PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical, laboratory, and imaging predictors for critical illness and mortality in patients with coronavirus disease 2019: protocol for a systematic review and meta-analysis
AUTHORS	Lai, Xinxing; Liu, Jian; Zhang, Tianyi; Feng, Luda; Jiang, Ping; Kang, Ligaoge; Liu, Qiang; Gao, Ying

VERSION 1 – REVIEW

REVIEWER	Ye Yuan Huazhong University of Science and Technology
REVIEW RETURNED	23-May-2020

GENERAL COMMENTS	This paper provides a good review for prognostic factors for COVID-19 patients. Prognostic factors and models may assist front-line clinicians in rapid identification of high-risk patients, early management of modifiable factors, appropriate triaging, and optimizing use of the limited healthcare resources. We aim to systematically assess the clinical, laboratory, and imaging predictors, as well as prediction model. The paper is timely and well-written. However, as there has been a surge of interests in this topic and some of the state-of-the-art methods were not included in this study, for example, Yan et. al., Nature Machine Intelligence, 2020.

REVIEWER	yi yang southeast university China
REVIEW RETURNED	29-Jun-2020

GENERAL COMMENTS	The authors want to perform a systemic review and meta-analysis to determine the risk factors of critically ill and mortality in patients with COVID-19. Numerous of studies have been reported the risk factors of severity and mortality of COVID-19. The risk factors seems clear. It is not very interesting to do this at current situation. 1. There was no new special methods in this protocol. 2. The aim of this study was not very clear. The risk factor of critically ill may be far different from that of mortality. Only determine some risk factors are not enough to predict the mortality 3. What's new can we get from this study. There are two meta-analysis discuss this question, why the authors want to repeat the work.

REVIEWER	Hai Hu West China Hospital of Sichuan University, PR China
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	This study is valuable for responce to the COVID-19 pandemic. But I think some improvment need to be done to strengthen the study.
	Page3 Line 56: I suggest the authors update the number of confirmed cases and deaths worldwide.
	Page4 Line 6:The authors mentioned "most patients with COVID-19 exhibit asymptomatic, mild, or moderate symptoms", so I suggest the authors explain the reason of the overwhelming number of patients who required hospital admission.
	Page4 Line 9: The authors need to show the criteria of severe or critically illness.
	Page7 Line 12: I suggest that the authors clarify the accepted criteria of COVID-19. In your research, are the diagnostic criteria of the included literatures from different periods and different regions consistent?
	Page7 Line 46: What is the "accepted criteria" of COVID related deterioration, progression, severe and critical illness

REVIEWER	Weikuan Gu UTHSC
REVIEW RETURNED	11-Aug-2020

GENERAL COMMENTS	In the section of exposures, please explain at least some of features or items of clinical, laboratory, and imaging predictors will be included. There is too little information on this section to the readers. In the section of Comparators, please explain in a more detail what sources of participants with and without specific information of COVID-19. You need to indicate the time of the start of the protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Ye Yuan
Institution and Country: Huazhong University of Science and Technology
Competing interests: None
Comments: This paper provides a good review for prognostic factors for COVID-19 patients. Prognostic factors and models may assist front-line clinicians in rapid identification of high-risk patients, early management of modifiable factors, appropriate triaging, and optimizing use of the limited healthcare resources. We aim to systematically assess the clinical, laboratory, and imaging predictors, as well as prediction model.
The paper is timely and well-written. However, as there has been a surge of interests in this topic and some of the state-of-the-art methods were not included in this study, for example, Yan et. al., Nature Machine Intelligence, 2020.
Response: First of all, we appreciate your positive comments and considering our manuscript as a timely and good review for COVID-19. We completely agree with you that there are an increasing number of great articles emerging with the worldwide pandemic of COVID-19. Based on your

suggestion, many high-quality papers have been identified when we updated our search and screening for eligible articles.

Reviewer: 2

Reviewer Name: yi yang

Institution and Country: southeast university China

Competing interests: No competing interests.

Comments: The authors want to perform a systemic review and meta-analysis to determine the risk factors of critically ill and mortality in patients with COVID-19. Numerous of studies have been reported the risk factors of severity and mortality of COVID-19. The risk factors seem clear. It is not very interesting to do this at current situation.

1. There was no new special methods in this protocol.

Response: Thanks for your comments. We did not aim to develop a new method to perform this systematic review. So well-acknowledged methods such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS-PF) checklist, and the Quality in prognosis Studies (QUIPS) tool, were used in this review.

Comments: 2. The aim of this study was not very clear. The risk factor of critically ill may be far different from that of mortality. Only determine some risk factors are not enough to predict the mortality.

Response: We agree with you that the risk factors of critically ill may be far different from that of mortality. Based on your suggestion, we have revised the research aims section (page 6) as "We aim to systematically assess the clinical, laboratory, and imaging predictors as well as models for severe or critical illness and mortality in patients with COVID-19. Predictors and models for critical illness may be different from that of mrtality, so it will be assessed according to different outcomes."

What's more, in the data synthesis section (page 11), we have added sentences as following "For severe or critical illness and mortality, the data will be synthesised according to different outcomes." Furthermore, we also agree with you that only determine some risk factors are not enough to predict the mortality. So we mentioned in the exposures section (page 8), interventions will be considered as potential predictors for critically illness or mortality, such as mechanical ventilation, Dexamethasone, or other interventions.

Comments: 3. What's new can we get from this study. There are two meta-analysis discuss this question, why the authors want to repeat the work.

Response: As we mentioned in the status of current literature section, two rapid systematic reviews focused on prognostic factors or models of COVID-19 had been published. However, these reviews focused on some specific perspectives and did not provided clinicians and researchers with an overview on this topic. For instance, Henry and colleagues published a systematic review which included only laboratory biomarkers, while excluded clinical and imaging predictor associated with severe illness and mortality in COVID-19 [1]. Wynants and colleagues only focused on prediction models for diagnosis and prognosis of COVID-19 infection. Moreover, there are a huge number of articles emerging recently with the worldwide pandemic. Many valuable articles on prognostic factors or models of COVID-19 were not included in these published reviews. Among them, some high-quality papers have been published on top journals [3-5], which provided us with more evidences and gave insights into this topic. Therefore, there is an urgent need for a systematic review to evaluate and synthesis the current studies from a comprehensive perspective. We have revised the sentences and added references in the status of current literature to make it more clear for the importance of this review. (page 5,6)

Reference:

[1] Henry BM, de Oliveira M, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020.

[2] Wynants L, Van Calster B, Bonten M, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ 2020;369:m1328.

[3] Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. 2020;180(8):1-9.

[4] Zhang K, Liu X, Shen J, et al. Clinically Applicable AI System for Accurate Diagnosis, Quantitative Measurements, and Prognosis of COVID-19 Pneumonia Using Computed Tomography. Cell. 2020;181(6):1423-1433.e11.

[5] Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020;31(6):1068-1077.e3.

Reviewer: 3

Reviewer Name: Hai Hu

Institution and Country: West China Hospital of Sichuan University, PR China

Competing interests: None declared

Comments: This study is valuable for response to the COVID-19 pandemic. But I think some improvement need to be done to strengthen the study.

Page3 Line 56: I suggest the authors update the number of confirmed cases and deaths worldwide.

Response: Thanks for your positive comments and valuable suggestion. We have updated the number of confirmed cases and deaths worldwide as "The infection has recently spread to at least 188 countries and regions, with more than 25 million confirmed cases and 850,000 deaths worldwide as of September 1, 2020."

Comments: Page 4 Line 6: The authors mentioned "most patients with COVID-19 exhibit asymptomatic, mild, or moderate symptoms", so I suggest the authors explain the reason of the overwhelming number of patients who required hospital admission.

Response: Thanks for your suggestion. We have mentioned the reason of the overwhelming number of patients who required hospital admission (page 4). Furthermore, sentences have been added in this section as "Patients who exhibited severe or critical symptoms or patients at high risk to develop severe conditions were the main reason behind the overwhelming number of patients who required admission or even intensive care." (page 5)

Comments: Page 4 Line 9: The authors need to show the criteria of severe or critically illness.

Response: We have revised the sentence as "Despite a variety of rapid public health responses aimed at containing the disease, many countries have been confronted with enormous challenges to the healthcare systems posed by the overwhelming number of patients requiring hospital admission, especially by those with progression to severe or critical illness according to the criteria in the WHO recommendations or the local guidelines." (Description of the condition section, page 4)

Comments: Page7 Line 12: I suggest that the authors clarify the accepted criteria of COVID-19. In your research, are the diagnostic criteria of the included literatures from different periods and different regions consistent?

Page7 Line 46: What is the "accepted criteria" of COVID related deterioration, progression, severe and critical illness

Response: We have revised the participants section (page 8) as "All patients with confirmed diagnosis of COVID-19, explicitly classified as mild, moderate, severe, or critically ill according to accepted diagnostic criteria such as the WHO recommendations or the local guidelines, will be included. The criteria in the guidelines may be modified over time. Thus, the criteria in different periods or regions will be acceptable."

Reviewer: 4

Reviewer Name: Weikuan Gu

Institution and Country: UTHSC

Competing interests: None declared

Comments: In the section of exposures, please explain at least some of features or items of clinical, laboratory, and imaging predictors will be included. There is too little information on this section to the readers.

Response: Thanks for your valuable suggestion, we have added some features in this section and revised as following: Any data related to demographics, symptoms and signs, pulmonary functions,

laboratory tests, radiological findings, comorbidities, and interventions will be considered potential predictors for critical illness or mortality in patients with COVID-19. This information may include factors such as the age, fever, shortness of breath, underlying diseases, mechanical ventilation, and dexamethasone or other interventions.

Comments: In the section of Comparators, please explain in a more detail what sources of participants with and without specific information of COVID-19.

Response: We have added more details in the comparators section as "Based on the published studies, many factors including older age; underlying diseases such as hypertension, diabetes, and cardiovascular diseases; and chest radiographic abnormalities were independent predictive factors for critical illness in hospitalised patients with COVID-19. [1, 2] Those potential variables will be considered the comparators." (page 8, 9)

Comments: You need to indicate the time of the start of the protocol.

Response: We started the protocol in early April and registered with PROSPERO on April 15, 2020. (CRD 42020178798)

References:

[1] Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. 2020;180(8):1-9.

[2] Zhu L, She ZG, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020;31(6):1068-1077.e3.

VERSION 2 – REVIEW

REVIEWER	Weikuan Gu UTHSC
REVIEW RETURNED	25-Sep-2020

GENERAL COMMENTS	Best wishes to the successful conducting this protocol.