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Complete List of Authors:	Zhou, Chenghui; Fuwai Hospital State Key Laboratory of Cardiovascular Disease, Anestheisiology Pei, Hanjun; First Affiliated Hospital of Baotou Medical College, Cardiology Gao, Yiming; Fuwai Hospital State Key Laboratory of Cardiovascular Disease, Echocardiology Zhang, Yulin; Chinese Academy of Medical Sciences and Peking Union Medical College Fuwai Hospital Cao, Liang; Fuwai Hospital State Key Laboratory of Cardiovascular Disease, Anestheisiology Fang, Zhongrong; Fuwai Hospital State Key Laboratory of Cardiovascular Disease, Anestheisiology Song, Jiangping; State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College
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Optimal Cutoff Value of Elevated Cardiac Troponin Level for Myocardial Injury Predicts Clinical Outcomes in Adult Patients with COVID-19: A Dose-response Analysis Protocol for Systematic Review

Chenghui Zhou[#,*,1], M.D, Ph.D; Hanjun Pei[#,2], M.D,Ph.D; Yiming Gao[3], M.D,Ph.D; Yulin Zhang[1], M.D, Ph.D; Liang Cao[1], M.D; Zhongrong Fang[1], M.D, Ph.D; Jiangping Song[*,4], M.D, Ph.D

[1]Department of Anesthesiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

[2] Department of Cardiology, The First Affiliated Hospital of Baotou Medical College, Baotou, Inner Mongolia, China

[3]Department of Echocardiography, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, China

[4]Department of Cardiac Surgery, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

[#]Dr. Zhou and Dr. Pei contributed equally as the first authors in this work.

[*]**Address for Correspondence**: Chenghui Zhou and Jiangping Song;

No. 167 Beilishi Road, 100037 Xicheng District, Beijing, China

Tel: 86-10-88398082, Fax: 86-10-88398082

E-mail: chenghuizhou@yahoo.com (Zhou Ch); fwsongjiangping@126.com (Song Jp);.

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ABSTRACT

Introduction Acute myocardial injury (AMI) in patients with COVID-19 infection has been recognized as one important complication associating with in-hospital mortality. The potential dose response effect of cardiac troponin (cTn) levels on adverse clinical outcomes has not been systematically studied. Hence, we will conduct a comprehensive dose-response meta-analysis to quantitatively evaluate the association between the elevated cTn levels and in-hospital adverse clinical outcomes in COVID-19 patients.

Methods We will search PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science database (from inception until October, 2021) to identify all retrospective, prospective cohort, and randomized controlled studies using the related keywords. The primary outcome will be all-cause mortality during hospitalization. The second outcome will be major adverse cardiovascular event (MACE). To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between elevated cTn levels and all-cause mortality or MACE, studies with three or more categories of cTn levels will be included. Univariate or multivariate meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of cTn level. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of all-cause mortality or MACE.

Ethics and dissemination In accordance with the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital, the ethical approval is waived for the protocol of systematic review. This meta-analysis will be disseminated through a peer-reviewing process for journal publication and conference communication.

Keywords: Acute myocardial injury, COVID-19, cardiac troponin, dose-response, meta-analysis

PROSPERO registration number CRD42020216059

Strengths and limitations of this study

1. This systematic review and meta-analysis will be the first one to comprehensively explore a potential linear or nonlinear dose-response relationship between cTn level and adverse clinical outcomes in COVID-19.
2. This protocol will encourage more and more researchers focusing on this issue and publishing the related prognostic outcome for different categories (>2) of cTn levels in COVID-19.
3. High sensitive cTn measurements at different time points are suggested for the potential prognostic role of tiny AMI (cTn levels between detection limit and URL) in early diagnosis for risk stratification， prompt therapy initiation, and thereby improving prognosis in patients with COVID-19 infection.
4. Both the retrospective and prospective study design will be included resulting the potential bias.
5. The sample size in each study may be small for the limitation of medical resources and economic decline.

Introduction

Acute myocardial injury (AMI) has been recognized as one important complication in adult patients with COVID-19 infection associating with in-hospital morbidity and mortality[1] [2]. By Oct 31st 2020, COVID-19 pandemic has cause 46,501,423 infections and 1,202,031 deaths worldwide in 215 countries[3].

Some studies have showed that the incidence of AMI is common as many as 20~40% based on cardiac troponin (cTn) levels, particularly in patients with obvious cardiovascular risk factors and severity of COVID-19. Although the main target of COVID-19 is the respiratory system, the cardiovascular system could also be influenced by affecting the neurohumoral regulation of the cardiovascular system, unbalancing the myocardial oxygen supply and demand with lung injury associated hypoxia, acute systemic inflammatory reaction and cytokine storm[4].

Up to now, different diagnostic thresholds of cTn levels for AMI in COVID-19 patients have been proposed. Some studies did not use 1xURL as the cutoff value of cTn levels[5]. Moreover, controversial prognostic relationships of AMI have been published by different researches using 1xURL for AMI diagnosis[6] [7]. Additionally, COVID-19 is a newly-breakout global pandemic with high mortality (at least 4 times increase), and will have a long-term coexistence with human beings[8]. Accordingly, the optimal cutoff value of cTn level for AMI with prognostic relevance needs to be identified in the very near future. However, there have been limited studies reporting the clinical outcomes for different categories of cTn levels in COVID-19. Hence, we

will conduct a comprehensive dose-response meta-analysis to quantitatively evaluate the association between the elevated cTn levels and adverse clinical outcomes in patients with COVID-19. We believe this protocol will encourage more and more researchers focusing on this issue and publishing the related prognostic outcome for different categories (>2) of cTn levels in COVID-19.

Objectives

The purpose of this systematic review and meta-analysis is to explore the potential optimal cutoff value of elevated cardiac troponin level for myocardial injury predicting clinical outcomes in adult patients with COVID-19.

METHODS AND ANALYSIS

Search Strategy

We will report this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline[9]. PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science database (from inception until October, 2021) will be systematically searched. Table 1 shows the related search keywords. Figure 1 shows the flow chart of searching process. This meta-analysis has been registered in the PROSPERO (CRD42020216059).

Type of Participants

We will include adult patients with confirmed COVID-19 infection as study participants.

Type of Studies

We will include all the retrospective, prospective cohort, or randomized controlled studies that have reported the associations of different cardiac troponin levels (>2) with the incidence of major adverse clinical outcomes. English-published trials will be included. The studies unable to extract odds ratio (OR) or hazard ratio (HR) and the corresponding 95% confidence intervals (CI) will be excluded.

Type of Outcomes

The primary outcome will be all-cause mortality during hospitalization. The second outcome will be major adverse cardiovascular event (MACE). MACE is a combined endpoint during hospitalization including: all-cause death, myocardial infarction, congestive heart failure, acute renal failure, pulmonary embolism, or stroke.

Data Extraction

Data will be extracted by two independent authors (Y.Gao and Y.Zhang). A third author (H. Pei) will make a final decision in case of discrepancies. The extracted data

included study design (author, publication year, country, sample size, percentage of positive cTn levels), patient characteristics (mean age, male proportion, race, body mass index, diabetes proportion, hypertension proportion, hyperlipidemia proportion, smoking proportion, coronary artery disease proportion, previous myocardial infarction, chronic heart failure, history of atrial fibrillation,, history of stroke or transient ischemic accident, kidney dysfunction, history of lung disease, history of liver disease,, beta-blocker usage, statin usage, angiotensin-converting enzyme inhibitor[ACEI] usage, angiotensin receptor blocker[ARB] usage, calcium channel blocker usage, aspirin usage), follow-up period, detection kit of cTn, URL of cTn, detection limit of cTn, cutoff value of cTn, and the different categories for cTn level.

Assessment of Risk of Bias

Newcastle-Ottawa quality assessment scale (NOS) will be used to evaluate the methodological quality of included studies[10].

Data synthesis

The ORs or HRs in each study will be extracted from the elevated versus non-elevated categories of cTn level for the pooled analysis. For studies only providing the Log-rank test or the Kaplan-Meier survival curve, the HR will be calculated based on time-to-event aggregate data[11]. The referent category with nonelevated cTn will be the lowest cTn level in each study. Random-effect model will

be used for the potential clinical inconsistency among the included studies in the pooled analysis by the DerSimonian and Laird method. If one study reported multiple categories (>2 categories), we will calculate the OR based on the number of cases and non-cases in all of the elevated categories and referent groups for the high vs low analysis. Univariate or multivariate meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of cTn level[12]. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of all-cause mortality or MACE. Publication bias evaluation will be conducted by the Begg's, Egger's test, and visualized symmetry of the funnel plot. A dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between different categorized elevated cTn levels and all-cause mortality or MACE will be performed. For study only providing the numerical value of each category of elevated cTn level, the related number of times the corresponding URL in each study will be calculated. The average level of elevated cTn in each category will be estimated by the mean of the lower and upper levels. If the highest category has an open upper level, the mean level will be estimated to be 1.2x the lower levels[13]. $P < 0.05$ (2-sided) will be considered to be statistically significant. All statistical analyses will be performed in Stata software (version 10.0, StataCorp., College Station, TX, USA) and RevMan software (version 5.0, Cochrane Collaboration, Oxford, United Kingdom).

DISCUSSION

Although the Fourth Universal Definition of Myocardial Infarction (UDMI) defines AMI as cTn concentrations >99th percentile URL under a broad clinical condition[14], some studies have used thresholds other than the URL[5] , whereas others using URL have obtained negative findings in patients with COVID-19[6] [7].Additionally, many studies have not used high sensitive cTn assays and only measured once at early time point, resulting in the underestimated incidence and extent of AMI in COVID-19.

Recently, a meta-analysis has indicated that the COVID-19 patients with AMI (mostly using URL as cutoff) showed a near 4 times higher mortality risk than those with non-AMI[8]. High mortality as high as 80 times with AMI has been reported in early univariate regression analysis[1]. Therefore, an optimal cutoff value of cTn levels for AMI need to be explored for early risk stratification， prompt therapy initiation, and thereby improving prognosis[15]. Similar findings have been showed by our previous analysis that a lower cutoff value of cTn levels for AMI than in fourth UDMI was proposed with prognostic relevance following elective percutaneous coronary intervention[16]. Fortunately, there has been several studies concerning this important issue[17-19]. In this protocol, we make an appeal for the future studies to release the related prognostic outcomes with different categories of cTn levels（>2） in patients with COVID-19. What's more, high sensitive cTn measurements at different time points[20] are encouraged for the potential prognostic role of tiny AMI

(cTn levels between detection limit and URL) in patients with COVID-19 infection[21-24] .

The major strength of this systematic review and meta-analysis is, for the first time, to comprehensively explore a potential linear or nonlinear dose-response relationship between cTn level and adverse clinical outcomes in COVID-19. Moreover, the significance of subclinical or tiny AMI below URL level will be focused for early diagnosis to improve prognosis and reduce the related mortality[21]. We believe this protocol will encourage more and more researchers focusing on this issue and publishing the related prognostic outcome for different categories (>2) of cTn levels in COVID-19. In addition, we will try to provide some new evidence for the new diagnostic criterion of the COVID-19 related AMI for a long-term coexistence of COVID-19 with human beings has been proposed. The limitations, on the other hand, are also existed in our analysis. Firstly, both the retrospective and prospective study design will be included resulting the potential bias. Secondly, the sample size in each study may be small for the limitation of medical resources and economic decline. Thirdly, we could not rule out the potential influence of different types of detection kit and method for the cTn level in the included studies. Fourthly, our analysis may not be sufficient for a diagnosis of myocardial infarction for lacking additional evidence of myocardial ischemia (electrocardiography, echocardiography, coronary CT or angiography) in accordance with the fourth UDMI definition.

ETHICS AND DISSEMINATION

In accordance with the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital, the ethical approval is waived for the protocol of systematic review. This meta-analysis will be disseminated through a peer-reviewing process for journal publication and conference communication.

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Author Contributions CZ, HP, and JS contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by CZ. YG and YZ will independently search and select the eligible studies and extract the data from the included studies. LC and ZF will assess methodological quality and the risk of bias. All the authors approved the protocol publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

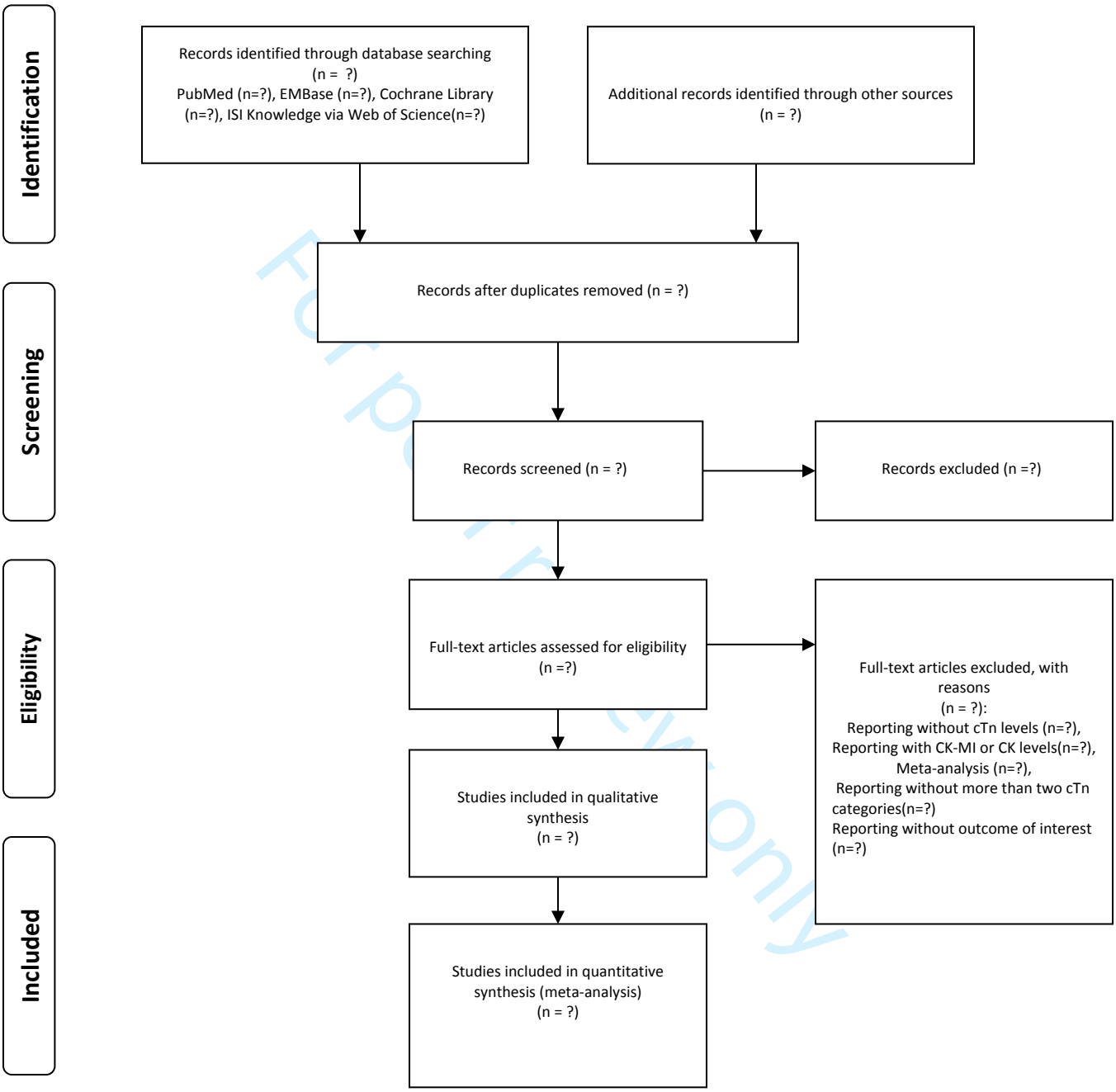
Figure Legends

Figure 1. Trial Searching and Selecting Flow Chart.

Table 1 Search strategy for PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science Database

Database	Search items
PubMed	
No.	
# 1	((cardiac injury) OR (myocardial injury)) OR (troponin)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2
EMBase	
# 1	cardiac AND injury OR (myocardial AND injury) OR troponin
# 2	'covid 19' OR 'sars cov 2'
# 3	# 1 and # 2
Cochrane Library	
# 1	cardiac injury in All Text OR myocardial injury in All Text OR troponin in All Text

# 2	COVID-19 in All Text OR SARS-CoV-2 in All Text
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	TOPIC: (cardiac injury) OR TOPIC: (myocardial injury) OR TOPIC: (troponin) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 2	TOPIC: (COVID-19) OR TOPIC: (SARS-CoV-2) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 3	# 1 and # 2



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		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	No update
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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 guarantor of the review	15
Amendments			Not Amendments
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Support			
Sources	#5a	Indicate sources of financial or other support for the review	15
Sponsor	#5b	Provide name for the review funder and / or sponsor	15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	15
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6
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	6
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	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	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)	7
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	7
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	7

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
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	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8,9
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 **T**)	8,9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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Chenghui Zhou[#,*,1], M.D, Ph.D; Hanjun Pei[#,2], M.D,Ph.D; Yiming Gao[3], M.D,Ph.D; Yulin Zhang[1], M.D, Ph.D; Liang Cao[1], M.D; Zhongrong Fang[1], M.D, Ph.D; Jiangping Song[*,4], M.D, Ph.D

[1]Department of Anesthesiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

[2]Department of Cardiology, The First Affiliated Hospital of Baotou Medical College, Baotou, Inner Mongolia, China

[3]Department of Echocardiography, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, China

[4]Department of Cardiac Surgery, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China

[#]Dr. Zhou and Dr. Pei contributed equally as the first authors in this work.

[*]**Address for Correspondence**: Chenghui Zhou and Jiangping Song;

No. 167 Beilishi Road, 100037 Xicheng District, Beijing, China

Tel: 86-10-88398082, Fax: 86-10-88398082

E-mail: chenghuizhou@yahoo.com (Zhou Ch); fwsongjiangping@126.com (Song Jp);.

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ABSTRACT

Introduction Acute myocardial injury in patients with COVID-19 infection has been recognized as one important complication associating with in-hospital mortality. The potential dose response effect of cardiac troponin (cTn) concentrations on adverse clinical outcomes has not been systematically studied. Hence, we will conduct a comprehensive dose-response meta-analysis to quantitatively evaluate the relationship between the elevated cTn concentrations and in-hospital adverse clinical outcomes in COVID-19 patients.

Methods We will search PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science database, as well as pre-print databases (medrxiv and biorxiv) (from inception until October, 2021) to identify all retrospective, prospective cohort, and randomized controlled studies using the related keywords. The primary outcome will be all-cause mortality during hospitalization. The second outcome will be major adverse event (MAE). To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between elevated cTn concentrations and all-cause mortality or MAE, studies with three or more categories of cTn concentrations will be included. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of cTn concentration. Sensitivity analyses will be used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of all-cause mortality or MAE.

Ethics and dissemination In accordance with the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital, the ethical approval is waived for the protocol of systematic review. This meta-analysis will be disseminated through a peer-reviewing process for journal publication and conference communication.

Keywords: Acute myocardial injury, COVID-19, cardiac troponin, dose-response, meta-analysis

PROSPERO registration number CRD42020216059

Strengths and limitations of this study

1. This systematic review and meta-analysis will be the first one to comprehensively explore a potential linear or nonlinear dose-response relationship between elevated cTn concentrations and adverse clinical outcomes in COVID-19.
2. Future data on the prognostic outcomes for different cTn categories (3 or more) in patients with COVID-19 are needed.
3. High sensitive cTn measurements at different time points are suggested for the potential prognostic role of tiny acute myocardial injury (cTn concentrations between detection limit and URL) in patients with COVID-19.
4. The inclusion of both retrospective and prospective studies may result in potential bias.
5. The sample size in each study and the number of included studies may be relative small.

Introduction

Acute myocardial injury has been recognized as one important complication in adult patients with COVID-19 infection associating with in-hospital morbidity and mortality[1 2]. By Oct 31st 2020, COVID-19 pandemic has cause 46,501,423 infections and 1,202,031 deaths worldwide in 215 countries[3].

Some studies have showed that the incidence of acute myocardial injury is common as many as 20~40% based on cardiac troponin (cTn) concentrations[4 5], particularly in patients with obvious cardiovascular risk factors and severity of COVID-19[6 7]. Although the main target of COVID-19 is the respiratory system, the cardiovascular system could also be influenced by affecting the neurohumoral regulation of the cardiovascular system, unbalancing the myocardial oxygen supply and demand with lung injury induced hypoxia, acute systemic inflammatory reaction, and cytokine storm[8-10].

Up to now, different diagnostic thresholds of cTn concentrations for acute myocardial injury in COVID-19 patients have been proposed. Some studies did not use 1xURL as the cutoff value of cTn concentrations [11]. Moreover, controversial prognostic relationships of acute myocardial injury have been published by various researchers using 1xURL for acute myocardial injury diagnosis[12 13]. Additionally, COVID-19 is a newly-breakout global pandemic with high mortality (at least 4 times increase), and will have a long-term coexistence with human beings[14]. Accordingly, the optimal cutoff value of cTn concentration for acute myocardial injury with

prognostic relevance needs to be identified to trigger a promptly beneficial intervention in the very near future. However, there have been limited studies reporting the clinical outcomes for different categories of cTn concentrations in COVID-19. Hence, we will conduct a comprehensive dose-response meta-analysis to quantitatively evaluate the association between the elevated cTn concentrations and adverse clinical outcomes in patients with COVID-19.

Objectives

The purpose of this systematic review and meta-analysis is to explore the potential optimal cutoff value of elevated cardiac troponin concentration for acute myocardial injury predicting adverse clinical outcomes in adult patients with COVID-19.

METHODS AND ANALYSIS

Search Strategy

We will report this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline[15]. PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science database, as well as pre-print databases (medrxiv and biorxiv) (from inception until October, 2021) will be systematically searched. Table 1 shows the related search keywords. Figure 1 shows the flow chart of searching process. This meta-analysis has been registered in the

PROSPERO (CRD42020216059).

Type of Participants

We will include adult patients with confirmed COVID-19 infection as study participants.

Type of Studies

We will include all the retrospective, prospective cohort, or randomized controlled studies that have reported the associations of different cTn categories (3 or more) with the incidence of major adverse clinical outcomes. English-published trials will be included. The studies unable to extract odds ratio (OR) or hazard ratio (HR) and the corresponding 95% confidence intervals (CI) will be excluded.

Type of Outcomes

The primary outcome will be all-cause mortality during hospitalization. The second outcome will be major adverse event (MAE). MAE is a combined endpoint during hospitalization including: all-cause death, myocardial infarction, congestive heart failure, acute kidney injury, pulmonary embolism, deep venous thrombosis, or stroke. Additional outcomes will include the incidence of heart failure, need and duration for mechanical ventilation, and incidence of multiple organ dysfunction syndromes.

Data Extraction

Data will be extracted by two independent authors (Y.Gao and Y.Zhang). A third author (H. Pei) will make a final decision in case of discrepancies. The extracted data will include study design (author, publication year, country, sample size, percentage of positive cTn concentrations), patient characteristics (mean age, male proportion, race, body mass index, diabetes proportion, hypertension proportion, hyperlipidemia proportion, smoking proportion, coronary artery disease proportion, previous myocardial infarction, chronic heart failure, history of atrial fibrillation,, history of stroke or transient ischemic accident, acute kidney dysfunction, chronic kidney dysfunction, history of lung disease, history of liver disease,, beta-blocker usage, statin usage, angiotensin-converting enzyme inhibitor usage, angiotensin receptor blocker usage, calcium channel blocker usage, aspirin usage), follow-up period, pattern, duration, number of total testing, detection kit of cTn, URL of cTn, detection limit of cTn, cutoff value of cTn, and the different categories for cTn concentration.

Assessment of Risk of Bias

Newcastle-Ottawa quality assessment scale (NOS) will be used to evaluate the methodological quality of included studies[16].

Data synthesis

The ORs or HRs in each study will be extracted from the elevated versus non-elevated categories of cTn concentration for the pooled analysis. For studies only

providing the Log-rank test or the Kaplan-Meier survival curve, the HR will be calculated based on time-to-event aggregate data[17]. The referent category with nonelevated cTn will be the lowest cTn concentration in each study. Random-effect model will be used for the potential clinical inconsistency among the included studies in the pooled analysis by the DerSimonian and Laird method. If one study reported multiple cTn categories (3 or more), we will calculate the OR based on the number of cases and non-cases in all of the elevated categories and referent groups for the high vs low analysis. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of cTn concentration including study design, demographic characteristics, and different cTn assay types[18]. Sensitivity analyses will be used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of all-cause mortality or MAE. Publication bias evaluation will be conducted by the Begg's, Egger's test, and visualized symmetry of the funnel plot. A dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between different categorized elevated cTn concentrations and all-cause mortality or MAE will be performed. For study only providing the numerical value of each category of elevated cTn concentration, the related number of times the corresponding URL in each study will be calculated. The average concentration of elevated cTn in each category will be estimated by the mean of the lower and upper concentrations. If the highest category has an open upper

concentration, the mean concentration will be estimated to be 1.2x the lower concentrations [19-21]. $P < 0.05$ (2-sided) will be considered to be statistically significant. All statistical analyses will be performed in Stata software (version 10.0, StataCorp., College Station, TX, USA) and RevMan software (version 5.0, Cochrane Collaboration, Oxford, United Kingdom).

DISCUSSION

Although the Fourth Universal Definition of Myocardial Infarction (UDMI) defines acute myocardial injury as cTn concentrations >99th percentile URL under a broad clinical condition[22], some studies have used thresholds other than the URL[11] , whereas others using URL have obtained negative findings in patients with COVID-19[12] [13].Additionally, many studies have not used high sensitive cTn assays and only measured once at early time point, resulting in the underestimated incidence and extent of acute myocardial injury in COVID-19.

Recently, a meta-analysis has indicated that the COVID-19 patients with acute myocardial injury (mostly using URL as cutoff) showed a near 4 times higher mortality risk than those with non-acute myocardial injury [14]. High mortality as high as 80 times with acute myocardial injury has also been reported in early univariable regression analysis[1]. Therefore, an optimal cutoff value of cTn concentrations for acute myocardial injury need to be explored for early risk stratification， prompt therapy initiation, and thereby improving prognosis[23]. Similar findings by our previous analysis showed that a lower cutoff value of cTn concentrations for acute

myocardial injury than in fourth UDMI has been proposed with prognostic relevance following elective percutaneous coronary intervention[20]. Fortunately, there has been several studies concerning this important issue[24-26]. What's more, high sensitive cTn measurements at different time points[27] are encouraged for the potential prognostic role of tiny acute myocardial injury (cTn concentrations between detection limit and URL) in patients with COVID-19 infection[28-31] .

The major strength of this systematic review and meta-analysis is, for the first time, to comprehensively explore a potential linear or nonlinear dose-response relationship between cTn concentrations and adverse clinical outcomes in COVID-19. Moreover, the significance of subclinical or tiny acute myocardial injury below URL level will be focused for early diagnosis to improve prognosis and reduce the related mortality[28]. In addition, we will try to provide some new evidence for the new diagnostic criterion of the COVID-19 related acute myocardial injury for a long-term coexistence of COVID-19 with human beings has been proposed. The limitations, on the other hand, are also existed in our analysis. Firstly, both the retrospective and prospective study design will be included resulting the potential bias. Secondly, the sample size in each study may be small for the limitation of medical resources and economic decline. Thirdly, we could not rule out the potential influence of different types of detection kit and method for the cTn concentration in the included studies. Fourthly, our analysis may not be sufficient for a diagnosis of myocardial infarction for lacking additional evidence of myocardial ischemia (electrocardiography,

echocardiography, coronary CT or angiography) in accordance with the fourth UDMI definition.

ETHICS AND DISSEMINATION

In accordance with the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital, the ethical approval is waived for the protocol of systematic review. This meta-analysis will be disseminated through a peer-reviewing process for journal publication and conference communication.

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Author Contributions CZ, HP, and JS contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by CZ. YG and YZ will independently search and select the eligible studies and extract the data from the included studies. LC and ZF will assess methodological quality and the risk of bias. All the authors approved the protocol publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Figure Legends

Figure 1. Trial Searching and Selecting Flow Chart.

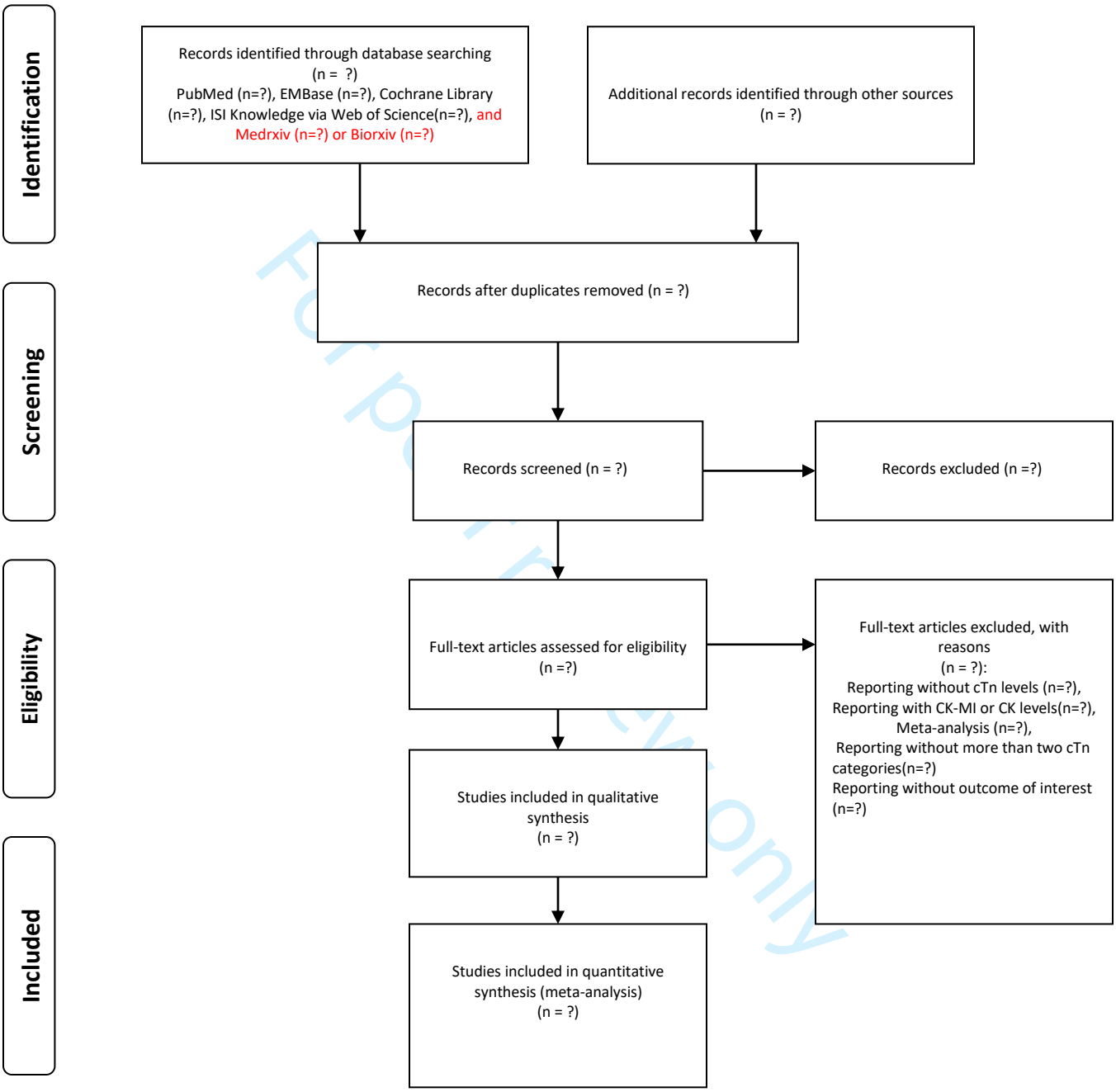
Table 1 Search strategy for PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science, and Medrxiv or Biorxiv

Database

Database	Search items
PubMed	
No.	
# 1	((cardiac injury) OR (myocardial injury)) OR (troponin)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2
EMBase	
# 1	cardiac AND injury OR (myocardial AND injury) OR troponin
# 2	'covid 19' OR 'sars cov 2'
# 3	# 1 and # 2
Cochrane Library	

# 1	cardiac injury in All Text OR myocardial injury in All Text OR troponin in All Text
# 2	COVID-19 in All Text OR SARS-CoV-2 in All Text
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	TOPIC: (cardiac injury) OR TOPIC: (myocardial injury) OR TOPIC: (troponin) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 2	TOPIC: (COVID-19) OR TOPIC: (SARS-CoV-2) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 3	# 1 and # 2
Medrxiv or Biorxiv	
# 1	title "cardiac injury" (match any words) and abstract or title "myocardial injury"

	(match any words) and full text or abstract or title "troponin" (match whole any)
# 2	title "COVID-19" (match any words) and abstract or title "SARS-CoV-2" (match any words)
# 3	# 1 and # 2



Reporting checklist for protocol of a systematic review.

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	No update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
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 guarantor of the review	15
Amendments			Not 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	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	15
Sponsor	#5b	Provide name for the review funder and / or sponsor	15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	15
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6
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	6
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	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - selection process	#11b	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)	7
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	7
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	7

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7,8
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	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8,9
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 **T**)	8,9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8,9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9