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Risk Factors for Contrast-Induced Nephropathy: Protocol for Systematic Review and Meta-analysis

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Keywords:	Coronary angiography, risk factor, contrast-induced nephropathy

Important Risk Factors for Contrast-Induced Nephropathy: Protocol for Systematic Review and Meta-analysis

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Abstract

Introduction: Identifying the patients who are at risk for contrast-induced nephropathy (CIN) is a valuable component for the targeted prevention strategies. The absolute and relative importance of risk factors over another has not been systematically evaluated, let alone new, controversial or modifiable risk factors of CIN.

Methods and analysis: According to MEDLINE, Embase, and Cochrane Central databases of Systematic Reviews, we performed systematic review and meta analysis to assess the important risk factors, induclidng modifiable, new and controversial ones for developing CIN, defined as an increase in serum creatinine after exposure to contrast media. The secondary endpoint is all-cause mortality. Two authors will then independently screen studies that meet the criteria for inclusion, consulting with a third author to resolve any dispute. The quality of the included studies will be assessed according to the Newcastle-Ottawa scale.

Ethics and dissemination: Ethics approval in this systematic review and meta-analysis protocol is not needed. We will disseminate the findings of this systematic review and meta-analysis via publications in peer-reviewed journals.

PROSPERO register number: CRD42019121534

Abbreviations: CIN=contrast induced nephropathy; GRADE=Grades of Recommendation, Assessment, Development and Evaluation; MACE=major adverse cardiovascular events; STEMI=ST-segment elevation myocardial infarction.

Keywords: Coronary angiography; risk factor; contrast-induced nephropathy.

Strengths and limitations of this study

This will be the first and largest comprehensive, systematic review of diverse risk factors associated with contrast-induced nephropathy (CIN).

The broad search strategy will identify clearly identify important risk factors of CIN to preferentially supply target prevention strategies, infrequently reported risk factors and identify new strategies to predict risk of CIN.

This study will also systematic evaluate modifiable, new and controversial factors, which may be the potential preventive target in the future.

This study will only identify English-language articles from the peer-reviewed literature.

Introduction

Contrast-induced nephropathy (CIN) has been reported to be associated with poor clinical outcomes including an increased short and long-term mortality, prolonging the duration of hospital stays, the need for renal replacement therapy, and an increase in major adverse cardiac events[1,2]. Critical predisposing factors for CIN include older age, preexisting renal failure, hemodynamic instability, congestive heart failure, diabetes mellitus, anemia, and the volume of contrast media[3,4]. Allen and Silve et al. [5,6] did systematically evaluatation for current predict models for CIN, but there has been

no systematic assessment absolute and relative importance of risk factors over another, let alone new, controversial risk factors of CIN.

To address this deficit in knowledge, we conducted a systematic review and a meta-analysis of the observational studies that examined the absolute and relative importance of risk factors of CIN.

Objectives

The objective of this study is to identity the relationship between multiple risk factors and CIN. More specifically, the goals of this study are the following:

1. To comprehensively and systematically assess the absolute and relative importance of current common risk factors for CIN;

2. To systematically assess the new, controversial risk factors for CIN.

Method

Patient and public involvement

This is a protocol for meta analysis and it was not appropriate or possible to involve patients or the public in this work.

Search strategy

A systematic computer-aided search of related studies was conducted in the following manner:

1. Ovid MEDLINE;
2. Ovid Embase;
3. Cochrane Database of Systematic Reviews.>

Initial keywords

The databases will be searched using the following initial keyword search terms:

coronary angiography；angiocardiograph；contrast medium；radiocontrast medium；acute kidney injury； contrast-induced nephropathy； risk factor； risk Assessment. We will search the databases we choose from the present with restrictions on the English language of publication. If we find additional relevant keywords during any of the electronic searches or others, we will modify the electronic search strategies to upgrade these terms and document the changes.

Types of studies

We will include all observational studies (registries, cohorts, etc.) analyzing the correlation between risk factors and CIN following procedures with contrast media. This review will also consider experimental and epidemiological study designs, including case-control and cohort studies as being appropriate for inclusion in the meta-analysis. However, we will exclude articles related to animal experiments.

Types of participants

We will include adults aged 18 years and above, identified with the CIN.

Types of outcomes

Primary outcome

The primary endpoint is CIN, defined as an increase in serum creatinine after exposure to contrast media.

Secondary outcome

Long-term all-cause mortality is defined as death from any cause within the follow-up time of patient's post-index procedure.

Selection of studies

We will filter all retrieved articles. Two authors (XCL and SJX) will browse the title and abstract independently, and the two authors will record the exclude documents and the reasons for the exclusion. If there is a dispute in the process of the screening of the article, there will be a third author (LY) to arbitrate. After the initial screening, the two authors will then read the full text and further filter the articles according to the inclusion and exclusion criteria mentioned above. The same queue of the population will be treated as the same study and then excluded. In the process of reading the full text, if there is doubt in the selection, the two authors (XCL and SJX) will discuss it. If it cannot be resolved, there will be a third author (LY) to arbitrate. Finally, all selected articles will be listed for further analysis, and the excluded articles will be classified according to the reasons for exclusion.

Quality assessment/assessment of the risk of bias in included studies

Two authors will independently assess the quality of selected articles using the ***Newcastle-Ottawa Scale***[7].

Observational studies using Newcastle-Ottawa Scale:

CASE-CONTROL STUDIES

Selection

1) Is the Case Definition Adequate?
2) Representativeness of the Cases
3) Selection of Controls
4) Definition of Controls

Comparability

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

Exposure

1) Ascertainment of Exposure

2) Non-Response Rate

COHORT STUDIES

Selection

1) Representativeness of the Exposed Cohort

2) Selection of the Non-Exposed Cohort

3) Ascertainment of Exposure

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

Comparability

1) Comparability of Cohorts on the Basis of the Design or Analysis

Outcome

1) Assessment of Outcome

2) Was Follow-Up Long Enough for Outcomes to Occur

3) Adequacy of Follow Up of Cohorts

We will rate each selected article with a rating of low, high or unclear and the results will be presented in the form of a table. Unpublished data will be considered in the evaluation of the publication bias, and we will try to contact the author for assistance in this regard.

Data synthesis:

We will use STATA Ver13.0 software and RevMan for data analysis, and risk factor

effect sizes will be expressed as an odds ratio and their 95% Cl. Using standard chi-square test to assess the heterogeneity and variable statistics, we will perform subgroup analysis to conduct data statistics. If there is data that cannot be counted in the selected article, the data will be listed in the form of a table or chart. EndNote will be used for managing references.

Sensitivity analysis. We will perform sensitivity analyses in order to explore the influence of the following factors on effect sizes.

1. Restricting the analysis to studies for coronary angiography.

2. Restricting the analysis to large cohort studies with more than 1000 subjects.

Conclusion:

The goal of this systematic review and meta-analysis is to clearly identify important risk factors of CIN to preferentially supply target prevention strategies, including contrast limiting and hydration, for those high risk factors[8,9,10]. In addtion modifiable, new and controversial factors may be the potential preventive target in the future.

Author affiliations

Contributions

Yong Liu, Xingchen Liang, Shaojun Xing, Jin Liu, Guoli Sun, Shiqun Chen, Xiaolin Cen, Xiaohua Dai, Yibo He, Feier Song, Yan Liang, Yuying Hu, Yingling Zhou, Zhujun Chen, Ning Tan, Jiyan Chen: conception and design of the work; Yong Liu, Xingchen Liang, Shaojun Xing, Xiaolin Cen, Xiaohua Dai: determining search terms, related literature search; Yong Liu, Xingchen Liang, Shaojun Xing, Jin Liu, Guoli Sun, Shiqun Chen, Xiaolin Cen, Xiaohua Dai, Yibo He, Feier Song: filter literature according to established standards; Yan Liang, Yuying Hu, Yingling Zhou, Zhujun Chen, Ning Tan, Jiyan Chen: as a third author, judge the doubtful literature; Yong Liu, Shiqun Chen: acquisition, analysis, or interpretation of data; Yong Liu, Shiqun Chen,

Jiyan Chen, Yong Liu, Ning Tan: drafting the work or revising it critically for important intellectual content. All authors agree that this is the final version of the article. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The authors declare no competing interests.

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Data sharing statement

All authors will share all data.

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Primary Subject Heading:	Cardiovascular medicine

Secondary Subject Heading:	Cardiovascular medicine
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Risk factors for contrast-induced acute kidney injury (CI-AKI): Protocol for systematic review and meta-analysis

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Abstract

Introduction: Identifying the patients who are at risk for contrast-induced acute kidney injury (CI-AKI), which is defined as an increase in serum creatinine after exposure to contrast media, is a critical step in targeted prevention strategies. The absolute and relative importance of individual risk factors have not been systematically evaluated, let alone the new, controversial, and modifiable risk factors of CI-AKI.

Methods and analysis: On December 17th, 2018, a search was performed on MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. We will perform a systematic review and meta-analysis to assess the important risk factors for developing CI-AKI, including those new, modifiable factors which are considered controversial. The secondary endpoint will be all-cause mortality. Two authors will then independently screen studies that meet the criteria for inclusion, consulting with a third author to resolve any dispute. The quality of the included studies will be assessed according to the Newcastle-Ottawa scale.

Ethics and dissemination: Ethics approval in this systematic review and meta-analysis protocol is not needed. We will disseminate the findings of this systematic review and meta-analysis via publications in peer-reviewed journals.

PROSPERO register number: CRD42019121534

Abbreviations: CI-AKI = contrast-induced acute kidney injury; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; MACE = major adverse cardiovascular events; STEMI = ST-segment elevation myocardial infarction.

Keywords: Coronary angiography; risk factor; contrast-induced nephropathy.

Strengths and limitations of this study

This will be the first, and largest, comprehensive systematic review of the diverse risk factors associated with CI-AKI.

Our broad search strategy will identify the important risk factors for CI-AKI for the purpose of preferentially supplying target prevention strategies, bringing attention to infrequently reported risk factors, and identifying new strategies to predict the risk of CI-AKI.

This study will also evaluate the new, modifiable risk factors, which are still considered controversial but may hold promise as preventive targets in the future.

This study will only select English-language articles from the peer-reviewed literature.

Introduction

Contrast-induced acute kidney injury (CI-AKI) has been reported to be associated with poor clinical outcomes including increased short and long-term mortality, prolonged duration of hospital stay, the need for renal replacement therapy, and an increase in major adverse cardiac events[1,2]. The use of a risk prediction tool for CI-AKI could have several benefits. Primarily, it may help identify those patients at high risk for the disorder who might benefit from perioperative strategies that protect the kidneys. Critical predisposing factors for CI-AKI include older age, preexisting renal failure, hemodynamic instability, congestive heart failure, diabetes mellitus, anemia, and the volume of contrast media[3,4]. Although Allen et al.[5] and Silver et al.[6] systematically evaluated the current predictive models for CI-AKI, there has been no systematic assessment of the absolute and relative importance of the individual risk factors for CI-AKI, let alone, the new, modifiable, and controversial ones. This will be the first, and largest systematic review about the risk factors associated with CI-AKI.

To address this deficit in knowledge, we will conduct a systematic review and a meta-analysis of the observational studies that have examined the absolute and relative importance of the risk factors of CI-AKI.

Objectives

The objective of this study is to identity the relationship between the multiple risk factors of CI-AKI. More specifically, the goals of this study are the following:

1. To comprehensively and systematically assess the absolute and relative importance of the current common risk factors for CI-AKI
2. To systematically assess the new, controversial risk factors for CI-AKI

Method

Patient and public involvement

This is a protocol for a meta-analysis, and it will be not appropriate or possible to involve patients or the public in this work.

Search strategy

A systematic computer-aided search of related studies will be conducted in the following databases:

1. Ovid MEDLINE
2. Ovid Embase
3. Cochrane Database of Systematic Reviews

Initial keywords

The databases will be searched using the following initial keyword search terms: coronary angiography；angiocardiograph；contrast medium；radiocontrast medium；acute kidney injury；contrast-induced nephropathy； acute renal insufficiency; risk factor; risk assessment; multivariate analysis; multivariable logistic regression; models. We will restrict the search on the databases to English language publications. If we find additional relevant keywords during any of the electronic searches, we will update the electronic search strategies with these terms and document the changes (details in Supplement).

Types of studies

We will include all observational studies (registries, cohorts, etc.) that analyze the correlation between risk factors and CI-AKI following procedures with contrast media. This review will also consider experimental and epidemiological study designs, including case-control and cohort studies, as being appropriate for inclusion in the meta-analysis. However, we will exclude articles related to animal experiments.

Types of participants

We will include adults identified with the CI-AKI who are aged 18 years and above.

Types of outcomes

Primary outcome

The primary endpoint will be CI-AKI, defined as an increase in serum creatinine after exposure to contrast media.

Secondary outcome

The secondary endpoint will be long-term all-cause mortality, defined as death from any cause within the follow-up time of patient's post-index procedure.

Selection of studies

We will filter all retrieved articles. Two authors (XCL and SJX) will browse the titles and abstracts independently, and will record the excluded documents and the reasons for the exclusion. If there is a dispute in the process of the screening of the article, there will be a third author (YL) to arbitrate. After the initial screening, the two authors (GLS and JY) will then read the full text and further filter the articles according to the inclusion and exclusion criteria mentioned above. To avoid overlapping patient data in duplicate publications, registry analyses will be cross-checked with institutional studies and compared with other registry studies, and the larger or more complete publication will be included. In the process of reading the full text, if there is doubt in the selection, the two authors (XCL and SJX) will discuss it. If it cannot be resolved, there will be a third author (LY) to arbitrate. Finally, all selected articles will be listed for further analysis, and the excluded articles will be classified according to the reasons for exclusion.

Quality assessment/assessment of the risk of bias in included studies

Two authors will independently assess the quality of selected articles using the ***Newcastle-Ottawa Scale***[7].

Observational studies using Newcastle-Ottawa Scale:

CASE-CONTROL STUDIES
Selection
1) Is the Case Definition Adequate?
2) Representativeness of the Cases
3) Selection of Controls
4) Definition of Controls
Comparability
1) Comparability of Cases and Controls on the Basis of the Design or Analysis
Exposure
1) Ascertainment of Exposure

2) Non-Response Rate

COHORT STUDIES

Selection

1) Representativeness of the Exposed Cohort
2) Selection of the Non-Exposed Cohort
3) Ascertainment of Exposure
4) Demonstration That Outcome of Interest Was Not Present at Start of Study

Comparability

1) Comparability of Cohorts on the Basis of the Design or Analysis

Outcome

1) Assessment of Outcome
2) Was Follow-Up Long Enough for Outcomes to Occur
3) Adequacy of Follow-Up of Cohorts

We will rate each selected article with a rating of low, high, or unclear, and the results will be presented in the form of a table. Unpublished data will be considered in the evaluation of the publication bias, and we will try to contact the author for assistance in this regard. In addition, we will use the Risk of Bias in Nonrandomized studies of Interventions tool (ROBINS-I)[8] to enhance the reproducibility and comparability of this review to future reviews of a similar topic.

Data synthesis:

We will use STATA Ver13.0 software and RevMan for data analysis, and risk factor effect sizes will be expressed as an odds ratio and their 95% Cl. Using standard chi-square test to assess the heterogeneity and variable statistics, we will perform subgroup analysis to conduct data statistics. If there are data that cannot be counted in the selected article, the data will be listed in the form of a table or chart. EndNote will be used for managing references.

Sensitivity analysis. We will perform sensitivity analyses in order to explore the influence of the following factors on effect sizes:

1. Restricting the analysis to studies of coronary angiography.

2. Restricting the analysis to large cohort studies with more than 1000 subjects.

Conclusion:

The goal of this systematic review and meta-analysis is to clearly identify the important risk factors for CI-AKI for the purpose of preferentially supplying target

prevention strategies, including contrast limiting and hydration for those high risk factors[9-11]. In addition, the modifiable, new, and controversial factors will also be evaluated, as they may have potential as preventive targets.

Author affiliations

Contributions

Yong Liu, Xingchen Liang, Shaojun Xin, Jin Liu, Guoli Sun, Shiqun Chen, Xiaolin Cen, Xiaohua Dai, Yibo He, Feier Song, Yan Liang, Yuying Hu, Yingling Zhou, Zhujun Chen, Ning Tan, Jiyan Chen: conception and design of the work; Yong Liu, Xingchen Liang, Shaojun Xin, Xiaolin Cen, Xiaohua Dai: determining search terms, related literature search; Yong Liu, Xingchen Liang, Shaojun Xin, Jin Liu, Guoli Sun, Shiqun Chen, Xiaolin Cen, Xiaohua Dai, Yibo He, Feier Song: filter literature according to established standards; Yan Liang, Yuying Hu, Yingling Zhou, Zhujun Chen, Ning Tan, Jiyan Chen: as a third author, judge the doubtful literature; Yong Liu, Shiqun Chen: acquisition, analysis, or interpretation of data; Yong Liu, Shiqun Chen, Jiyan Chen, Yong Liu, Ning Tan: drafting the work or revising it critically for important intellectual content. All authors agree that this is the final version of the article. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

None declared

Funding

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Data sharing statement

All authors will share all data.

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-10. 4 and 8 and 9

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a-P1	Identify the report as a protocol of a systematic review
Update	NO	If the protocol is for an update of a previous systematic review, identify as such
Registration	2-P2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a-P1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b-P1	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	NO	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
Support:		
Sources	5a-P8	Indicate sources of financial or other support for the review
Sponsor	5b-P8	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c-P8	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6-P3	Describe the rationale for the review in the context of what is already known
Objectives	7-P3	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8-P6	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
Information sources	9-P4	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
Search strategy	10-P4	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a-P7	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b-P6	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c-P6	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
Data items	12-P6	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13-P5	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14-P7	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
Data synthesis	15a-P7	Describe criteria under which study data will be quantitatively synthesised
	15b-P7	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 I^2, Kendall's τ)
	15c-P7	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d-P7	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Risk factors for contrast-induced acute kidney injury (CI-AKI): Protocol for systematic review and meta-analysis

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Coronary angiography, risk factor, contrast-induced nephropathy

Risk factors for contrast-induced acute kidney injury (CI-AKI): Protocol for systematic review and meta-analysis

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Abstract

Introduction: Identifying the patients who are at risk for contrast-induced acute kidney injury (CI-AKI), which is defined as an increase in serum creatinine after exposure to contrast media, is a critical step in targeted prevention strategies. The absolute and relative importance of individual risk factors have not been systematically evaluated, let alone the new, controversial, and modifiable risk factors of CI-AKI.

Methods and analysis: On July 1st, 2019, a search was performed on MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. We will perform a systematic review and meta-analysis to assess the important risk factors for developing CI-AKI, including those new, modifiable factors which are considered controversial. The secondary endpoint will be all-cause mortality. Two authors will then independently screen studies that meet the criteria for inclusion, consulting with a third author to resolve any dispute. The quality of the included studies will be assessed according to the Newcastle-Ottawa scale.

Ethics and dissemination: Ethics approval in this systematic review and meta-analysis protocol is not needed. We will disseminate the findings of this systematic review and meta-analysis via publications in peer-reviewed journals.

PROSPERO register number: CRD42019121534

Abbreviations: CI-AKI = contrast-induced acute kidney injury; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; MACE = major adverse cardiovascular events; STEMI = ST-segment elevation myocardial infarction.

Keywords: Coronary angiography; risk factor; contrast-induced nephropathy.

Strengths and limitations of this study

This will be the first, and largest, comprehensive systematic review of the diverse risk factors associated with CI-AKI.

Our broad search strategy will identify the important risk factors for CI-AKI for the purpose of preferentially supplying target prevention strategies, bringing attention to infrequently reported risk factors, and identifying new strategies to predict the risk of CI-AKI.

This study will also evaluate the new, modifiable risk factors, which are still considered controversial but may hold promise as preventive targets in the future.

This study will only select English-language articles from the peer-reviewed literature.

Introduction

Contrast-induced acute kidney injury (CI-AKI) has been reported to be associated with poor clinical outcomes including increased short and long-term mortality, prolonged duration of hospital stay, the need for renal replacement therapy, and an increase in major adverse cardiac events.[1 2] The use of a risk prediction tool for CI-AKI could have several benefits. Primarily, it may help identify those patients at high risk for the disorder who might benefit from some prevention strategies like intravenous isotonic saline hydration which has been proven to be effective, statins and acetylcysteine that are controversial, or other interventions targeting the risk factors that will be identified in this meta-analysis in progress.[3] Critical predisposing factors for CI-AKI include older age, preexisting renal failure, hemodynamic instability, congestive heart failure, diabetes mellitus, anemia, and the volume of contrast media.[4 5] Although Allen et al.[6] and Silver et al.[7] systematically evaluated the current predictive models for CI-AKI, there has been no systematic assessment of the absolute and relative importance of the individual risk factors for CI-AKI, let alone, the new, modifiable, and controversial one, for example, the usage of ACEI/ARB or diuretics, smoking and body mass index.[3] This will be the first, and largest systematic review about the risk factors associated with CI-AKI. To address this deficit in knowledge, we will conduct a systematic review and a meta-analysis of the observational studies that have examined the absolute and relative importance of the risk factors of CI-AKI.

Objectives

The objective of this study is to identity the relationship between the multiple risk factors of CI-AKI. More specifically, the goals of this study are the following:

1. To comprehensively and systematically assess the absolute and relative importance of the current common risk factors for CI-AKI

2. To systematically assess the new, controversial risk factors for CI-AKI

Method

Patient and public involvement

This is a protocol for a meta-analysis, and it will be not appropriate or possible to

involve patients or the public in this work.

Search strategy

A systematic computer-aided search of related studies will be conducted in the following databases:

1. Ovid MEDLINE (1946 to June 30, 2019, including epub ahead of print, in process and other non-indexed citations and daily)
2. Ovid Embase (1947 to June 2019)
3. Cochrane Database of Systematic Reviews （published on or before 30th June 2019）

Initial keywords

The databases will be searched using the following initial keyword search terms: coronary angiography；angiocardiograph；contrast medium；radiocontrast medium；acute kidney injury；contrast-induced nephropathy；acute renal insufficiency; risk factor; risk assessment; multivariate analysis; multivariable logistic regression; models. We will restrict the search on the databases to English language publications. If we find additional relevant keywords during any of the electronic searches, we will update the electronic search strategies with these terms and document the changes (details in Supplement).

Types of studies

We will include all observational studies (registries, cohorts, etc.) that analyze the correlation between risk factors and CI-AKI following procedures with contrast media. This review will also consider experimental and epidemiological study designs, including case-control and cohort studies, as being appropriate for inclusion in the meta-analysis. However, we will exclude articles related to animal experiments.

Types of participants

We will include adults identified with the CI-AKI who are aged 18 years and above.

Types of outcomes

Primary outcome

The primary endpoint will be CI-AKI, defined as an increase in serum creatinine after exposure to contrast media.

Secondary outcome

The secondary endpoint will be long-term all-cause mortality, defined as death from any cause within the follow-up time of patient's post-index procedure.

Selection of studies

We will filter all retrieved articles. Two authors (XCL and SJX) will browse the titles and abstracts independently, and will record the excluded documents and the reasons for the exclusion. If there is a dispute in the process of the screening of the article, there will be a third author (YL) to arbitrate. After the initial screening, the two authors (GLS and JY) will then read the full text and further filter the articles according to the inclusion and exclusion criteria mentioned above. To avoid overlapping patient data in duplicate publications, registry analyses will be cross-checked with institutional studies and compared with other registry studies, and the larger or more complete publication will be included. In the process of reading the full text, if there is doubt in the selection, the two authors (XCL and SJX) will discuss it. If it cannot be resolved, there will be a third author (LY) to arbitrate. Finally, all selected articles will be listed for further analysis, and the excluded articles will be classified according to the reasons for exclusion.

Quality assessment/assessment of the risk of bias in included studies

Two authors will independently assess the quality of selected articles using the ***Newcastle-Ottawa Scale***.[8]

Observational studies using Newcastle-Ottawa Scale:

CASE-CONTROL STUDIES

Selection

1) Is the Case Definition Adequate?
2) Representativeness of the Cases
3) Selection of Controls
4) Definition of Controls

Comparability

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

Exposure

1) Ascertainment of Exposure
2) Non-Response Rate

COHORT STUDIES

Selection

1) Representativeness of the Exposed Cohort
2) Selection of the Non-Exposed Cohort
3) Ascertainment of Exposure
4) Demonstration That Outcome of Interest Was Not Present at Start of Study

Comparability

1) Comparability of Cohorts on the Basis of the Design or Analysis

Outcome

1) Assessment of Outcome
2) Was Follow-Up Long Enough for Outcomes to Occur
3) Adequacy of Follow-Up of Cohorts

We will rate each selected article with a rating of low, high, or unclear, and the results will be presented in the form of a table. In addition, we will use the Risk of Bias in Nonrandomized studies of Interventions tool (ROBINS-I)[9] to enhance the reproducibility and comparability of this review to future reviews of a similar topic.

Data synthesis:

We will use STATA Ver13.0 software and RevMan for data analysis, and risk factor effect sizes will be expressed as an odds ratio and their 95% Cl. Using standard chi-square test to assess the heterogeneity and variable statistics, we will perform subgroup analysis to conduct data statistics. If there are data that cannot be counted in the selected article, the data will be listed in the form of a table or chart. EndNote will be used for managing references.

Sensitivity analysis. We will perform sensitivity analyses in order to explore the influence of the following factors on effect sizes:

1. Restricting the analysis to studies of coronary angiography.

2. Restricting the analysis to large cohort studies with more than 1000 subjects.

Meta-biases

We will evaluate the possibility of publication bias using funnel plots and take Egger's

test of bias as a complement. Unpublished data will also be considered in the evaluation of the publication bias, and we will try to contact the author for assistance in this regard.

Confidence in cumulative evidence

We will evaluate the strength of evidence for all outcomes by performing the Grading of Recommendations Assessment, Development and Evaluation working group methodology. The quality of evidence will be assessed across the domains of risk of bias, precision, directness, consistency, and publication bias. Strength will be judged as high (further research is improbable to alter our confidence in the estimate of effect), moderate (further research will probably generate an important impact on our confidence in the estimate of effect and may alter the estimate), low (further research is very likely to generate an important impact on our confidence in the estimate of effect and change the estimate), or very low (the estimate of effect is indeterminable).[10]

Conclusion:

The goal of this systematic review and meta-analysis is to clearly identify the important risk factors for CI-AKI for the purpose of preferentially supplying target prevention strategies, including contrast limiting and hydration for those high risk factors. In addition, the modifiable, new, and controversial factors will also be evaluated, as they may have potential as preventive targets.

Author affiliations

Contributions

Yong Liu, Xingchen Liang, Shaojun Xin, Jin Liu, Guoli Sun, Shiqun Chen, Xiaolin Cen, Xiaohua Dai, Yibo He, Feier Song, Yan Liang, Yuying Hu, Yingling Zhou, Zhujun Chen, Ning Tan, Jiyan Chen: conception and design of the work; Yong Liu, Xingchen Liang, Shaojun Xin, Xiaolin Cen, Xiaohua Dai: determining search terms, related literature search; Yong Liu, Xingchen Liang, Shaojun Xin, Jin Liu, Guoli Sun,

Shiqun Chen, Xiaolin Cen, Xiaohua Dai, Yibo He, Feier Song: filter literature according to established standards; Yan Liang, Yuying Hu, Yingling Zhou, Zhujun Chen, Ning Tan, Jiyan Chen: as a third author, judge the doubtful literature; Yong Liu, Shiqun Chen: acquisition, analysis, or interpretation of data; Yong Liu, Shiqun Chen, Jiyan Chen, Yong Liu, Ning Tan: drafting the work or revising it critically for important intellectual content. All authors agree that this is the final version of the article. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

None declared

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Data sharing statement

All authors will share all data.

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-9. ((risk adj3 model*) or score* or prognostic factor* or predict* or regression* or (logistic adj2 model*) or multivariable logistic regression or multivariable analyses or logistic regression or algorithm* or equation* or (multivariate adj3 analysis or Forecasting or "Predictive Value of Tests" or multivariate analysis or mathematical concepts or Models, Biological or models, statistical or area under curve)).ti,ab.

-10. 4 and 8 and 9

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a-P1	Identify the report as a protocol of a systematic review
Update	NO	If the protocol is for an update of a previous systematic review, identify as such
Registration	2-P2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a-P1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b-P1	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	NO	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
Support:		
Sources	5a-P8	Indicate sources of financial or other support for the review
Sponsor	5b-P8	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c-P8	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6-P3	Describe the rationale for the review in the context of what is already known
Objectives	7-P3	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8-P6	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
Information sources	9-P4	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
Search strategy	10-P4	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a-P7	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b-P6	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c-P6	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
Data items	12-P6	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13-P5	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14-P7	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
Data synthesis	15a-P7	Describe criteria under which study data will be quantitatively synthesised
	15b-P7	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 I^2, Kendall's τ)
	15c-P7	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d-P7	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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