Dear Editor-in-Chief

World Journal of Meta-Analysis

On behalf of my coauthors, I would like to thank you for the accurate review and precious comments on our work. We really appreciate all of the efforts and time which were put into this. We carefully read your comments and tried to address your comments. A point-by-point response letter, a reference to revisions, and answers to the comments are included below. We used Track Changes to mark all new changes in the revised version of the manuscript.

Comment	Reply and action
Reviewer #1:	The authors would like to thanks the honorable reviewer for the precise review of the manuscript and this comment.
1) This article provides an in-depth analysis of the effectiveness and feasibility of troponin I as a biomarker in predicting the mortality and poor prognosis of Covid-19. But there are too many such articles, and the originality and innovation are not enough.	This paper has completed an updated systematic review and meta-analysis on a contextual topic important for clinical practice given current circumstances, which have not been formally published as a review article type, though there are previous publications that discuss Cardiac Trop I as a prognostic indicator in patients with COVID-19.
Reviewer #2:	The authors would like to thanks the honorable reviewer for the insightful and constructive comments.
1) I think that the main issue on the prognostic value of Troponin-I in COVID is whether this test is an independent variable in prognostication, as outlined by the authors in the discussion when they describe the quadrilateral mediator loop of Troponin. I am not sure if any multivariate analysis have been performed in these studies to assess if Tropo-I is really an independent and better prognostic marker than D-Dimer levels, right ventricular strain, CRP levels and so on. Neither I am sure if the multivariate analysis contained in the studies can be included in a formal meta-analysis, but It could be helpful for non-experts in meta-analysis to touch on this point in the discussion.	Although Troponin-I is elevated in acute coronary syndrome, the etiology of increased Troponin-I is multifactorial. In patients with Covid-19, this elevation is related to the inflammatory response to disease. Though inflammatory cascade activation may lead to myocardial infarction, Singh et al. found that less than 1% of the study patients with elevated Troponin-I had clinical evidence of acute coronary syndrome. In the studies that were included in our study, the baseline characteristic and initial clinical data of the patients were included as a variable in univariate analysis. Any significant variable was entered into multivariate analysis. Troponin-I can be used as a valuable factor to predict disease sequels including ARDS, kidney injury, and need for ICU admission. regardless of the history of myocardial injuries or the presence of cardiovascular risk profile, the value of Troponin-I should be accurately assessed on admission because of its high predicting value for COVID-19 related mortality and morbidity

2)	Only Baseline Troponin-I at hospital admission was considered in the various studies. Is there any study taking into account the difference in Troponin- levels between hospital admission and subsequent time points (Delta Troponin-I)?	To the best of our knowledge before writing this article, there was no article discussing about delta Troponin and Covid19. Though, in a recent study by Ronaldo Go et al, published on 2021 May 3, in journal of American College of Cardiology, entitled "INITIAL, MAXIMUM, AND DELTA TROPONIN AND MORTALITY IN COVID-19", 586 COVID-19 patients with troponin values were reviewed. They concluded that maximum troponin and change in troponin, but not initial troponin, were predictive of mortality, suggesting the value of serial troponins
3)	Abstract lines 14-18: better to describe HR with 95% C.I. rather than with p values -	It is amended in the abstract part.
4)	Abstract: lines 16-18 The sentence "The pooled analysis led to point significantly higher concentration of this marker between the two survived and non-survived groups" is twisted. It should be better said.	The pooled analysis showed significantly higher concentration of this marker in the survived group compared to non-survived group
5)	Introduction: line 5. It is clear that accurate and early diagnosis may prevent COVID diffusion, but it is counter-intuitive that assessment of severity can do the same, since patients with no or few symptoms are the main route of transmission.	Accurate and early diagnosis, in addition to preventing the spread of the disease, can also prevent the disease from becoming more severe. Disease severity can lead to irreparable damage or even death. Therefore, early diagnose of the disease is important, because we can prevent the disease severity and possible complications or mortality following it.
6)	Introduction: lines 22 and following. Please quote the recent CDC document on medical conditions associated with high risk for severe COVID. It contains a thorough description of the various HR of comorbidities for severe disease (March 20. 2021: https://cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)	It is amended in the Introduction part.
7)	Methods: the authors tried to collect studies in any language through an explicit English translation, but de-facto all 5 non-English studies were excluded (Fig.1 Flow chart). Better said that non English studies were excluded from the meta-analysis.	Non English studies were excluded from the meta-analysis.
8)	The English text needs some revision since it contains some slips and misspellings	The whole text was revised and the misspelling or slips were amended in it.

Reviewer #3:	The authors would like to thanks the honorable reviewer for the precise review of the manuscript and this comment.
This is a paper which completed an updated systematic review and meta-analysis on a contextual topic important for clinical practice given current circumstances, which have not been formally published as a review article type - though there are previous publications in Letter to the Editor Format e.g. Lippi et al, 2020 Prog Cardiovasc Dis completed a meta-analysis re Cardiac Trop I as a prognostic indicator in patients with COVID-19. That said, the general methodology on how the authors completed their search is robust and clearly described. The completion of meta-analysis has also been clear, and addresses the pitfalls in their collated data i.e. bias and heterogeneity etc., which was generally consistent with previous published findings on this topic.	
1) Language - there are some phrases throughout the paper which appear awkward and grammatically erroneous, please review.	The whole text was revised and the misspelling or slips were amended in it.
2) Please acknowledge previous meta-analysis completed on this topic from Lippi et al. 2020, Prog Cardiovasc Dis and Vrsalovic et al. 2020, J Infect in the discussion and reference	This meta-analysis is discussed and acknowledged in discussion part.
3) Please describe search terms used in completing the systematic search in the methods section.	The main keywords were 'covid-19' OR 'sars-cov-2' OR '2019-ncov' AND 'troponin' AND 'mortality' OR 'death'
Reviewer #4:	The authors would like to thanks the honorable reviewer for the insightful and constructive comments.
1) Explain about study eligibility criteria Please explain about the study interval What is the reason for the high heterogeneity? Justify it if possible Discuss limitations at study and outcome level	all prospective and retrospective comparative studies that evaluated the link between the serum level of Troponin-I and two COVID-19 related parameters including disease severity and mortality were considered to be eligible for primary assessment. heterogeneity can be explained by first the difference insignificant divergent in the cutoff points defined for Troponin-I raising, also by the difference in the baseline characteristics of study populations especially with respect to the presence of

	cardiovascular risk profiles, the sample size of the studies, the time for patients' following–up, as well as the techniques for measuring Troponin-I concentration. One of our study limitation was that we could not obtain some articles full-text despite trying to contact the correspondence author of the article. And also, some articles were non-English articles that we exclude them from our study.
LANGUAGE QUALITY	The authors would like to thanks for the insightful and constructive comments.
1) Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.	The whole text was revised and the misspelling or slips were amended in it.
(1) *Science editor*	The authors would like to thanks for the insightful and constructive comments.
1) The "Author Contributions" section is missing. Please provide the author contributions	The "Author Contributions" section is added after the text before the references.
2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;	It is amended in the reference part.
3) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.	The "Article Highlights" section is added at the end of the main text before the reference part.
(3) *Company editor-in-chief:*	The authors would like to thanks for the insightful and constructive comments.
1) The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).	The title is changed to: Troponin I biomarker as a strong prognostic

	factor for predicting mortality of Covid-19: A systematic review and meta-analysis