and has been a major healthcare burden worldwide.[1-4] AKI is also associated with serious complications, increased health care costs, length of stay and mortality. More than 1.7 million deaths have been reported indirectly due to AKI annually related to chronic kidney disease (CKD), cardiovascular and cerebrovascular events.[5-8]

AKI can originate from heterogeneous causes, and stratifying cases according to characteristics and biomarkers would raise possibility of early prediction of AKI. Biomarkers including serum creatinine (sCr) and urine output are commonly used ones to define AKI. [9] More recently, several other frequently used and new candidate biomarkers have been found to predict AKI in clinics at different stage of the disease condition, but many of them are found to have low sensitivity and specificity.[10-16]

Clinical prediction models are widely used in real-world clinical practice. They are proved to be useful for informing healthcare systems to distinguish high risk patients, guide diagnostic and therapeutic intervention selection, thus early measurements could be taken to improve outcomes.[17] The application of multidimensional indicators to predict the risk of AKI in critical ill patients may provide a more comprehensive approach of disease assessment. Furthermore, in

critically ill patients, multivariable risk prediction models for AKI could be used in clinical practice to assist decision making on hospital admission or admission to ICUs and treatment options.[18-20]

Several prediction models, incorporating multiple predictors for the prediction of AKI, have been developed. Wang et al found that hypertension, chronic kidney disease, acute pancreatitis, cardiac failure, shock, pH ⩽ 7.30, creatine kinase (CK) > 1000 U/L, hypoproteinemia, nephrotoxin exposure, and male gender were independent predictors of AKI.[21] Ferrari and colleagues established a novel prediction score to quickly predict AKI at any stage up to 7 days.[22] However, to the best of our knowledge, no prognostic model for AKI has been endorsed. In routine clinical practice, no a standardised prediction model have been widely accepted or routinely been used.

In this study, we aim to systematically summarise the reported multivariable models developed for predicting AKI in critically ill patients, to map their characteristics and laboratory features, and to test whether they have been carried out external validation. We will apply the Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess the risk of bias of the methodological aspects of the included studies developing or validating prediction models. For prediction models involving several validation studies, we will perform a meta-analysis for performance and calibration of each model to yield more accurate effect estimates.

METHODS AND ANALYSIS

We will design and conduct this systematic review according to Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guideline [23] and the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[24] and the guidance by Debray et al.[25] We have registered the protocol on the website of open science framework (OSF) (https://osf.io/x25at/).

Literature search

We systematically searched PubMed, Embase and Cochrane Library from inception to October 2020 to capture all relevant studies developing and/or validating a prediction model for AKI in critically ill patients. The following search strategy with related key words was developed: (predict* OR progn* OR "risk prediction" OR "risk score" OR "risk calculation" OR "risk assessment" OR "C statistic" OR discrimination OR calibration OR AUC OR "area under the curve" OR "area under the receiver operator characteristic curve") AND ("acute kidney failure" OR "acute tubular necrosis" OR "acute kidney tubule necrosis" OR AKI OR ARI OR AKF OR ARF) AND ("emergency care unit" OR "intensive care unit" OR "critical ill patient" OR "acute ill*" OR ICU). Two independent investigators will undertake the literature search and screening, and discrepancies will be resolved by a senior author. We will

further hand search the reference list of each eligible study for potential missing eligible studies.

Eligibility criteria

We will include all cohort studies that described development and external validation of original multivariable models for predicting AKI in critical ill patients. We present the detailed description of the PICOTS for this systematic review in Table 1. Based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guideline,[26] we will screen and select eligible prognostic model studies when the following inclusion criteria are satisfied. 1) studies that reported the development or validation multivariable model(s) of AKI with or without external validation; 2) studies that yielded at least two predictors; 3) studies that evaluated or updated the quantitative measure of model performance of an existing model in an independent population in terms of overall performance, discriminative ability and calibration of a certain prediction model. We will exclude conference abstracts, editorials, clinical case reviews, letters, commentaries, book chapters and surveys.

Data abstraction

Data extraction will be conducted using a standardised data extraction form by at least two independently reviewers based on the recommendations in the CHARMS checklist.[24] If the needed data are not reported or unclear, the corresponding authors

will be contacted for detailed information. The following general study information will be extracted including first author, publication year, model name, publication source and research country. For model development study, we will extract the following specific data: modelling method, method for selection of predictors for inclusion in multivariable modeling combined with criteria used and shrinkage of predictor weights or regression coefficients. For model performance study, measures of calibration and discrimination with confidence intervals will be abstracted. For studies reporting model evaluation, method used for testing model performance will also be abstracted. Besides, the method for treating the missing data involving the prediction model of each eligible study will also be abstracted.

Critical appraisal

We will critically appraise each included prediction model using the PROBAST technique, a tool to assess risk of bias and applicability of prediction model studies.[27] Based on the checklist of PROBAST, 20 separate questions across 4 domains (participants, predictors, outcome, and analysis) will be asked. Details for the assessment rules are summarized in Table 2. Two authors of the research team will independently assess the risk of bias of the included studies and cross-check the results. Any discrepancies will be resolved by discussion or by a senior author.

Statistical analysis

We will calculate and report descriptive statistics to summarise the characteristics of the AKI models. For binary or categorical variables, we will calculate frequencies or

percentages, while for continuous variables, means, medians, and interquartile ranges (IQRs) will be calculated. For the prediction model of AKI developed from different populations, a random effects □□□ will be applied to calculate a summary estimate for models' performance and calibration. For studies that did not provide measurements of mean C statistics, we will use a formula to estimate the standard error of mean C statistic according to the methods proposed by Snell and colleagues.[28] Due to the relatively small sample size of validation studies for each prediction model, we will meta-analyse C statistic with its 95% CI using a random-effects model based on the restricted maximum likelihood (REML) estimation and the Hartung-Knapp-Sidik-Jonkman (HKSJ) method.[25 29] 95% prediction interval (PI) integrating the heterogeneity will also be calculated to pool C statistics to predict a possible range of C statistics of future validation studies. Heterogeneity between studies will be quantified using the I^2 statistic, defined significant heterogeneity when I^2 statistic more than 50%. [30] The potential of publication bias will be assessed by funnel plots when more than 10 studies are meta-analysed for the prediction model. All statistical analyses will be carried out using R Statistical Software version 3.2.3(R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and Stata version 15.0 (Stata Corporation, College Station, TX, USA).

Patient and public involvement

The current study is a systematic review of what is already reported in the literature. It does not involve patient and public in the design, conduct or reporting of this study.

Ethics and dissemination

Ethical approval and patient informed consent are not required because all information will be abstracted from published literatures. We plan to share our results with clinicians and publish them in a general or critical care medicine peer- reviewed journal. We also plan to present our results at critical care international conferences.

Amendments

The protocol for this systematic review will be amended when necessary during the peer-review process.

DISCUSSION

Although there have been numerous original reports and narrative reviews focusing on the prediction model of AKI,[31-39] several factors may limit the interpretation and application of these prediction models. To the best of our knowledge, this will be the first systematic review that aims to evaluate the published evidence on the prediction models for AKI. This study will provide a clear overview for clinicians to identify some most effective prediction models for AKI among critical ill patients or patients in ICUs. By synthesising data including predictive accuracy such as C statistics across studies, we may get some evidence-based data to stratify disease severity and help inform the clinical management of critical ill patients.

Strengths and limitations

There will be several strengths of this study. Firstly, we will strictly adhere to the Cochrane Handbook's method recommendations during the conduct and reporting of this systematic review to make the results more reliable.[25 40] The purpose of this study is to achieve high-quality evidence regarding the prediction model of AKI in critical ill patients and provide practice recommendations on its applicability for policy makers. Secondly, we will present a detailed description of the characteristics of the reported prediction models for AKI. Moreover, another important strength is the critical appraisal of prediction models for AKI by using the PROBAST tool. Finally, we will perform a meta-analysis of C statistics for prediction models that are externally validated in different independent cohorts.

There are also limitations to this study. One is that large between study heterogeneity is expected in the meta-analyses. There may be several potential sources of heterogeneity including the differences in clinical scenarios, patients' characteristics, cohort regions or races and statistical methods. However, due to the small number of development or validation studies, subgroup analyses or meta-regression analyses cannot be performed.

In summary, this study will provide an overall mapping of the available research on prediction models for AKI in critical ill patients.

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Tables and legends

Table 1. Primary elements for formulating study purpose, search strategy, inclusion and exclusion criteria for the study according to the following PICOTS guidance

Item	Definition
Population	Patients who were critically ill
Intervention	Any prediction model to predict the risk of acute kidney injury (AKI) in patients with critical illness, to distinguish critical ill patients with poor outcome (who will develop AKI), or to aid in clinical decision making in acute care, planning therapeutic intervention and monitoring treatment response
Comparator	Not applicable
Outcomes	AKI reported by prediction models
Timing	Predictive variables measured at any timepoint during the clinical course of the disease; no specific limitation applied in prediction horizon
Setting	Patients with critical illness who were admitted to hospital, treated in intensive care unit (ICU), or emergency department

Table 2. Twenty key questions assessing the risk of bias for 4 domains of participants, predictors, outcome and analysis.

Domain 2: Participants
1.1 Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study data?
1.2 Were all inclusions and exclusions of participants appropriate?
Domain 2: Predictors
2.1 Were predictors defined and assessed in a similar way for all participants?
2.2 Were predictor assessments made without knowledge of outcome data?
2.3 Are all predictors available at the time the model is intended to be used?
Domain 3: Outcome
3.1 Was the outcome determined appropriately?
3.2 Was a prespecified or standard outcome definition used?
3.3 Were predictors excluded from the outcome definition?
3.4 Was the outcome defined and determined in a similar way for all participants?
3.5 Was the outcome determined without knowledge of predictor information?
3.6 Was the time interval between predictor assessment and outcome determination appropriate?
Domain 4: Analysis
4.1 Were there a reasonable number of participants with the outcome?
4.2 Were continuous and categorical predictors handled appropriately?
4.3 Were all enrolled participants included in the analysis?

4.4 Were participants with missing data handled appropriately?

4.5 Was selection of predictors based on univariable analysis avoided?

4.6 Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately?

4.7 Were relevant model performance measures evaluated appropriately?

4.8 Were model overfitting and optimism in model performance accounted for?

4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

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Dr. Zubing Mei and Dr. Danqiong Wang have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zubing Mei and Danqiong Wang

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Abstract

Introduction

Acute kidney injury (AKI) has high morbidity and mortality in intensive care units (ICUs), which can lead to chronic kidney disease (CKD), more costs and longer hospital stay. Early identification of AKI is crucial for clinical intervention. Though various risk prediction models have been developed to identify AKI, the overall predictive performance varies widely across studies. Due to the different disease scenarios and the small number of externally validated cohorts in different prediction models, the stability and applicability of these models for AKI in critically ill patients are controversial. Moreover, there are no current risk-classification tools that are standardised for prediction of AKI in critically ill patients. The purpose of this systematic review is to map and assess prediction models for AKI in critical ill patients based on a comprehensive literature review.

Methods and analysis

A systematic review with meta-analysis is designed and will be conducted according to the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS). Three databases including Pubmed, Cochrane Library and EMBASE from inception through October 2020 will be searched to identify all studies describing development and/or external validation of original multivariable models for predicting AKI in critical ill patients. Random-effects meta-analyses for external validation studies will be performed to

estimate the performance of each model. The restricted maximum likelihood (REML) estimation and the Hartung-Knapp-Sidik-Jonkman (HKSJ) method under a random-effects model will be applied to estimate the summary C statistic and 95% CI. 95% prediction interval (PI) integrating the heterogeneity will also be calculated to pool C-statistics to predict a possible range of C-statistics of future validation studies. Two investigators will extract data independently using the CHARMS checklist. Study quality or risk of bias will be assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST).

Ethics and dissemination

Ethical approval and patient informed consent are not required because all information will be abstracted from published literatures. We plan to share our results with clinicians and publish them in a general or critical care medicine peer- reviewed journal. We also plan to present our results at critical care international conferences.

OSF registration number 10.17605/OSF.IO/X25AT

Key words

Prediction model; acute kidney injury (AKI); critical ill; systematic review; cohort study

Strengths and limitations of this study

- This study will provide an overall mapping of the available studies on prediction models for acute kidney injury (AKI) in critical ill patients.
- This study will be carried out and reported according to the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS).
- Prediction models for AKI in critical ill patients will be evaluated using the PROBAST tool.
- Meta-analysis of C statistics will be conducted for prediction models that are externally validated in different individual populations.
- Several potential sources of heterogeneity including AKI definition, AKI type, window of prediction and other study characteristics will need further investigation.

Introduction

Acute kidney injury (AKI) is a common condition among hospitalized critical patients, especially in intensive care units (ICUs), and has been a major healthcare burden worldwide.[1-4] AKI is also associated with serious complications, increased health care costs, length of stay and mortality. More than 1.7 million deaths have been reported indirectly due to AKI annually related to chronic kidney disease (CKD), cardiovascular and cerebrovascular events.[5-8]

AKI can originate from heterogeneous causes, and stratifying cases according to characteristics and biomarkers would raise possibility of early prediction of AKI. Currently, there is a great need for multi-modal data in the development of these models as the clinical trajectory of critical illness involves multiple organ dysfunction and organ cross-talk, which can be captured with different data types. Biomarkers including serum creatinine (sCr) and urine output are commonly used ones to define AKI. [9] More recently, several other frequently used and new candidate biomarkers have been found to predict AKI in clinics at different stage of the disease condition, but many of them are found to have low sensitivity and specificity.[10-16]

Clinical prediction models are widely used in real-world clinical practice. They are proved to be useful for informing healthcare systems to distinguish high risk patients, guide diagnostic and therapeutic intervention selection, thus early measurements could be taken to improve outcomes.[17] The application of

multidimensional indicators to predict the risk of AKI in critical ill patients may provide a more comprehensive approach of disease assessment. Furthermore, in critically ill patients, multivariable risk prediction models for AKI could be used in clinical practice to assist decision making on hospital admission or admission to ICUs and treatment options.[18-20]

Several prediction models, incorporating multiple predictors for the prediction of AKI, have been developed. Wang et al found that hypertension, chronic kidney disease, acute pancreatitis, cardiac failure, shock, pH $\leqslant$ 7.30, creatine kinase (CK) > 1000 U/L, hypoproteinemia, nephrotoxin exposure, and male gender were independent predictors of AKI.[21] Ferrari and colleagues established a novel prediction score to quickly predict AKI at any stage up to 7 days.[22] However, to the best of our knowledge, no prognostic model for AKI has been endorsed. Moreover, in routine clinical practice, there are no current risk-classification tools that are standardised for prediction of AKI in critically ill patients.

In this study, we aim to systematically summarise the reported multivariable models developed for predicting AKI in critically ill patients, to map their characteristics and laboratory features, and to test whether they have been carried out external validation. We will apply the Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess the risk of bias of the methodological aspects of the included studies developing or validating prediction models. For prediction models

involving several validation studies, we will perform a meta-analysis for performance and calibration of each model to yield more accurate effect estimates.

METHODS AND ANALYSIS

We will design and conduct this systematic review according to Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) guideline [23] and the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[24] and the guidance by Debray et al.[25] We have registered the protocol on the website of open science framework (OSF) (https://osf.io/x25at/).

Literature search

We systematically searched PubMed, Embase and Cochrane Library from inception to October 2020 to capture all relevant studies developing and/or validating a prediction model for AKI in critically ill patients. The following search strategy with related key words was developed: (predict* OR progn* OR "risk prediction" OR "risk score" OR "risk calculation" OR "risk assessment" OR "C statistic" OR discrimination OR calibration OR AUC OR "area under the curve" OR "area under the receiver operator characteristic curve") AND ("acute kidney failure" OR "acute tubular necrosis" OR "acute kidney tubule necrosis" OR AKI OR ARI OR AKF OR ARF) AND ("emergency care unit" OR "intensive care unit" OR "critical ill patient" OR "acute ill*" OR ICU). Two independent investigators will undertake the literature

search and screening, and discrepancies will be resolved by a senior author. We will further hand search the reference list of each eligible study for potential missing eligible studies.

Eligibility criteria

We will include all cohort studies that described development and external validation of original multivariable models for predicting AKI in critical ill patients. We present the detailed description of the PICOTS for this systematic review in Table 1. Based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guideline,[26] we will screen and select eligible prognostic model studies when the following inclusion criteria are satisfied. 1) studies that reported the development or validation multivariable model(s) of AKI with or without external validation; 2) studies reporting AKI models involving medical-AKI related critical ill patients and using AKI definitions of Kidney Disease Improving Global Outcomes (KDIGO),[27] Acute Kidney Injury Network (AKIN),[28] and Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE);[29] 3) studies that yielded at least two predictors; 4) studies that evaluated or updated the quantitative measure of model performance of an existing model in an independent population in terms of overall performance, discriminative ability and calibration of a certain prediction model. We will exclude conference abstracts, editorials, clinical case reviews, letters, commentaries, book chapters and surveys. Studies involving only post-surgical critical ill patients will also be excluded.

Data abstraction

Data extraction will be conducted using a standardised data extraction form by at least two independently reviewers based on the recommendations in the CHARMS checklist.[24] If the needed data are not reported or unclear, the corresponding authors will be contacted for detailed information. The following general study information will be extracted including first author, publication year, model name, publication source and research country. For model development study, we will extract the following specific data: modelling method, method for selection of predictors for inclusion in multivariable modeling combined with criteria used and shrinkage of predictor weights or regression coefficients. For model performance study, measures of calibration and discrimination with confidence intervals will be abstracted. For studies reporting model evaluation, method used for testing model performance will also be abstracted. Besides, the method for treating the missing data involving the prediction model of each eligible study will also be abstracted.

Critical appraisal

We will critically appraise each included prediction model using the PROBAST technique, a tool to assess risk of bias and applicability of prediction model studies.[30] Based on the checklist of PROBAST, 20 separate questions across 4 domains (participants, predictors, outcome, and analysis) will be asked. Details for the assessment rules are summarized in Table 2. Moreover, we will also use the Modified Downs and Black Checklist and Sackett's Level of Evidence for assessment of risk of

bias and methodological quality of included studies.[31 32] Two authors of the research team will independently assess the risk of bias of the included studies and cross-check the results. Any discrepancies will be resolved by discussion or by a senior author.

Statistical analysis

We will calculate and report descriptive statistics to summarise the characteristics of the AKI models. For binary or categorical variables, we will calculate frequencies or percentages, while for continuous variables, means, medians, and interquartile ranges (IQRs) will be calculated. For the prediction model of AKI developed from different populations, a random effects meta-analysis will be applied to calculate a summary estimate for models' performance and calibration. For studies that did not provide measurements of mean C statistics, we will use a formula to estimate the standard error of mean C statistic according to the methods proposed by Snell and colleagues.[32] Due to the relatively small sample size of validation studies for each prediction model, we will meta-analyse C statistic with its 95% CI using a random-effects model based on the restricted maximum likelihood (REML) estimation and the Hartung-Knapp-Sidik-Jonkman (HKSJ) method.[25 33] 95% prediction interval (PI) integrating the heterogeneity will also be calculated to pool C statistics to predict a possible range of C statistics of future validation studies. Heterogeneity between studies will be quantified using the I^2 statistic, defined significant heterogeneity when I^2 statistic more than 50%. [34] To explore the sources of potential heterogeneity, we will conduct stratified analyses by summarising estimates based on AKI definition

(KDIGO vs. AKIN vs. RIFLE), AKI type (any AKI vs. severe AKI or stage 1 AKI vs. stage 2/3 by KDIGO criteria), window of prediction (first 24h vs. 48-96h) and lack of evaluation of key characteristics of AKI such as duration, need for renal replacement therapy,etc (yes vs. no). The potential of publication bias will be assessed by funnel plots when more than 10 studies are meta-analysed for the prediction model. All statistical analyses will be carried out using R Statistical Software version 3.2.3(R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and Stata version 15.0 (Stata Corporation, College Station, TX, USA).

Patient and public involvement

The current study is a systematic review of what is already reported in the literature. It does not involve patient and public in the design, conduct or reporting of this study.

Ethics and dissemination

Ethical approval and patient informed consent are not required because all information will be abstracted from published literatures. We plan to share our results with clinicians and publish them in a general or critical care medicine peer- reviewed journal. We also plan to present our results at critical care international conferences.

Amendments

The protocol for this systematic review will be amended when necessary during the peer-review process.

DISCUSSION

Although there have been numerous original reports and narrative reviews focusing on the prediction model of AKI,[35-43] several factors may limit the interpretation and application of these prediction models. To the best of our knowledge, this will be the first systematic review that aims to evaluate the published evidence on the prediction models for AKI. This study will provide a clear overview for clinicians to identify some most effective prediction models for AKI among critical ill patients or patients in ICUs. By synthesising data including predictive accuracy such as C statistics across studies, we may get some evidence-based data to stratify disease severity and help inform the clinical management of critical ill patients.

Strengths and limitations

There will be several strengths of this study. Firstly, we will strictly adhere to the Cochrane Handbook's method recommendations during the conduct and reporting of this systematic review to make the results more reliable.[25 44] The purpose of this study is to achieve high-quality evidence regarding the prediction model of AKI in critical ill patients and provide practice recommendations on its applicability for policy makers. Secondly, we will present a detailed description of the characteristics of the reported prediction models for AKI. Moreover, another important strength is the critical appraisal of prediction models for AKI by using the PROBAST tool.

Finally, we will perform a meta-analysis of C statistics for prediction models that are externally validated in different independent cohorts.

There are also limitations to this study. One is that large between study heterogeneity is expected in the meta-analyses. There may be several potential sources of heterogeneity including the differences in clinical scenarios, patients' characteristics, cohort regions or races and statistical methods. However, due to the small number of development or validation studies, subgroup analyses or meta--regression analyses cannot be performed.

In summary, this study will provide an overall mapping of the available research on prediction models for AKI in critical ill patients.

Contributorship statement:

Dr. Zubing Mei and Dr. Danqiong Wang have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Danqiong Wang, Weiwen Zhang and Zubing Mei

Administrative, technical, or material support: All authors.

Study supervision: Zubing Mei and Danqiong Wang

Competing interests:

The authors declare that they have no conflict of interest.

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Tables and legends

Table 1. Primary elements for formulating study purpose, search strategy, inclusion and exclusion criteria for the study according to the following PICOTS guidance

Item	Definition
Population	Patients who were critically ill
Intervention	Any prediction model to predict the risk of acute kidney injury (AKI) in patients with critical illness, to distinguish critical ill patients with poor outcome (who will develop AKI), or to aid in clinical decision making in acute care, planning therapeutic intervention and monitoring treatment response
Comparator	Not applicable
Outcomes	AKI reported by prediction models
Timing	Predictive variables measured at any timepoint during the clinical course of the disease; no specific limitation applied in prediction horizon
Setting	Patients with critical illness who were admitted to hospital, treated in intensive care unit (ICU), or emergency department

Table 2. Twenty key questions assessing the risk of bias for 4 domains of participants, predictors, outcome and analysis.

Domain 2: Participants
1.1 Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study data?
1.2 Were all inclusions and exclusions of participants appropriate?
Domain 2: Predictors
2.1 Were predictors defined and assessed in a similar way for all participants?
2.2 Were predictor assessments made without knowledge of outcome data?
2.3 Are all predictors available at the time the model is intended to be used?
Domain 3: Outcome
3.1 Was the outcome determined appropriately?
3.2 Was a prespecified or standard outcome definition used?
3.3 Were predictors excluded from the outcome definition?
3.4 Was the outcome defined and determined in a similar way for all participants?
3.5 Was the outcome determined without knowledge of predictor information?
3.6 Was the time interval between predictor assessment and outcome determination appropriate?
Domain 4: Analysis
4.1 Were there a reasonable number of participants with the outcome?
4.2 Were continuous and categorical predictors handled appropriately?
4.3 Were all enrolled participants included in the analysis?

4.4 Were participants with missing data handled appropriately?

4.5 Was selection of predictors based on univariable analysis avoided?

4.6 Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately?

4.7 Were relevant model performance measures evaluated appropriately?

4.8 Were model overfitting and optimism in model performance accounted for?

4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the	2-3

		guarantor of the review	
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	2
Sponsor	#5b	Provide name for the review funder and / or sponsor	2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	3
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	7-8
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Study records -	#11b	State the process that will be used for selecting studies (such	10

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11-12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12-13
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12-13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11-12