PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optimal Cutoff Value of Elevated Cardiac Troponin Concentrations for Myocardial Injury Predicts Clinical Outcomes in Adult Patients with COVID-19: A Dose-response Analysis Protocol for Systematic Review
AUTHORS	Zhou, Chenghui; Pei, Hanjun; Gao, Yiming; Zhang, Yulin; Cao, Liang; Fang, Zhongrong; Song, Jiangping

VERSION 1 – REVIEW

REVIEWER	John Pickering University of Otago, Christchurch New Zealand
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	This manuscript suggests a protocol to address a perceived concern about how to interpret troponin concentrations in patients with COVID-19. Unfortunately, the manuscript fails to adequately describe what exactly is being meta-analysed and how a desired "optimal" cutoff of cTn will be derived. In the introduction it is stated "the optimal cutoff value of cTn level for AMI with prognostic relevance needs to be identified... ." What is meant by "optimal"? Is this something to do with sensitivity or specificity for a particular outcome or a cutoff that would trigger a beneficial intervention or something else? P6 "We believe this protocol ...." I fail to see the value of stating a "belief" – don't all authors of all papers hope that others will be inspired to focus more on the topic of their paper? If the authors, as they say in the discussion, want to "make an appeal" then a simple letter to an appropriate journal would do that. I suggest removing this sentence (and elsewhere in the manuscript where it referenced). P6 it is unclear what "different categories (>2) of cTn levels" means. P7 talks of "different cardiac troponin levels (>2)" which is a different wording, but I suspect is meant to be the same thing. I think what is being talked about is where outcomes have been reported for 3 or troponin groupings. It appears to me that this meta-analysis will attempt to meta-analyse troponin studies with different assays. This needs some very robust justification because the various troponin assays in use do not all measure the same thing, nor are they necessarily well correlated across their whole range of concentrations. I fail to see how studies using different assays can be meta-analysed together. Furthermore, any cutoff for a troponin will necessarily be assay specific.

	A definition of MACE that includes non-cardiac events of “acute renal failure” or PE is unusual. This is not really MACE. Also, the common term now is Acute Kidney Injury (AKI) rather than acute renal failure. Minor Please use cTn “concentrations” not “levels” (because we don’t measure levels of troponin, we measure its concentration). I think the authors may need to use “multivariable” (many variables) instead of multivariate (“many outcomes”). There are several grammar errors. Finally, I am a little concerned that there may be insufficient published papers with the required data for a meta-analysis. There have been a lot of pre-prints published that have yet to complete peer review and be published in journals. I would not recommend including them in the main meta-analysis, but it may be valuable to search for them as a secondary analysis.

REVIEWER	Ajay Kumar Mishra Saint Vincent Hospital, Worcester, MA, USA
REVIEW RETURNED	03-Dec-2020

GENERAL COMMENTS	Abstract: None Article: Authors aim to study the cutoff value of troponin level for myocardial injury in patients with COVID 19. I congratulate them for their hypothesis and wish them the best. I have the following suggestions. 1. Kindly remove AMI which can imply acute myocardial infarction. As authors are implying myocardial injury not the former. 2. Kindly include acute and chronic kidney dysfunction separately if possible as they can have different implications on the result 3. A significant proportion of sick COVID patients get embolic complications, please include pulmonary embolism and DVT if possible 4. Try to include the pattern, duration, number of total testing in appendix 5. Please note that myocardial injury is both diagnostic and prognostic of severe COVID 19 based on the level of multiple cardiac markers. Consider looking for other soft outcomes like worsening ejection fraction, need for mechanical ventilation, multiple organ involvement if available 6. There has been a significant amount of work on this from the west. Kindly refer and include these on your citation. PMID: 33169595, PMID: 32315733, PMID: 32306491, PMID: 32640385, PMID: 32169400, PMID: 32427432

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

Major

1 This manuscript suggests a protocol to address a perceived concern about how to interpret troponin concentrations in patients with COVID-19. Unfortunately, the manuscript fails to adequately describe what exactly is being meta-analysed and how a desired “optimal” cutoff of cTn will be derived.
Re: Thank you for your concerns. We will conduct a linear or non-linear dose–response meta-analysis based on the different cTn groups with according clinical adverse outcomes. This is a protocol for the future analysis based on adequate publications. The method of this analysis has been successfully used in our previous work [EuroIntervention.2020 Mar 20;15(16):1444-1450.].

2 In the introduction it is stated “the optimal cutoff value of cTn level for AMI with prognostic relevance needs to be identified... .” What is meant by “optimal”? Is this something to do with sensitivity or specificity for a particular outcome or a cutoff that would trigger a beneficial intervention or something else?
Re: Sorry for the unclear statement. The “optimal” cutoff value of cTn level for COVID-19 related acute myocardial injury is a threshold that would trigger a promptly beneficial intervention. We have revised the statement as follows: “Accordingly, the optimal cutoff value of cTn level for acute myocardial injury with prognostic relevance needs to be identified to trigger a promptly beneficial intervention in the very near future.”

3 P6 “We believe this protocol ....” I fail to see the value of stating a “belief” – don’t all authors of all papers hope that others will be inspired to focus more on the topic of their paper? If the authors, as they say in the discussion, want to “make an appeal” then a simple letter to an appropriate journal would do that. I suggest removing this sentence (and elsewhere in the manuscript where it referenced).
Re: Sorry for the inappropriate statement. We have deleted this sentence and other related ones.

4 P6 it is unclear what “different categories (>2) of cTn levels” means. P7 talks of “different cardiac troponin levels (>2)” which is a different wording, but I suspect is meant to be the same thing. I think what is being talked about is where outcomes have been reported for 3 or troponin groupings.
Re: Sorry for the inaccurate expression. These two expressions are meant to be the same thing. We have corrected it as “different cTn categories (3 or more)” and other related ones.

5 It appears to me that this meta-analysis will attempt to meta-analyse troponin studies with different assays. This needs some very robust justification because the various troponin assays in use do not all measure the same thing, nor are they necessarily well correlated across their whole range of concentrations. I fail to see how studies using different assays can be meta-analysed together. Furthermore, any cutoff for a troponin will necessarily be assay specific.
Re: Thank you for the constructive advice. This is a very important issue as we stated in the Data synthesis. Indeed, different assays of cTns have different cutoff value. We will convert the numerical value of each category of elevated cTn level as the related number of times the corresponding URL of each assay in each study. The URL is a widely used unit in each version of Universal Definition of Myocardial Infarction Task force[J Am Coll Cardiol 2018; 72: 2231-64.]. This method has been used in previous meta-analysis[JAMA . 2011 Feb 9;305(6):585-91.] as well as our recent work[EuroIntervention . 2020 Mar 20;15(16):1444-1450.].In addition, we will perform a meta

regression and subgroup analysis of different assays. Therefore, according to your concerns, we have added the two references and the missing information in the Section of Data synthesis. “Univariate or multivariate 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 types18” and “For study only providing the numerical value of each category of elevated cTn concentrations, 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 concentration, the mean concentration will be estimated to be 1.2x the lower concentrations19-21”.

6 A definition of MACE that includes non-cardiac events of “acute renal failure” or PE is unusual. This is not really MACE. Also, the common term now is Acute Kidney Injury (AKI) rather than acute renal failure.
Re: Sorry for the inappropriate expressions. We have corrected the MACE as MAE for the abbreviation of “major adverse event”. Additionally, the expression of “acute renal failure” has been revised as acute kidney injury.

Minor

1. Please use cTn “concentrations” not “levels” (because we don’t measure levels of troponin, we measure its concentration).
Re: Thank you for the suggestion. We have replaced all the related ones.

2. I think the authors may need to use “multivariable” (many variables) instead of multivariate (“many outcomes”).
Re: Thank you for the suggestion. We have corrected it.

3. There are several grammar errors.
Re: Thank you for the suggestion. We have corrected it.

4. Finally, I am a little concerned that there may be insufficient published papers with the required data for a meta-analysis. There have been a lot of pre-prints published that have yet to complete peer review and be published in journals. I would not recommend including them in the main meta-analysis, but it may be valuable to search for them as a secondary analysis.
Re: Thank you for your concerns. We have stated this as a limitation: “ 5.The sample size in each study and the number of included studies may be relative small.”, and set the cut-off time as October, 2021. In addition, we have updated the search database in the Section of Search Strategy as follows:” PubMed, EMBase, Cochrane Library, ISI Knowledge via Web of Science database, as well as pre-print databases (medxriv and bioxriv) (from inception until October, 2021) will be systematically searched”. In addition, we have updated the related search in the Table 1.

Special thanks for your constructive advices.

Reviewer: 2

1. Kindly remove AMI which can imply acute myocardial infarction. As authors are implying myocardial injury not the former.
Re: Thank you for the suggestion. We have corrected it.

2. Kindly include acute and chronic kidney dysfunction separately if possible as they can have different implications on the result

Re: Thank you for the suggestion. We have revised it.

3. A significant proportion of sick COVID patients get embolic complications, please include pulmonary embolism and DVT if possible
Re: Thank you for the suggestion. We have already included pulmonary embolism as the complications. We have also added the DVT at this time.

4. Try to include the pattern, duration, number of total testing in appendix
Re: Thank you for the suggestion. This is a protocol for future meta-analysis. We will add the pattern, duration, number of total testing in the future analysis. We have added your advice in the section of Data Extraction.

5. Please note that myocardial injury is both diagnostic and prognostic of severe COVID 19 based on the level of multiple cardiac markers. Consider looking for other soft outcomes like worsening ejection fraction, need for mechanical ventilation, multiple organ involvement if available
Re: Thank you for the suggestion. We have added other soft outcomes such as heart failure, need for mechanical ventilation, and multiple organ dysfunction syndromes in the Section of Type of Outcomes as follows: “Additional outcomes will include the incidence of heart failure, need and duration for mechanical ventilation, and incidence of multiple organ dysfunction syndromes.”.

6. There has been a significant amount of work on this from the west. Kindly refer and include these on your citation. PMID: 33169595, PMID: 32315733, PMID: 32306491, PMID: 32640385, PMID: 32169400, PMID: 32427432
Re: Thank you for your carefulness and providing several well-design, reliable and informative citations. We have added these publications in the revision.

Thank you for your comments and suggestions.

We tried our best to improve the manuscript and made some corrections in the manuscript according to the Editorial and Reviewers’ comments. These changes will not affect the content and framework of the paper. We did not list the minor changes in the response letter. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the corrections will meet with approval.
Once again, thank you very much for your comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Ajay Mishra St Vincent Hospital, MA, USA
REVIEW RETURNED	15-Dec-2020

GENERAL COMMENTS	Authors have incorporated all the modifications suggested. I have no further recommendations.