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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 has been recognised 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 secondary 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.

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Strengths and limitations of this study

- The potential linear or nonlinear dose–response relationship between postoperative cardiactroponin (cTn) levels and adverse clinical outcomes in adult noncardiac surgery will be explored.
- The prognostic significance of subclinical or tiny myocardial injury below the upper reference limit of cTn will be focused.
- This meta-analysis will pool the data from a number of studies to form the largest prospective data set to date.
- The baseline cTn level is not a routine test for patients undergoing noncardiac surgery.
- This work cannot 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 recognised as an important complication associated with short-term and long-term morbidity and mortality.[1] Some studies have shown that the incidence of MINS is as 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 ischaemia-related evidence in

the myocardium including that from ECG, echocardiography, coronary 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 hospitalisation.

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-term/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 guidelines.[18] We will search 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. 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 cTn levels and the incidence of major adverse clinical outcomes. No language restrictions 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 and (3) detection above

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

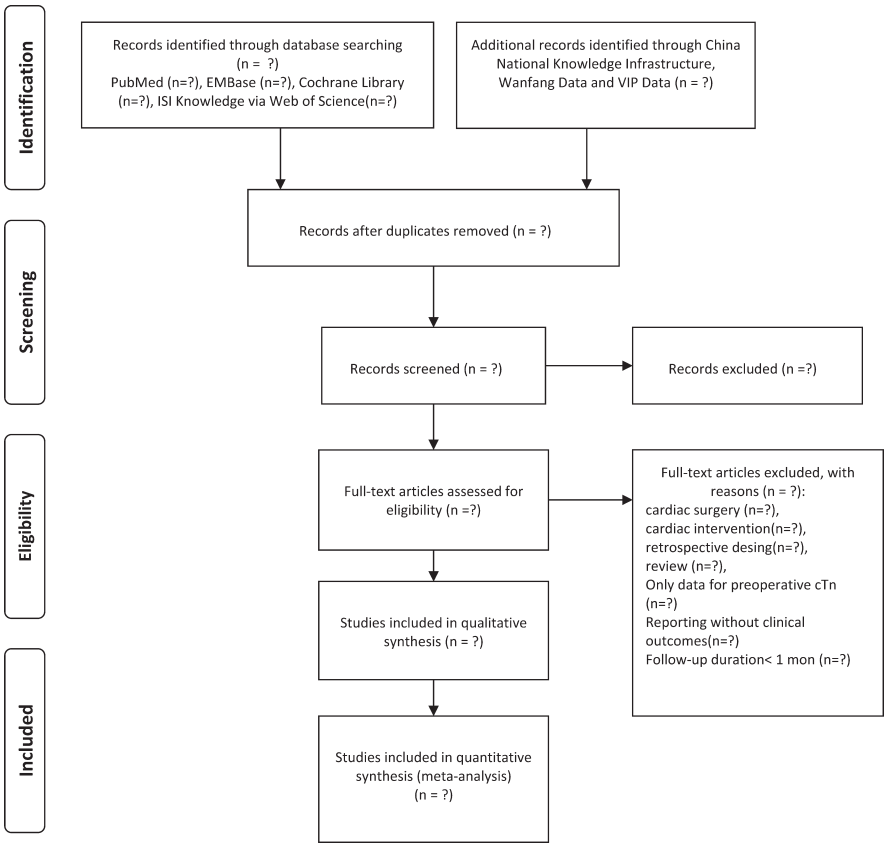

Figure 1 Flowchart of the trial searching process.

the URL. This definition based only on biomarkers of myocardial injury is not based on the UDMI[6] or Standardised Endpoints in Perioperative Medicine initiative[19] due to the lack of availability of additional information such as ECG, 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 revascularisation 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 outcomes and secondary outcomes will be included in the dose–response analysis.

Data extraction

The data will be extracted by two independent authors (TA and YT). 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, hyperlipidaemia 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 ischaemic accident, kidney dysfunction, history of lung disease, history of liver disease, elective surgery proportion, vascular surgery proportion, general anaesthesia, 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.[20]

Data synthesis

The ORs or HRs in each study will be extracted or calculated from patients categorised 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 vs nonhigh sensitive, cTnI vs cTnT, baseline cTn vs 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 versus 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] $p<0.05$ (two sided) will be considered statistically significant. All statistical analyses will be performed in Stata software (V.10.0, Stata, College Station, Texas) and RevMan software (V.5.0, Cochrane Collaboration, Oxford, UK).

DISCUSSION

Although there have been several meta-analyses concerning the prognostic effect of preoperative and/or postoperative troponin levels in adult noncardiac surgery, there are obvious pitfalls in these studies (including a large number of retrospective studies,[16] 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 ischaemia (ECG, echocardiography, coronary CT or angiography) required in the fourth UDMI. Finally, 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.

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Contributors 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.

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REFERENCES

1 Puelacher C, Lurati Buse G, Seeberger D, *et al*. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. *Circulation* 2018;137:1221–32.
2 Kavsak PA, Walsh M, Srinathan S, *et al*. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. *Clin Biochem* 2011;44:1021–4.
3 Hietala P, Strandberg M, Kiviniemi T, *et al*. Usefulness of troponin T to predict short-term and long-term mortality in patients after hip fracture. *Am J Cardiol* 2014;114:193–7.
4 Gillies MA, Shah ASV, Mullenheim J, *et al*. Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the optimise trial. *Br J Anaesth* 2015;115:227–33.
5 Liem VGB, Hoeks SE, Mol KHJM, Khjm M, *et al*. Postoperative hypotension after noncardiac surgery and the association with myocardial injury. *Anesthesiology* 2020;133:510–22.
6 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231–64.
7 Sousa J. Myocardial injury after non-cardiac surgery (MINS) in EVAR patients: a retrospective single-centre study. *J Cardiovasc Surg* 2020;62:130–5.
8 Gualandro DM, Campos CA, Calderaro D, *et al*. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. *Atherosclerosis* 2012;222:191–5.
9 Sheth T, Chan M, Butler C, *et al*. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. *BMJ* 2015;350:h1907.
10 Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. *Eur Heart J* 2020;41:3083–91.
11 Park J, Hyeon CW, Lee SH, *et al*. Mildly elevated cardiac troponin below the 99th-Percentile upper reference limit after noncardiac surgery. *Korean Circ J* 2020;50:925–37.
12 Millán-Figueroa A, López-Navarro JM, Pérez-Díaz I, *et al*. Evaluation of perioperative high-sensitive cardiac troponin I as a predictive biomarker of major adverse cardiovascular events after noncardiac surgery. *Rev Invest Clin* 2020;73. [Epub ahead of print: 07 May 2020].
13 Conti D, Ballo P, Ruggiano P, *et al*. Very early postoperative troponin increase and clinical outcome in patients admitted to the recovery room after noncardiac surgery with suspected cardiac events. *Indian Heart J* 2020;72:197–9.
14 Humble CAS, Huang S, Jammer I, *et al*. Prognostic performance of preoperative cardiac troponin and perioperative changes in cardiac troponin for the prediction of major adverse cardiac events and mortality in noncardiac surgery: a systematic review and meta-analysis. *PLoS One* 2019;14:e0215094.
15 Nagele P, Rao LK, Penta M, *et al*. Postoperative myocardial injury after major head and neck cancer surgery. *Head Neck* 2011;33:1085–91.
16 Levy M, Heels-Ansdell D, Hiralal R, *et al*. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology* 2011;114:796–806.
17 Cho SW. Subclinical and tiny myocardial injury within upper reference limit of cardiac troponin should not be ignored after noncardiac surgery. *Korean Circ J* 2020;50:938–9.
18 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
19 Beattie WS, Lalu M, Bocock M, *et al*. Systematic review and consensus definitions for the standardized endpoints in perioperative medicine (step) initiative: cardiovascular outcomes. *Br J Anaesth* 2021;126:56–66.
20 Murad MH, Sultan S, Haffar S, *et al*. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60–3.
21 Williamson PR, Smith CT, Hutton JL, *et al*. Aggregate data meta-analysis with time-to-event outcomes. *Stat Med* 2002;21:3337–51.
22 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
23 Berlin JA, Longnecker MP, Greenland S. Meta-Analysis of epidemiologic dose-response data. *Epidemiology* 1993;4:218–28.
24 Shen J-T, Xu M, Wu Y, *et al*. Association of pre-operative troponin levels with major adverse cardiac events and mortality after noncardiac surgery: a systematic review and meta-analysis. *Eur J Anaesthesiol* 2018;35:815–24.
25 Zhang L-J, Li N, Li Y, *et al*. Cardiac biomarkers predicting mace in patients undergoing noncardiac surgery: a meta-analysis. *Front Physiol* 2018;9:9.