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Potential Dose-response Effect of Postprocedural Elevated Cardiac Troponin Level on Adverse Clinical Outcomes Following Noncardiac Surgery: A Systematic Review Protocol of Prospective Studies

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Dose-response Effect of Postprocedural Elevated Cardiac Troponin Level on Adverse Clinical Outcomes Following Adult Noncardiac Surgery: A Systematic Review Protocol of Prospective Studies

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ABSTRACT

Introduction Myocardial injury after noncardiac surgery (MINS) has been recognized as one important complication in association with short-term and long-term morbidity and mortality. The potential dose response effect of postprocedural cardiac troponin (cTn) levels on adverse clinical outcomes has not been studied. Hence, we will conduct a comprehensive dose-response meta-analysis based on the all related prospective studies to quantitatively evaluate the association between the postoperative elevated cTn levels and short-/long-term adverse clinical outcomes following noncardiac surgery.

Methods We will search PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science database (from inception until Oct, 2020) to identify all prospective cohort studies using the related keywords. The primary outcome will be all-cause mortality. The second outcomes will include cardiovascular mortality and major adverse cardiovascular event (MACE). Univariate or multivariate meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of postoperative 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. To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between postoperative elevated cTn levels and all-cause mortality or MACE, studies with three or more categories will be included.

Ethics and dissemination Ethical approval is waived for the systematic review protocol according to the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication and conference presentations.

Keywords: myocardial injury, noncardiac surgery, postoperative cardiac troponin,

dose-response

PROSPERO registration number CRD42020173175.

Strengths and limitations of this study

1. This meta-analysis will be the first one to explore the potential linear or nonlinear dose-response relationship between postoperative cTn level and adverse clinical outcomes in adult non-cardiac surgery.

2. This meta-analysis will be the first one focusing the prognostic significance of subclinical or tiny myocardial injury below URL.

3. This meta-analysis will include the largest study population with only prospective enrollment.

4. The baseline cTn level is not a regular test for patients undergoing noncardiac surgery resulting insufficient data.

5. This work could not rule out the potential influence of different detection kit and method for the cTn level in the included studies

Introduction

Myocardial injury after noncardiac surgery (MINS) has been recognized as one important complication in association with short-term and long-term morbidity and mortality[1]. Some studies have showed that the incidence of MINS is common as many as 30~45% based on postoperative high sensitive cardiac troponin(cTn) level[2-4]. The major proposed mechanism of MINS is imbalance of myocardial oxygen supply-demand including perioperative hypotension[5], hypoxia[6], anemia[7], previous coronary artery disease[8], and coronary thrombosis[9]. Postoperative cTn measurement is recommended in high-risk patients undergoing noncardiac surgery. According to the latest fourth Universal Definition of Myocardial Infarction (UDMI) in 2018[6], the cutoff value for regularly diagnosing MINS is the 99th percentile upper reference limit (URL) of postoperative cTn level. However, increase in the prognostic effect of cTn still requires the newly-onset ischemia-related evidence of myocardium including electrocardiogram, echocardiography, coronary computed tomography (CT), or coronary angiography[6]. However, these cardiac-specific examinations are not regularly used in patients undergoing noncardiac surgery, and may increase a large amount of cost during hospitalization.

Given the limited high-quality evidence and controversial findings from available studies concerning the long-term prognostic significance following noncardiac surgery, whether there is an optimal cutoff value for postoperative cTn level to diagnose MINS with improved prognostic significance remains unknown[10-16]. Moreover, quantitative analysis for the myocardial injury below the recommended URL has not been systematically studied[17]. Hence, we will conduct a comprehensive dose-response meta-analysis based on the all related prospective studies to quantitatively evaluate the association between the postoperative elevated cTn levels and short-/long-term adverse clinical outcomes following noncardiac surgery.

Objectives

The purpose of this systematic review and meta-analysis is to explore the potential dose-response relationship between postoperative elevated cTn levels and adverse clinical outcomes after adult noncardiac surgery.

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[18]. We will search PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science database (from inception until Oct, 2020), and the reference lists of the retrieved articles. The related search keywords are listed in Table 1. This meta-analysis has been registered in the PROSPERO with registration ID CRD42020173175. The searching process is shown in Figure 1.

Type of Participants

We will include adult patients undergoing noncardiac surgery as study participants.

Type of Studies

We will include prospective cohort studies that have reported the associations of the postoperative cardiac troponin levels with the incidence of major adverse clinical outcomes. The publication language will be limited as English. The studies unable to extract odds ratio(OR) or hazard ration(HR) and the corresponding 95% confidence intervals (CI) will be excluded.

Type of Outcomes

The primary outcome will be all-cause mortality. The second outcomes will include cardiovascular mortality and major adverse cardiovascular event (MACE).

MACE is a combined endpoint including at least three of the following events: death, cardiovascular death, any cause for coronary revascularization, unstable angina, myocardial infarction, congestive heart failure, major adverse arrhythmias requiring treatment, cardiac arrest, pulmonary embolism, or stroke. The follow-up duration will be divided into three time periods: ‘short term (1-3 months)’, ‘medium term (3~12 months)’, and ‘long term (≥1 year)’. Both primary outcome and second outcome will be included in the analysis of potential dose-response effect.

Data Extraction

Data will be extracted by two independent authors (T. An and T. Yue). Discrepancies will be resolved by group discussion. The extracted data included study design (author, publication year, country, sample size, percentage of positive cTn levels), patient characteristics (mean age, male proportion, diabetes proportion, hypertension proportion, hyperlipidemia proportion, smoking proportion, coronary artery disease[CAD] proportion, previous myocardial infarction, chronic heart failure, atrial fibrillation, history of valvular heart disease, history of peripheral vascular disease, history of stroke or transient ischemic accident, kidney dysfunction, history of lung disease, history of liver disease, elective surgery proportion, vascular surgery proportion, general anesthesia, revised cardiac risk index[RCRI], beta-blocker usage, statin usage, angiotensin-converting enzyme inhibitor[ACEI]/ 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 postoperative cTn level.

Risk of Bias Assessment

The methodological quality of the studies will be evaluated in accordance with the Newcastle-Ottawa quality assessment scale (NOS)[19].

Data synthesis

The ORs or HRs in each study will be extracted or calculated from the elevated versus non-elevated categories of postoperative cTn level for the pooled analysis. Specifically, the HR will be calculated based on the Log-rank test or the Kaplan-Meier survival curve[20]. Nonelevated category at the lowest cTn level will be chose as the reference. The DerSimonian and Laird random-effects model will be used in the pooled analysis for the potential clinical inconsistency regardless of heterogeneity test. Univariate or multivariate meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of postoperative cTn level[21]. 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 assessment will be performed by the Begg's and Egger's test. If one study reported multiple categories (>2 categories), we will calculate the OR by using the number of event and total in all of the elevated categories and referent one for the high vs low analysis. To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between postoperative elevated cTn levels and all-cause mortality or MACE, studies with three or more categories will be included. If the category only provides the numerical value of elevated cTn level, we will convert this into the number of times the corresponding URL in each individual study. 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 had an open upper level, the mean level was estimated to be 1.2x the level of the lower levels[22]. $P<0.05$ (2-sided) was considered to be statistically significant. All statistical analyses were 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 there has been several meta-analyses concerning about the perioperative troponin levels and adverse clinical outcomes in adult cardiac surgery, there are obvious weakness for these works (including a large amount of retrospective studies[16], only focusing on preoperative troponin levels[14 23], without distinguishing preoperative and postoperative troponin levels [24]. Moreover, no previous meta-analysis has studied the potential linear or non-linear dose-response relationship between postoperative troponin level and adverse clinical outcomes in adult cardiac surgery. In addition, several recent studies have reported the prognostic role of subclinical or tiny myocardial injury (below URL)[17], which need to be paid attention for early risk stratification and improved outcomes in the future.

The strengths of this systematic review and meta-analysis include the prospective design in all the included studies, and its ability in gathering a large study population in this area. Moreover, for the first time, we will explore a potential linear or nonlinear dose-response relationship between postoperative cTn level and adverse clinical outcomes. In addition, the significance of subclinical or tiny myocardial injury below URL will firstly be focused[17]. The limitations, on the other hand, are also existed in our analysis. Firstly, the univariate or multivariate meta-regression and subgroup analyses are mainly based on the aggregate patient data, but not individual patient data. Other confounding factors may be underestimated. Secondly, we will focus the effect of baseline cTn level in the analysis. However, the baseline cTn level is not a regular test for patients undergoing noncardiac surgery resulting insufficient data. Thirdly, we could not rule out the potential influence of different 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) required in the fourth UDMI.

ETHICS AND DISSEMINATION

Ethical approval is waived according to the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication and conference presentations.

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Author Contributions CZ and TT contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by TA. TA and JG will independently search and select the eligible studies and extract the data from the included studies. YT and WK 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

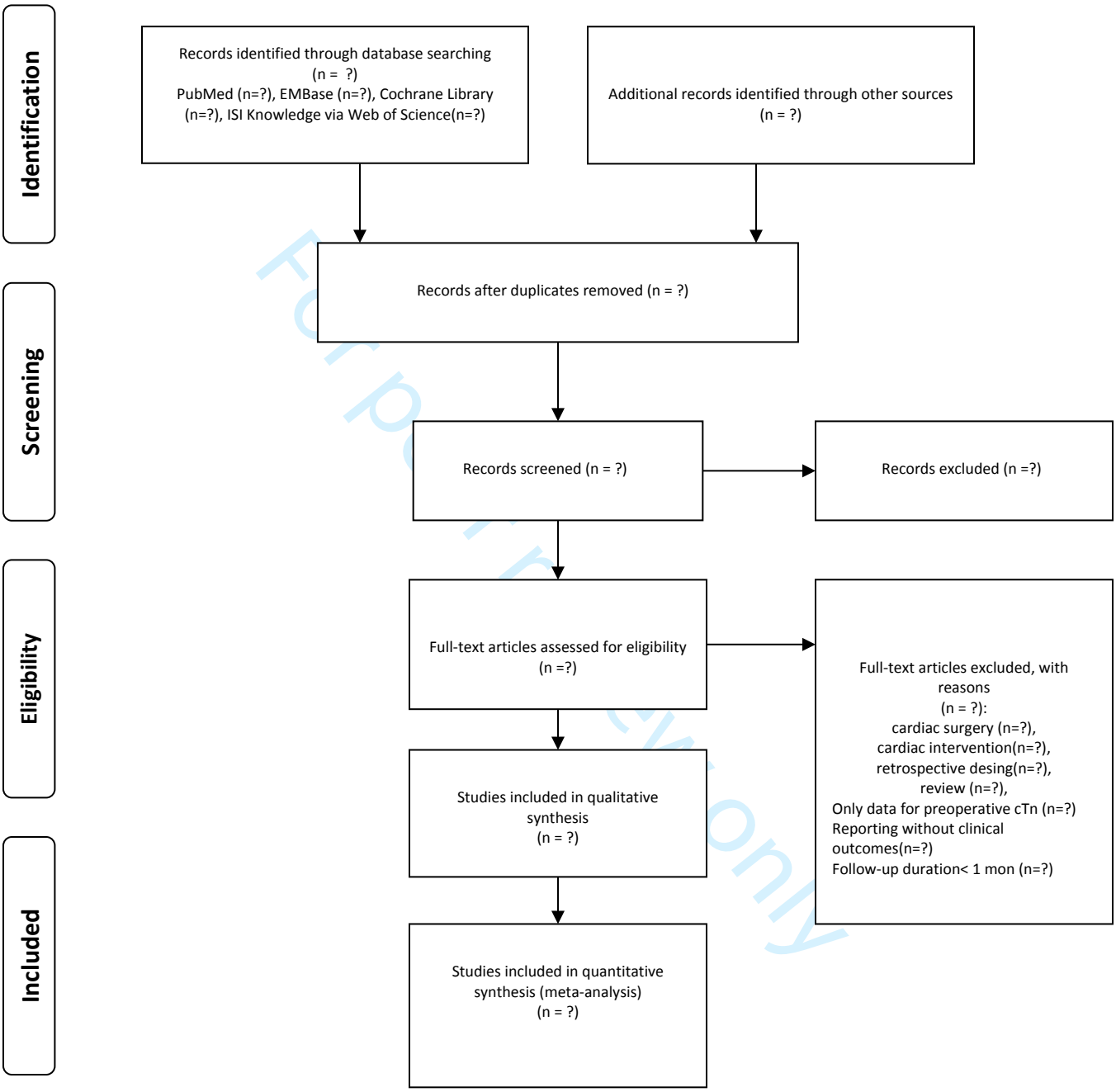
Figure 1. Flow Chart of the Trial Searching Process.

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

Database	Search items
PubMed	
No.	
# 1	((((troponin) OR (troponins)) OR (TnI)) OR (TnT)) OR (myocardial injury)
# 2	(noncardiac surgery) OR (non-cardiac surgery)
# 3	# 1 and # 2
EMBase	
# 1	troponin OR troponins OR tni OR tnt OR (myocardial AND injury)
# 2	noncardiac AND surgery OR ('non cardiac' AND surgery)
# 3	# 1 and # 2

Cochrane Library	
# 1	troponin in All Text OR troponins in All Text OR TnI in All Text OR TnT in All Text OR myocardial injury in All Text
# 2	noncardiac surgery in All Text OR non-cardiac surgery in All Text
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	(troponin) OR TOPIC: (troponins) OR TOPIC: (TnI) OR TOPIC: (TnT) OR TOPIC: (myocardial injury)
	Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto

# 2	TOPIC: (noncardiac surgery) OR TOPIC: (non-cardiac surgery) 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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Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			Not Amendments
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Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	12
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	12
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)	6
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	6
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	6

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6,7
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	7
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8
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
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

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ABSTRACT

Introduction Myocardial injury after noncardiac surgery (MINS) has been recognized as one important complication in association with short-term and long-term morbidity and mortality. However, whether higher level of postoperative cardiac troponin (cTn) possess higher incidence of major complications remains controversial. Hence, we will conduct a comprehensive dose-response meta-analysis based on the all related prospective studies to quantitatively evaluate the association between the postoperative elevated cTn levels and short-/long-term adverse clinical outcomes following adult noncardiac surgery.

Methods We will search PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science, China National Knowledge Infrastructure, Wanfang and VIP database (from inception until Oct, 2020) to identify all prospective cohort studies using the related keywords. The primary outcome will be all-cause mortality. The second outcomes will include cardiovascular mortality and major adverse cardiovascular event (MACE). Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of postoperative cTn level. 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 MACE. To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between postoperative elevated cTn levels and all-cause mortality or MACE, studies with three or more categories will be included.

Ethics and dissemination Ethical approval is waived for the systematic review protocol according to the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication and conference presentations.

Keywords: myocardial injury, noncardiac surgery, postoperative cardiac troponin,

dose-response

PROSPERO registration number CRD42020173175.

Strengths and limitations of this study

1. This meta-analysis will be the first one to explore the potential linear or nonlinear dose-response relationship between postoperative cTn level and adverse clinical outcomes in adult non-cardiac surgery.

2. This meta-analysis will firstly focus on the prognostic significance of subclinical or tiny myocardial injury below URL of cTn.

3. This meta-analysis will include the largest prospective study population.

4. The baseline cTn level is not a regular test for patients undergoing noncardiac surgery.

5. This work could not rule out the potential influence of different cTn detection kits and methods.

Introduction

Myocardial injury after noncardiac surgery (MINS) has been recognized as one important complication in association with short-term and long-term morbidity and mortality[1]. Some studies have showed that the incidence of MINS is common as many as 30~45% based on postoperative high sensitive cardiac troponin(cTn) level[2-4]. The major proposed mechanisms of MINS include imbalance of myocardial oxygen supply-demand including perioperative hypotension[5], hypoxia[6], anemia[7], previous coronary artery disease(CAD)[8], and coronary thrombosis[9]. Postoperative cTn measurement is recommended in high-risk (previous CAD, previous heart failure, previous atrial fibrillation, previous heart disease, etc) patients undergoing noncardiac surgery. According to the latest fourth Universal Definition of Myocardial Infarction (UDMI) in 2018[6], the cutoff value for regularly diagnosing MINS is the 99th percentile upper reference limit (URL) of postoperative cTn level. However, increase in prognostic effect of cTn still requires the newly-onset ischemia-related evidence of myocardium including electrocardiogram, echocardiography, coronary computed tomography (CT), or coronary angiography[6]. However, these cardiac-specific examinations are not regularly used in patients undergoing noncardiac surgery, and may increase a large amount of cost during hospitalization.

Given the limited high-quality evidence and controversial findings from available studies concerning the long-term prognostic significance following noncardiac surgery, whether there is an optimal cutoff value for postoperative cTn level to diagnose MINS with improved prognostic significance remains unknown[10-16]. Moreover, quantitative analysis for myocardial injury below the recommended URL has not been systematically studied[17]. Hence, we will conduct a comprehensive dose-response meta-analysis based on the all related prospective studies to quantitatively evaluate the association between the postoperative elevated cTn levels and short-/long-term adverse clinical outcomes following noncardiac surgery.

Objectives

The purpose of this systematic review and meta-analysis is to explore the potential dose-response relationship between postoperative elevated cTn levels and adverse clinical outcomes after adult noncardiac surgery.

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[18]. We will search PubMed, EMBase, Cochrane Library, and ISI Knowledge via Web of Science database (from inception until Oct, 2020), and the reference lists of the retrieved articles. The related search keywords are listed in Table 1. We will also search China National Knowledge Infrastructure, Wanfang and VIP Database (from inception until Oct, 2020) using the translated Chinese search keywords accordingly. This meta-analysis has been registered in the PROSPERO with registration ID CRD42020173175. The searching process is shown in Figure 1.

Type of Participants

We will include adult patients undergoing noncardiac surgery as study participants.

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.

Type of Studies

We will include prospective cohort studies that have reported the associations of the postoperative cardiac troponin levels with the incidence of major adverse clinical outcomes. No language restriction will be used. For the studies unable to extract

odds ratio (OR) or hazard ratio (HR) and the corresponding 95% confidence intervals (CI) , we will perform a related systematic review in a section.

Definition of MINS

We will not set a constant value for the definition of MINS. If a precise cutoff value has been provided in each study, the definition of MINS will be accepted. Three types of cutoff value will be existed: ① detection limit below URL; ② URL; ③ a value above URL. This definition is not according to the UDMI[6] or Standardized Endpoints in Perioperative Medicine initiative[19] for the exploration of dose-response relationship.

Type of Outcomes

The primary outcome will be all-cause mortality. The second outcomes will include cardiovascular mortality and major adverse cardiovascular event (MACE). MACE is a combined endpoint including at least three of the following events: death, cardiovascular death, any cause for coronary revascularization, unstable angina, myocardial infarction, congestive heart failure, major adverse arrhythmias requiring treatment, cardiac arrest, pulmonary embolism, or stroke. The follow-up duration will be divided into three time periods: ‘short term (1-3 months)’, ‘medium term (3~12 months)’, and ‘long term (≥1 year)’. Both primary outcome and second outcome will be included in the dose-response analysis.

Data Extraction

Data will be extracted by two independent authors (T. An and T. Yue). Discrepancies will be resolved by group discussion. The extracted data included study design (author, publication year, country, sample size, percentage of positive cTn levels), patient characteristics (mean age, male proportion, diabetes proportion, hypertension proportion, hyperlipidemia proportion, smoking proportion, CAD proportion, previous myocardial infarction, chronic heart failure, atrial fibrillation,

history of valvular heart disease, history of peripheral vascular disease, history of stroke or transient ischemic accident, kidney dysfunction, history of lung disease, history of liver disease, elective surgery proportion, vascular surgery proportion, general anesthesia, revised cardiac risk index, beta-blocker usage, statin usage, angiotensin-converting enzyme inhibitor/ Angiotensin Receptor Blocker 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 postoperative cTn level.

Risk of Bias Assessment

The methodological quality of the studies will be evaluated in accordance with the Newcastle-Ottawa quality assessment scale (NOS)[20].

Data synthesis

The ORs or HRs in each study will be extracted or calculated from the elevated versus non-elevated categories of postoperative cTn level for the pooled analysis. Specifically, the HR will be calculated based on the Log-rank test or the Kaplan-Meier survival curve[21]. Nonelevated category at the lowest cTn level will be chose as the reference. The DerSimonian and Laird random-effects model will be used in the pooled analysis for the potential clinical inconsistency regardless of heterogeneity test. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between elevated versus non-elevated categories of postoperative cTn level including but not limited to age, surgical types, sex, and cTn types (high sensitive versus non-high sensitive, cTnI versus cTnT, baseline cTn versus without baseline cTn)[22]. 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 MACE. Publication bias assessment will be performed by the Begg's and Egger's test. If one

study reported multiple categories (>2 categories), we will calculate the OR by using the number of event and total in all of the elevated categories and referent one for the high vs low analysis. To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between postoperative elevated cTn levels and all-cause mortality or MACE, studies with three or more categories will be included. If the category only provides the numerical value of elevated cTn level, we will convert this into the number of times the corresponding URL in each individual study. 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 had an open upper level, the mean level will be estimated to be 1.2x the level of the lower levels[23]. 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 there have been several meta-analyses concerning about the prognostic effect of pre- and/or post-operative troponin levels in adult noncardiac surgery, there are obvious pitfalls for these works (including a large amount of retrospective studies[16], only focusing on preoperative troponin levels[14 24], without distinguishing preoperative and postoperative troponin levels [25]). Moreover, none of them have studied the potential linear or non-linear dose-response relationship between postoperative troponin level and adverse clinical outcomes in adult noncardiac surgery. In addition, the prognostic role of subclinical or tiny myocardial injury (below URL)[17] has been largely ignored for early risk stratification and improved outcomes in adult noncardiac surgery.

The strengths of this systematic review and meta-analysis include the prospective design in all the included studies, and its ability in gathering a large study population

in this area. Moreover, for the first time, we will explore a potential linear or nonlinear dose-response relationship between postoperative cTn level and adverse clinical outcomes. In addition, the prognostic significance of subclinical or tiny myocardial injury below URL will firstly be focused[17]. The limitations, on the other hand, are also existed in our analysis. Firstly, the univariablee or multivariable meta-regression and subgroup analyses are mainly based on the aggregate patient data, but not individual patient data. Other confounding factors may be underestimated. Secondly, we will focus the effect of baseline cTn level in the analysis. However, the baseline cTn level is not a regular test for patients undergoing noncardiac surgery. Thirdly, we could not rule out the potential influence of different detection kits and methods 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) required in the fourth UDMI. Lastly, elevated troponin has been observed in non-cardiac situations such as pulmonary embolism or renal dysfunction, and thus might not be a marker of only direct cardiac problems.

ETHICS AND DISSEMINATION

Ethical approval is waived according to the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication and conference presentations.

Author Contributions CZ and TT contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by TA. TA and JG will independently search and select the eligible studies and extract the data from the included studies. YT and WK will assess methodological quality and the risk of bias. All the authors approved the protocol publication.

Competing interests None declared.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Figure Legends

Figure 1. Flow Chart of the Trial Searching Process.

Table 1 Search strategy for PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science, China National Knowledge Infrastructure, Wanfang and VIP Database

Database	Search items
PubMed	
No.	
# 1	((((troponin) OR (troponins)) OR (TnI)) OR (TnT)) OR (myocardial injury)
# 2	(noncardiac surgery) OR (non-cardiac surgery)
# 3	# 1 and # 2
EMBase	
# 1	troponin OR troponins OR tni OR tnt OR (myocardial AND injury)
# 2	noncardiac AND surgery OR ('non cardiac' AND surgery)
# 3	# 1 and # 2
Cochrane Library	

# 1	troponin in All Text OR troponins in All Text OR TnI in All Text OR TnT in All Text OR myocardial injury in All Text
# 2	noncardiac surgery in All Text OR non-cardiac surgery in All Text
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	(troponin) OR TOPIC: (troponins) OR TOPIC: (TnI) OR TOPIC: (TnT) OR TOPIC: (myocardial injury) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 2	TOPIC: (noncardiac surgery) OR TOPIC: (non-cardiac surgery) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO.Search language=Auto
# 3	# 1 and # 2

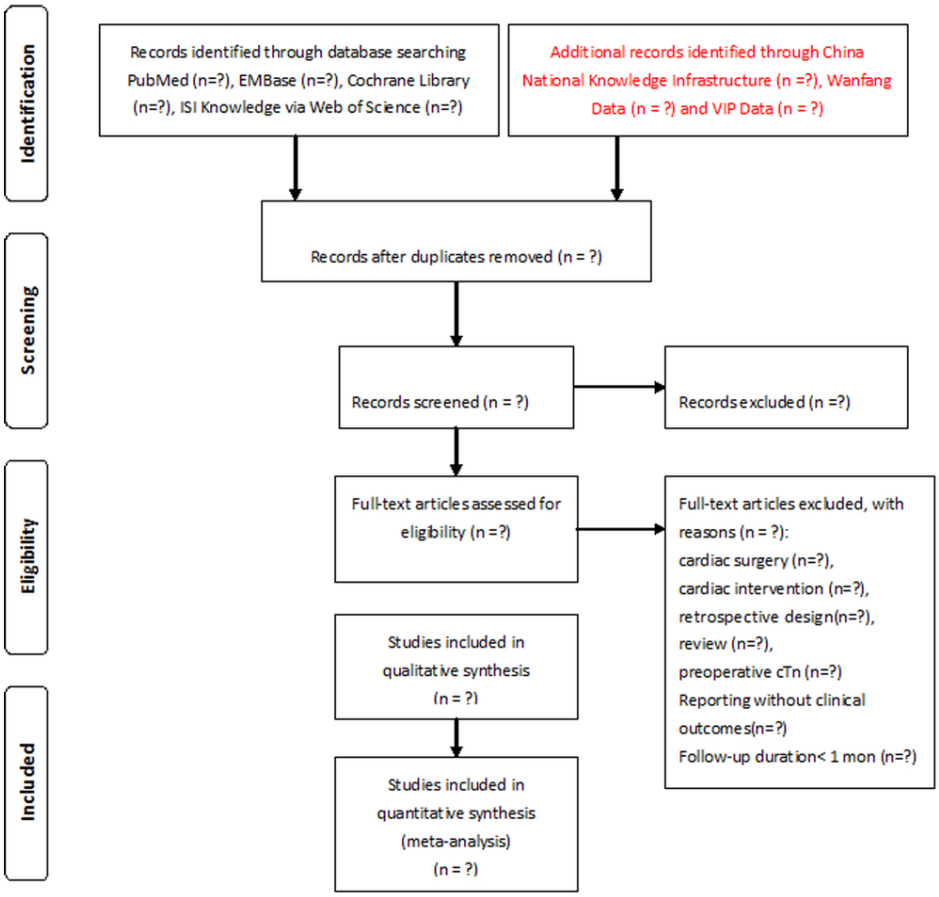

Figure 1. Flow Chart of the Trial Searching Process

90x90mm (300 x 300 DPI)

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.

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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
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	10
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	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
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
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)	8,9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8,9

BMJ Open

Dose-response Effect of Postprocedural Elevated Cardiac Troponin Level on Adverse Clinical Outcomes Following Adult Noncardiac Surgery: A Systematic Review Protocol of Prospective Studies

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Secondary Subject Heading:	Evidence based practice, Intensive care, Epidemiology, Diagnostics
Keywords:	Adult anaesthesia < ANAESTHETICS, Adult intensive & critical care < ANAESTHETICS, Anaesthesia in cardiology < ANAESTHETICS

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Dose-response Effect of Postprocedural Elevated Cardiac Troponin Level on Adverse Clinical Outcomes Following Adult Noncardiac Surgery: A Systematic Review Protocol of Prospective Studies

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Word Count: 3387 words.

ABSTRACT

Introduction Myocardial injury after noncardiac surgery (MINS) has been recognized as an important complication associated with short-term and long-term morbidity and mortality. However, whether a higher level of postoperative cardiac troponin (cTn) is associated with a higher incidence of major complications remains controversial. Hence, we will conduct a comprehensive dose-response meta-analysis based on all relevant prospective studies to quantitatively evaluate the association between elevated postoperative cTn levels and short-/long-term adverse clinical outcomes following adult noncardiac surgery.

Methods We will search the PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science, China National Knowledge Infrastructure, Wanfang and VIP databases (from inception until October 2020) to identify all prospective cohort studies using the relevant keywords. The primary outcome will be all-cause mortality. The second outcomes will include cardiovascular mortality and major adverse cardiovascular events (MACEs). Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between elevated versus nonelevated categories of postoperative cTn levels. 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 MACE. To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between postoperative elevated cTn levels and all-cause mortality or MACE, studies with three or more categories will be included.

Ethics and dissemination Ethical approval is waived for the systematic review protocol according to the Institutional Review Board/Independent Ethics Committee of Fuwai Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication and conference presentations.

Keywords: myocardial injury, noncardiac surgery, postoperative cardiac troponin, dose-response

PROSPERO registration number CRD42020173175.

Strengths and limitations of this study

1. The potential linear or nonlinear dose-response relationship between postoperative cTn levels and adverse clinical outcomes in adult noncardiac surgery will be explored.

2. The prognostic significance of subclinical or tiny myocardial injury below the URL of cTn will be focused.

3. This meta-analysis will pool the data from a number of studies to form the largest prospective dataset to date.

4. The baseline cTn level is not a routine test for patients undergoing noncardiac surgery.

5. This workcannot rule out the potential influence of different cTn detection kits and methods used in the included studies.

Introduction

Myocardial injury after noncardiac surgery (MINS) has been recognized as an important complication associated with short-term and long-term morbidity and mortality[1]. Some studies have shown that the incidence of MINS isas high as 30~45% based on postoperative high-sensitive cardiac troponin (cTn) levels[2-4]. The major proposed mechanisms of MINS include animbalance in myocardial oxygen supply and demand due to perioperative hypotension[5], hypoxia[6], anaemia[7], previous coronary artery disease(CAD)[8], and coronary thrombosis[9]. Postoperative cTn measurement is recommended for high-risk (previous CAD, previous heart failure, previous atrial fibrillation, previous heart disease, etc) patients undergoing noncardiac surgery. According to the fourth Universal Definition of Myocardial Infarction (UDMI) published in 2018[6], the cut-off value for the diagnosis of MINS is the 99th percentile upper reference limit (URL) of the postoperative cTn level. However, an increase in the prognostic effect of cTn levels still requires the new-onset ischemia-related evidence in the myocardium including that from electrocardiogram, echocardiography, coronary computed tomography (CT), or coronary angiography[6]. However, these cardiac-specific examinations are not regularly used in patients undergoing noncardiac surgery, and may increase the cost of hospitalization.

Given the limited high-quality evidence available and the controversial findings revealed by available studies concerning the long-term prognostic significance of cTn levels following noncardiac surgery, whether there is an optimal cut-off value for postoperative cTn level to diagnose MINS with improved prognostic significance remains unknown[10-16]. Moreover, quantitative analysis for myocardial injury below the recommended URL has not been systematically studied[17]. Hence, we will conduct a comprehensive dose-response meta-analysis based on all relevant prospective studies to quantitatively evaluate the association between elevated postoperative cTn levels and short-/long-term adverse clinical outcomes following noncardiac surgery.

Objectives

The purpose of this systematic review and meta-analysis is to explore the potential dose-response relationship between postoperative elevated cTn levels and adverse clinical outcomes after adult noncardiac surgery.

METHODS AND ANALYSIS

Search Strategy

We will conduct this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines[18]. We will search the PubMed, EMBase, Cochrane Library, and ISI Knowledge via the Web of Science databases (from inception until October 2020), and the reference lists of the retrieved articles. The related search keywords are listed in Table 1. We will also search the China National Knowledge Infrastructure, Wanfang and VIP Databases (from inception until October 2020) using same search keywords translated into Chinese. This meta-analysis has been registered in PROSPERO with the registration ID CRD42020173175. The proposed search process is shown in Figure 1.

Type of Participants

We will include adult patients undergoing noncardiac surgery as the study participants.

Patient and public involvement

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

Type of Studies

We will include prospective cohort studies that have reported the associations between postoperative cardiac troponin levels and the incidence of major adverse

clinical outcomes. No language restriction will be used.

Definition of MINS

The definition of MINS with a precise cut-off value in each study will be accepted. The following three types of cut-off value will exist: ① detection limit below the URL; ② detection at the URL; ③ detection above the URL.This definition based only on biomarkers of myocardial injury is not based on the UDMI[6] or Standardized Endpoints in Perioperative Medicine initiative[19] due to the lack of availability of additional information such as electrocardiography, echocardiography, coronary CT or angiography data .

Type of Outcomes

The primary outcome will be all-cause mortality. The secondary outcomes will include cardiovascular mortality and major adverse cardiovascular events (MACEs). MACEs constitute a combined endpoint including at least three of the following events: death, cardiovascular death, coronary revascularization of any cause, unstable angina, myocardial infarction, congestive heart failure, major adverse arrhythmias requiring treatment, cardiac arrest, pulmonary embolism, or stroke. The follow-up duration will be divided into the following three time periods: ‘short term (1-3 months)’, ‘medium term (3~12 months)’, and ‘long term (≥1 year)’. Both the primary outcome and secondary outcomes will be included in the dose-response analysis.

Data Extraction

The data will be extracted by two independent authors (T. An and T. Yue). Discrepancies will be resolved by group discussion. The extracted data will include study design (author, publication year, country, sample size, percentage of positive cTn levels), patient characteristics (mean age, male proportion, diabetes proportion, hypertension proportion, hyperlipidemia proportion, smoking proportion, CAD

proportion, previous myocardial infarction, chronic heart failure, atrial fibrillation, history of valvular heart disease, history of peripheral vascular disease, history of stroke or transient ischemic accident, kidney dysfunction, history of lung disease, history of liver disease, elective surgery proportion, vascular surgery proportion, general anesthesia, revised cardiac risk index, beta-blocker usage, statin usage, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker usage, calcium channel blocker usage, aspirin usage), follow-up period, kit used to detect cTn, the URL of cTn, the detection limit of cTn, cut-off value of cTn, and the different categories of postoperative cTn levels.

Risk of Bias Assessment

The methodological quality of the studies will be evaluated in accordance with the Newcastle-Ottawa quality assessment scale (NOS)[20].

Data synthesis

The ORs or HRs in each study will be extracted or calculated from patients categorized as having elevated versus nonelevated postoperative cTn levels for the pooled analysis. Specifically, the HR will be calculated based on the log-rank test or the Kaplan-Meier survival curve[21]. Patients in the nonelevated cTn level category with the lowest cTn levels will be chosen as the reference points. The DerSimonian and Laird random-effects model will be used in the pooled analysis for potential clinical inconsistency regardless of the heterogeneity test result. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the comparison between patients with elevated versus nonelevated postoperative cTn levels to assess the impact of multiple potential influential factors such assurgical types, patient characteristics, and cTn types (high sensitive versus non-high sensitive, cTnI versus cTnT, baseline cTn versus without baseline cTn)[22]. 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 MACEs. Publication bias assessment will be performed by the Begg's and Egger's tests. If one study reported multiple categories (>2 categories), we will calculate the OR by using the number of events and the total in all of the elevated categories and reference one for the high vs low analysis. To conduct a dose-response meta-analysis for the potential linear or restricted cubic spline regression relationship between postoperative elevated cTn levels and all-cause mortality or MACEs, studies with three or more categories will be included. If only the numerical value of the elevated cTn levels is provided, we will convert this into the number of times the corresponding URL in each individual study. The average level of elevated cTn in each category will be estimated by determining 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 level of the lower levels[23]. $P<0.05$ (2-sided) will be considered 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 there have been several meta-analyses concerning the prognostic effect of pre- and/or postoperative troponin levels in adult noncardiac surgery, there are obvious pitfalls in these studies (including a large number of retrospective studies[16], and studies focused onlyon preoperative troponin levels[14 24] or, did not distinguish between preoperative and postoperative troponin levels [25]). Moreover, the potential linear or nonlinear dose-response relationship between postoperative troponin level and adverse clinical outcomes in adult noncardiac surgery has not been studied. In addition, the prognostic role of subclinical or tiny myocardial injury (below the URL)[17] has been largely ignored for early risk stratification and prediction of improved outcomes in adult noncardiac surgery.

The strengths of this systematic review and meta-analysis include the prospective design of all the included studies, and its ability to gather a large relevant study population. Moreover, for the first time, we will explore the potential linear or nonlinear dose-response relationship between postoperative cTn levels and adverse clinical outcomes. In addition, we will focus on the prognostic significance of subclinical or tiny myocardial injury below the URL for the first time[17]. The limitations, on the other hand, also exist in our analysis. First, the univariable or multivariable meta-regression and subgroup analyses are mainly based on aggregate patient data, not individual patient data. Other confounding factors may be underestimated. Second, we will focus on the effect of baseline cTn level in the analysis. However, the baseline cTn level is not a routine test for patients undergoing noncardiac surgery. Third, we cannot rule out the potential influence of different detection kits and methods used to measure the cTn levels in the included studies. Fourth, our analysis may not be sufficient for a diagnosis of myocardial infarction due to the lack of additional available evidence for myocardial ischemia (electrocardiography, echocardiography, coronary CT or angiography) required in the fourth UDMI. Last, elevated troponin has been observed in noncardiac situations such as pulmonary embolism or renal dysfunction and thus might not solely be a direct marker of cardiac problems.

ETHICS AND DISSEMINATION

Ethical approval is waived according to the Institutional Review Board /Independent Ethics Committee of Fuwai Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication and conference presentations.

Author Contributions CZ and TT contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by TA. TA and JG will independently search and select the eligible studies and extract the data from the included studies. YT and WK will assess methodological quality and

the risk of bias. All the authors approved the protocol publication.

Competing interests None declared.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Figure Legends

Figure 1. Flow Chart of the Trial Searching Process.

Table 1 Search strategy for PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science, China National Knowledge Infrastructure, Wanfang and VIP Database

Database	Search items
PubMed	
No.	
# 1	((((troponin) OR (troponins)) OR (TnI)) OR (TnT)) OR (myocardial injury)
# 2	(noncardiac surgery) OR (non-cardiac surgery)
# 3	# 1 and # 2
EMBase	
# 1	troponin OR troponins OR tni OR tnt OR (myocardial AND injury)
# 2	noncardiac AND surgery OR ('non cardiac' AND surgery)
# 3	# 1 and # 2
Cochrane Library	

# 1	troponin in All Text OR troponins in All Text OR TnI in All Text OR TnT in All Text OR myocardial injury in All Text
# 2	noncardiac surgery in All Text OR non-cardiac surgery in All Text
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	(troponin) OR TOPIC: (troponins) OR TOPIC: (TnI) OR TOPIC: (TnT) OR TOPIC: (myocardial injury) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 2	TOPIC: (noncardiac surgery) OR TOPIC: (non-cardiac surgery) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO.Search language=Auto
# 3	# 1 and # 2

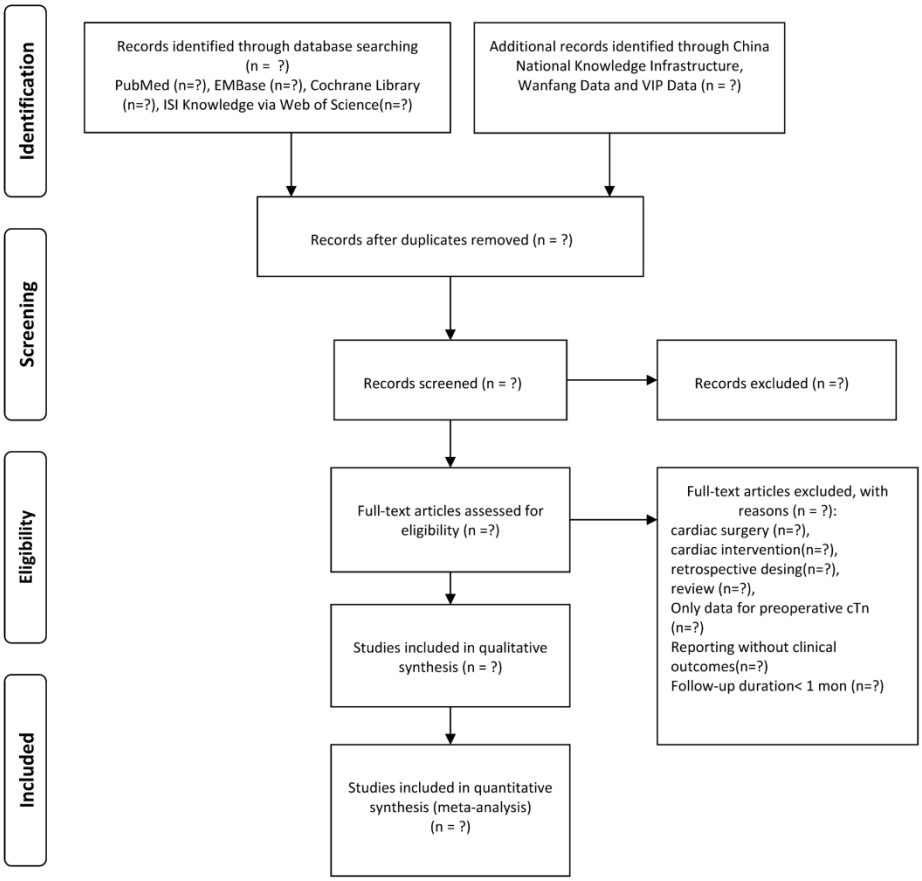

Figure 1. Flow Chart of the Trial Searching Process.

127x116mm (600 x 600 DPI)

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	10

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	11
Sponsor	#5b	Provide name for the review funder and / or sponsor	11
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	11
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	8
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	8
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
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 τ)	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)	8,9
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8,9

evidence