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Clinical, laboratory, and imaging predictors for critically illness and mortality in patients with coronavirus disease 2019 (COVID-19): protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: With the threat of a worldwide pandemic of COVID-19, it is important to identify the prognostic factors of critical conditions among patients with non-critical COVID-19 initially. 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 models for severe or critically illness and mortality in patients with COVID-19.

Methods and analysis: All peer-reviewed and pre-printed primary articles with a longitudinal design that focus on prognostic factors or models of COVID-19 related critically illness and mortality will be considered eligible through eleven databases including PubMed, EMBASE, Web of Science, Cochrane library, CNKI, VIP, Wanfang Data, SinoMed, as well as bioRxiv, Arxiv and MedRxiv. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with data extraction using the modified version of Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS-PF) checklist, and quality will be evaluated by the Newcastle-Ottawa Scale and the Quality in prognosis Studies (QUIPS) tool. The association of prognostic factors and outcomes of interest will be synthesized, and a meta-analysis will be conducted with three or more studies in a consistent manner reporting on a particular factor.

Ethics and dissemination: We will disseminate our findings through a publication in a peer reviewed journal.

PROSPERO registration number: CRD 42020178798

Strengths and limitations of this study

1) The evidence synthesis on prognostic factors and models of COVID-19 related critical conditions will play a pivotal role in assisting front-line clinical decision making.
2) The quality of included studies will be evaluated using a validated tool (QUIPS) specifically developed to assess the risk of bias of prognosis studies.
3) Given that primary studies can be conducted in different region, population, or setting, prognostic factors or models can be assessed using different tools, heterogeneity in the pooled data may be a limitation of this review; however, subgroup analyses will help overcome this limitation.

INTRODUCTION

Description of the condition

Coronavirus disease 2019 (COVID-19), a newly emerged respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December, 2019.[1 2] The infection has recently spread to at least 185 countries and regions, with more than 2.9 million confirmed cases and 200,000 deaths worldwide as of April 26, 2020.[3] The number of people infected is probably much higher due to the shortage of tests for COVID-19. Despite a variety of rapid public health responses

aimed to contain the disease, many countries have been confronted with enormous challenges of healthcare systems by the overwhelming number of patients who required hospital admission, especially those with progression to severe or critically illness.[4-8]

Why is important to do this review?

A report of 72314 cases from the Chinese Center for Disease Control and Prevention shown that most patients with COVID-19 exhibit asymptomatic, mild, or moderate symptoms.[9] The vast majority of mild and moderate patients are recommended to stay at home or admitted in shelter/field hospitals.[10-14] However, patients with mild symptoms may developed rapidly worsening respiratory failure that required intubation.[7] There were approximately 5% to 29% progress to severe or critical condition, such as acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure, requiring intensive care unit (ICU) admission.[9 15-18] It is crucially important to determine the prognostic factors that associated with the risk of experiencing a subsequently critical outcome, among patients with non-critical COVID-19 initially. Prognostic factors and prediction model of severe or critical COVID-19 have many potential uses in various setting, including informing individuals about the future course of their illness, aiding triage and referral, early management of modifiable factors, treatment as well as other clinical decision making.

Status of current literature

Evidence is rapidly accumulating about prognostic factors and models on COVID-19 related critical conditions or mortality. Recently, two systematic review of prediction on COVID-19 has been published.[19 20] 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.[19] The other review that focused on the prediction models for diagnosis and prognosis of COVID-19 infection was published by Wynants and colleagues.[20] Eight studies of prognostic models on severe state or mortality were included. However, only studies aimed to develop or validate a model or scoring system were included, while those aimed to predictor finding were excluded in this systematic review. [20] In addition, given that China was the first epicenter of COVID-19, many studies of prediction on COVID-19 may be published in Chinese journals. According to our preliminary results, there are more than fifteen studies of prognostic factors or models have been published in four Chinese databases (CNKI, WANFANG, CBM, and VIP), which were not searched in this published systematic review. Limited data are available on the overview of evidence that focus on clinical, laboratory, imaging prognostic factors for critical or mortality of COVID-19. Furthermore, with the increasing number of cases across the globe, data from other countries out of China will rapidly emerge over time. There is, therefore, a need for a systematic review and meta-analysis to evaluate and synthesis the current studies of clinical, laboratory, imaging prognostic factors and prediction models for critical and mortality of COVID-19.

Research aims

We aim to systematically assess the clinical, laboratory, and imaging predictors, as well as models for severe or critically illness and mortality in patients with COVID-19.

METHODS

This systematic review protocol followed the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols recommendations (PRISMA-P)[21] and Cochrane Handbook. This review protocol has already been registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD 42020178798).[22]

Search strategy

A systematic search of eleven public-domain databases including PubMed, EMBASE, Web of Science, Cochrane library, China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), Wanfang database (Wanfang Data), China Biology Medicine disc (SinoMed), bioRxiv, Arxiv, as well as MedRxiv will be performed. We will use exploded Medical Subject Headings and the appropriate corresponding keywords relating to the population, combined with exposure and outcomes, such as: “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” “novel coronavirus” AND “critically” OR “severe” OR “mortality” OR “deterioration” AND “predictor” OR “prediction” OR “prognostic” OR “factor”. Further, publication list of the COVID-19 Living Systematic Review[23] and other resources[24] will be screened for additional relevant references. There will be no restrictions on language or publication status (preprint or peer reviewed articles). The research will be restricted to articles concerning humans from December 2019 to the present. We will include additional papers from other sources including the references of review articles or studies identified during screening. A sample search strategy for PubMed is shown in online supplementary appendix 1.

Eligibility criteria

Participants

All patients with confirmed diagnosis of coronavirus disease 2019 (COVID-19), with an explicit classification of mild, moderate, severe, or critically ill according to accepted criteria.

Exposures

Any information related to demographics, symptoms and signs, pulmonary functions, laboratory tests, radiological findings, comorbidities, as well as interventions will be considered as potential predictors for critically illness or mortality in patients of COVID-19.

Comparators

Participants with and without specific clinical, laboratory, imaging information will be compared to clarify its significance to predict the critically illness and mortality of COVID-19.

Outcomes

COVID related deterioration, progression, severe, critical illness or death according to accepted criteria.

Timing and setting

There will be no restriction on the time point when the prognostic factors were under review, as well as the time period when the outcomes were predicted. No restriction will be made on the setting (e.g., inpatients, outpatients, and shelter hospitals).

Types of study to be included

Both experimental and longitudinal observational studies such as randomized controlled trial, cohort study, case-control study, and registry study will be included. Review articles, editorials, letters, comments, case reports, cross-sectional study, as well as those failing to investigate the prognostic factors or models for critically illness or mortality will be excluded.

Study selection

Two reviewers (Jian Liu, Luda Feng) will independently perform initial search and examine the titles, abstracts, and if necessary, full-texts to identify eligible studies according to the inclusion and exclusion criteria. Disagreement between reviewers will be resolved by consensus and in case of persistent disagreement by adjudication of a third reviewer (Qiang Liu). The selection process will be illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Figure 1. Flow diagram of the study selection process).[25]

Data extraction

Data extraction will be conducted by two reviewers (Tianyi Zhang, Ping Jiang) independently, using a standard data extraction form developed according to CHARMS checklist for prediction model studies and its modified edition (CHARMS-PF),[26 27] as well as PROBAST (prediction model risk of bias assessment tool).[28] For each included trial, the following key information will be extracted where available: name of first author, year of publication, study location, study design, study setting, participants, sample size, follow-up period, outcomes of interest, risk and prognostic factors, missing data, summary statistics, results, interpretation and discussion. Authors of studies will

be contacted through email or telephone in case of missing relevant data.

Risk of bias assessment

We will evaluate risk of bias using the Newcastle-Ottawa Scale[29] and the QUIPS checklist (quality in prognostic factor studies) which has been recommended by the Cochrane Group to assess the risk of bias in prognostic factor studies.[30] Quality assessment will be done independently by two reviewers (Tianyi Zhang, Ligaoge Kang), and discrepancies will be resolved through consensus.

Data synthesis

Essential data will be summarized in tables for evaluation. Estimates of risk difference in terms of critically illness and mortality will be calculated. For categorical variables, ORs, RRs, or HRs will be analyzed to compare these variables between mild/moderate and severe/critical COVID-19 cases. Studies reporting adjusted or unadjusted results will be analyzed separately. Only unadjusted effect estimates for prognostic factor will be combined, while effect estimates from multivariate models will be described qualitatively. With three or more studies in a consistent manner reporting on a particular factor, a meta-analysis will be conducted using the Review Manager software (RevMan 5.3, the Cochrane Collaboration) to synthesize the association of prognostic factors and critically illness or mortality in patients with COVID-19. Heterogeneity among the include studies will be tested using the I^2 statistic.[31] Forest plots will be presented for significant predictors. In case of substantial heterogeneity, subgroup analyses will be conducted to examine or explore the causes of heterogeneity. Subgroup analysis will base on the categories defined by characteristics as following: study location/region,

risk of bias, and particular population such as children, elder people.

Ethics and dissemination

Ethical approval is not required for this systematic review. We will disseminate our findings through a publication in a peer reviewed journal.

Patient and public involvement

There is no patient and public involvement in the whole process of conducting this systematic review.

DISCUSSION

With the unprecedented threat of a worldwide pandemic of COVID-19, there has been an increasing need for early identification of patients at higher risk of progression to critical illness, or even to death. This systematic review will comprehensively summarize the existing evidence on clinical, laboratory, and imaging factors and models for predicting critical conditions and mortality in patients with COVID-19. The findings will provide front-line clinicians an early surrogate of disease severity before the onset of critical illness, which may play a key role in assisting clinicians to early manage modifiable factors, triage patients appropriately and optimize use of the limited healthcare resources.

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improvement of methodology of this protocol.

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Contributors

XL, YG conceived the research question. TZ, LF, PJ and LK developed the search strategy and performed the preliminary search, screening and data extraction. QL and YG contributed to the methodological development of the protocol. XL and JL drafted the manuscript. QL and YG revised the manuscript and all authors developed and approved the final manuscript before submission.

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Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

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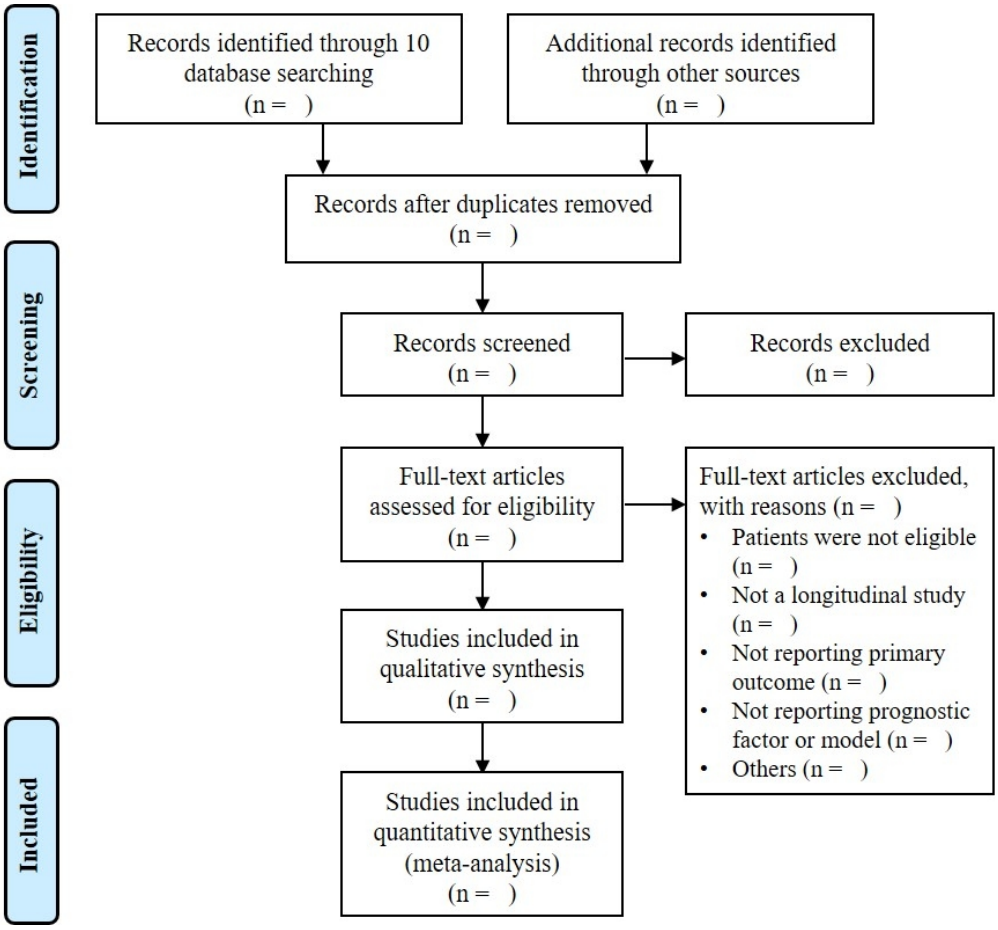

Figure 1. Flow diagram of the study selection process

146x134mm (150 x 150 DPI)

Appendix 1. Search Strategy Example: PubMed search

No	Search items
1	"Covid-19"[All Fields]
2	"coronavirus disease 2019""[All Fields]
3	"SARS-CoV-2"[All Fields]
4	"novel coronavirus"[All Fields]
5	"new coronavirus"[All Fields]
6	"severe acute respiratory syndrome coronavirus 2"[All Fields]
7	"novel coronavirus-infected pneumonia"[All Fields]
8	"2019-nCoV"[All Fields]
9	"Wuhan coronavirus"[All Fields]
10	"NCP"[All Fields]
11	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10**
12	"Critical*"[title/abstract]
13	"intensive"[title/abstract]
14	"ICU" [title/abstract]
15	"severe" [title/abstract]
16	"death" [title/abstract]
17	"mortality" [title/abstract]
18	"decease*" [title/abstract]
19	"survival" [title/abstract]
20	"deteriorate*" [title/abstract]
21	"worsen*" [title/abstract]
22	"progress*" [title/abstract]
23	**12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22**
24	"predict*" [title/abstract]
25	"prognos*"[title/abstract]
26	"risk"[title/abstract]
27	"factor"[title/abstract]
28	"algorithm"[title/abstract]
29	"score" [title/abstract]
30	"marker*" [title/abstract]
31	"biomarker*" [title/abstract]
32	**24 OR 25 26 OR 27 OR 28 OR 29 OR 30 OR 31**
33	"humans"[filter]
34	"review"[filter]
35	"case reports" [filter]
36	"editorial" [filter]
37	**33 OR 34 OR 35 OR 36**
38	**(11 AND 23 AND 32 AND 33) NOT 37**

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐	☐	NA
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4, 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	7, 8
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	6

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	8
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	8
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	9
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	9
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA

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Complete List of Authors:	Lai, Xinxing; Tsinghua University, MOE Key Laboratory of Bioinformatics, TCM-X Center/Bioinformatics Division; Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital Liu, Jian; China-Japan Friendship Hospital, Department of TCM Pulmonary Diseases, Center of Respiratory Medicine Zhang, Tianyi; Beijing University of Chinese Medicine Feng, Luda; Beijing University of Chinese Medicine, Jiang, Ping; Beijing University of Chinese Medicine Kang, Ligaoge; Fangshan Hospital, Beijing University of Chinese Medicine, Department of Emergency Liu, Qiang; The Word Federation of Chinese Medicine Societies, Center for Evidence-based Medicine Gao, Ying; Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Medical management, Public health
Keywords:	INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, COVID-19, Adult intensive & critical care < ANAESTHETICS

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Title: Clinical, laboratory, and imaging predictors for critical illness and mortality in patients with coronavirus disease 2019: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: With the threat of a worldwide pandemic of coronavirus disease 2019 (COVID-19), it is important to identify the prognostic factors for critical conditions among patients with non-critical COVID-19. Prognostic factors and models may assist front-line clinicians in rapid identification of high-risk patients, early management of modifiable factors, appropriate triaging, and optimising the use of limited healthcare resources. We aim to systematically assess the clinical, laboratory, and imaging predictors as well as prediction models for severe or critical illness and mortality in patients with COVID-19.

Methods and analysis: All peer-reviewed and pre-print primary articles with a longitudinal design that focussed on prognostic factors or models for critical illness and mortality related to COVID-19 will be eligible for inclusion. A systematic search of 11 databases including PubMed, EMBASE, Web of Science, Cochrane library, CNKI, VIP, Wanfang Data, SinoMed, bioRxiv, Arxiv, and MedRxiv will be conducted. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Data extraction will be performed using the modified version of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist and quality will be evaluated using the Newcastle-Ottawa Scale and the Quality In Prognosis Studies tool. The association between prognostic factors and outcomes of interest will be synthesised and a meta-analysis will be conducted with three or more studies reporting a particular factor in a consistent manner.

Ethics and dissemination: Ethical approval was not required for this systematic

review. We will disseminate our findings through publication in a peer-reviewed journal.

PROSPERO registration number: CRD 42020178798

KEYWORDS: COVID-19; predictor; critical illness; mortality; prediction model; systematic review

Strengths and limitations of this study

1) The evidence synthesis on prognostic factors and models of COVID-19 related critical conditions will play a pivotal role in assisting front-line clinical decision making.
2) The quality of included studies will be evaluated using a validated tool (QUIPS) specifically developed to assess the risk of bias of prognosis studies.
3) Given that primary studies can be conducted in different region, population, or setting, prognostic factors or models can be assessed using different tools, heterogeneity in the pooled data may be a limitation of this review; however, subgroup analyses will help overcome this limitation.

INTRODUCTION

Description of the condition

Coronavirus disease 2019 (COVID-19), a newly emerged respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019.[1, 2] 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 1 September 2020.[3] The number of people infected is probably much higher due to the shortage of tests for COVID-19. 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.[4-8]

Why is it important to do this review?

A report of 72314 cases from the Chinese Center for Disease Control and Prevention showed that most of the patients with COVID-19 are asymptomatic or exhibit mild or moderate symptoms.[9] The vast majority of patients with mild and moderate symptoms are recommended to stay at home or are admitted in shelter/field hospitals.[10-14] However, patients with mild symptoms may develop rapidly worsening respiratory failure that requires intubation.[7] Approximately 5% to 29% of the patients progressed to a severe or critical condition such as acute respiratory distress

syndrome or septic shock and/or multiple organ failure that required admission to the intensive care unit.[9, 15-18] 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. Hence, it is crucial to determine the prognostic factors associated with the risk of a subsequent critical outcome among patients with non-critical COVID-19. Prognostic factors and prediction models for severe or critical COVID-19 have many potential uses in various settings including informing individuals about the future course of their illness, aiding triage and referral, early management of modifiable factors, treatment, and other factors related to clinical decision making.

Status of the current literature

Evidence is rapidly accumulating about prognostic factors and models for critical conditions or mortality related to COVID-19. Recently, two systematic reviews focusing on specific perspectives of COVID-19 have been published.[19, 20] Henry and colleagues published a systematic review that included only the laboratory biomarkers and excluded the clinical and imaging predictors associated with severe illness and mortality in COVID-19.[19] Another review by Wynants and colleagues focused on the prediction models for diagnosis and prognosis of COVID-19 infection.[20] Eight studies regarding prognostic models for severe state or mortality were included. However, only the studies aimed at developing or validating a model or a scoring system were included, while those aimed at predictor findings were excluded

from this systematic review.[20] In addition, since China was the first epicentre of COVID-19, many studies on the prediction of COVID-19 may have been published in Chinese journals. According to our preliminary results, more than 15 studies regarding prognostic factors or models have been published in four Chinese databases (CNKI, WANFANG, CBM, and VIP) that were not included in the aforementioned systematic review. Limited data are available on the overview of evidence that focuses on clinical, laboratory, and imaging prognostic factors for critical illness or mortality associated with COVID-19. Moreover, a huge number of recent articles have emerged with the worldwide pandemic. Many valuable articles on prognostic factors or models of COVID-19 have not been included in these published reviews. Among these, some high-quality papers have been published in leading journals,[21, 22] which provided us with more evidence and insights into this topic. Therefore, there is a need for a systematic review to evaluate and synthesise the data from the current studies from a comprehensive perspective on clinical, laboratory, and imaging prognostic factors and prediction models for critical illness and mortality associated with COVID-19.

Research aims

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 mortality, so it will be assessed according to different outcomes.

METHODS

This systematic review protocol followed the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) recommendations [23] and the Cochrane Handbook. The PRISMA-P checklist is presented in online supplementary appendix 1. This review protocol was started in early April and has been registered with the International Prospective Register of Systematic Reviews (registration number: CRD 42020178798). [24]

Search strategy

A systematic search of 11 public-domain databases including PubMed, EMBASE, Web of Science, Cochrane library, China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), Wanfang database (Wanfang Data), China Biology Medicine disc (SinoMed), bioRxiv, Arxiv, and MedRxiv will be performed. We will use exploded Medical Subject Headings and the appropriate corresponding keywords related to the population, combined with exposure and outcomes such as: “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” OR “novel coronavirus” AND “critically” OR “severe” OR “mortality” OR “deterioration” AND “predictor” OR “prediction” OR “prognostic” OR “factor”. Additionally, a publication list of the COVID-19 Living Systematic Review[25] and other resources[26] will be screened for additional relevant references. There will be no restrictions on language or publication status (pre-print or peer-reviewed articles). The research will be restricted to articles concerning humans from December 2019 to the present. We will include

additional papers from other sources including the references of review articles or studies identified during screening. A sample search strategy for PubMed is shown in online supplementary appendix 2.

Eligibility criteria

Participants

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.

Exposures

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.

Comparators

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.[21, 22] These potential variables will be

considered the comparators. Participants with and without specific clinical, laboratory, and imaging information will be compared to clarify the significance of this information in predicting critical illness and mortality associated with COVID-19.

Outcomes

The outcomes will include deterioration, progression, severe critical illness, or death related to COVID-19 according to accepted criteria.

Timing and setting

There will be no restriction on the time point when the prognostic factors were under review as well as on the period when the outcomes were predicted. No restriction will be imposed on the setting.

Types of study to be included

Both experimental and longitudinal observational studies including randomised controlled trials, cohort studies, case-control studies, and registry studies will be included. Review articles, editorials, letters, comments, case reports, cross-sectional studies, and studies that failed to investigate the prognostic factors or models for critical illness or mortality will be excluded.

Study selection

Two reviewers (Jian Liu, Luda Feng) will independently perform the initial search and examine the titles, abstracts, and full texts (if necessary) to identify eligible studies according to the inclusion and exclusion criteria. Disagreements between the reviewers will be resolved by consensus and by adjudication of a third reviewer (Qiang Liu) in

case of persistent disagreement. The selection process is illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Figure 1).[27]

Data extraction

Data extraction will be independently conducted by two reviewers (Tianyi Zhang, Ping Jiang), using a standard data extraction form developed according to the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist for prediction model studies and its modified version (CHARMS-PF)[28, 29] as well as according to the Prediction model Risk Of Bias Assessment Tool.[30] For each included trial, the following key information will be extracted based on availability: name of the first author, year of publication, study location, study design, study setting, participants, sample size, follow-up period, outcomes of interest, risk and prognostic factors, missing data, summary statistics, results, interpretation, and discussion. The authors of the studies will be contacted through email or telephone in case of missing relevant data.

Assessment of the risk of bias

We will evaluate the risk of bias using the Newcastle-Ottawa Scale[31] and the Quality In Prognosis Studies checklist, which has been recommended by the Cochrane Group to assess the risk of bias in studies related to prognostic factors.[32] Quality assessment will be performed independently by two reviewers (Tianyi Zhang, Ligaoge Kang) and discrepancies will be resolved through consensus.

Data synthesis

Essential data will be summarised in tables for evaluation. Estimates of risk difference in terms of critical illness and mortality will be calculated. For categorical variables, odds ratios, relative risks, or hazard ratios will be analysed to compare these variables between mild/moderate and severe/critical COVID-19 cases. Studies reporting adjusted or unadjusted results will be analysed separately. Only the unadjusted effect estimates for prognostic factors will be combined, while effect estimates from multivariate models will be described qualitatively. With three or more studies reporting a particular factor in a consistent manner, a meta-analysis will be conducted using the Review Manager software (RevMan 5.3, the Cochrane Collaboration, London, UK) to synthesise the association of prognostic factors and critical illness or mortality in patients with COVID-19. For severe or critical illness and mortality, the data will be synthesised according to different outcomes. Heterogeneity among the included studies will be tested using the I^2 statistic.[33] Forest plots will be presented as significant predictors. In case of substantial heterogeneity, subgroup analyses will be conducted to examine or to explore the causes of heterogeneity. Subgroup analysis will be based on the categories defined by the following characteristics: study location/region, risk of bias, and particular population such as children and elderly people.

Ethics and dissemination

Ethical approval was not required for this systematic review. We will disseminate

our findings through publication in a peer-reviewed journal.

Patient and public involvement

There is no patient or public involvement in the whole process of conducting this systematic review.

DISCUSSION

With an unprecedented threat of a worldwide COVID-19 pandemic, there has been an increasing need for early identification of patients at higher risk of progression to critical illness or even death. This systematic review will comprehensively summarise the existing evidence on clinical, laboratory, and imaging factors and models for predicting critical conditions and mortality in patients with COVID-19. The findings of this review will provide front-line clinicians an early surrogate for disease severity before the onset of critical illness, which may play a key role in assisting the clinicians in early management of modifiable factors, appropriate triaging of patients, and optimising the use of limited healthcare resources.

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Contributors

XL, YG conceived the research question. TZ, LF, PJ and LK developed the search strategy and performed the preliminary search, screening and data extraction. QL and YG contributed to the methodological development of the protocol. XL and JL drafted the manuscript. QL and YG revised the manuscript and all authors developed and approved the final manuscript before submission.

Funding

None.

Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Figure 1. Flow diagram of the study selection process

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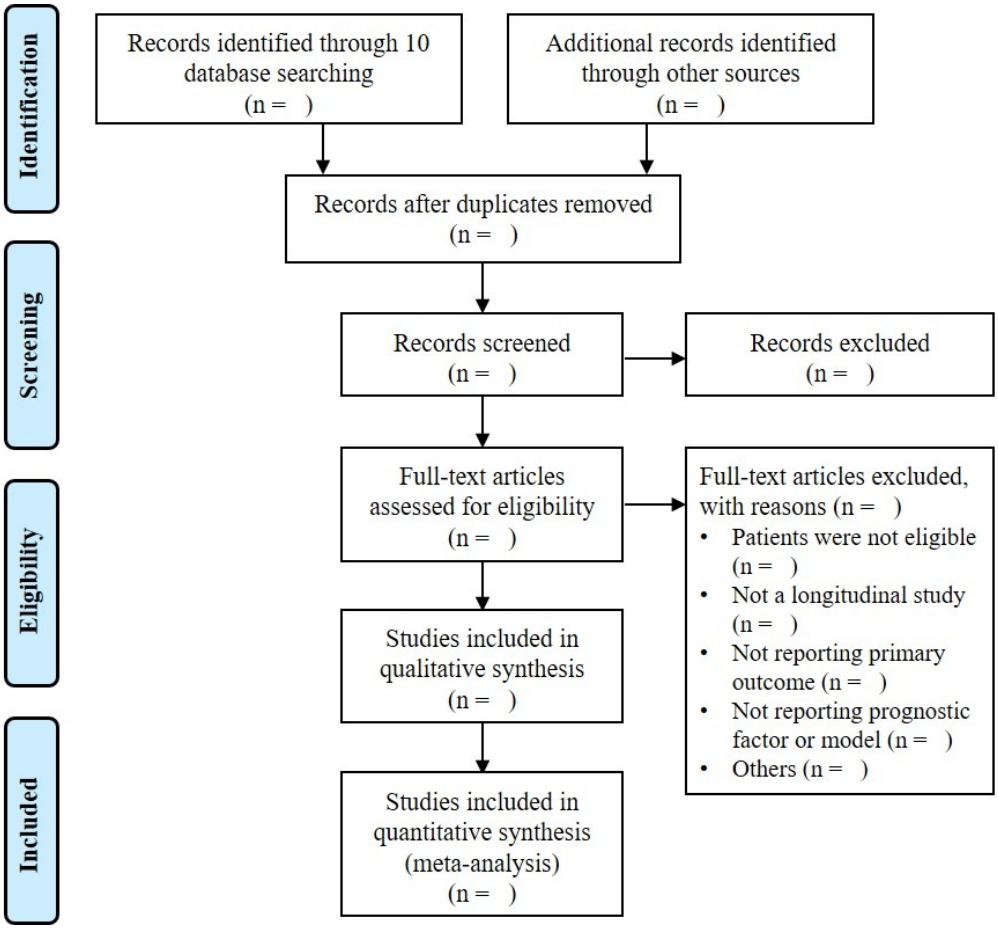

Figure 1. Flow diagram of the study selection process

146x134mm (150 x 150 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☐	3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐	☐	NA
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	5, 6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	6
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	8, 9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	7, 8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	9
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	9, 10
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	10
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	10
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	11
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA

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From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2. Search Strategy Example: PubMed search

No	Search items
1	"Covid-19"[All Fields]
2	"coronavirus disease 2019""[All Fields]
3	"SARS-CoV-2"[All Fields]
4	"novel coronavirus"[All Fields]
5	"new coronavirus"[All Fields]
6	"severe acute respiratory syndrome coronavirus 2"[All Fields]
7	"novel coronavirus-infected pneumonia"[All Fields]
8	"2019-nCoV"[All Fields]
9	"Wuhan coronavirus"[All Fields]
10	"NCP"[All Fields]
11	**1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10**
12	"Critical*"[title/abstract]
13	"intensive"[title/abstract]
14	"ICU" [title/abstract]
15	"severe" [title/abstract]
16	"death" [title/abstract]
17	"mortality" [title/abstract]
18	"decease*" [title/abstract]
19	"survival" [title/abstract]
20	"deteriorate*" [title/abstract]
21	"worsen*" [title/abstract]
22	"progress*" [title/abstract]
23	**12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22**
24	"predict*" [title/abstract]
25	"prognos*"[title/abstract]
26	"risk"[title/abstract]
27	"factor"[title/abstract]
28	"algorithm"[title/abstract]
29	"score" [title/abstract]
30	"marker*" [title/abstract]
31	"biomarker*" [title/abstract]
32	**24 OR 25 26 OR 27 OR 28 OR 29 OR 30 OR 31**
33	"humans"[filter]
34	"review"[filter]
35	"case reports" [filter]
36	"editorial" [filter]
37	**34 OR 35 OR 36**
38	**(11 AND 23 AND 32 AND 33) NOT 37**