Original Article

Coronavirus disease (COVID 2019): protocol for a living overview of systematic reviews

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Background: The coronavirus disease 2019 (COVID-19) pandemic continues to grow worldwide, and systematic reviews (SRs)/meta-analyses (MAs) on COVID-19 can efficiently guide evidence-based clinical practice. However, SRs/MAs with weaknesses can mislead clinical practice and pose harm to patients, and too many useless SRs/MAs could pose confusion and waste sources. A "living" overview of SRs/MAs aims to provide an open, accessible and frequently updated resource summarizing the highest-level evidence of COVID-19, that can help evidence-users to quickly identify trusted evidence to guide the practice. This study aims to systematically give an overview SRs/MAs of COVID-19, assess their quality, and identify the best synthesis of evidence.

Methods: Databases including Medline, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) and WanFang were systematically searched on May 1, 2020 using relevant terms for identify SRs/MAs related to COVID-19. The study selection, data extraction and quality assessment will be performed by independent reviewers, and results will be cross-checked. The authoritative tools (AMSTAR-2, PRISMA and its extensions) will be used to assess the methodological quality and reporting quality of included SRs/MAs, and potential influence factors will be explored. The consistency of conclusions will be compared among reviews and the best evidence will be summarized. In addition, we will conduct exploratory meta-analyses (MAs) of individual studies when applicable. Data will be reported as number with (or) percentage, risk ratio (RR) or odds ratio (OR), mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI) according to the specific results. R3.6.1 and Microsoft Excel 2016 will be used to analyze and manage data.

Results: The results of this overview will be submitted to a peer-reviewed journal for publication.

Conclusions: In this study, we will present for the first time, an overview of SRs/MAs, which provides a comprehensive, dynamic evidence landscape on prevalence, prevention, diagnosis, treatment, and prognosis of COVID-19.

Keywords: COVID-19; living overview; systematic review (SR); meta-analysis; evidence quality; AMSTAR-2; PRISMA

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Introduction

At the end 2019, the novel coronavirus disease 2019 (COVID-19) that could spread from person to person was firstly identified and reported in the world (1). In addition to severe acute respiratory syndrome coronavirus (SARS) and middle east respiratory syndrome coronavirus (MERS), COVID-19 is the third coronavirus that is severely harmful to human health (2). On February 1, 2020, the World Health Organization (WHO) declared COVID-19 as a public health emergency of international concern that presently has spread around the world (3). According to WHO report published at May 1, 2020, the cumulative number of confirmed cases and deaths worldwide reached 3145407 and 221823, respectively (https://covid19.who.int/).

After the COVID-19 outbreak, the number of research evidence of COVID-19 is rapidly increasing (4-11), includes basic research, epidemiology research, clinical studies, narrative reviews, bibliometric studies, systematic reviews (SRs)/MAs, guidelines or recommendations, etc. The topics of these publications cover but are not limited to the underlying mechanism of action, prevention, diagnosis, treatment and prognosis (4). However, in several studies, concerns have been expressed on quality, reliability and normalization of COVID-19 studies (12-14). Evidence based medicine (EBM) emphasizes that all clinical decisions should be based on the best evidence currently available (15). In addition, SR/MA as a key tool in EBM, that through summarizing multiple individual studies on same or similar clinical question including etiology, prevention, diagnosis, treatment and prognosis topics, provide guidance for EBM clinical practice (16). However, poor methodological guidance, selection report and duplications will pose significant confusion, and may even mislead practice, thus sources waste will be companied (16-18). Recently, many SRs/MAs on COVID-19 have been published (9,10,19-21), however, the quality of the studies remains unknown. Moreover, these SRs/MAs may have posed confusion for relevant stakeholders in applying these evidences. An overview could summarize multiple SRs/MAs into a single usable document and provide a comprehensive 'friendly front end' of the evidence for clinicians, decision-makers, and patients (22-24). Evidence users be able to quickly capture and understand the evidence by reading the overview, and do not have to spend much time to assimilate data from separate SRs/MAs (24).

By increasing of SRs/MAs on COVID-19 and substantially increased the clinical workload, it has been a challenge for clinicians to update their knowledge on COVID-19 for evidence-based practice. Therefore, we plan this "living" overview (which will be updated regularly) to summarize evidence of SRs/MAs on COVID-19 to guide clinical practice, assess their quality, and identify current gaps in evidence to inform future studies.

Methods

In this study, we reported this protocol by referencing the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines (25). Considering the urgency of the study, we have not yet registered this in a public website, but if some modifications were to occur, any changes as well as the reasoning will be reported in the main text.

Eligibility criteria

We will include all types of SRs/MAs (such as qualitative SR, traditional MA, network MA) on COVID-19 that have been published in the Chinese or English language, and they should conform the following definition (26): "*A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant studies, and collect and analyze data from the studies included in the review (qualitative SR), or the statistical combination of at least two studies to produce a single estimate (such as traditional MA or network MA)*". The clinical topics could involve all aspects of COVID-19, including prevalence, prevention, diagnosis, treatment and prognosis. We will exclude preclinical studies, narrative reviews, overviews, guidelines, and other publications that do not present key information, such as protocols, letters, abstracts, newsletters, etc.

Search method

A systematically search in Medline (Ovid), EMBASE (Ovid), Web of Science, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) and WanFang databases was performed on May 1, 2020. Main search terms included "coronavirus", "COVID-19", "2019-nCoV", "SARS-CoV-2", "novel coronavirus", "WN-CoV", "systematic", "systematic review", "systematic literature review", "meta-analysis", "meta analyses", and "evidence synthesis", etc. The search was performed by QW and BP with the guidance of two senior researchers (LG, KHY) (27). The initial database search yielded 447 records, and this

search will be updated monthly. The detailed search strategy is shown in Appendix 1. To identify any potentially eligible studies, the references list of included SRs/MAs will be manual checked. We did not search preprints websites, such as medRxiv (https://www.medrxiv.org/), which has the following statement: "Preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information."

Study selection

All identified records will be imported into Endnote X9 software (Thomson Reuters, NY, USA). After removing duplications, teams of three reviewers (TTL, LYH, YuHW, YR, LC, CCL) will independently screen titles and abstracts according to the eligibility criteria. Potential studies and conflicted studies will be subjected to full-text review. Any disagreement or conflict will be solved through discussion, and in any case the conflict exists, a senior reviewer (LG) will be making an arbitrary decision.

Data extraction

For data extraction, teams of two reviewers (BP, LYH, YuHW, TZQ, HHL, QW, TTL, QZ) will independently extract key information from included SRs/MAs. This information includes the following: title, first author, publication date or online date, language, journal and impact factor, number of authors, country of the corresponding author or the last author, number of patients (participants) and their details (age, gender, clinical symptoms, co-morbidities, diagnostic methods, interventions, risk factors, and disease severity, etc.), clinical topics, data sources, number of primary studies, type of primary studies, assessment tools for the quality of primary studies, synthesis methods, outcomes, and their effect sizes, and key findings or conclusions, etc. Any conflict will be resolved by consensus.

Quality assessment

The tools, Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) (28) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (29) and its extensions (such as PRISMA-DTA for diagnostic MA, PRISMA-NMA for network MA) (30,31), will be used to evaluate the methodological quality and reporting quality of included SRs/MAs, respectively. AMSTAR-2 consists of 16 items, among which seven (item 2, 4, 7, 9, 11, 13 and 15) are considered critical items. The overall confidence on quality of SRs/MAs will be classified into four categories: (I) high quality: no or only one non-critical weakness, (II) moderate quality: >1 non-critical weakness, (III) low quality: only one critical weakness, with or without non-critical weakness, and (IV) critically low quality: > one critical weakness, with or without non-critical weakness. However, considering that AMSTAR-2 was developed for interventional SRs/MAs (28), modifications will be conducted when necessary. The PRISMA consists of 27 items, and we will assess the compliance of SRs/MAs against each item using "Yes", "Partial", "No", or "Not applicable". In addition, the aforementioned four options for its extensions are appropriate. Prior to the assessment, all investigators will discuss the items of the tools, and all reviewers will use 5–10 SRs/MAs to test the consistency until a consensus is reached. Then, teams of two reviewers (BP, LYH, YiHW, HHL, TZQ, QW, TTL, QZ) will assess the quality of included SRs/MAs. Any conflict will be resolved by discussion or by adjudication of a senior reviewer (LG, or CCL). In addition, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to assess evidence quality based on each of the outcomes of MAs that focus on randomized controlled trials (32), when applicable.

Data analysis

In this study, qualitative description and quantitative synthetization will be used. The results of quality assessment will be reported as number with (or) percentage. We will explore the differences of the quality of included SRs/MAs by subgroup analysis based on the type of reviews, country, journals' impact factor, and clinical topic, etc., and the results will be reported as the risk ratio (RR) with 95% confidence interval (CI). In addition, based on AMSTAR-2 assessment, we will categorize reviews into "Trusted evidence" (high and moderate quality) and "Questionable evidence" (low and critically low quality). For "Trusted evidence", we will summarize the conclusion of each review in tabular format and will stratify according to the type of SR. Where MA is performed within a review, we will also extract forest plot and pooled effect sizes. Where no quantitative pooling of effect sizes is reported, we will use standardized language indicating

the direction of the effect and statistical significance. For continuous outcomes, we will summarize data using the mean difference (MD) or standardized mean difference (SMD) with 95% CI as reported in the included reviews. For dichotomous outcomes, we will present the RR or odds ratio (OR) or absolute effect and 95% CI as appropriate. For "questionable evidence", we will try to reconduct an exploratory MA or indicate the necessary of future research. For all analyses, significance level will be set at 0.05 (two-sided test). R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel 2016 (Microsoft, Richmond, WA, USA) will be used to analyze and manage the data obtained.

Discussion

SRs/MAs as high-level evidence source for supporting clinical practice, their methodology and reporting can influence their applicability in clinical practice (16,17). At present, many SRs/MAs related to COVID-19 have been published, however, their quality remains unknown. Moreover, many reviews may have posed confusion on relevant stakeholders. To fill this gap, the present study was designed to present comprehensive evidence from SRs/MAs, and the results of this study will be updated regularly. The study will employ AMSTAR-2, PRISMA and its extensions to assess the quality of included SRs/MAs, and data will be re-synthesized when applicable. Furthermore, because the number of SRs/MAs is growing, we will keep updating our results and this involves a dynamic process that we named "living overview". We believe this living overview will promote the use of SRs/MAs evidence to improve clinical service quality while reducing research waste (18).

Strengths and limitations

This research has several strengths and limitations. Firstly, this is the first living overview of SRs/MAs related to COVID-19. This study will provide a comprehensive and dynamic evidence landscape on prevalence, prevention, diagnosis, treatment and prognosis of COVID-19. Secondly, the validated tools, AMSTAR-2, PRISMA and its extensions will be used to judge the quality of included SRs/MAs, and data will be re-synthesized when applicable. Regarding limitations, we will only include SRs/MAs published in the English and Chinese language, therefore, language bias may be an important limitation.

Presenting and reporting of results

The results of this study will be reported by referencing the PRISMA statement (29). A flow diagram will be used to show the process of the screening and selection of the eligible SRs/MAs. Finally, this work will be submitted to a peer-reviewed journal for publication.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1130). The authors have no conflicts of interest to declare.

Ethical Statement: All authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All data used to support the present research will be from published publications, and there will be no any identifiable patient information. No ethical approve or informed consent is required for the purposes of the present study.

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Supplementary

Search strategy and results (May 1st 2020)

Databases	Results
Medline (Ovid)	177
EMBASE (Ovid)	132
Web of Science	82
China National Knowledge Infrastructure (CNKI)	31
WanFang	15
China Biology Medicine (CBM)	10
Total records	447

Medline ALL (Ovid)

1	Coronavirus:ti,ab,kw	13525
2	((corona* OR corono*) adj1 (virus* OR viral* OR virinae*)):ti,ab,kw	818
3	(coronavirus* OR coronovirus* OR coronavirinae* OR Coronavirus* OR Coronovirus* OR Wuhan* OR Hubei* OR Huanan OR "2019-nCoV" OR 2019nCoV OR nCoV2019 OR "nCoV-2019" OR "COVID-19" OR COVID19 OR "CORVID-19" OR CORVID19 OR "WN-CoV" OR WNCoV OR "HCoV-19" OR HCoV19 OR CoV OR "2019 novel*" OR Ncov OR "n-cov" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese* OR "2019 novel coronavirus" OR "Wuhan coronavirus" OR "novel coronavirus" OR "Wuhan seafood market pneumonia virus" OR "Wuhan virus"):ti,ab,kw	24144
4	(((respiratory* adj2 (symptom* OR disease* OR illness* OR condition*)) OR "seafood market*" OR "food market*") adj10 (Wuhan* OR Hubei* OR China* OR Chinese* OR Huanan*)):ti,ab,kw	487
5	((outbreak* OR wildlife* OR pandemic* OR epidemic*) adj1 (China* OR Chinese* OR Huanan*)):ti,ab,kw	189
6	"severe acute respiratory syndrome*":ti,ab,kw	5489
7	OR/1-6	26857
8	(((((Systematic OR "systematic review" OR (systematic$ adj review$)) OR (Systematic$adj2 review$)) OR (Systematic$adj2 overview$)) OR "systematic literature review")):ti,ab,kw	360354
9	Meta-Analysis.pt.	114021
10	(("meta-analysis" OR "meta analysis" OR "meta analyses" OR "evidence synthesis" OR ((metaanalysis*) OR meta analysis*) OR "meta-analysis*" OR (meta-reviews OR metareviews)) OR metasyntheses):ti,ab,kw	171605
11	OR/ 8-10	466461
12	7 AND 11 limited 2019-2020	177

http://dx.doi.org/10.21037/apm-20-1130

EMBASE (Ovid)

1	coronavirus/exp	18488
2	((corona* OR corono*) adj1 (virus* OR viral* OR virinae*)):ti,ab,kw	608
3	(coronavirus* OR coronovirus* OR coronavirinae* OR Coronavirus* OR Coronovirus* OR Wuhan* OR Hubei* OR Huanan OR "2019-nCoV" OR 2019nCoV OR nCoV2019 OR "nCoV-2019" OR "COVID-19" OR COVID19 OR "CORVID-19" OR CORVID19 OR "WN-CoV" OR WNCoV OR "HCoV-19" OR HCoV19 OR CoV OR "2019 novel*" OR Ncov OR "n-cov" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese* OR "2019 novel coronavirus" OR "Wuhan coronavirus" OR "novel coronavirus" OR "Wuhan seafood market pneumonia virus" OR "Wuhan virus"):ti,ab,kw	24480
4	(((respiratory* adj2 (symptom* OR disease* OR illness* OR condition*)) OR "seafood market*" OR "food market*") adj10 (Wuhan* OR Hubei* OR China* OR Chinese* OR Huanan*)):ti,ab,kw	570
5	((outbreak* OR wildlife* OR pandemic* OR epidemic*) adj1 (China* OR Chinese* OR Huanan*)):ti,ab,kw	81
6	"severe acute respiratory syndrome*":ti,ab,kw	5722
7	OR/1-6	
8	(((((Systematic OR "systematic review" OR (systematic$ adj review$)) OR (Systematic$ adj2 review$)) OR (Systematic$ adj2 overview$)) OR "systematic literature review")):ti,ab,kw	420773
9	(("meta-analysis" OR "meta analysis" OR "meta analyses" OR "evidence synthesis" OR ((metaanalysis*) OR meta analysis*) OR "meta-analysis*" OR (meta-reviews OR metareviews)) OR metasyntheses):ti,ab,kw	222786
10	OR/ 8-9	492
11	7 AND 10 limited 2019.12.1-2020.5.1	132

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Web of Science

Science Citation Index Expanded (SCI-EXPANDED) –from 2019 to now
Social Sciences Citation Index (SSCI) – from 2019 to now

1	TS= coronavirus/	1948
2	TS=((corona* OR corono*) ? (virus* OR viral* OR virinae*))	1318
3	TS=(coronavirus* OR coronovirus* OR coronavirinae* OR Coronavirus* OR Coronovirus* OR Wuhan* OR Hubei* OR Huanan OR "2019-nCoV" OR 2019nCoV OR nCoV2019 OR "nCoV-2019" OR "COVID-19" OR COVID19 OR "CORVID-19" OR CORVID19 OR "WN-CoV" OR WNCoV OR "HCoV-19" OR HCoV19 OR CoV OR "2019 novel*" OR Ncov OR "n-cov" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese* OR "2019 novel coronavirus" OR "Wuhan coronavirus" OR "novel coronavirus" OR "Wuhan seafood market pneumonia virus" OR "Wuhan virus")	4428
4	TS= (((respiratory*?? (symptom* OR disease* OR illness* OR condition*)) OR "seafood market*" OR "food market*") ? (Wuhan* OR Hubei* OR China* OR Chinese* OR Huanan*))	907
5	TS= ((outbreak* OR wildlife* OR pandemic* OR epidemic*)? (China* OR Chinese* OR Huanan*))	1890
6	TS="severe acute respiratory syndrome*"	289
7	OR/1-6	6818
8	TS=Systematic OR TS="systematic review" OR TS=(systematic$? review$) OR TS=(Systematic$? review$) OR TS="systematic literature review"	70270
9	TS="Meta-Analysis" OR TS="meta analysis" OR TS="meta analyses" OR TS="evidence synthesis" OR TS=((metaanalysis*) OR meta analysis*) OR TS=meta-analysis* OR TS=(meta-reviews OR metareviews) OR TS="metasyntheses"	49702
10	OR/ 8-9	100026
11	7 AND 10 Limited 2019.12.1-2020.5.1	82

China National Knowledge Infrastructure

1	SU=COVID-19 OR SU=COVID19 OR SU=COVID-19 OR SU=COVID-2019 OR SU=SARS-CoV-19 OR SU=SARS-CoV-2019 OR SU=SARS-CoV-2 OR SU=SARS2 OR SU=2019-nCoV OR SU= 严重急性呼吸综合征冠状病毒 2 型 OR SU= 冠状病毒感染 OR SU= 武汉冠状病毒 OR SU= 武汉海鲜市场肺炎病毒 OR SU= 冠状病毒 2019 OR SU=2019 新型冠状病毒 OR SU=2019 新型冠状病毒感染 OR SU=2019 冠状病毒 OR SU= 新型冠状病毒 -19 OR SU= 冠状病毒	124367
2	SU= 系统评价 OR SU=meta 分析 OR SU= 荟萃分析 OR SU= 系统综述	51118
3	1 AND 2 limited 2019.12.1-2020.5.1	31

WanFang

1	主题 :COVID-19 OR 主题 :COVID19 OR 主题 :COVID-19 OR 主题 :COVID-2019 OR 主题 :SARS-CoV-19 OR 主题 :SARS-CoV-2019 OR 主题 :SARS-CoV-2 OR 主题 :SARS2 OR 主题 :2019-nCoV OR 主题 : 严重急性呼吸综合征冠状病毒 2 型 OR 主题 : 冠状病毒感染 OR 主题 : 武汉冠状病毒 OR 主题 : 武汉海鲜市场肺炎病毒 OR 主题 : 冠状病毒 2019 OR 主题 :2019 新型冠状病毒 OR 主题 :2019 新型冠状病毒感染 OR 主题 :2019 冠状病毒 OR 主题 : 新型冠状病毒 -19 OR 主题 : 冠状病毒	15469
2	主题 : 系统评价 OR 主题 :meta 分析 OR 主题 : 荟萃分析 OR 主题 : 系统综述	123
3	1 AND 2 limited 2019.12.1-2020.5.1	15

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1	((“COVID-19”[常用字段 : 智能] OR “ COVID19”[常用字段 : 智能] OR “ COVID-19”[常用字段 : 智能] OR “ COVID-2019”[常用字段 : 智能] OR “ SARS-CoV-19”[常用字段 : 智能] OR “ SARS-CoV-2019”[常用字段 : 智能] OR “ SARS-CoV-2”[常用字段 : 智能] OR “ SARS2”[常用字段 : 智能] OR “ 2019-nCoV”[常用字段 : 智能] OR “ 严重急性呼吸综合征冠状病毒 2 型 ”[常用字段 : 智能] OR “ 冠状病毒感染 ”[常用字段 : 智能] OR “ 武汉冠状病毒 ”[常用字段 : 智能] OR “ 武汉海鲜市场肺炎病毒 ”[常用字段 : 智能] OR “ 冠状病毒 2019”[常用字段 : 智能] OR “ 2019 新型冠状病毒 ”[常用字段 : 智能] OR “ 2019 新型冠状病毒感染 ”[常用字段 : 智能] OR “ 2019 冠状病毒 ”[常用字段 : 智能] OR “ 新型冠状病毒 -19”[常用字段 : 智能] OR “ 冠状病毒 ”[常用字段 : 智能]))	5531
2	“ 系统评价 ” [常用字段 : 智能] OR “meta 分析 ” [常用字段 : 智能] OR“ 荟萃分析 ” [常用字段 : 智能] OR“ 系统综述 ” [常用字段 : 智能]	19299
3	1 AND 2 2019-2020[日期]	10

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