PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence, Risk factors, and Prognostic Effect of Imaging Right Ventricular Involvement in Patients with COVID-19: a Dose-response Analysis Protocol for Systematic Review
AUTHORS	Zhou, Chenghui; Lou, Baohui; Li, Hui; Wang, Xin; Ao, Hushan; Duan, Fujian

VERSION 1 – REVIEW

REVIEWER	Pastore, Maria University of Siena
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	The Authors aim to conduct a meta-analysis on the current available studies on right ventricular involvement in patients with COVID-19, its prognostic value, and a special focus on the imaging methods to detect RV damage. This could be an useful attempt to highlight the evaluation of RV in COVID19 patients, which could have important prognostic implications. Since timely evidence is needed on this topic, and the study protocol is overall well written, I think that it could be considered publication, after undergoing these revisions: -The term “risk factors” for cardiac imaging is ambiguous. I suggest changing or clarifying it. -Please define if you will measure either global or free-wall right ventricular longitudinal strain, or both. -Will acute pulmonary embolism be registered? It is a possible COVID19 complication which strongly affects right ventricular function, therefore it should not be overlooked. -Among medications, will sacubitril/valsartan and diuretics be registered? Please include them -For the statistical analysis methods, there were past and future tenses alternatively used, both in the abstract and in the main text. Please revise -Discussion I suggest expanding the discussion with further description on the rationale for this meta-analysis, for example, discussing the importance of cardiac imaging in COVID-19 patients, with a focus on its optimal indication [PMID: 32242891, PMID: 32654210, PMID: 32762885] and specifying the reasons for their choice to study echocardiographic parameters as secondary outcome. -Page 7 line 7 : “the” was written two times -The paper needs undergoing further English proofreading

REVIEWER	Bertini, Pietro

	Azienda Ospedaliero Universitaria Pisana
REVIEW RETURNED	14-Mar-2021

GENERAL COMMENTS	Please, clearly state the difference between right ventricular enlargement, right ventricular failure and the means to assess it. Also, a comprehensive review should investigate the role of pulmonary hypertensio

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
-The term “risk factors” for cardiac imaging is ambiguous. I suggest changing or clarifying it.
Re: Thank you for the advice. The risk factors are only for the incidence of right ventricular dilation and/or dysfunction assessed by cardiac imaging including echocardiography, CT or MRI. We have updated the related statements.

-Please define if you will measure either global or free-wall right ventricular longitudinal strain, or both.
Re: Sorry for the missing information. Both the two strains will be analyzed, and we have corrected the related content in the whole manuscript accordingly.

-Will acute pulmonary embolism be registered? It is a possible COVID19 complication which strongly affects right ventricular function; therefore it should not be overlooked.
Re: Sorry for the missing information. The acute pulmonary embolism will be also extracted as the patient demographic data, and included in the risk factor analyses, subgroup and meta-regression analyses.

-Among medications, will sacubitril/valsartan and diuretics be registered? Please include them
Re: Sorry for the missing information. The sacubitril/valsartan and diuretics will be also extracted as the patient demographic data, and included in the risk factor analyses, subgroup and meta-regression analyses.

-For the statistical analysis methods, there were past and future tenses alternatively used, both in the abstract and in the main text. Please revise
Re: Sorry for the inappropriate expressions. We have revised these contents accordingly.

-Discussion
I suggest expanding the discussion with further description on the rationale for this meta-analysis, for example, discussing the importance of cardiac imaging in COVID-19 patients, with a focus on its optimal indication [PMID: 32242891, PMID: 32654210, PMID: 32762885] and specifying the reasons for their choice to study echocardiographic parameters as secondary outcome.
Re: Thank you for your constructive advice. We have added the related content in the Discussion section. “The imaging tools for RV structure and function assessment includes echocardiography, CT, and CMR in a direct way with more information than other indirect methods (such as electrocardiography, X-ray, or central venous pressure), Although CT and CMR possess some unique advantages, 2D with 3D echocardiography could also provide noninvasive, convenience, fast, and comprehensive RV assessment with low cost for subsequent therapeutic treatment guidance25, In addition, point-of-care evaluation using echocardiography is quite meaningful for critical patients with COVID-19 infection in intensive care unit. Specifically, echocardiographic evaluation for patients with COVID-19 could reduce the time of transportation and thereby the cross-over contamination in hospital. In this study, TAPSE, FAC, RV-GLS, RV-FWLS. and RV diameter will be chose as the second outcomes. These echocardiographic parameters are regular and useful for RV structural and

function assessment, and have been recommended in recent guideline for patients with COVID-1926-28."

-Page 7 line 7 : "the" was written two times
Re: Thank you for the wrong writing. We have corrected it.

-The paper needs undergoing further English proofreading
Re: Thank you for the advice. We have asked for and completed a professional copyediting service via BMJOPEN submission system (AJE).
Special thanks for your constructive advices.

Reviewer: 2
Please, clearly state the difference between right ventricular enlargement, right ventricular failure and the means to assess it. Also, a comprehensive review should investigate the role of pulmonary hypertension
Re: Thank you for your constructive advice. We have clearly stated the definitions and assessing means of right ventricular enlargement and failure in the Types of Outcomes Section" The primary outcome will be the incidence of RV involvement (dysfunction and/or dilation) assessed by echocardiography, CT, or MRI. The definition criteria of RV dysfunction will be as follows; ① fractional area change (FAC) < 35%, tricuspid annular plane systolic excursion (TAPSE) < 17 mm, and/or S' <10 mm/seg; ② 3D-(RV ejection fraction) RVEF< 45%; ③ RV free wall longitudinal strain (RV-FWLS)>-20%. The definition criteria of RV dilation will be as follows; ① RV to left ventricular (LV) basal diameter classified as mild (0.67–0.9), moderate (1.0), and severe (>1.0) enlargement; ② RV basal diameter > 41 mm.". The role of pulmonary hypertension will be also extracted as the patient demographic data, and included in the risk factor analyses, subgroup and meta-regression analyses. 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	Pastore, Maria University of Siena
REVIEW RETURNED	05-Apr-2021

GENERAL COMMENTS	I have no further comments.

REVIEWER	Bertini, Pietro Azienda Ospedaliero Universitaria Pisana
REVIEW RETURNED	17-Apr-2021

GENERAL COMMENTS	I am satisfied with the revision, thank you.