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Evidence on the effectiveness and safety of pharmacological treatments for COVID-19: A rapid scoping review

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ABSTRACT

Objectives: The current global pandemic of Coronavirus Disease 2019 (COVID-19) has produced a high burden of disease and mortality. For current research efforts to support optimal decision-making for front-line healthcare workers, rigorous and systematic knowledge synthesis must be made available.

Design: Rapid scoping review

Setting: Secondary care

Participants: Adults of any age treated for COVID-19

Interventions: Pharmacologic interventions for COVID-19

Primary and secondary outcome measures: Lab-confirmed coronavirus infection (primary outcome of interest), hospitalization, Intensive Care Unit (ICU) admission, mortality, and adverse events (e.g., cardiovascular events, changes in liver enzymes, thromboembolism)

Results: The search and screening identified 152 potentially relevant full-text articles, of which 107 were excluded, resulting in 28 articles (8 randomised controlled trials, 1 quasi-randomised trial, and 19 cohort studies). The most commonly studied interventions were antiviral drugs, followed by hydroxychloroquine/chloroquine, corticosteroids, monoclonal antibodies, convalescent plasma, immunoglobulins, and interferons. Reported outcomes included admission to intensive care unit or need for mechanical ventilation, changes in pneumonia symptoms, morality, and adverse events. Overall results from the studies were inconclusive or conflicted with one another, preventing any clearly effective treatment candidates from being identified. Additionally, some potentially serious adverse events such as ventricular arrythmia have been reported in relation to interventions like hydroxychloroquine/chloroquine; highlighting the need to carefully evaluate the safety of interventions as well as their effectiveness.

Conclusions: The current body of evidence shows there are a number of pharmacologic treatment options under study; however, results regarding their effectiveness have been inconclusive. The need for evidence to support clinical guidance during the rapidly evolving COVID-19 global pandemic show an ideal use for responsive knowledge synthesis methods. Specifically, a living systematic review and network meta-analysis of all potential COVID-19 treatments under study in human trials would provide a current and reliable source of evidence to support treatment decisions.

Keywords: COVID-19; RESPIRATORY MEDICINE; Clinical trials<THERAPEUTICS

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Automated search and screening techniques allowed for a more comprehensive search to be conducted compared to non-automated searches
- The reduced workload from implementing automated search and screening allowed for more rigorous review methods to be used despite the short timeline
- Information sources still had to be carefully selected to complete the project on a short timeline and some international sources could not be searched

INTRODUCTION

The current global pandemic of Coronavirus Disease 2019 (COVID-19) has resulted in a high burden of disease and mortality worldwide [1, 2]. Aside from a recent trial of dexamethasone, a corticosteroid, that reduced 28-day mortality in people requiring oxygen or mechanical ventilation, there are few studies providing strong evidence to support specific pharmacological treatments for COVID-19 [3]. The lack of clearly promising treatments for COVID-19 has resulted in the almost constant production of trials and observational studies testing potential pharmacological options. Attempts to synthesize this evidence thus far have resulted in various reviews focusing on single drugs or isolated drug classes [4-10]. While attempts to leverage this disparate evidence into clinical guidelines have produced weak recommendations that provide little direction for pharmacological treatment of COVID-19 [11-13]. For these research efforts to support optimal decision-making for front-line healthcare workers, rigorous and systematic syntheses that compare all of the current evidence must be available.

The objective of this rapid scoping review was to identify pharmacological interventions for COVID-19 that were evaluated in human studies to determine if there is any evidence of their effectiveness or safety.

METHODS

The rapid scoping review conduct was guided by the updated Joanna Briggs Guide [14] for scoping reviews, alongside the World Health Organization (WHO) Guide to rapid reviews [15]. The protocol for the review was registered using the Open Science Framework (https://osf.io/ypz7x). An integrated knowledge translation approach was used to engage with the knowledge users from Health Canada throughout the conduct of the rapid review including during: research question development, literature search, study inclusion, interpretation of

results, and draft report. The knowledge user also commissioned our team to conduct a prior rapid review focusing on antiviral or antibody treatments for COVID-19 that was published as a pre-print article [16] so some of the studies reported in that review are also reported in this manuscript given the overlap in subject matter. Reporting of results was guided using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension to Scoping Reviews (PRISMA-ScR) Statement [17] (Appendix 1); as a PRISMA extension specific to rapid reviews is currently under development.

Patient and Public Involvement

Since this work was carried out as part of a rapid response to the COVID-19 pandemic project timelines did not allow for participation of any patients or members of the public in this scoping review.

Literature search

Comprehensive literature searches and automated search and citation screening [18] were used in combination to gather relevant evidence from MEDLINE, EMBASE, Cochrane library, and pre-print servers (biorxiv/medrxiv). Grey (i.e., difficult to locate or unpublished) literature was searched via international clinical trial registries (e.g., clinical trials.gov, European Union [EU] clinical trial register, Chinese Clinical Trial Registry, WHO international clinical trials register) and Google Scholar. The EMBASE search strategy is available in Appendix 2.

The literature was searched from inception up to and including May 21, 2020. Titles and abstracts from public archives were identified for screening using Continuous Active Learning® (CAL®) [18], which uses supervised machine learning. For archives that could be retrieved in their entirety (e.g., MEDLINE), the entire archive was processed and searched using CAL®. For those archives that could only be accessed using keywords (e.g., clinicaltrials.gov), broad

relevant search terms were applied (e.g., COVID-19, treatment). CAL® then identified and ranked the titles and abstracts most likely to meet specific inclusion criteria, based on the screening results that were previously identified and reviewed. This process continued iteratively until none of the identified articles met the inclusion criteria. The automated search was supplemented by searching unique citations that were not available in MEDLINE via EMBASE. Hence, a combination of an automated search plus an electronic literature search of EMBASE was conducted.

Eligibility criteria

The eligibility criteria followed the PICOST framework and consisted of:

- Population: Individuals of any age diagnosed with COVID-19.
- Intervention: Antiviral agents, antibiotics, antiparasitics, antimalarials, interferons, non-specific anti-inflammatories, anticoagulants, immunosuppressive therapies, monoclonal antibodies, kinase inhibitors, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, convalescent plasma, intravenous immunoglobulin, interleukin inhibitors, and other compounds under investigation in human clinical trials as potential COVID-19 therapies (see Appendix 3). Chinese medicine and complementary and alternative medicine – either alone or in combination with these medications – were excluded.
- Comparator: Any of the interventions listed above, no intervention, or placebo.
- Outcomes: Lab-confirmed coronavirus infection (primary outcome of interest), hospitalization, Intensive Care Unit (ICU) admission, mortality, and adverse events (e.g., cardiovascular events, changes in liver enzymes, thromboembolism).
- Study designs: Randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs, e.g., such as quasi-RCTs, non-randomized trials, interrupted time series, controlled

before-after), and observational studies (e.g., cohort, case control) were included. Studies must have a control or comparator in order to be eligible for inclusion and as such, cross-sectional, case series, case reports, and qualitative studies were excluded.

- Time periods: All periods of time and duration of follow-up were included.

Study selection

In order to meet the short timeline requested by the knowledge users, a streamlined approach to study selection was employed. An automated approach to initial screening with CAL® was used to process all results from the database search (Embase) and other sources (e.g., Medline, Cochrane Library, clinical trial registries) to identify the most relevant citations that were then retained for further for full-text screening [18]. A calibration exercise was conducted prior to full-text screening using a random sample of 10 articles until reviewers reached at least 75% agreement. A screening form based on the eligibility criteria was prepared for reviewers to aid in making consistent judgements on article relevance. Subsequently, screening was completed by a single reviewer and verified by independent secondary reviewers whereby one secondary reviewer screened a sample of excluded citations (approximately 500) and another secondary reviewer screened all excluded full-text studies.

Data items and data charting

A charting form was developed and calibrated amongst the entire review team using two randomly selected full-text articles to ensure a standard approach to data collection. Following successful completion of the calibration exercise, included studies were charted by single reviewers and all outcome data were verified by a second reviewer to ensure accuracy. As this project was a scoping review, quality appraisal of included studies was not conducted.

The items collected in data charting included study characteristics (e.g., study duration, study design, country of conduct), patient characteristics (e.g., type of diagnosis, mean age, co-morbidities), intervention details (e.g., type of intervention, dose, timing of treatment), comparator details (e.g., comparator intervention, dose), and outcome results (e.g., hospitalizations due to coronavirus, adverse events, mortality) at the longest duration of follow-up.

Synthesis

The characteristics of the included studies were summarized narratively and the results were summarized descriptively including summary statistics. Detailed tables of study characteristics and results were prepared to support the data presented in the text; tables of study results are organized according to study design.

RESULTS

Literature Search

The database search, grey literature search, and automated screening returned a total of 2,075 potentially relevant citations, of which 1,923 were excluded after further review. This left 152 articles to undergo full-text screening; 107 were excluded subsequently, resulting in 28 articles included in the review (Figure 1; Appendix 4).

Characteristics of included studies

Of the 28 studies included in this review, 8 were randomised controlled trials, 1 was a quasi-randomised controlled trial, and 19 were cohort studies. The majority of included articles (n=16) were obtained from pre-print servers and the rest (n=12) were published in peer-reviewed journals. All included studies were published in 2020, with the majority conducted in China (n=17), followed by the USA (n=6), and single studies each from Brazil, France, Hong Kong,

Spain, and South Korea; all articles were published in English or had English translations available. Sample sizes for the controlled trials ranged from 28 to 236 participants, while the cohorts ranged from 21 to 1,820 participants. All of the studies were conducted in adult populations ranging from 38 to 68 years and 45 to 62 years for the controlled trials and cohort studies, respectively. Comorbidities were reported in most of the studies (n=25) and commonly included conditions such as diabetes, heart disease, hypertension, and renal failure (Table 1; Appendix 5)

Interventions examined in the included studies

The most commonly studied interventions were antiviral therapies including lopinavir/ritonavir (Kaletra), umifenovir (Arbidol), oseltamivir, ganciclovir, favipravir, and remdesivir (n=11) as well as lopinavir/ritonavir combined with interferons (n=1), and the drugs hydroxychloroquine and chloroquine either alone (n=10) or combined with azithromycin (n=3). The next most common treatment categories were corticosteroids (n=5), monoclonal antibodies (n=2), convalescent plasma (n=1), immunoglobulins (n=1), and interferons (n=1; Table 1; Appendix 5).

Outcomes reported in the included studies

All of the included studies reported exclusively on hospitalized patients, thus there are no results for the specific outcome 'hospitalization' that was included in the review protocol. The most commonly reported outcome was mortality (n=22), followed by adverse events (n=14), transfer to ICU or initiation of mechanical ventilation (n=11), and finally, evidence/progression of pneumonia (n=5; Table 1; Appendix 5).

205 *Table 1: Summary of study and patient characteristics*

Characteristics (value type)	**Controlled Trials (n=9)**	**Cohort Studies (n=19)**
Age (years) of population *(range)*	44.7 – 62	37.9 – 68
Sample size *[median (range)]*	127 (28 – 236)	181 (21 – 1820)
Study duration (days) *[median (range)]*	21 (10 – 39)	38.5 (7 – 122)
Comorbidities reported in study population	Yes (8)/No (1)	Yes (17)/No (2)
Publication Type		
Pre-print server	4	12
Peer-reviewed journal	5	7
Country of conduct		
	China (6); USA (1); Brazil (1); Hong Kong (1)	China (11); USA (5); France (1); Spain (1); South Korea (1)
Interventions*		
Antivirals *(lopinavir/ritonavir, umifenovir, favipravir, ganciclovir, oseltamivir, remdesivir)*	4	7
+interferon	1	--
Hydroxychloroquine, Chloroquine	3	7

+antibiotics	--	3
Convalescent Plasma	--	1
Corticosteroids	1	4
Immunoglobulins	--	1
Interferons	--	1
Monoclonal Antibodies *(meplazumab, tocilizumab)*	1	1
Outcomes Reported		
ICU admission/Mechanical ventilation	5	6
Clinically confirmed pneumonia	3	2
Mortality	7	16
Adverse Events	8	6

*Total number of interventions exceeds the number of included studies due to the presence of combination therapies and studies with more than 2 treatment arms or active comparator groups

Results from studies of antiviral treatment

Four RCTs [19-22] and seven cohort studies [23-29] examined antiviral medications including lopinavir/ritonavir (n=6), umifenovir (n=5), lopinavir/ritonavir + umifenovir (n=2), lopinavir/ritonavir + interferon beta-1b (n=1), favipravir (n=1), ganciclovir (n=1), oseltamivir (n=1), and remdesivir (n=1). Outcomes reported among these studies include ICU admission/mechanical ventilation (n=4), confirmation of or changes in pneumonia (n=4), mortality (n=8), and adverse events (n=7).

Three controlled trials [19, 21, 22] found that fewer patients in the antiviral treatment group (remdesivir, umifenovir, lopinavir/ritonavir) were admitted to ICU or required mechanical ventilation compared to control; however, the differences were not statistically significant (data not shown, Table 2, Appendix 6). Two cohort studies [23, 29] found signs of improvement in pneumonia in patients treated with lopinavir/ritonavir + umifenovir and with umifenovir alone, the difference was only statistically significant for lopinavir/ritonavir + umifenovir compared to umifenovir alone (69% showing improvement vs 25%; $p<0.05$). Of the eight studies reporting mortality outcomes, three controlled trials [20-22] and one cohort study [24] examining umifenovir, favipravir, lopinavir/ritonavir, and lopinavir/ritonavir + interferon beta-1b reported no deaths in their patient population at study end. One controlled trial [19] and one cohort study [25] found non-statistically significant reductions in mortality for patients treated with remdesivir compared to placebo (1.1; 95% confidence interval (CI) -8.1% to 10.3%) and lopinavir/ritonavir + umifenovir compared to lopinavir/ritonavir (2.6% v 2.9%), and two cohort studies [27, 28] found no difference in mortality rates between patients treated with antivirals compared to corticosteroids (data not shown, Table 2, Appendix 6).Four trials [19-22] and three cohort studies [24, 26, 29] examining antiviral therapies reported adverse events including gastrointestinal symptoms (n =5), arrythmia or abnormal ECG findings (n=1), and changes in liver function (n=4; Table 2, Appendix 6).

Results from studies of hydroxychloroquine and chloroquine

Three controlled trials [30-32] and seven cohort studies [24, 33-38] examined hydroxychloroquine either alone (n=10) or combined with azithromycin (n=3) compared to control/standard care (n=6) or other treatments (n=3), and one study compared low-dose to high-dose chloroquine. Outcomes reported among these studies included ICU admission/mechanical

ventilation (n=6), confirmation of or changes in pneumonia (n=1), mortality (n=7), and adverse events (n=6).

Three cohort studies [33, 34, 37] reporting ICU admission or mechanical ventilation found a decrease in admission rates for patients taking hydroxychloroquine + azithromycin (hazard ratio [HR] 0.43; 95% CI 0.16 to 1.12) and hydroxychloroquine alone (relative risk [RR] 0.91; 95% CI 0.47 to 1.8 and RR 0.81; 95% CI 0.55 to 1.18) compared to control, but the differences were not statistically significant. Two cohort studies [24, 35] also found that fewer patients taking hydroxychloroquine were admitted to ICU compared to hydroxychloroquine + azithromycin (9 patients vs 21, statistical significance not reported) or lopinavir/ritonavir (1 patient vs 4, p=0.375). In contrast, two cohort studies [33, 36] found patients taking hydroxychloroquine had non-statistically significant increased risk of being admitted to ICU compared to control (HR 1.43; 95% CI 0.55 to 3.79 and 19.2% vs 12.2%, statistical significance not reported) and one cohort study [36] found more patients taking hydroxychloroquine and azithromycin were admitted to ICU compared to control (30.7% vs 12.2%, statistical significance not reported). One trial found [31] that more patients taking hydroxychloroquine showed improvement in pneumonia symptoms compared to control (80.6% vs 54.8%, statistical significance not reported). Three cohort studies [30, 33, 38] reporting mortality found statistically significant results, Yu et al. (2019) found a statistically significant decrease in the risk of death (P<0.001) in the hydroxychloroquine group compared to control while Magagnoli et al. (2020) found a significant increase in the risk of death from any cause after adjusting for age, race, sex, body mass index, comorbid conditions, and clinical characteristics at hospital admission (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P=0.03) in patients treated with hydroxychloroquine compared to control. There was a trend for increased mortality in patients treated with hydroxychloroquine

plus azithromycin compared to control (adjusted HR; 1.14; 95% CI, 0.56 to 2.32; P=0.72), yet this was not statistically significant[33]. The trial by Borba et al. (2020) comparing different dosage regimens of chloroquine also found a statistically significant increase in the risk of death associated with the higher-dose regimen (odds ratio [OR] 3.6; 95%CI, 1.2-10.6) however the statistical significance of the association was no longer present when adjusted for age (OR 2.8; 95% CI 0.9 to 8.5). Three cohort studies [34, 36, 37] reported non-statistically significant decreases in risk of mortality among patients taking hydroxychloroquine compared to control (RR 0.61; 95% CI 0.13 to 2.89; RR 0.95; 95% CI 0.74 to 1.23; RR 0.56; 95% CI 0.26 to 1.21) and one cohort study [24] comparing hydroxychloroquine, lopinavir/ritonavir, and a standard care control group reported no deaths among any of the treatment groups at study end. Two cohort studies [33, 36] reporting mortality also found an increased risk of death for patients taking hydroxychloroquine (adjusted HR 1.08; 95% CI 0.63 to 1.85) and hydroxychloroquine + azithromycin (adjusted HR 1.35; 95% CI 0.76 to 2.4 and HR 1.14; 95% CI 0.56 to 2.32) but the association was not statistically significant. Adverse events were reported in three trials [30-32] and three cohort studies [24, 35, 36] and included decreased hemoglobin (n=1), increased creatinine/creatinine phosphokinase (n=1), altered liver function (n=1), rash (n=1), headache (n=1), gastrointestinal symptoms (n=1), and arrythmia or abnormal ECG findings (n=3; Table 2, Appendix 6).

Results from studies of corticosteroid treatments

Four cohort studies [27, 28, 39, 40] and one RCT [41] examined corticosteroid therapy including adjuvant corticosteroids added to antiviral therapy (n=2), early administration of corticosteroids (n=1), corticosteroids compared to standard care (n=1), and methylprednisolone compared to

lopinavir/ritonavir (n=1). Outcomes reported among these studies include ICU admission/mechanical ventilation (n=1) and mortality (n=5).

One controlled trial [41] reported rates of admission to ICU and found that early corticosteroid treatment (defined as within 48 hours of admission) statistically significantly reduced the risk of transfer to ICU (OR 0.47; 95% CI 0.25 to 0.88) or need for mechanical ventilation (OR 0.47; 95% CI 0.25 to 0.92; p=0.025). Two studies reporting on mortality found statistically significant results, one trial [41] found early corticosteroid treatment (received within 48 hours of hospital admission) statistically significantly reduced the risk of death compared to control (OR 0.45; 95% CI 0.22 to 0.91; p=0.024) and one cohort study [39] found in-hospital mortality was statistically significantly higher in patients receiving corticosteroids compared to control (HR 1.77; 95% CI 1.08 to 2.89; p=0.023). The three other cohort studies that reported mortality rates also found divergent results: one study [27] found corticosteroids had no effect on risk of death (OR 1.05; 95% CI -1.92 to 2.01), one study [28] reported two deaths in the corticosteroid treatment arm compared to one death in patients treated with antivirals (statistical significance not reported), and the third study [40] reported no deaths in either the corticosteroid treatment group or control (Table 2, Appendix 6).

Results from studies of immune supporting therapies

Five studies examined immune supporting/modifying therapies such as meplazumab (one controlled trial), tocilizumab (one cohort study), interferon beta-1b (one cohort study), intravenous immunoglobulin (one cohort study), and convalescent plasma (one cohort study). Outcomes reported among these studies include ICU admission (n=1), mortality (n=5), and adverse events (n=2).

The trial [42] comparing meplazumab to a standard care control arm found a greater rate of recovery from ICU and hospital discharge in patients receiving meplazumab (n=11) compared to control (n=5, p=0.021) and reported no deaths. The cohort study [43] examining tocilizumab only reported on mortality rates and found a significantly increased survival rate in the treatment group compared to control (61.36% vs 48%, p<0.00001). The remaining three cohort studies [44-46] that reported mortality found no statistically significant differences between treatment and controls for intravenous immunoglobulins (33 patients vs 21 patients, p=0.222), interferon beta-1b (20.8% vs 27.3%, p=0.229), and convalescent plasma (5 patients vs 14 patients, p=0.5). Adverse events were reported in two studies: one trial [42] found altered liver function (elevated ALT/AST ≥2 ULN) in patients receiving meplazumab that lasted for the duration of treatment and the cohort study [46] reported no adverse events associated with treatment with convalescent plasma (Table 2, Appendix 6).

315 *Table 2: Summary of Effectiveness and Safety Results*

Treatment comparisons	**ICU admission/ Mechanical ventilation[a]**		**Pneumonia[a]**		**Mortality[a]**		**Adverse Events[a]**	
	Trial	**Cohort**	**Trial**	**Cohort**	**Trial**	**Cohort**	**Trial**	**Cohort**
Antivirals vs control	3+			2+	4+	1+	2[b]	2
vs antivirals				**1+**		1+	2	1
vs corticosteroids						2		
Antimalarials vs control		3+/2-	1+			4+/**1+/2-**	2	
vs high dose					**1-**		1	
vs antimalarial +antibiotic		1+/3-						2
vs antivirals		1+				1+		1
Antimalarial + antibiotic vs control		1+/1-			1-	1-		
Corticosteroids vs control						1+/2-		
vs early administration	**1+**				**1+**			

vs antivirals				1-	
Monoclonal antibodies vs control	**1+**		1+	**1+**	1
Interferons vs control				1+	
Intravenous immunoglobulin vs control				1-	
Convalescent plasma vs control				1+	1+

[a]Bolded values indicated statistically significant outcomes

[b]No symbol indicates results that did not indicate direction of effectiveness of intervention

+ study results indicate: decreased risk of or number of patients admitted to ICU/receiving mechanical ventilation or mortality; improvement in symptoms/clinical signs of pneumonia

- study results indicate: increased risk of or number of patients admitted to ICU/receiving mechanical ventilation or mortality; worsening symptoms/clinical signs of pneumonia

DISCUSSION

We completed a rapid scoping review for Health Canada to identify which pharmacologic interventions have been studied to treat patients with COVID-19. A comprehensive search of electronic databases, trial registries, and other grey literature sources identified 9 controlled trials and 19 cohort studies lasting between 7 and 122 days that included approximately 8,000 patients examining various interventions for COVID-19.

It is important to emphasize that a scoping review cannot be used to establish practice or policy recommendations, as the purpose is to provide an overall summary of the literature that has been conducted on a given concept [14]. The current evidence indicates there is a broad range of interventions under study and that there is a heavy emphasis on antivirals, antimalarials, and corticosteroids in the current literature. The results of the studies that are available thus far often report conflicting results on the effectiveness of interventions such as hydroxychloroquine, corticosteroids, and antivirals. Additionally, the majority of the available evidence comes from observational cohort studies, mostly retrospective, and do not include some of the most recent data from large scale trials (e.g., RECOVERY in the UK) or include trials for treatments like anticoagulants for patients at high risk of clots due to COVID-19. Some adverse events have been reported in relation to interventions such as hydroxychloroquine/chloroquine (ventricular arrythmia or abnormal ECG findings) which indicate both safety and effectiveness need to be explored in future studies before they could be considered for use in COVID-19 treatment.

This review is part of a rapidly growing body of knowledge synthesis products related to treatments for COVID-19, currently there are 184 treatment reviews registered in the PROSPERO database. To date the published reviews focus on single treatments or single classes of drugs [4-10] and to our knowledge, there is no other published review examining more than

one type of potential COVID-19 treatment. The results of these prior reviews are concordant with our findings, reporting little certainty in the clinical potential of the interventions they have examined and often finding conflicting results between individual studies. Future efforts in this area should focus on using living systematic review methods to keep pace with the rapid growth of evidence and network meta-analysis methods to allow indirect comparisons of the effectiveness and safety of all treatments of interest in the clinical community such as antivirals, monoclonal antibodies, corticosteroids, or antimalarial drugs.

There are several strengths to the conduct of this rapid scoping review. The integration of machine learning allowed for a much more comprehensive search to be completed in a shorter time while also reducing the workload on reviewers so that more robust rapid review methods such as using a single reviewer plus verifier for study selection and data charting could be used. There are some limitations to this review however, as the number of information sources searched had to be narrowed to accommodate rapid timelines and may have resulted in some studies being missed. Nonetheless, the methods used in this review were thoughtfully selected according to our knowledge user needs and the urgent need to provide timely results.

CONCLUSIONS

The current state of research for COVID-19 therapies shows a broad range of pharmacologic options have been evaluated and have largely resulted in inconclusive or conflicting findings regarding their effectiveness. Additionally, the evidence reported here is largely observational and does not include a number of large-scale trials that are ongoing but have not yet reported results. The urgent need for evidence to support clinical guidance and the rapidly evolving nature of the COVID-19 global pandemic point to a need for responsive knowledge synthesis methods. Specifically, a living systematic review and network meta-analysis of all potential COVID-19

treatments under study in human trials would provide an ongoing and timely source of high-quality evidence to support clinical decision making.

List of abbreviations

AST/ALT: aspartate transaminase/alanine aminotransferase

CAL: Continuous Active Learning

COVID-19: Coronavirus disease 2019

HR: hazard ratio

ICU: Intensive Care Unit

NRCT: non-randomized clinical trial

OR: odds ratio

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension to Scoping Reviews

RCT: randomized controlled trial

RR: relative risk

WHO: World Health Organization

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors have no competing interests to declare.

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Authors' contributions

PR screened full-text articles, abstracted and verified data, interpreted results and wrote the manuscript; AR, ND, JA, CW, and NR screened full-text articles, abstracted or verified data, and reviewed the manuscript; BP, GVC, and MG developed and ran the automated search and citation screening process and reviewed the manuscript; MPM reviewed and edited the

manuscript; SES and ACT developed the protocol, obtained funding, developed review methods, interpreted results, and edited the manuscript.

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Additional File

File Format: Microsoft Word (.docx)

Title of Data: Additional File 1 (Appendices 1-6)

Description of Data: The appendices include the following additional information:

Appendix 1 – PRISMA-ScR checklist

Appendix 2 – Embase literature search

Appendix 3 – Interventions of interest

Appendix 4 – Studies excluded during full-text screening

Appendix 5 – Detailed study and patient characteristics

Appendix 6 – Detailed effectiveness and safety results

FIGURE LEGEND

Figure 1. Flow chart of studies included in the review

Study flow diagram.

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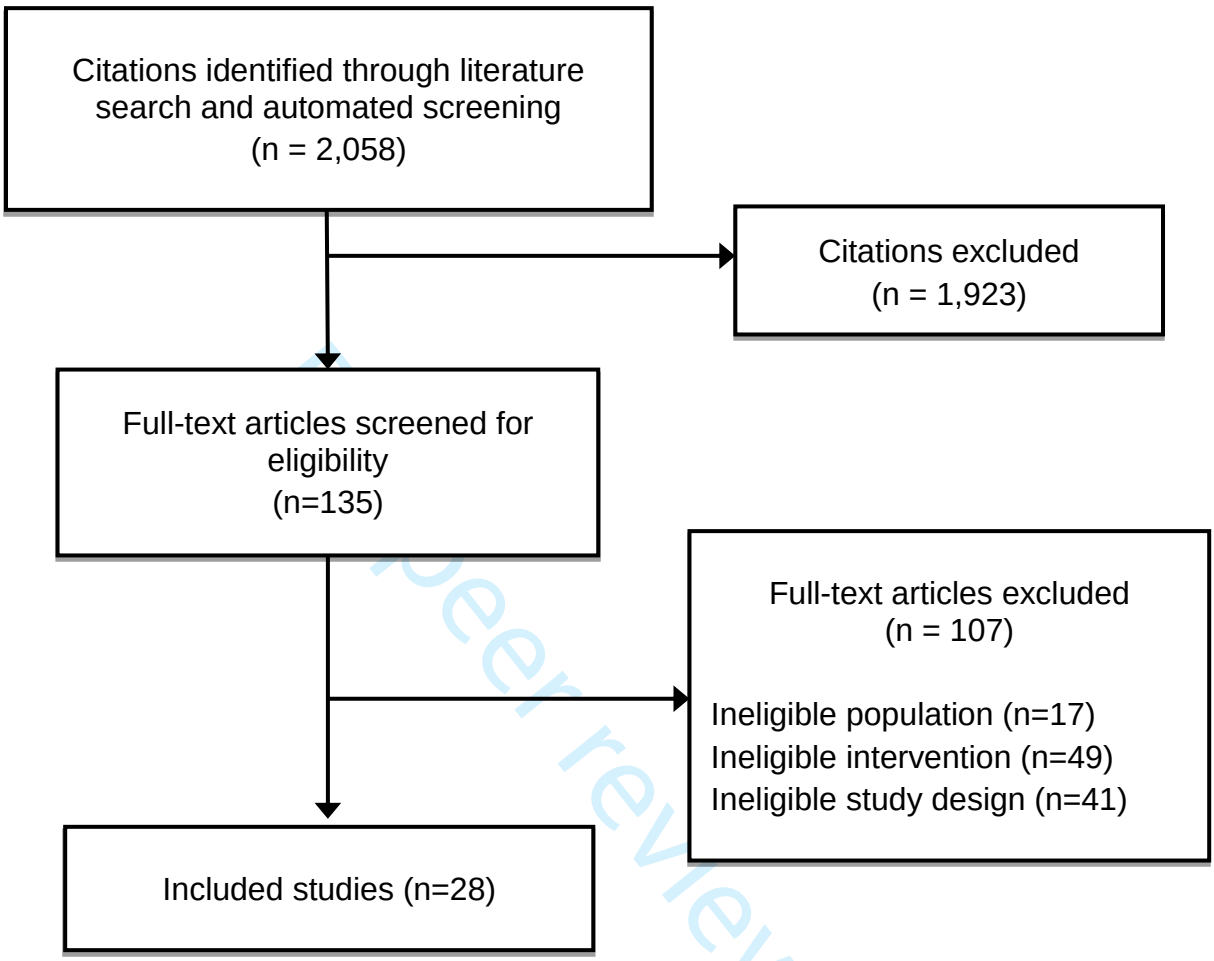

Appendix 1 – PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	3
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4-5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4, Appendix 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5-6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6

Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7, Figure 1, Appendix 4
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8-9, Table 1, Appendix 3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9-14, Table 2, Appendix 5
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	9-14, Table 2
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17, Table 2
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	17-18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	20

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Appendix 2 – Embase literature search

Database: Embase <1974 to 2020 May 01>

Search Strategy:

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1 exp coronaviridae/ or exp Coronaviridae infection/ or exp Coronavirus infection/ or SARS coronavirus/

2 ((wuhan or hubei or huanan) and (severe acute respiratory or pneumonia* or virus*) and outbreak*).mp.

3 (coronavir* or "corona virus*" or "coronavirus pneumonia" or betacoronavir* or COVID or COVID-19).mp.

4 ("nCoV" or "cov 2" or cov2 or 2019ncov or 2019-nCoV or "2019 ncov" or "2019-ncov" or "2019 novel cov" or "2019 ncov disease*" or "2019 novel coronavirus*").mp.

5 ("severe acute respiratory syndrome coronavirus*" or "wuhan virus*" or "sars cov 2 mers" or "middle east respiratory syndrome*" or "Severe Acute Respiratory" or SARS or SARS-CoV or SARScov2 or MERS-CoV).mp.

6 or/1-5

7 exp Interferons/ or interleukin-2/ or exp Immunoglobulin/ or anakinra/ or Sarilumab/ or Siltuximab/ or tumor necrosis factor/ or granulocyte macrophage colony stimulating factor/ or beta1a interferon/ or interferon beta serine/

8 (interferon* or "Interferon-alpha" or "Interferon-beta" or "avonex" or "interferon beta-1a" or "Betaseron" or "Extavia" or "betaferon" or "beneseron" or "beta 1-b interferon" or "recombinant interferon beta-1b" or "Rebif" or "Interferon-gamma" or immunoglobulin* or "immuno globulin*" or "immune-globulin*" or anakinra or kineret or Sarilumab or kevzara or regn88 or sar153191 or Siltuximab or sylvant or cnto328 or "cnto 328" or "tumor necrosis factor*" or "tumor necrosis serum*" or cachectin or cachetin or "anti-TNF-alpha" or "TNF alfa" or "TNF alpha" or anti-granulocyte macrophage or anti-GM-CSF or "GM CSF" or gmcsf or Flebogamma or Gamunex or "Globulin-N" or "Globulin N" or Intraglobin Gammagard or Gamimune or Gamimmune or Privigen or Sandoglobulin or Venoglobulin or "Venoglobulin-I" or "Venoglobulin I" or Venimmune or Iveegam or Alphaglobin or Endobulin or "Gamimune N" or "Gamimmune N" or Gammonativ or beriglobin or biggam or carimune or cuvitru or gammagen or gammaplex or gamunex or hizentra or kiovig or norga or panzyga or sandoglobulin* or subcuvia or venogamma or vigam or interleukin-2 or interleukin).tw.

9 umifenovir/ or riamilovir/ or favipiravir/ or sofosbuvir/ or Arbidol/ or Galidesivir/

10 (Favipiravir or Triazavirin or Umifenovir or riamilovir or sofusbivir or sofosbuvir or sovaldi or psi7851 or psi7976 or psi7977 or "EIDD-2801" or "EIDD 2801" or arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.

11 Darunavir/ or Lopinavir/ or Ritonavir/ or danoprevir/ or remdesivir/

12 (ASC09 or Azvudine or Danoprevir or Darunavir or Lopinavir or ritonavir or Remdesivir or "gs 5734" or "gs5734" or prezista or "tmc 114" or tmc114 or "uic 94017" or uic94017 or abt378 or norvir).tw.

13 baloxavir marboxil/ or baloxavir marboxil.tw.

14 exp antimalarial agent/ or exp quinoline derivative/

15 (Amodiaquine or Basoquin or Camoquin or Flavoquine or Chloroquine or Resochin or Dawaquin or Lariago or Aarlen or Hydroxychloroquine or Hydroxy-chloroquine or chloroquinol or hydrochloroquine or hydrocloroquine or oxychloroquine or quensyl or "sn 8137" or ercoquin or Plaquenil or Hydroquin or Axemal or Dolquine or Quensyl or Quinoric or Imiquimiod or Aldara or Vyloma or Zyclara or Primaquine or Jasoprim or Malirid or Neo-Quipenyl or Pimaquin or Pmq or Primachina or Primacin or Primaquina or Primaquine or Primaquine or Remaquin or Tafenoquine or Krinfatel or Kozenis or Arakoda or Krintafel or Pamaquine or Plasmochin or Plasmoquine or Plsamaguine or Neo-Quipenyl or Primachin or Dihydroartemisinin or Mefloquine or lariam or laricam or mefliam or mephaquin* or tropicur or Nitazoxanide or Alinia or colufase or daxon or heliton or "salicylamide acetate" or nodik or "ph 5776" or ph5776 or ambilhar or "ba 32644" or ba32644 or "ciba 32644 ba" or "ciba 32644ba" or ciba32644ba or niradazol* or nitrothiamidazol* or nitrothiazole or "nsc 136947" or nsc136947 or yarocen or Nitrothiazole or Amokin or amokine or anoclor or aralan or aralen or arechin or arechine or arequine or arthrochin or arthrochine or arthroquine or artrichin or artrichine or artriquine or avloclor or bemaphata or bemaphate or bemasulph or bipiquin or cadiquin or chemochin or chemochine or chingamine or chingaminum or chloraquine or chlorochin or chlorochine or chlorofoz or chloroquin or chloroquin* or cidanchin or "clo-kit junior" or clorichina or clorichine or cloriquine or clorochina or delagil or delagyl or dichinalex or diclokin or diquinalex or diroquine or emquin or genocin or gontochin or gontochine or gontoquine or heliopar or imagon or iroquine or klorokin or klorokine or klorokinfosfat or lagaquin or malaquin or malarex or malarivon or malaviron or maliaquine or maquine or mesylith or mexaquin or mirquin or nivachine or nivaquin* or roquine or quinachl or quingamine or repal or resochen* or resochin or resochina or resochine or resochinon resoquina or resoquine or reumachlor or roquine or rp3377 or sanoquin or sanoquine or silbesan or siragan or sirajan or sn7618 or solprina or solprine or tresochin or tresochine or tresoquine or trochin or trochine or troquine).tw.

16 suramin/

17 (Carriomycin or Suramin).tw.

18 exp steroid/ or exp meprednisone/ or exp corticosteroid/ or fingolimod/ or leflunomide/ or thalidomide/

19 (steroid* or methylprednisone or meprednisone or Prednisolone or Fluprednisolone or Corticosteroid* or Fingolimod or Leflunomid* or Thalidomid*).tw.

20 ruxolitinib/

21 (Jakotinib or Ruxolitinib).tw.

22 exp monoclonal antibody/

23 (Ruxolitinib or Tocilizumab or Adalimumab or Camrelizumab or Eculizumab or Mepolizumab or "PD-1 mAb" or Tocilizumab or Adamumab or tozumab or meplazumab or monoclonal antibod*).tw.

24 ("SARS-Cov-2 specific neutralizing antibod*" or "SARS-Cov specific neutralizing antibod*" or "MERS-Cov specific neutralizing antibod*" or "Anti C5a monoclonal antibod*").tw.

25 acetylcysteine/ or exp angiotensin receptor antagonist/ or exp angiotensin derivative/ or exp dipeptidyl carboxypeptidase inhibitor/ or citrate potassium/ or glycyrrhizic acid/ or dipyridamole/ or hydrogen peroxide/ or polyinosinic polycytidylic acid/ or thymosin/ or ascorbic acid/

26 (Acetylcysteine or Angiotensin or Angiotensin or "ACE inhibitor*" or ACE-2 or "Angiotensin II receptor blocker*" or ARBs or "potassium citrate" or Bromhexine or "Diammonium glycyrrhizinate" or Glycyrrhizic or Dipyridamole or Ebastine or "Hydrogen peroxide" or Pirfenidone or Polyinosinic-polycytidylic or "Polyinosinic-polycytidylic" or "Poly I-C" or "rhG-CSF" or Thymosin* or Tranilast or "Vitamin C" or "Ascorbic Acid*").tw.

27 ("inhal*" adj2 gas*).tw.

28 Cyclosporine/

29 (Cyclosporin or cequa or "cgc 1072" or "cgc1072" or ciclomulsion or cyclasol or de076 or deximune or implanta or imusporin or neuro-stat or neurostat or opsisporin or "otx 101" or padciclo or papilock or "sp 14019" or verkazia).tw.

30 Fenretinide/

31 (fenretinide or "mcn r 1967" or "4 hydroxyphenylretinamide" or Ifendopril).tw.

32 Dalteparin/ or enoxaparin/ or tinzaparin/ or fondaparinux/ or edoxaban/ or rivaroxaban/ or apixaban/ or betrixaban/ or heparin/ or danaparoid/ or warfarin/ or dabigatran.hw.

33 (dalteparin or fragmin* or "low liquemin" or enoxaparin or clexan or clexane or inhixa or lexane or lovenox or neoparin or neoparin-nx or thorinane or tinzaparin or innohep or logiparin or fondaparinux or quixidar or dabigatran or edoxaban or lixiana or roteas or savaysa or rivaroxaban or xarelto or "bay 59 7939" or apixaban or eliques or eliquis or warfarin or adoisine or carfin or coumadan or coumadin* or marevan or panwarfarin or panwarfin or sofarin or warnerin or betrixaban or bevyxxa or dexxience or heparin or Disebrin or hepalean or lipo-hepin or menaven or multiparin or nevparin or panheparin or panheprin or praecivenin or thrombareduct or thromboliquine or vetren or danaparoid or lomoparan or orgaran).tw.

34 (Azilsartan or candesartan or eprosartan or Irbesartan or telmisartan or valsartan or losartan or olmesartan).hw. or cobicistat/ or losartan/

35 (Azilsartan or Edarbi or "tak 536" or tak536 or candesartan or amcandin or amlodipine or amlopres or camlostar or candam or candeamio or candezek or caramlo or framsyl or unisia or zenicamo or Atacand or eprosartan or epratenz or futuran or naviten or navixen or regulaten or "skf 108566" or "skf108566" or tevesten or tevetan or teveten or tevetenz or Irbesartan or irbertan or Avapro or telmisartan or approvel or aprovel or "arbez lr" or avapro or ifirmasta or irban or irbetan or iretensa or irovel or irvell or karvea or sabervel or Micardis or valsartan or Diovan* or Prexxartan or saval or losartan or Cozaar or entrizen or lavestra or lorista or Olmesartan or Benicar or sarten or entresto or sacubitril or valsartan or byvalson or nebivolol or Aviptadil or Losartan or cozaar or cobicistat or tybost or actelsar or kinzal mono or kinzalmono or micardis or predxal or pritor or pritoral or semintra or telma-20 or tolura or angiosan or cordinate or dalzad ordiovan or diovane or kalpress or miten or nisis or prexxartan or provas or rixil or saval or tareg or tazea or troval or valpression or vals or valsocard or valtan or valtsu or alteis or belsar or benetor or benevas or benicar or cs866 or ixia or laresin or mencord or mesar or olartan or olmeblo or olmec or olmes or Olmesartan or olmetec or olpresor olsar or omesar or openvas or plaunac or rnh6270 or santini or sarten or tensar or tensiol or vivactra or votum or byvalson or cozaar).tw.

36 (benazepril or Captopril or Cilazapril or Enalapril or Fosinopril or Lisinopril or Perindopril Quinapril or Ramipril or Trandolapril).hw.

37 (Benazepril or Lotensin or Captopril or Benace or boncordin or briem or brien or "cgs 148241" or "cgs 14824a" or "cgs148241" or "cgs14824a" or cibace or cibacen* or fortekor or lotensin or tenkuoren or zinadril or ace-bloc or acenorm or acepress or acepril or aceprilex or aceril or aceten or adocor or alopresin or altran or apuzin or asisten or capace or capocard or caposan or capoten* capotril or capril or captace or captensin or capti or captoflux or captohexal or captolane or captomax or capton or captopren or captoprilan or captoril or captral or cardiopril or cardipril or catona or catoplin or catopril or cesplon or cryopril or debax or dexacap or dextro captopril or ecapres or ecaten or epicordin or epsitron or farcopril or farmoten or hiperil or hypopress or hypotensor or insucar or iopril or isopresol or katopil or ketanine or keyerpril or lapril or locap or lopirin or lopril or medepres or midrat or minitent or nolectin or "oltens ge" or petacilon or praten or primace or rilcapton or ropril or smarten or tenofax or tensicap tensiomen or tensiomin or tensobon or tensoprel or tensoril or tenzib or topace or toprilem or typril-ace or vasosta or zapto or orkaptil or Cilazapril or dynorm or inhibace or inibace or initiss or inocar).tw.

38 (justor or vascace or Enalapril or Vasotec or bpnorm or dynacil or eliten or fosenopril or fosinil or fosinonorm or fosinopril or fosinorm or fosipres or fositen or fositens or fovas or fozitec or monopril or newace or sapril or sq28555 or staril or vasopril or acerbon or alapril or alfaken or carace or cipril or coric or dapril or fibsol or inopril or linopril or linvas or lipril or lisi abz orlisibeta or lisigamma or lisihexal or lisinopril dihydrate or lisipril or lisodur or lisopress or lisopril orlisoril or lispril or listril or lysinopril or "mk 0521" or "mk 521" or "mk 522" or "mk0521or mk521" or "mk522" or noperten or novatec or presiten or prinil or prinivil or qbrelis or sinopril or tensopril or tensyn or vivatec or zestomax or zestril or Monopri or Lisinopril or Prinivil or Zestril or Perindopril or Coversyl or Quinapril or Accupril or accuprin or accupro or accupron or acequin or acuitel or acuprel or acupril or asig or "ci906" or conan or ectren or korec or quinalapril or quinaten or quinazi or quinhexal or quinipril or Ramipril or acovil or altace or carasel or cardace or corpril or delix or "hoe 498" or hypren or hytren or lostapres or ramace or ramilich or triatec or tritace or unipril or vesdil or vivace or Altace or Trandolapril or Mavik or gopten or Odace or odric or udrik).tw.

39 Colistin/ or (Teicoplanin or Ivermectin or azithromycin).hw.

40 (Colistin or belcomycin or colimycin* or belcomycin or Colicort or colimycin or colistine or colomycin or coly mycin or colymicin or multimycin or polymyxin or Teicoplanin or planium or tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichoplanin or teichoplanine or teicomid or teicopix or teiplamil or Planium or Tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichomycin or teichoplanin* or teicomid or teicopix or teiplamil or Ivermectin or Avermectin or cardomec or diapec or efacti or epimekor or eqvalan or eqvalenor or ivermectina or ivermectol or ivexterm or ivomec or mectizan or "mk 933" or "mk933" or oramec or quanox or revectina or securo or sklice or soolantra or stromectol or azithromycin or aruzilina or atizor or azadose or azasite or azatril or azenil or azibiot or azimin or azithral or azithromycin or azitrocin or azitromax azitromicin* or aziwok or azomyne or aztrin or azydrop or azyter or azithromycin or bazyt or "cp 62933" or "cp 62993" or "cp62933" or "cp62993" or erythromycin or Forcin or Inedol or infectoazit or "isv 401" or "isv401" or kromicin or macrozit or mezatrin or octavax or ordipha or ribotrex or sumamed or tobyl or tromix or trozocina or ultreon or vinzam or xithrone or "xz 450"

or "xz450" or Zaret or Zarom or zetamax or zeto or zibramax or zifin or zimericina or zistic or zithromax or zithrox or zitinn or zitrim or zitrobifan or zitrocin or zitromax or zmax).tw. (63618)

41 Tamoxifen.hw. or dasatinib/ or Epirubicin/ or Gemcitabine/ or Homoharringtonin/ or Imatinib/ or toremifene/ or Valrubicin/

42 (dasatinib or Ellence or Epirubicin* or epid or epifil or epiham or epilem or epirubicine or farmorrubicina or farmorubicin or pharmorubicin or Gemcitabine or difluorodeoxycytidine or Gemcite or gemtro or gemzar or infugem or "ly188011" or Homoharringtonine or harringtonine or omacetaxine or ceflatonin or omapro or synribo or Imatinib or "cgp 57148" or "cgp57148b" or gleevac or gleevec or glivec or glivic or ruvise or Tamoxifen or ebefen or kessar or tamoplac or tamoxasta or tamoxifene or toremifene or estrimex or fareston or fc1157a or Valrubicin or valstar or valtaxin).tw.

43 Disulfiram/ or Emetine/ or Clomipramine/ or Loperamide/ or Caspofungin/ or Terconazole/ or Colchicine/ or Promethazine/ or Azelastine/ or Aprepitant/ or Chlorpromazine/ or Icatibant/ or Bepotastine/ or prostacyclin/ or Vapreotide/ or Conivaptan/ or Nitric oxide/ or (Perphenazine or Metformin).hw.

44 (Disulfiram or antabus or Antabuse or esperal or disulfizam or Emetine or Emetin or Clomipramine or Anafranil or anafranilin or anafranyl or clomicalm or hydiphen or Loperamide or immodium or Caspofungin or Cancidas or Terconazole or fungistat or terazol or "r 42470or Colchicine" or colchysat or mitigare or "nsc 757" or Promethazine or allerfen or antiallersin or atosil or fenergan or hiberna or Phenergan or Pipolphen or Prothazine or Romergan or Sayomol or Azelastine or Astelin or "a5610 or afluon" or alerdual or alergodil or allergodrop or allergospray or allespray or allestin or astepro or azedil or azelamed or azelavision or azep or azeptin or carelastin or corifina or "e 0659" or "e0659" or lasticom or lastin or lastinaz or loxin or oculastin or optivar or pollival or proallergodil or radethacin or radethazin or rhinolast or rinelaz or tebarat or visuzel or vividrin or vivispray or Aprepitant or cinvanti or emend or aprepitant or "l754030" or "mk 0869" or "ono7436").tw.

45 (Perphenazine or decentan or etaperazine or ethaperazine or "sch 3940" or thilatazin or tranquisan or trifalon or trilafan or trilafon or trilifan or triliphan or Chlorpromazine or hibernal or contomin or largactil or megaphen or neurazine or plegomazin or promacid or promapar or propaphenin or solidon or sonazine or taroctil or "thor prom" or thorazine or vegetamin or zuledin or Icatibant or firazyr or Metformin or diabetosan or diabex or dianben or diformin or fluamine or flumamine or fortamet or glifage or gliguanid or glucoformin or gluconil or glucophage or glucophage-mite or glucostop or glukophage or glumetza or haurymellin or meguan or merckformin or metforal or metformax or metiguanide or riomet or risidon or siofor or Bepotastine or bepreve or talion or Epoprostenol or prostacyclin or caripul or cycloprostin or epoprostenol or flolan or Vapreotide or docrised or octastatin or Conivaptan or vaprisol or "Nitric oxide" or inomax or noxivent).tw.

46 (convalescence/ and plasma transfusion/) or (Convalesc* adj2 plasma).tw.

47 Natural killer cell/ or exp mesenchymal stem cell/

48 ("Recombinant human ACE-2" or "APN0" or "Natural killer cell" or "natural killer cells" or "NK cell" or "NK cells" or mesenchymal).tw.

49 Arbidol/ or Galidesivir/

50 (arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.

51 n methyl dextro aspartic acid receptor blocking agent/

52 ("n methyl dextro aspartic acid receptor" or "n methyl d aspartate a" or " NMDA antagonist*" or " NMDA inhibitor*" or " NMDA block*" or " NMDA receptor*").tw.

53 or/7-52

54 6 and 53

55 exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.

56 55 not human/

57 54 not 56

Appendix 3 – Interventions of interest

Categories	**Drug names/descriptions**
ACE Inhibitors	• Benazepril (Lotensin), Captopril (Capoten), Cilazapril (Inhibace), Enalapril (Vasotec), Fosinopril (Monopril), Lisinopril (Prinivil, Zestril), Perindopril (Coversyl), Quinapril (Accupril), Ramipril (Altace), Trandolapril (Mavik)
Angiotensin II Receptor Blocker (ARB)	• Azilsartan (Edarbi), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), telmisartan (Micardis), valsartan (Diovan, Prexxartan), losartan (Cozaar), olmesartan (Benicar), entresto (sacubitril/valsartan), byvalson (nebivolol/valsartan),
Antibiotics/antiparasitic	• Suramin, Carriomycin, Suramin sodium, Colistin, Teicoplanin, Ivermectin, azithromycin
Antibodies	• SARS-Cov-2 specific neutralizing antibodies • Bevicizumab, Ruxolitinib, Tocilizumab, Adalimumab, Camrelizumab, Eculizumab, Mepolizumab, "PD-1 mAb", Tocilizumab, tozumab, abciximab (Reopro), adalimumab (Humira/Amjevita), alefacept (Amevive), alemtuzumab (Campath), basiliximab (Simulect), belimumab (Benlysta), bezlotoxumab (Zinplava), canakinumab (Ilaris), certolizumab (Cimzia), cetuximab (Erbitux), daclizumab (Zenapax/Zinbryta), denosumab (Prolia/Xgeva), efalizumab (Raptiva), golimumab (Simponi), inflectra (Remicade), ipilimumab (Yervoy), ixekizumab (Taltz), natalizumab (Tysabri), nivolumab (Opdivo), olaratumab (Lartruvo), omalizumab (Xolair), palivizumab (Synagis), panitumumab (Vectibix), pembrolizumab (Keytruda), rituximab (Rituxan), tocilizumab (Actemra/ RoActemra), trastuzumab (Herceptin), secukinumab (Cosentyx), ustekinumab (Stelara), Meplazumab
Anticancer/chemotherapy	• Dasatinib, Epirubicin, Gemcitabine hydrochloride, Homoharringtonine , Imatinib mesylate, Tamoxifen, Toremifene, Valrubicin
Anticoagulants	• dalteparin, enoxaparin, tinzaparin, fondaparinux heparin, dabigatran, edoxaban, rivaroxaban, apixaban, warfarin, betrixaban, heparin, danaparoid
Antimalarials	• Amodiaquine, Basoquin, Camoquin, Flavoquine, Chloroquine, Resochin, Dawaquin, Lariago, Aarlen, Hydroxychloroquine, Hydroxy-chloroquine, Plaquenil, Hydroquin, Axemal, Dolquine, Quensyl, Quinoric, Imiquimiod, Aldara, Vyloma,, Zyclara, Primaquine, Jasoprim, Malirid, Neo-Quipenyl, Pimaquin, Pmq, Primachina, Primacin, Primaquina, Primaquine, Primaquine, Remaquin, Tafenoquine, Krinfatel, Kozenis, Arakoda, Krintafel, Pamaquine, Plasmochin,

	Plasmoquine, Plsamaguine, Neo-Quipenyl, Primachin, Dihydroartemisinin, mefloquine, Nitazoxanide, Nitrothiazole
Antiviral – Direct acting	• Protease inhibitors: boceprevir, telaprevir, lopinavir, ritonavir, lopinavir/ritonavir (Kaletra), darunavir/cobicistat (Prezcobix), indinavir (Crixivan), saquinavir (Invirase) • Integrase inhibitors: raltegravir, elvitegravir, dolutegravir • Entry (fusion) inhibitors: maraviroc (celsentri) • Nucleoside reverse transcriptase inhibitors: abacavir, ziagen, emtricitabine, emtriva, lamivudine, epivir, tenofovir (Viread), zidovudine, azidothymidine, retrovir • Nonnucleoside reverse transcriptase inhibitors : , doravirine, pifeltro, efavirenz, sustiva, etravirine, intelence, nevirapine, viramune, rilpivirine, edurant • Acyclic nucleoside phosphonate analogues: cidofovir diphosphates • Acyclic guanosine analogues: acyclovir • Pyrophosphate analogues: foscarnet, fomivirsen • Oligonucleotides • Nucleotide analog inhibitor: sofusbivir • Nucleoside inhibitor: ribavirin (Ibavyr) • Matrix 2 protein inhibitors: amantadine • RNA polymerase inhibitors: Rimantadine • Neuraminidase inhibitors: oseltamivir (Tamiflu), peramivir (Rapivab), zanamivir (Relenza) • Antiretrovirals: ASC09, Azvudine, Danoprevir, Darunavir, Lopinavir, ritonavir, Remdesivir
Antiviral – Other	• Baloxavir, marboxil, EIDD-2801
Antivirals – Broad spectrum	• Favipiravir, Triazavirin, Umifenovir (arbidol hydrochloride), Galidesivir
Immune support/modulating	• Convalescent plasma • Recombinant human ACE-2: APN01 • Natural killer (NK) cells • Mesenchymal stem cells • Interferons: Interferon-alpha, Interferon-beta, Interferon-gamma, interferon β – 1b (Betaseron/Extavia), interferon beta – 1a (Rebif) • Intravenous Immunoglobulin: Flebogamma DIF; Gamunex; Globulin-N; Globulin N; Intraglobin; Intraglobin F, Gammagard; Gamimune; Gamimmune, Privigen; Sandoglobulin; Venoglobulin;

	Venoglobulin-I; Venoglobulin I; Venimmune; Iveegam; Alphaglobin; Endobulin; Gamimune N; Gammimune N; Gammonativ
Interleukin Inhibitors	• Interleukin (IL)-1 Inhibitor: Anakinra • Interleukin (IL)-6 Inhibitors: Sarilumab (Kevzara); Siltuximab • Anti-Tumor necrosis factor-alpha (anti-TNF-alpha) • Anti-Granulocyte-macrophage colony-stimulating factor (anti-GM-CSF)
Kinase Inhibitors	• Baricitinib, Acalabrutinib (Calquence), Fedratinib, Ruxolitinib, Jakotinib, Ruxolitinib, Sunitinib, Erlotinib
Nonspecific anti-inflammatory and immunosuppressive drugs	• Fingolimod Hydrochloride, Leflunomide, Thalidomide, Methylprednisone, Prednisolone, Fluprednisolone, Corticosteroids, Cyclosporin A, Glycyrrhizic Acid/Glycyrrhizic
Other	• Disulfiram (acetaldehyde dehydrogenase inhibitor), Emetine (alkaloid emetic), Clomipramine (antidepressant), Loperamide (antidiarrheal), Caspofungin (antifungal), Terconazole (antifungal), Colchicine (anti-gout agent), Promethazine hydrochloride (antihistamine), Azelastine (antihistamine), Aprepitant (anti-nausea/antiemetic), Perphenazine (antipsychotic), Chlorpromazine hydrochloride (antipsychotic), Icatibant (Bradykinin B2 Receptor Antagonists), Metformin (diabetes), Bepotastine (histamine 1 antagonist), Epoprostenol (prostaglandin), Vapreotide (somatostatin), Conivaptan (vasopressin inhibitor), Nitric oxide (vasodilator), Acetylcysteine (prodrug), Potassium citrate (alkalinizer), Dipyridamole (vasodilator), Hydrogen peroxide, Cobicistat (Tybost), Bromhexine (mucolytic), Ebastine (H1 receptor agonist), Pirfenidone (antifibrotic), Polyinosinic-polycytidylic (Poly I-C), rhG-CSF, Thymosin, Tranilast, Ascorbic Acid, Aviptadil (neuropeptide), Ifendopril (NMDA inhibitor), fenretinide (synthetic rentinoid), famotidine (H2 receptor antagonist)

Appendix 4 – Studies excluded during full-text screening

Title	Reason for exclusion
A retrospective study of the clinical characteristics of COVID-19 infection in 26 children	Ineligible intervention
Acute gastrointestinal injury in critically ill patients with coronavirus disease 2019 in Wuhan, China	Ineligible intervention
Impact of COVID-19 pandemic on severity of illness and resources required during intensive care in the greater New York City area	Ineligible intervention
A major outbreak of severe acute respiratory syndrome in Hong Kong	Ineligible intervention
Temporal Patterns of Hepatic Dysfunction and Disease Severity in Patients with SARS	Ineligible intervention
Serum LD1 isoenzyme and blood lymphocyte subsets as prognostic indicators for severe acute respiratory syndrome	Ineligible intervention
Factors associated with psychosis among patients with severe acute respiratory syndrome: A case-control study	Ineligible intervention
Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience	Ineligible intervention
Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019	Ineligible intervention
Clinical characteristics of 50466 patients with 2019-nCoV infection	Ineligible intervention
Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China	Ineligible intervention
Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series	Ineligible intervention
Clinical Features of COVID-19 Related Liver Damage	Ineligible intervention
Epidemiological and Clinical Characteristics of Children with Coronavirus Disease 2019	Ineligible intervention

Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China	Ineligible intervention
Association of Cardiovascular Manifestations with In-hospital Outcomes in Patients with COVID-19: A Hospital Staff Data	Ineligible intervention
Epidemiological and clinical features of 2019-nCoV acute respiratory disease cases in Chongqing municipality, China: a retrospective, descriptive, multiple-center study	Ineligible intervention
Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China	Ineligible intervention
Clinical features and outcomes of 2019 novel coronavirus-infected patients with cardiac injury	Ineligible intervention
Clinical Characteristics of SARS-CoV-2 Pneumonia Compared to Controls in Chinese Han Population	Ineligible intervention
Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19	Ineligible intervention
Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan, China	Ineligible intervention
Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study	Ineligible intervention
The first report of the prevalence of COVID-19 in Chronic myelogenous leukemia patients in the core epidemic area of China:multicentre, cross-sectional survey	Ineligible intervention
Influence factors of death risk among COVID-19 patients in Wuhan, China: a hospital-based case-cohort study	Ineligible intervention
Clinical characteristics and durations of hospitalized patients with COVID-19 in Beijing: a retrospective cohort study	Ineligible intervention
Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients	Ineligible intervention
Clinical features and the maternal and neonatal outcomes of pregnant women with coronavirus disease 2019	Ineligible intervention
Clinical features and outcomes of 197 adult discharged patients with COVID-19 in Yichang, Hubei	Ineligible intervention
Radiographic Findings and other Predictors in Adults with Covid-19	Ineligible intervention

Anaesthetic managment and clinical outcomes of parturients with COVID-19: a multicentre, retrospective, propensity score matched cohort study	Ineligible intervention
SARS-COV-2 comorbidity network and outcome in hospitalized patients in Crema, Italy	Ineligible intervention
Clinical features and management of severe COVID-19: A retrospective study in Wuxi, Jiangsu Province, China	Ineligible intervention
A Randomized, Single-blind, Group sequential, Active-controlled Study to evaluate the clinical efficacy and safety of α-Lipoic acid for critically ill patients with coronavirus disease 2019（COVID-19）	Ineligible intervention
Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study	Ineligible intervention
Critically ill healthcare workers with the middle east respiratory syndrome (MERS): A multicenter study	Ineligible intervention
Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome	Ineligible intervention
Long-term consequences in lung and bone associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study.	Ineligible intervention
Association of HLA class I and II alleles with susceptibility to Severe acute respiratory syndrome infection in North China.	Ineligible intervention
Clinical characteristics of 2019 novel coronavirus infection in China	Ineligible intervention
Clinical features and outcomes of severe acute respiratory syndrome and predictive factors for acute respiratory distress syndrome.	Ineligible intervention
Clinical Manifestations, Laboratory Findings, and Treatment Outcomes of SARS Patients	Ineligible intervention
Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.	Ineligible intervention
Comparison of clinical course of patients with severe acute respiratory syndrome among the multiple generations of nosocomial transmission.	Ineligible intervention
Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome.	Ineligible intervention
Noninvasive positive pressure ventilation treatment for acute respiratory failure in SARS	Ineligible intervention

Serum hepatic enzyme manifestations in patients with severe acute respiratory syndrome: Retrospective analysis.	Ineligible intervention
Severe acute respiratory syndrome (SARS) in Singapore: Clinical features of index patient and initial contacts.	Ineligible intervention
Severe acute respiratory syndrome in Taiwan: analysis of epidemiological characteristics in 29 cases.	Ineligible intervention
Effective Treatment of Severe COVID-19 Patients with Tocilizumab	Ineligible study design
Key to successful treatment of COVID-19: accurate identification of severe risks and early intervention of disease progression	Ineligible study design
Treatment of severe acute respiratory syndrome with convalescent plasma	Ineligible study design
Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong	Ineligible study design
Critically ill patients with severe acute respiratory syndrome	Ineligible study design
Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS)	Ineligible study design
Epidemiologic features, clinical diagnosis and therapy of first cluster of patients with severe acute respiratory syndrome in Beijing area	Ineligible study design
Management of severe acute respiratory syndrome: the Hong Kong University experience	Ineligible study design
Severe acute respiratory syndrome: Clinical outcome and prognostic correlates	Ineligible study design
Short-term outcome of critically ill patients with severe acute respiratory syndrome	Ineligible study design
Clinical Description of a Completed Outbreak of SARS in Vietnam February-May 2003	Ineligible study design
Factors of avascular necrosis of femoral head and osteoporosis in SARS patients' convalescence	Ineligible study design
Six month radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors	Ineligible study design

Pentaglobin in steroid-resistant severe acute respiratory syndrome	Ineligible study design
Use of convalescent plasma therapy in SARS patients in Hong Kong	Ineligible study design
Reduced bone mineral density in male Severe Acute Respiratory Syndrome (SARS) patients in Hong Kong	Ineligible study design
Steroid-induced osteonecrosis in severe acute respiratory syndrome: a retrospective analysis of biochemical markers of bone metabolism and corticosteroid therapy.	Ineligible study design
Characteristic features and outcomes of severe acute respiratory syndrome found in severe acute respiratory syndrome intensive care unit patients	Ineligible study design
Clinical findings in critical ill patients infected with SARS-Cov-2 in Guangdong Province, China: a multi-center, retrospective, observational study	Ineligible study design
First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naive and Experienced COVID-19 Patients	Ineligible study design
Dynamic profile of severe or critical COVID-19 cases	Ineligible study design
Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in patients with SARS-CoV-2 infection	Ineligible study design
Medical treatment of 55 patients with COVID-19 from seven cities in northeast China who fully recovered: a single-center, retrospective, observational study	Ineligible study design
Associations of clinical characteristics and antiviral drugs with viral RNA clearance in patients with COVID-19 in Guangzhou, China: a retrospective cohort study	Ineligible study design
Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: A multicenter retrospective cohort study	Ineligible study design
Clinical characteristics of 34 COVID-19 patients admitted to ICU in Hangzhou, China	Ineligible study design
COVID-19 in Iran, a comprehensive investigation from exposure to treatment outcomes	Ineligible study design
Critically Ill Patients With the Middle East Respiratory Syndrome	Ineligible study design
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial	Ineligible study design

Influence of factors on production of IgG antibody in SARS patients. [Chinese]	Ineligible study design
Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia.	Ineligible study design
Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study.	Ineligible study design
Avascular necrosis of bone in severe acute respiratory syndrome	Ineligible study design
Avascular osteonecrosis after treatment of SARS: a 3-year longitudinal study.	Ineligible study design
Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study.	Ineligible study design
QT Interval Prolongation and Torsade De Pointes in Patients with COVID-19 treated with Hydroxychloroquine/Azithromycin	Ineligible study design
Treatment of severe acute respiratory syndrome in health-care workers.	Ineligible study design
Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis.	Ineligible study design
Early Treatment of COVID-19 Patients With Hydroxychloroquine and Azithromycin: A Retrospective Analysis of 1061 Cases in Marseille, France	Ineligible study design
Sarilumab use in severe SARS-CoV-2 pneumonia	Ineligible study design
Treatment of COVID-19 Patients with Convalescent Plasma in Houston, Texas	Ineligible study design
The use of corticosteroids in SARS	Ineligible study population
Temporal relationship of viral load, ribavirin, interleukin (IL)-6, IL-8, and clinical progression in patients with severe acute respiratory syndrome	Ineligible study population
Hydroxychloroquine (HCQ): an observational cohort study in primary and secondary prevention of pneumonia in an at-risk population	Ineligible study population

Outcomes associated with corticosteroid dosage in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease	Ineligible study population
No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection	Ineligible study population
Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients.	Ineligible study population
Early preemptive immunomodulators (Corticosteroids) for severe pneumonia patients infected with SARS-COV-2.	Ineligible study population
Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure.	Ineligible study population
Convalescent plasma: A possible treatment of COVID-19 in India.	Ineligible study population
Pharmaceutical care of chloroquine phosphate in elderly patients with coronavirus pneumonia (COVID-19).	Ineligible study population
COVID-19 and Chloroquine/Hydroxychloroquine: is there Ophthalmological Concern?.	Ineligible study population
Prolonged disturbances of in vitro cytokine production in patients with severe acute respiratory syndrome (SARS) treated with ribavirin and steroids.	Ineligible study population
COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases	Ineligible study population
Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients.	Ineligible study population

The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study	Ineligible study population
Clinical Manifestations, Laboratory Findings, and Treatment Outcomes of SARS Patients	Ineligible study population
Prolonged disturbances of in vitro cytokine production in patients with severe acute respiratory syndrome (SARS) treated with ribavirin and steroids.	Ineligible study population

Appendix 5 – Detailed study and patient characteristics

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
Controlled Trials n=9			
Bian, 2020; China Pre-print	28 days, Tangdu Hospital of Fourth Military Medical University; COVID-19, Lab-confirmed	median (IQR): 51 (49-67); 28 Female: 42.86, Male:57.14	Diabetes (3/28), Hypertension (9/28), Cardiovascular disease (3/28), Chronic obstructive pulmonary disease (1/28), Parkinson's disease (1/28)
Borba, 2020; Brazil Peer-reviewed	Mar 23 to Apr 5, 2020, Hospital e Pronto-Socorro Delphina Rinaldi Abdel Aziz; COVID-19, Lab-confirmed	mean (SD): 51.1 (13.9); 81 Female: 24.7, Male:75.3	Hypertension (25/55), Alcoholism (14/51), Heart disease (5/55), Asthma (4/54), Chronic kidney disease (4/54), Rheumatic diseases (3/55), Liver diseases (2/55), Tuberculosis (2/55), HIV/AIDS (1/55)
Chen, 2020a; China Pre-print	Feb 20 to Mar 1, 2020, Zhonghan Hospital of Wuhan University (ZNWU), Leishenshan Hospital (LSS) and the Third Hospital of Hubei Province (HBTH); COVID-19, Lab-confirmed	NR (NR); 236 Female: 53.39, Male:46.61	Hypertension (66/236), Diabetes (27/236), Insomnia (45/236), Conjunctivitis (15/236)
Chen, 2020b; China Pre-print	10 days, Renmin Hospital of Wuhan University; COVID-19, Lab-confirmed	mean (SD): 44.7 (15.3); 62 Female: 53.2, Male:46.8	None reported

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
Fadel, 2020; USA Peer reviewed	Mar 12 to Mar 27, 2020, five hospitals in southeast and south-central Michigan; COVID-19, WHO or CDC Criteria	Median (IQR): 52 (32-62); 127 Female: 46.46, Male: 53.54	Diabetes (17/127), Hypertension (36/127), Coronary artery disease (10/127), Cerebrovascular disease (2/127), Hyperlipidaemia (29/127), Thyroid disease (4/127), Obstructive sleep apnoea (2/127), Crohn's disease (1/127), Epilepsy (1/127), Tuberculosis (2/127), Chronic hepatitis B (3/127), Chronic hepatitis C (1/127), Malignancy (2/127), Smoker (7/127)
Hung, 2020; Hong Kong Peer reviewed	Feb 10 to Mar 20, 2020, Queen Mary Hospital, Pamela Youde Nethersole Hospital, Ruttonjee Hospital, United Christian Hospital, Queen Elizabeth Hospital, and Tuen Mun Hospital; COVID-19, Lab-confirmed	Mean: 46; 150 Female: NR, Male: 55	Diabetes (21/150), Hypertension (9/150), Others [unspecified] (31/150)
Li, 2020; China Pre-print	21 days, Guangzhou Eighth People's Hospital; COVID-19, Lab-confirmed	mean (range): 49.4 (19-79); 86 Female: 53.49, Male:46.51	Diabetes (2/86), Hypertension (7/86), Coronary heart disease (2/86), Chronic liver disease (4/86)
Tang, 2020; China Peer-reviewed	Feb 11 to Mar 14, 2020, 16 government-designated COVID-19 treatment centers in three provinces in China (Hubei, Henan	Median (IQR): 62 (51-62) 213 Female: NR, Male: 51.2	Asthma (33/213), Chronic kidney disease (98/213), Chronic obstructive pulmonary disease (27/213), Congestive heart failure (26/213),

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
	and Anhui); COVID-19, Lab-confirmed		Coronary artery disease (38/213), Diabetes (105/213), Hypertension (158/231), Malignancy (24/213), Smoking history (88/213)
Wang, 2020a; China Peer-reviewed	28 days, ten hospitals in Hubei China; COVID-19, Lab-confirmed	median (IQR): 66 (57-73)[intervention]; 64 (53-70) [control]; 236 Female: 40.68, Male:59.32	Any comorbidity (167/236), Hypertension (102/236), Diabetes (56/236), Coronary heart disease (17/236)
Cohort Studies n=19			
Deng, 2020; China Peer-reviewed	21 days, The Fifth Affiliated Hospital of Sun Yat-Sen University; COVID-19, Lab-confirmed	mean (SD): 44.56 (15.73); 33 Female: NR, Male:51.51	Chronic obstructive pulmonary disease (1/33), Chronic liver disease (3/33), Diabetes mellitus (5/33), Coronary heart disease (5/33), Hypertension (5/33), Obesity (3/33)
Estebanez, 2020; Spain Pre-print	Feb 23 to Apr 4, 2020, Central Defense Hospital; COVID-19, Lab-confirmed	Mean: 64 256 Female: NR, Male: 59.4	Hypertension (114/256), Diabetes Mellitus (47/256), Dyslipidaemia (78/256), Cardiopathy (57/256), Cancer (29/256), Dementia (21/256), Pulmonary disease (37/256)
Kim, 2020; South Korea Pre-print	Feb 28 to Apr 28, 2020, Korea Worker's Compensation &	Mean (SD): 38 (15.1); 270 Female: 64.4, Male: NR	Hypertension (11/270), Diabetes mellitus (2/270), Dyslipidemia (5/270), Thyroid (4/270)

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
	Welfare Service Daegu Hospital; COVID-19, Lab-confirmed		
Lan, 2020; China Pre-print	Feb 21 to Mar 18, 2020, Lishui Central Hospital, Zhejiang, China and Wuhan fourth hospital hospital, Hubei , China; COVID-19, Lab-confirmed	mean (SD): 52.3 (15.8)[intervention] 59.5 (13.6)[control]; 73 Female: 49.32, Male:50.68	Cardiovascular and cerebrovascular disease (20/73), Endocrine system disease (10/73), Malignant tumor (4/73), Respiratory system disease (1/73), Digestive system disease (1/73), Renal disease (1/73), Liver disease (1/73)
Lian, 2020; China Peer-reviewed	Feb 2 to Mar 20, 2020, non-ICU Ward at Wuhan Jinyintan Hospital; COVID-19, Lab-confirmed	median (IQR): 60 (49-66); 81 Female: NR, Male:56	Hypertension (16/81), Diabetes (8/81), Coronary Heart Disease (7/81)
Lu, 2020; China Pre-print	28 days, intensive care wards of Tongji hospital in Wuhan, China; COVID-19, NR	median (range): 62 (50-71); 244 Female: NR, Male:52	Hypertension (95/244), Diabetes (44/244), Cerebrovascular Disease (28/244), Chronic Obstructive Pulmonary Disease (12/244)
Magagnoli, 2020; USA Pre-print	NR, all United States Veterans Health Administration medical centers; COVID-19, NR	median (IQR): 70 (60-75)[intervention]; 68 (59-74)[intervention]; 69 (59-75)[control]; 368 Female: 0, Male:100	Hyperlipidemia (58/368), Asthma (22/368), Myocardial infarction (18/368), Congestive heart failure (75/368), Peripheral vascular disease (68/368), Cerebrovascular disease (47/368), Dementia (31/368), Chronic pulmonary disease (72/368), Connective tissue disease/Rheumatic disease (5/368), Peptic ulcer disease

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
			(2/368), Mild liver disease (30/368), Diabetes without complications (159/368), Diabetes with complications (90/368), Paraplegia/Hemiplegia (8/368), Renal disease (92/368), Cancer (59/368), Moderate/severe liver disease (4/368), Metastatic carcinoma (7/368), HIV/AIIDS (9/368)
Mahévas, 2020; France Pre-print	7 days, four French tertiary care centres providing care to patients with COVID-19 pneumonia; COVID-19, Lab-confirmed	median (IQR): 60 (52-68); 181 Female: NR, Male:71.1	Chronic respiratory disease - including asthma (20/181), Chronic heart failure - NYHA III or IV (6/181), Cardiovascular diseases - incl. hypertension (94/181), Diabetes requiring insulin (15/181), Chronic kidney failure (9/181), Liver cirrhosis - Child-Pugh B or more (1/181), Immunodepression (21/181)
Mercuro, 2020; USA Peer-reviewed	NR, Beth Israel Deaconess Medical Center; COVID-19, Lab-confirmed	mean (SD): 60.1 (16.7); 90 Female: 48.9, Male:NR	Hypertension (48/90), Congestive heart failure (9/90), Diabetes mellitus (26/90), Coronary artery disease (10/90), Atrial fibrillation (12/90), Chronic obstructive pulmonary disease or asthma (18/90)

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
Rosenberg, 2020; USA Peer-reviewed	Mar 15 to Apr 24, 2020, hospitals in NYC, Nassau County, Suffolk County, and all but one hospital in Westchester County; COVID-19, Lab-confirmed	NR; 1438 Female: NR, Male: 59.67	Obesity [BMI ≥30] (438/1030), Cancer (55/1438), Any kidney disease (187/1438), Any chronic lung conditions (259/1438), Diabetes (504/1438), Any cardiovascular diseases (438/1438), Hypertension (816/1438), Coronary artery disease (173/1438), Congestive heart failure (96/1438), Dementia (93/1438)
Shao, 2020; China Pre-print	Dec 2019 to Apr 2020, eight government designated treatment centers for COVID-19 patients (4 ICUs and 4 general wards) in 3 cities in China, including Wuhan, Guangzhou, and Shenzhen; COVID-19, Lab-confirmed	mean (SD): 58 (46-69); 325 Female: 42, Male:58	Hypertension (98/325), Coronary heart disease (31/325), Chronic kidney disease (5/325), Diabetes (38/325), Chronic obstructive lung disease (10/325), Stroke (16/325), Carcinoma (10/325), Other (61/325)
Singh, 2020; USA Pre-print	Jan 20 to May 1, 2020, 40 million patients from 34 healthcare organizations (HCOs) in the United States; COVID-19, Lab-confirmed	NR; 1820 Female: NR, Male: 54.45	Hypertensive diseases (1120/1820), Diabetes mellitus (342/1820), Obesity (550/1820), Ischemic heart diseases (525/1820), Chronic kidney disease (408/1820), Heart failure (339/1820), Prolonged QT interval or Long QT Syndrome (46/1820), Atrial fibrillation and flutter (308/1820), Cerebrovascular diseases (242/1820), Chronic obstructive pulmonary

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
			disease (259/1820), Asthma (239/1820), Diseases of liver (181/1820), Malignant neoplasms of lymphoid, hematopoietic and related tissue (62/1820), Rheumatoid arthritis (49/1820), Malignant neoplasm of breast (44/1820), Malignant neoplasm of colon (32/1820), Malignant neoplasm of prostate (31/1820), Systemic lupus erythematosus (SLE) (25/1820), Human immunodeficiency virus [HIV] disease (20/1820), Nicotine dependence (208/1820), Alcohol related disorders (86/1820)
Wadud, 2020; USA Pre-print	Mar 15 to Apr 20, 2020, Orange Regional Medical Center; COVID-19, Lab-confirmed	NR; 94 Female: 23.4, Male: 76.6	None reported
Wang, 2020b; China Pre-print	Jan 20 to Feb 25, 2020, Wuhan Union Hospital; COVID-19, Lab-confirmed	median (IQR): 54 (48-64); 46 Female: NR, Male:57	Chronic cardiac disease (6/46), Chronic pulmonary disease (3/46), Cerebrovascular disease (2/46), Malignancy (2/46), Diabetes (4/46), Hypertension (14/46)
Wu, 2020; China Pre-print	Dec 26 to Mar 15, 2020, Wuhan Hankou Hospital and No. Six Hospital of Wuhan;	Median (IQR): 61 (51-70); 1514	Diabetes (181/1514), Hypertension (354/1514), COPD (42/1514), Cancer

Author, Year; Country of Conduct Publication Type	Study Period, Setting; Diagnosis, Criteria	Age (variance), Sample Size, % Female, % Male	Co-morbidities (n/N)
	COVID-19, Lab-confirmed	Female: 52.2, Male: NR	(22/1540), CKD (29/1514), Smoking (185/1540)
Yu, 2020; China Pre-print	Feb 1 to Apr 8 2020, Tongji Hospital, Wuhan; COVID-19, Lab-confirmed	median (NR): 68 (NR); 568 Female: 36.97, Male:63.03	Hypertension (252/568), Coronary heart disease (59/568), Chronic obstructive pulmonary disease (16/568), Diabetes (97/568)
Zeng, 2020; China Peer-reviewed	NR, The First Affiliated Hospital of Zhengzhou University and The Sixth People's Hospital of Zhengzhou City; COVID-19, Lab-confirmed	median (NR): 61.5 (NR)[intervention] 73 (NR)[control]; 21 Female: NR, Male:76.19	Diabetes (6/21), Hypertension (4/21), Chronic liver diseases (2/21), Cardiovascular diseases (1/21), Respiratory system diseases (1/21), Chronic kidney disease (1/21)
Zha, 2020; China Peer-reviewed	Jan 24 to Feb 29, 2020, Second People's Hospital of Wuhu and Yijishan Hospital; COVID-19, Lab-confirmed	median (IQR): 39 (32-54); 31 Female: NR, Male:64	Hypertension (7/31), Diabetes (1/31), Coronary heart disease (1/31), Chronic hepatitis B virus infection (2/31)
Zhu, 2020; China Peer-reviewed	Jan 23 to Feb 29, 2020, Third People's Hospital of Changzhou and the Second People's Hospital of Wuhu; COVID-19, Lab-confirmed	NR (NR) 50 Female: NR, Male:52	None reported

IQR – interquartile range, NR – Not reported, SD – standard deviation

[§] Multiple analyses of overlapping cohorts of patients

Appendix 6 – Detailed effectiveness and safety results

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Controlled trials n=9		
Study: Bian, 2020 **Condition:** COVID-19		
Meplazumab (n=17) [10mg meplazumab administered on day 1, day 2 and day 5 by intravenous infusion (60–90 min); lopinavir/ritonavir (17); recombinant human interferon alfa-2b (17); glucocorticoid (16); antibiotic (17)]	**Critical cases (ICU/mechanical ventilation) change from baseline to day 28: 7->1 patients;** **Mortality: 0 patients** **'Compared to control group, meplazumab treatment significantly improved the discharged (p=0.006) and case severity (p=0.021) in critical and severe patients...at day 28, 4 severe cases and 1 critical case were improved to common and no case was discharged in control group. In meplazumab group, 9 cases (6 severe and 3 critical) were discharged, 2 critical cases were improved to common, and 1 critical case was improved to severe, demonstrating a significantly beneficial outcome compared to control group (p=0.021)'**	elevated ALT/AST: 2/17 patients; duration 7days, treatment procedure was not affected by their fluctuation

Drug therapy (sample size) **[dose, route of administration, frequency, duration; additional therapies]**	**Effectiveness outcome:** **quantitative results;** **'study conclusions'**	**Safety outcome:** **quantitative results;** **duration, clinical response**
Control (n=11) [lopinavir/ritonavir (n=11); recombinant human interferon alfa-2b (n=11); glucocorticoid (n=7); antibiotic (n=10)]	**Critical cases (ICU/mechanical ventilation) change from baseline to day 28: 3->0 patients;** **Mortality: 0 patients**	elevated ALT/AST: 1/11 patients; duration 7 days, treatment procedure was not affected by their fluctuation
Study: Borba, 2020 **Condition:** COVID-19		
High dose chloroquine (n=41) [oral 600mg CQ, 4 × 150mg tablets twice daily for 10 days, total dose 12 g; intravenous ceftriaxone (1 g twice daily for 7 days), azithromycin (500mg once daily for 5 days), systematically, starting on day 0]	Mortality (day 13): 16 patients; "**The high-dosage group was associated with lethality (odds ratio, 3.6; 95%CI, 1.2-10.6)**. Despite the small sample size, in an exploratory multivariate analysis, the high-dosage CQ was no longer associated with death when controlled by age (odds ratio, 2.8; 95%CI, 0.9-8.5)."	Decreased hemoglobin: 7/24 patients Creatinine increase: 9/23 patients Creatinine phosphokinase increase: 7/23
Low dose chloroquine (n=40) [oral 450mg CQ; 3 × 150mg and 1 placebo tablet twice daily on day 0, 3 × 150mg plus 1 placebo tablet once a day followed by 4 placebo tablets from day 1 to day 4, 4 placebo tablets twice daily from day 5 to day 9, total dose 2.7 g; intravenous ceftriaxone (1 g twice daily for 7 days) plus azithromycin (500mg once daily for 5 days), systematically, starting on day 0]	Mortality (day 13): 6 patients	Decreased hemoglobin: 4/18 patients Creatinine increase: 7/19 patients Creatinine phosphokinase increase: 6/19 patients
Study: Chen, 2020a **Condition:** COVID-19		

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Arbidol (n=120) [200mg, three times daily; plus standard care for 7 days, standard care could comprise: Traditional Chinese herbal medicine, antibiotics, antiviral treatment, immunomodulatory drugs, steroids, psychotic drugs, nutrition support, cardiovascular drugs, supportive oxygen, noninvasive positive pressure ventilation or invasive ventilation]	All-cause Mortality: 0 patients	Total adverse events: 28/120 patients
Favipravir (n=116) [1600mg, twice first day followed by 600mg, twice daily; plus standard care for 7 days, standard care components same as listed above]	All-cause Mortality: 0 patients;	Total adverse events: 37/116 patients
Study: Chen, 2020b **Condition:** COVID-19		
Hydroxychloroquine (n=31) [oral 400 mg/d (200 mg/bid) between days 1 and 5; antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids]	Pneumonia improvement (based on chest CT): 25 patients; 'Surprisingly, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31). Besides, 61.3% of patients in the HCQ treatment group had a significant pneumonia absorption.'	Rash: 1/31 patients Headache: 1/31 patients

Drug therapy (sample size) **[dose, route of administration, frequency, duration; additional therapies]**	**Effectiveness outcome:** **quantitative results;** **'study conclusions'**	**Safety outcome:** **quantitative results;** **duration, clinical response**
Control (n=31) [antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids]	Pneumonia improvement based on chest CT): 17 patients	Rash: 0/31 patients Headache: 0/31 patients
Study: Fadel, 2020 **Condition:** COVID-19		
Early corticosteroid treatment (n=132) [Patients with moderate COVID-19 (required ≥4 liters O^2/min) received IV methylprednisolone 0.5 to 1 mg/kg/day in 2 divided doses for 3 days; Patients in ICU received IV methylprednisolone 0.5 to 1 mg/kg/day in 2 divided doses for 3 to 7 days; methylprednisolone median dose 40mg (IQR 35-50mg); hydroxychloroquine 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2-5 (n=104); empiric antibiotic n=98; lopinavir/ritonavir n=1; tocilizumab n=6]	**Escalation from medical ward to ICU: 32 patients** **Odds Ratio (v control): 0.47 (95% CI 0.25-0.88, p=0.017)** **Respiratory failure requiring mechanical ventilation: 26 patients** **Odd Ratio (v control): OR 0.47 (95% CI 0.25-0.92, p=0.025)**	
Control (n=81) [supportive care with or without a combination of the following: empiric antibiotic n=65, duration median 5 days (IQR 3-5); hydroxychloroquine n=57; lopinavir/ritonavir n=9; remdesivir n=5; tocilizumab n=8; methylprednisolone use n=43, median dose 40mg (IQR 40-50mg), oral prednisone n=5]	**Escalation from medical ward to ICU: 31 patients** **Respiratory failure requiring mechanical ventilation: 26 patients**	

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Study: Hung, 2020 **Condition:** COVID-19		
Combination therapy (n=86) [lopinavir-ritonavir + interferon beta-1b]	Required ventilator support: 0 patients 30-day mortality: 0 patients	Nausea: 30 patients, duration [median (IQR)]: 2 (1-2) Diarrhea: 34 patients, duration [median (IQR)]: 3 (3-3) Increased ALT: 11 patients Hyperbilirubinemia: 4 patients Sinus bradycardia: 3 patients Serious adverse events: 0 patients
Control (n=41) [lopinavir-ritonavir]	Required ventilator support: 1 patient 30-day mortality: 0 patients	Nausea: 13 patients, duration [median (IQR)]: 2 (1-2) Diarrhea: 18 patients, duration [median (IQR)]: 3 (3-3) Increased ALT: 7 patients Hyperbilirubinemia: 3 patients Sinus bradycardia: 1 patient Serious adverse events: 1 patient
Study: Li, 2020 **Condition:** COVID-19		

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Arbidol (n=35) [arbidol (100mg), orally administered, 200mg three times daily for 7-14 days; All three groups were treated with supportive care and effective oxygen therapy if in need]	Deterioration in clinical status - requiring ICU monitoring or mechanical ventilation (7 days): 3 patients; 'At day 7, eight (23.5%) patients in the LPV/r group, 3 (8.6%) in the arbidol group and 2(11.8%) in the control group deteriorated from mild/moderate clinical status to severe/critical clinical status, without statistical difference (P =0.206)…In order to rule out the influence of the time from onset to treatment on the clinical status, we compared the time from onset to treatment in patients who deteriorated to severe/critical clinical status [5 (IQR 2, 8) days] with those who did not [4 (IQR 2, 7) days], and did not find any significant difference between them (P =0.619)' Mortality: 0 patients; Evidence of pneumonia based on chest CT imaging: 33 patients; 'The results showed that LPV/r and arbidol did not...improve the symptoms of COVID-19 or pneumonia on lung CT imaging at 7 days and 14 days'	Diarrhea: 3/35 patients Nausea: 2/35 patients ALT enzymes >2.5 normal: 0/34 patients

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Lopinavir/ritonavir (n=34) [lopinavir (200mg)/ritonavir (50mg); orally administed twice daily for 7-14 days; all three groups were treated with supportive care and effective oxygen therapy if in need]	Deterioration in clinical status - requiring ICU monitoring or mechanical ventilation (7 days): 8 patients Mortality: 0 patients Evidence of pneumonia based on chest CT imaging: 28 patients	Diarrhea: 9/34 patients Loss of appetite: 5/34 patients ALT enzymes >2.5 normal: 1/34 patients
Control (n=17) [patients were not given any antiviral therapy, all three groups were treated with supportive care and effective oxygen therapy if in need]	Deterioration in clinical status - requiring ICU monitoring or mechanical ventilation (7 days): 2 patients; Mortality: 0 patients; Evidence of pneumonia based on chest CT imaging: 14 patients;	Diarrhea: 0/34 patients Loss of appetite: 0/34 patients ALT enzymes >2.5 normal: 0/34 patients
Study: Tang, 2020 **Condition:** COVID-19		

Drug therapy (sample size) **[dose, route of administration, frequency, duration; additional therapies]**	**Effectiveness outcome:** **quantitative results;** **'study conclusions'**	**Safety outcome:** **quantitative results;** **duration, clinical response**
Hydroxychloroquine (n=75) [loading dose of 1200 mg daily for three days followed by a maintained dose of 800 mg daily, total treatment duration: 2 or 3 weeks for mild/moderate or severe patients, respectively; additional antiviral agents (47): arbidol (37), virazole (13), lopinavir–ritonavir (13), oseltamivir (8), entecavir (1); Antibiotics (32); Systemic glucocorticoid treatment (6)]		Any adverse event*: 21/70; Serious adverse event: 2/70 *Multiple occurrences of the same adverse event in one patient were counted
Control (n=75) [Standard care (including, not limited to): antiviral agents (48): arbidol (33), virazole (15), lopinavir–ritonavir (12), oseltamivir (9), entecavir (1); Antibiotics (27); Systemic glucocorticoid treatment (4)]		Any adverse event*: 7/80 Serious adverse event: 0/80 *Multiple occurrences of the same adverse event in one patient were counted
Study: Wang, 2020a **Condition:** COVID-19		

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Remdesivir (n=158) [intravenous, 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions; interferon alfa-2b at baseline (n=29), lopinavir–ritonavir at baseline (n=27), Antibiotic treatment at baseline (n=121), Corticosteroids therapy at baseline (n=60)]	Patients requiring extracorporeal membrane oxygenation or invasive mechanical ventilation at study end (day 28): 2/150 patients; 'Our trial found that intravenous remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo.' Mortality at study end (day 28): 22/150 patients	Any adverse event[1]: 102/155 patients Serious adverse events[2]: 28/155 patients
Placebo (n=78) [same volume of placebo infusions for a total of 10 days; interferon alfa-2b at baseline (n=15), lopinavir–ritonavir at baseline (n=15), Antibiotic treatment at baseline (n=63), Corticosteroids therapy at baseline (n=31)]	Patients requiring extracorporeal membrane oxygenation or invasive mechanical ventilation at study end (day 28): 3/77 patients; Mortality at study end (day 28): 10/77 patients	Any adverse event[1]: 50/78 patients Serious adverse events[2]: 20/78
Cohort Studies n=19		
Study: Deng, 2020 **Condition:** COVID-19		

Drug therapy (sample size) **[dose, route of administration, frequency, duration; additional therapies]**	**Effectiveness outcome:** **quantitative results;** **'study conclusions'**	**Safety outcome:** **quantitative results;** **duration, clinical response**
Arbidol + lopinavir ritonavir (n=16) [arbidol 200 mg every 8h, lopinavir (400 mg)/ritonavir (100 mg) orally every 12 h, duration approximately 5–21 days; all patients received Immunoglobulin therapy, some received broad-spectrum antibacterial therapy (n=20) or corticosteroid therapy (n=1)]	**Pneumonia improvement based on chest CT: 11 patients;** **'Chest CT scans were improving for 11 (69%) of 16 patients in the combination group after 7 days, compared with 5 (29%) of 17 in the monotherapy group (p<0.05)'**	
Lopinavir/ritonavir (n=17) [lopinavir (400 mg)/ritonavir (100 mg) orally every 12 h duration approximately 5–21 days; all patients received Immunoglobulin therapy, some received broad-spectrum antibacterial therapy (n=20) or corticosteroid therapy (n=7)]	**Pneumonia improvement based on chest CT: 5 patients**	
Study: Estebanez, 2020 **Condition:** COVID-19		
Interferon beta-1b (n=106) [subcutaneous injection at a dose of 250 µg on alternate days. Patients included in the interferon group had received at least one dose; Hydroxychloroquine (101); Lopinavir/ritonavir (47); Azythromycin (64); Corticosteroids (24); Tocilizumab (3)]	Overall mortality: 22 patients (p=0.229) In the multivariate analysis age (older than 65 years old), clinical severity at admission, and not have received hydroxychloroquine were significantly associated with in-hospital mortality (Table 2). The interferon treatment was not associated with survival benefit neither univariate analysis nor multivariate analysis	

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Control (n=150) [Hydroxychloroquine (96); Lopinavir/ritonavir (45); Azythromycin (94); Corticosteroids (42); Tocilizumab (2)]	Overall mortality: 41 patients	
Study: Kim, 2020 **Condition:** COVID-19		
Lopinavir/ritonavir (n=35) [lopinavir 200mg/ritonavir 50mg twice daily; azithromycin 500 mg once daily for 3 days, cefixime 100mg twice daily]	Referral to tertiary hospital or ICU: 4 patients Lopinavir/ritonavir v Hydroxychloroquine: p=0.375 All three treatment groups: p=0.189 Mortality: 0 patients	Nausea/vomiting: 4 patients Abdominal discomfort/diarrhea: 3 patients Tachycardia: 0 patients Increased total bilirubin: 0 patients Elevated BUN: 1 patient Elevated AST/ALT: 4 patients
Hydroxychloroquine (n=22) [200 mg hcq tablets twice daily; azithromycin 500 mg once daily for 3 days, cefixime 100mg twice daily]	Referral to tertiary hospital or ICU: 4 patients Mortality: 0 patients	Nausea/vomiting: 2 patients Abdominal discomfort/diarrhea: 1 patient Tachycardia: 1 patient Increased total bilirubin: 1 patient Elevated BUN: 0 patients Elevated AST/ALT: 4 patients

Drug therapy (sample size) **[dose, route of administration, frequency, duration; additional therapies]**	**Effectiveness outcome: quantitative results; 'study conclusions'**	**Safety outcome: quantitative results; duration, clinical response**
Conservative treatment (n=40) [azithromycin 500 mg once daily for 3 days, cefixime 100mg twice daily]	Referral to tertiary hospital or ICU: 0 patients Mortality: 0 patients	Nausea/vomiting: 0 patients Abdominal discomfort/diarrhea: 0 patients Tachycardia: 0 patients Increased total bilirubin: 0 patients Elevated BUN: 0 patients Elevated AST/ALT: 1 patient
Study: Lan, 2020 **Condition:** COVID-19		
Lopinavir/ritonavir (n=34) [lopinavir-ritonavir (400 mg and 100mg, orally) twice daily]	Transferred to ICU: 0 patients Mortality: 1 patient	
Lopinavir/ritonavir + Arbidol (n=39) [lopinavir-ritonavir (400 mg and 100mg, orally) twice daily combined with arbidol (200 mg, orally) three times a day]	Transferred to ICU: 2 patients Mortality: 1 patient	
Study: Lian, 2020 **Condition:** COVID-19		
Umifenovir (n=45) [0.2 gram three times a day; some patients were given umifenovir for five days (n=8) and the rest for 7-10 days (n=37)]		Digestive symptoms (diarrhea and nausea): 5/45 patients

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Control (n=36) [Not reported]		Digestive symptoms (diarrhea and nausea): 3/36 patients
Study: Lu, 2020 **Condition:** COVID-19		
Adjuvant corticosteroid therapy (n=151) [hydrocortisone-equivalent dosage range: 100-800mg/d, median (IQR) administration duration was 8 (4-12) days; antiviral therapy (e.g., oseltamivir, arbidol, lopinavir/ritonavir, ganciclovir, interferon-α)]	Mortality: NR 'Multivariate analysis that adjusted for major mortality-associated variables and propensity score indicated that corticosteroid treatment was independent from overall mortality (adjusted OR: 1.05; 95% CI: -1.92-2.01)'	
Antiviral therapy only (n=93) [oseltamivir, arbidol, lopinavir/ritonavir, ganciclovir, interferon-α]	Mortality: NR	
Study: Magagnoli, 2020 **Condition:** COVID-19		

Drug therapy (sample size) **[dose, route of administration, frequency, duration; additional therapies]**	**Effectiveness outcome:** **quantitative results;** **'study conclusions'**	**Safety outcome:** **quantitative results;** **duration, clinical response**
Hydroxychloroquine (n=97) [Not reported]	Mechanical ventilation: 12 patients; 'We did not observe a significant difference in the risk of ventilation in either the HC group (adjusted HR, 1.43; 95% CI, 0.53 to 3.79; P=0.48) or the HC+AZ group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; P=0.09), compared to the no HC group' Mortality: 27 patients; **'Compared to the no HC group, there was a higher risk of death from any cause in the HC group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P=0.03)** but not in the HC+AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72)...No significant difference was observed in the risk of death after ventilation in either the HC group (adjusted HR, 4.08; 95% CI, 0.77 to 21.70; P=0.10) or the HC+AZ group (adjusted HR, 1.20; 95% CI, 0.25 to 5.77; P=0.82), compared to the no HC group'	
Hydroxychloroquine + azithromycin (n=113) [Not reported]	Mechanical ventilation: 7 patients Mortality: 25 patients	
No hydroxychloroquine (n=158) [Not reported]	Mechanical ventilation: 25 patients Mortality: 18 patients	

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Study: Mahévas, 2020 **Condition:** COVID-19		
Hydroxychloroquine (n=84) [600 mg in the first 48 hours after hospitalisation; azithromycin (n=17), amoxicillin/clavulanic acid (n=64)]	Death or transfer to ICU: 16 patients; 'In the weighted analysis, 20.2% patients in the HCQ group were transferred to the ICU or died within 7 days vs 22.1% in the no-HCQ group (16 vs 21 events, relative risk [RR] 0.91, 95% CI 0.47–1.80).' Day 7 Mortality: 3 patients; 'In the HCQ group, 2.8% of the patients died within 7 days vs 4.6% in the no-HCQ group (3 vs 4 events, RR 0.61, 95% CI 0.13–2.89)'	
Control (n=97) [Standard care (unspecified)]	Death or transfer to ICU: 21 patients Day 7 Mortality: 4 patients	
Study: Mercuro, 2020 **Condition:** COVID-19		
Hydroxychloroquine (n=37) [400mg of hydroxychloroquine twice on day 1, then 400 mg daily on days 2 through 5]		QTc prolongation developed into torsades de pointes and other ventricular arrhythmias: 10/37 patients

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Hydroxychloroquine and azithromycin (n=53) [400mg of hydroxychloroquine twice on day 1, then 400 mg daily on days 2 through 5 and azithromycin]		QTc prolongation developed into torsades de pointes and other ventricular arrhythmias: 18/53 patients
Study: Rosenberg, 2020 **Condition:** COVID-19		
Hydroxychloroquine + azithromycin (n=735) [Hydroxychloroquine was initiated at a median of 1 day (Q1-Q3, 1-2) following admission and azithromycin was given at a median of 0 days (Q1-Q3, 0-1)]	Mechanical ventilation required after treatment initiation: 94 patients (27.1%) ICU admission after treatment initiation: 226 patients (30.7%) Mortality: 189 patients Following adjustment for demographics, specific hospital, preexisting conditions, and illness severity, no significant differences in mortality were found between patients receiving hydroxychloroquine + azithromycin (adjusted HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (adjusted HR, 1.08[95%CI,0.63-1.85]), or azithromycin alone (adjusted HR,0.56 [95%CI,0.26-1.21]), compared with neither drug	Abnormal ECG findings (compared to control): odds ratio 1.55 (95% CI 0.89-2.67)

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Hydroxychloroquine (n=271) [Hydroxychloroquine was initiated at a median of 1 day (Q1-Q3, 1-2) following admission]	Mechanical ventilation required after treatment initiation: 31 patients (18.8%) ICU admission after treatment initiation: 52 patients (19.2%)	Abnormal ECG findings (compared to control): odds ratio 1.50 (95% CI 0.88-2.58)
Azithromycin (n=211) [azithromycin was given at a median of 0 days (Q1-Q3, 0-1)]	Mechanical ventilation required after treatment initiation: 5 patients (6.2%) ICU admission after treatment initiation: 23 patients (10.9%)	Abnormal ECG findings (compared to control): odds ratio 0.95 (95% CI 0.47-1.94)
Control (n=221) [unspecified]	Mechanical ventilation required after treatment initiation: 18 patients (8.1%) ICU admission after treatment initiation: 27 patients (12.2%)	Abnormal ECG findings (compared to control): odds ratio 1.58 (95% CI 0.77-3.24)
Study: Shao, 2020 **Condition:** COVID-19		
Intravenous immunoglobulin (n=174) [>15 g/day or ≤15 g/day]	60-day Mortality: 33 patients; 'There was no significant difference in 28-day and 60-day mortality between the IVIG group and non-IVIG group (P=0.872 and P=0.222, respectively), and no significant difference in survival time (P= 0.225)	
Control (n=151) [Not reported]	60-day Mortality: 21 patients	

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Study: Singh, 2020 **Condition:** COVID-19		
Hydroxychloroquine (n=910) [Not reported]	Mechanical ventilation: 46 patients Relative risk (vs control): 0.81 (95% CI 0.55 to 1.18) Risk difference (vs control): -1.21% (95% CI -3.33% to 0.91%) 30-day mortality: 104 patients Relative risk (vs control): 0.95 (95% CI 0.74 to 1.23) Risk difference (vs control): -0.55% (95% CI -3.50% to 2.40%)	
Control (n=910) [Not reported]	Mechanical ventilation: 57 patients 30-day mortality: 109 patients	
Study: Wadud, 2020 **Condition:** COVID-19		

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Tocilizumab (n=44) [Not reported]	**Survival rate: 61.36%** **Survival rate was much lower at 48 % in the control group and 61.36 % in patients who received Tocilizumab with significant P value of < 0.00001. The number needed to treat (NNT) was 7.48, if we treat 8 patients with Tocilizumab, 1 will not die.**	
Control (n=50) [Not reported]	**Survival rate: 48%**	
Study: Wang, 2020b **Condition:** COVID-19		
Lopinavir/ritonavir (n=20) [a-interferon, immunoenhancement therapy (thymosin)]	Mortality: 1 patient	
Methylprednisolone (n=26) [1- 2mg/kg/d for 5-7 days via intravenous injection; antiviral therapy(a-interferon, Kaletra [lopinavir/ritonavir]), immunoenhancement therapy (thymosin)]	Mortality: 2 patients	
Study: Wu, 2020 **Condition:** COVID-19		

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Corticosteroid (n=983) [Accumulative corticosteroid dose, mg: 280.0 (140.0, 480.0); Duration of corticosteroid use, d: 6.0 (3.0, 10.0); Daily average corticosteroid dose, mg: 40.0 (37.3, 57.1)]	**28-day mortality: 83 patients** **For all 1514 severe cases, we analysed the factors associated with in-hospital mortality. Kaplan-Meier survival curve showed that in-hospital mortality was significantly higher in the corticosteroid use group than in the no corticosteroid use group (log-rank test p<0.001). The 28-day in-hospital mortality was 20.6% (95% CI: 16.5%-25.6%) in the corticosteroid use group while 3.7% (95% CI: 2.3%-6.0%) for no corticosteroid use...In the multivariable Cox model, systemic corticosteroid use was independently associated with in-hospital mortality (HR=1.77, 95% CI: 1.08-2.89, p=0.023)**	
No corticosteroid (n=531) [Not reported]	**28-day mortality: 26 patients**	
Study: Yu, 2020 **Condition:** COVID-19		
Hydroxychloroquine (n=48) [oral 200 mg twice per day for 7-10 days]	**Mortality: 9 patients** **'In total of 568 patients, 247 patients died (mortality was 43.5%). Nine out of 48 HCQ patients (18.8%) died, while in NHCQ group, 238/520 (45.8%) patients died (p<0.001)'**	

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Control (n=520) [antiviral drugs: Lopinavir and Ritonavir, Entecavir hydrate, or Ribavirin]	**Mortality: 238 patients**	
Study: Zeng, 2020 **Condition:** COVID-19		
Convalescent plasma (n=6) [volume [median (IQR)] 300mL (200mL to 600mL), one dose (n=3), two doses (n=3); Antibiotics (n=6), Antiviral therapy (n=4), Intravenous immunoglobulin therapy (n=5), Glucocorticoid pulse therapy (n=4)]	Mortality: 5 patients, p=0.500	None reported
Control (n=15) [Antibiotics (n=15), Antiviral therapy (n=12), Intravenous immunoglobulin therapy (n=14), Glucocorticoid pulse therapy (n=12)]	Mortality: 14 patients	None reported
Study: Zha, 2020 **Condition:** COVID-19		

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Corticosteroid (n=20) [40 mg methylprednisolone once or twice per day (n=11) within 24 hours of admission for a median 5 days (IQR, 4.5–5.0 days); Moxifloxacin (n=6), duration [median (IQR)] 7 (5.5–7) days, lopinavir/ritonavir and interferon alfa (n=16), umifenovir and lopinavir/ritonavir and interferon alfa (n=4), duration of interferon alfa (days), [median (IQR)] 14.5 (10.5–17), duration of antiviral drug (days), [median (IQR)] 10 (7.75–13)]	Mortality: 0 patients	
Control (n=11) [Moxifloxacin (n=8), duration [median (IQR)] 7 (6–8.75) days, lopinavir/ritonavir and interferon alfa (n=10), Umifenovir and lopinavir/ritonavir and interferon alfa (n=1), duration of interferon alfa (days), [median (IQR)] 16 (10.5–17.5), duration of antiviral drug (days), [median (IQR)] 9 (8–10)]	Mortality: 0 patients	
Study: Zhu, 2020 **Condition:** COVID-19		
Arbidol (n=16) [arbidol group was given 0.2g arbidol, three times a day; All patients received conventional therapy, including oxygen inhalation (2L/min for half an hour, three times a day), atomized inhalation of recombinant human interferon-α 2b injection (5 million units, twice a day)]		elevated levels of ALT (<125 U/L): 3/16 patients, occurred during 1st week of admission

Drug therapy (sample size) [dose, route of administration, frequency, duration; additional therapies]	Effectiveness outcome: quantitative results; 'study conclusions'	Safety outcome: quantitative results; duration, clinical response
Lopinavir/ritonavir (n=34) [Lopinavir/ritonavir group received 400mg/100mg twice a day for a week; All patients received conventional therapy, including oxygen inhalation (2L/min for half an hour, three times a day), atomized inhalation of recombinant human interferon-α 2b injection (5 million units, twice a day)]		elevated levels of ALT (<125 U/L): 3/34, occurred during 1st week of admission

[1] includes: Hypoalbuminaemia; Hypokalaemia; Increased blood glucose; Anaemia; Rash; Thrombocytopenia; Increased total bilirubin; Increased blood lipids; Increased white blood cell count; Hyperlipidaemia; Increased blood urea nitrogen; Increased neutrophil; Aspartate aminotransferase increased; Constipation; Nausea; Diarrhoea; Vomiting; Reduced serum sodium; Increased serum potassium

[2] includes: Respiratory failure or acute respiratory distress syndrome; Cardiopulmonary failure; Pulmonary embolism; Recurrence of COVID-19; Cardiac arrest; Acute coronary syndrome; Tachycardia; Septic shock; Lung abscess; Sepsis; Bronchitis; Thrombocytopenia; Increased D-dimer; Haemorrhage of lower digestive tract; Ileus; Deep vein thrombosis; Acute kidney injury; Diabetic ketoacidosis; Multiple organ dysfunction syndrome

[§] Multiple analyses of overlapping cohorts of patients

Bolded text indicates statistically significant results

PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	3
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4-5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4, Appendix 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5-6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6

Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7, Figure 1, Appendix 4
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8-9, Table 1, Appendix 3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9-14, Table 2, Appendix 5
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	9-14, Table 2
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17, Table 2
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	17-18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	20

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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ABSTRACT

Objectives: The COVID-19 pandemic has stimulated growing research on treatment options. We aim to provide an overview of the characteristics of studies evaluating COVID-19 treatment.

Design: Rapid scoping review

Data sources: Medline, Embase and biorxiv/medrxiv from inception to May 15, 2021

Setting: Hospital and community care

Participants: COVID-19 patients of all ages

Interventions: COVID-19 treatment

Results: The literature search identified 630 relevant primary studies of which 190 were randomized controlled trials and 303 relevant evidence syntheses. The studies and evidence syntheses were conducted in 51 and 41 countries, respectively.

Most studies enrolled patients admitted to acute care hospitals (84%), included on average 172 participants, with an average age of 60 years, study duration of 28 days, number of effect outcomes of four and number of harm outcomes of one. The most common primary outcome was death (33%).

The included studies evaluated 215 treatment options. The most common treatments were tocilizumab (11%), hydroxychloroquine (9%), and convalescent plasma (7%). The most common therapeutic categories were non-steroidal immunosuppressants (18%), steroids (15%), and antivirals (14%). The most common therapeutic categories involving multiple drugs were antimalarials/antibiotics (16%), steroids/non-steroidal immunosuppressants (9%), and antimalarials/antivirals/antivirals (7%). The most common treatments evaluated in systematic reviews were steroids (11%), hydroxychloroquine (11%), and remdesivir (7%).

The evaluated treatment was in favour 50% and 35% of the evaluations, according to the conclusion of the authors of primary studies and evidence syntheses, respectively.

Conclusions: This scoping review characterized a growing body of comparative-effectiveness primary studies and evidence syntheses. The results suggest future studies should focus on children, elderly ≥65 years of age, patients with mild symptoms, outpatient treatment, multi-mechanism therapies, harms and active comparators. The results also suggest that future living evidence synthesis and network meta-analysis would provide additional information for decision-makers on managing COVID-19.

Keywords: COVID-19; RESPIRATORY MEDICINE; Clinical trials<THERAPEUTICS, scoping review, knowledge synthesis, evidence synthesis

Strengths and limitations of this study

- Broad literature search and study selection yielded 933 study reports, including 630 relevant studies (190 randomized controlled trials) and 303 evidence syntheses.
- Detailed charting of study populations, interventions and outcomes of included studies and reviews were conducted to analyze characteristics and trends in the included literature and to elucidate lessons for future research.
- Practical implications for future research with respect to study design, populations, interventions, comparators, outcomes and methodological approaches were identified.
- Semi-automation approach to study selection, allowing for a very broad literature search and screening approximately 290,000 titles/abstracts in about 40 person-hours over 2.3 weeks.
- This is a scoping review and as such, we did not assess the risk of bias of the included studies and evidence syntheses.

INTRODUCTION

The current global pandemic of Coronavirus Disease 2019 (COVID-19) has resulted in a high burden of disease and mortality worldwide(1, 2). The lack of effective treatments for COVID-19 has resulted in the almost constant production of studies and evidence syntheses evaluating potential treatment options, as illustrated by thousands of study protocols in clinical trial registries and hundreds of review protocols in systematic review registries(3, 4). Attempts to synthesize this evidence thus far have resulted in various scoping reviews focusing on single drugs or isolated drug classes(5-9). Better understanding of the characteristics of study populations, treatments and outcomes of this research is a prerequisite to the design and conduct of future comparative-effectiveness research.

The objective of this rapid scoping review was to provide an overview of the characteristics of studies examining COVID-19 treatment.

METHODS

The conduct of the rapid scoping review was guided by the JBI (formally Joanna Briggs Institute) Guide for scoping reviews, alongside the World Health Organization (WHO) Guide to rapid reviews(10, 11). An integrated knowledge translation approach was used to engage with the knowledge users from Health Canada (MK) and Public Health Agency of Canada (MP) throughout the conduct of the rapid scoping review, including during: research question development, literature search, study inclusion, interpretation of results, and draft report. The protocol for the review was registered using the Open Science Framework (https://osf.io/ypz7x). The discussion section includes minor amendments that occurred to the conduct of the review from the original protocol. Reporting of results was guided using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension to Scoping Reviews (PRISMA-ScR) Statement(12). Our research question was "What evidence exists on

the treatments for COVID-19 in primary studies and reviews", which is appropriate for the scoping review methodology(13).

Patient and Public Involvement

Since this work was carried out as part of a rapid response to the COVID-19 pandemic project, timelines did not allow for participation of any patients or members of the public in this scoping review.

Literature search

Comprehensive literature searches and citation screening were used in combination to gather relevant evidence from MEDLINE, EMBASE and pre-print servers (biorxiv/medrxiv)(14). The literature was initially searched from inception to May 21, 2020 and subsequently updated to May 15, 2021. Titles/abstracts were identified for screening using the Continuous Active Learning® (CAL®) tool, which uses supervised machine learning (see Appendix 1 for the description and performance of the tool)(14). For archives that could be retrieved in their entirety (e.g., MEDLINE, pre-print servers), the CAL® tool applied broad relevant search terms (Appendix 1). This search was supplemented by a literature search conducted by an experienced librarian in EMBASE (Appendix 2). The literature search was not restrict by language or publication status.

Eligibility criteria

The eligibility criteria followed the PICOS framework and consisted of:

- Population: Individuals of any age who were clinically and/or laboratory diagnosed with COVID-19.
- Intervention: Any compounds under investigation in human clinical trials as potential COVID-19 therapies (Appendix 3). Chinese medicine and complementary and alternative medicine – either alone or in combination with these medications – were excluded.

- Comparator: Any of the interventions listed above, no intervention or placebo.
- Outcomes: Any reported outcome.
- Study designs: Primary studies of any design with a comparator group. Evidence syntheses of such studies were included, including systematic reviews, scoping reviews, rapid reviews, meta-analysis and overviews of reviews.

Study selection

A streamlined approach to study selection was used for the rapid scoping review. In combination with manual screening by reviewers, the CAL® tool was used to identify and rank the titles and abstracts most likely to meet the inclusion criteria. This process continued iteratively until none of the identified articles met the inclusion criteria. For manual screening, a screening form based on the eligibility criteria was prepared for reviewers to aid in making consistent judgements on article relevance. A pilot-test was conducted using a random sample of 10 titles/abstracts until reviewers reached at least 75% agreement. Subsequently, screening was completed by single reviewers.

Data charting and coding

A charting form was developed and calibrated amongst the entire review team using two randomly selected full-text articles to ensure a standard approach to data collection. Following successful completion of the pilot-test, included studies were charted by single reviewers and verified by a second reviewer to ensure accuracy. Methodological quality or risk of bias appraisal of included studies was not conducted since this is scoping review(10). The items collected included study characteristics (e.g., study duration, study design, country of conduct), patient characteristics (e.g., type of diagnosis, mean age), intervention and comparator details (e.g., type of intervention, dose, frequency, duration) and outcome measures details (e.g., mortality, viral clearance, and hospital admission).

Pharmacological agents were grouped by their therapeutic category(15). Study primary outcomes were grouped together to reflect the clinical, virology, respiratory, inflammatory, cardiology and olfactory status and measures of COVID-19(16, 17). The numbers of effect and harm measures were derived by counting the outcomes from the description of study outcomes. Authors' conclusions were coded into the following categories: favor treatment, favor control, indeterminate and other(18). Pairs of reviewers conducted the data coding independently, with discrepancies reviewed and resolved through discussion by a pair of reviewers.

Synthesis

The charted and coded data were summarized descriptively for all patient population, interventions, comparators and outcomes. The data were stratified by study design (randomized controlled trials versus non-RCT) and review type (review conducted according to a review protocol or otherwise).

Data repository

All material related to this review, including EndNote databases, extracted data in MS Excel, coding categories and analysis procedures written in the statistical software R are available at https://knowledgetranslation.net/comparative-effectiveness-research-of-covid-19-treatment-a-rapid-scoping-review-data-repository/.

RESULTS

Literature Search

Figure 1 displays the literature search results. The semi-automation process with CAL® and human reviewers allowed for the screening of approximately 290,000 titles/abstracts in about 40 person-hours over 2.3 weeks. Specifically, CAL® identified 289,844 Covid-19 records and 4,183 potentially relevant titles/abstracts. Title/abstract screening by reviewers resulted in

1,542 potentially relevant reports. Report screening by reviewers resulted in 933 relevant reports, including 630 studies and 303 knowledge syntheses. The list of included primary studies and knowledge syntheses is in Appendix 4 and 5, respectively.

Characteristics of included studies

Figure 2 displays the timing when the studies were available online; on average 48 primary studies per month were published from July 2020 to April 2021. Table 1 displays the characteristics of the 630 included studies of varying design, including randomized controlled trials (190 studies [30%]), retrospective cohort studies (314 [50%]) and prospective cohort studies (71 [11%]), amongst others. The median study duration was 28 days and the median sample size was 172 participants. Public sources provided funding for about a third of the studies; RCTs were funded often by private funding sources (27% relative to 3% for non-RCT). The primary studies were conducted in 51 countries, including the United States (26%), China (17%), Italy (8%), France (7%), Spain (7%), India (4%), Iran (3%), United Kingdom (3%) and Brazil (3%), among others (Table A1, Appendix 6).

Most studies were conducted with participants admitted to acute care hospital (84%). Participants were on average 60 years of age, including 61% male, and mostly with confirmed COVID-19 via PCR test (Table 1). About a third of the included studies enrolled participants with severe or critical COVID-19 conditions. Few studies (0.3%) enrolled children (e.g., <16 years of age, 0.3%) or the elderly (e.g., ≥65 years of age, 2%). Figure A1 displays the cloud of words often used to describe the participants (Appendix 6). Typical words used were COVID-19, COVID-19 patients, hospitalized, severe, pneumonia, ICU, outpatient, respiratory distress, invasive mechanical ventilation, critically ill and supplemental oxygen, among others.

The median number of effect outcomes was four, and the corresponding number of harm outcomes was one (Table 1). Common primary outcomes included death/survival (33% of the

included studies), clinical status/measures (20%), virology status/measures (10%), respiratory status/measures (9%), safety/adverse events excluding death (7%) and composite outcomes involving death (7%, e.g., intubation and death, or intensive care admission and death), among others.

The included studies evaluated 828 treatment arms (712 single-drug and 116 multiple-drug treatment arms) against 630 control arms, of which 137 (22%) control arms involved active comparators (Table 2). The treatment arms consisted of 215 unique treatment options (Table A2, Appendix 6). The most common treatments were tocilizumab (11%), hydroxychloroquine (9%), convalescent plasma (7%), steroid (4%), lopinavir combined with ritonavir (4%), methylprednisolone (3%), remdesivir (3%), enoxaparin (2%), hydroxychloroquine combine with azithromycin (2%), and anakinra (2%), among others. Table 2 also displays the common therapeutic categories of the evaluated treatment. The most common therapeutic categories were non-steroidal immunosuppressant (18%), steroid (15%), antiviral (14%), antimalarial (12%), anticoagulant (5%), convalescent plasma (8%), antibiotic (4%), anti-inflammatory (3%), interferon therapy (2%), anti-parasitic (2%) and immunomodulatory (2%), among others (details in Table A3, Appendix 6). Common therapeutic categories involving multiple drugs were the combination of antimalarial/antibiotic (16%), steroid/non-steroidal immunosuppressant (9%), antimalarial/antiviral/antiviral (7%), 2-antivirals (4%) and antiviral/interferon (4%), among others (Table A4, Appendix 6).

Characteristics of included knowledge syntheses

Figure 2 displays the timing when the knowledge syntheses were available online, on average 22 reviews appeared each month from May 2020 to April 2021. Table 3 displays characteristics of the 303 included knowledge syntheses, including 89 (29%) knowledge syntheses and 214 (71%) knowledge syntheses conducted with and without a review

protocol, respectively. Commonly conducted knowledge syntheses included systematic review with meta-analysis (63%), systematic review (24%), meta-analysis (4%, none mentioned the use of a review protocol), scoping review (3%) and rapid review (3%), among others. Most reviews (83%) included RCT and non-RCT studies. The median number of data sources was five and the median number of included studies was 14. The evidence syntheses were conducted in 41 countries, including the United States (19%), China (14%), India (11%), Iran (6%) and the United Kingdom (6%), among others (Table A5, Appendix 6). The evidence syntheses evaluated 540 treatment arms against 303 control arms (see Table 4). The treatment arms consisted of 140 unique treatment options. Table 5 displays common treatment options, including steroid (11%), hydroxychloroquine (11%), remdesivir (7%), tocilizumab (7%), convalescent plasma (6%), and lopinavir/ritonavir (4%), chloroquine (4%) and antiviral (4%), among others (Table A6, Appendix 6).

Treatment evaluation according to authors' conclusion

Table 5 displays the results of the treatment evaluation according to authors' conclusion. Among the included studies and knowledge syntheses, the conclusion was in favour of treatment 50% and 35% of the evaluated treatment arms, respectively.

DISCUSSION

We completed a rapid scoping review for Health Canada and Public Health Agency of Canada to identify pharmacologic treatments for COVID-19. A comprehensive search of electronic databases, trial registries and other grey literature sources from inception to May 2020 identified 9 controlled trials and 19 cohort studies with approximately 8,000 participants. Updated to May 15, 2021, the search of electronic databases identified 933 relevant reports, including 630 studies with approximately 15.4 million participants, and 303 knowledge syntheses.

With respect to study population, existing studies put much emphasis on adult patients admitted to acute care hospitals. Future studies need to focus on children, older adults aged ≥65 years and patients with mild symptoms in community settings. Future study populations will need to reflect a broader range of age groups as the current pandemic evolves to affect younger age groups(19, 20).

With respect to treatment, many studies and reviews evaluated antimalarial agents. Existing studies emphasised preventing and treating cytokine surge with steroids and non-steroidal immunosuppressants, including interleukin-6 inhibitors (e.g., tocilizumab, sarilumab), interleukin-1 antagonist (e.g., anakinra), anti-IL-1β monoclonal antibody (e.g., canakinumab), TNF-alpha inhibitor (e.g., adalimumab) and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib). Future studies may need to explore treatment for patients not responding to these agents, such as immunomodulators (e.g., thymosin-α1). Existing studies put much emphasis on monotherapy; future studies need to evaluate combination therapy that addresses the multiple aspects of COVID-19, such as virology, respiratory, inflammatory and cardiology. Future studies may also need to explore outpatient treatment for patients with mild symptoms, and treatment options not frequently evaluated in existing studies, such as therapeutic anticoagulants.

With respect to comparators, most existing randomized controlled trials used placebo comparators while most observational studies used standard of care as comparator; future studies may consider active treatment as comparators, especially when evaluating treatments aiming to produce incremental improvement against effective treatments. Methodological issues related to the selection and delineation of comparators in studies evaluating combination therapies deserve attention. For example, a study evaluated multi-mechanism approach with medications targeting early immunomodulation, anticoagulation, and viral suppression to prevent catastrophic cytokine release syndrome encountered large variation in

clinical characteristics of study participants and standard-of-care comparators in the five participant hospitals in two countries, including differences in disease severity and different doses of colchicine and types of steroids used across comparative groups(17).

With respect to outcomes, about a third of the included studies used mortality as the primary outcome. Tracking this outcome may require sufficiently long study duration, perhaps longer than the median duration of less than a month observed among existing studies, especially in patients with prolonged respiratory problems, suggesting longer follow-up duration for future studies. Of note, few existing studies used composite endpoints involving death, including endpoints such as intubation and intensive care admission. This use seems to be particularly suitable to capture the respiratory, immunology and cardiovascular aspects of COVID-19, as well as mortality. Few existing studies focused on harms due to treatment and among those that evaluated benefits and harms, the median number of reported harms was one; future studies need to put more emphasis on harm evaluation. Existing RCTs put much emphasis on the use of clinical status/measures as primary outcome measures. Future trials may consider other primary outcomes that are relevant to patients, such as pneumonia, acute respiratory distress syndrome, multi-organ failure, and septic shock, among others.

With respect to study design, our results showed a breakdown of 30% and 70% for RCTs and observational studies, respectively. Future trials are needed for evaluating combination therapies. Observational studies will remain pertinent in the evaluation of combination therapies, especially when rich data becomes available with their use in practice. Our review excluded qualitative studies, but we wish to emphasize the importance of these studies in elucidating the experience of COVID-19 patients.

With respect to evidence synthesis, we identified a small number of meta-analyses conducted without the associated systematic review and review protocol (n=13). This practice needs to be scrutinized because of the associated high risk of bias in the results, which could be

wrong, but appeared to be convincingly precise(21). Existing knowledge syntheses mostly evaluated monotherapy; future evidence syntheses will need to include data from the evaluation of combination therapy. The number of existing network meta-analyses was low (n=4); future network meta-analyses are needed to identify effective treatment given a plethora of treatment options, as well as to identify effective component treatment options addressing multiple aspects of COVID-19(22). Given the growing literature, there is a definitive need for living knowledge synthesis, in which the synthesis is updated regularly as new studies become available(23). The results suggest that monthly updates may become necessary.

With respect to the growing literature, the use of automation tools like CAL® for study selection will become essential to ensure a highly sensitive yield of relevant studies, responsive timelines for decision-making and reduced workload for reviewers. In this scoping review, we used a continuous active learning approach that integrates machine learning with feedback instructions from reviewers. This approach allowed the screening of approximately 290,000 titles/abstracts in about 40 person-hours over 2.3 weeks. We believe this approach is indispensable for future reviews involving large body of literature. This approach called for slight changes in our review conduct and reporting, of note the reported number of the titles/abstracts excluded by the automation tool in the flowchart (see Figure 1).

There are several limitations of this review. This is a scoping review, and as such, we did not assess the risk of bias in the included studies and reviews. Initially, the review protocol called for a borrowing strength of evidence approach, including studies evaluating treatment for SARS and MERS. The initial literature search in May 2020 included electronic databases, trial registries, Cochrane Library and other grey literature sources. Given the growing literature on COVID-19 by May 2021, the current review was focused only on COVID-19 treatment, with relevant studies identified from MEDLINE, EMBASE and pre-print servers.

In this review, the evaluated treatment options appeared to attain a reasonable chance of being more effective than their comparators, approximately 30% and 50% according to the authors' conclusions from the included studies and reviews, respectively. However, we did not extract outcome data and combined them to verify the authors' conclusions. To provide a broad overview of the comparative effectiveness research on Covid-19 treatment, we included reports from preprint servers, but these reports had not gone through peer review. Despite these limitations, the methods used in this review were carefully selected to address the needs of our knowledge users from Health Canada and Public Health Agency of Canada. In addition, we made the material from this scoping review available in an online data repository as the data may be useful for conducting systematic reviews of specific therapies or for updating the current review(24).

CONCLUSIONS

This scoping review characterized a growing body of comparative-effectiveness studies and evidence syntheses evaluating hundreds of monotherapy and combination therapy options addressing the multiple sequelae of COVID-19. The results suggest future studies in children, elderly (e.g., ≥65 years of age) and patients with mild symptoms, with additional data on outpatient treatment, multi-mechanism therapy, harms and active comparators. The results also suggest that future living evidence synthesis and network meta-analysis would provide additional information for decision-makers on managing COVID-19.

DECLARATIONS

Ethics approval and consent to participate

Not applicable. This research is exempt from ethics approval because the work is carried out on published documents.

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors have no competing interests to declare.

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Authors' contributions

PR and BP analyzed the data, interpreted the results and drafted the original and revised manuscript, respectively. ACT and SES conceived and designed the study, helped obtain funding, interpreted the results and helped write sections of the manuscript. GVC and MRG provided methodological and technical support and edited the manuscript. AR, ND, JA and FY coordinated the review, screened citations and full-text articles, abstracted data, resolved discrepancies and edited the manuscript. MK, MP and MM helped conceive the study, provided methodological support and content expertise and edited the manuscript. RR and MG provided methodological support, screened citations and full-text articles and assisted with drafting the manuscript. CW, NR, EM and RW screened citations and full-text articles, abstracted data and assisted with data analysis. All authors read and approved the final manuscript.

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Additional File

File Format: Microsoft Word (.docx)

Title of Data: Additional File 1 (Appendices 1-6)

Description of Data: The appendices include the following additional information:

Appendix 1 – The Continuous Active Learning (CAL®) tool

Appendix 2 – EMBASE search strategy

Appendix 3 – List of drugs from Health Canada and Public Health Agency of Canada

Appendix 4 – List of included primary studies

Appendix 5 – List of included knowledge syntheses

Appendix 6 – Additional details for the Results section

FIGURE LEGEND

Figure 1. Flow diagram of included studies

Study Flow Diagram

Figure 2. Timing of available online of included studies*

Online timing chart of included studies

TABLES

Table 1. Study, participant and outcome characteristics

Study characteristics	Total (n=630)	RCT (n=190)	Non-RCT (n=440)
Study design			
RCT	190 (30%)	190	
Retrospective cohort	314 (50%)		314 (71%)
Prospective cohort	71 (11%)		71 (16%)
Case-control	28 (4%)		28 (6%)
Controlled clinical trial	23 (4%)		23 (5%)
Controlled before-after	4 (1%)		4 (1%)
Study setting			
Acute care hospital	528 (84%)	147 (77%)	381 (87%)
Intensive care unit	44 (7%)	4 (2%)	40 (9%)
Community	42 (7%)	34 (18%)	8 (2%)
Community and hospital	7 (1%)	3 (2%)	4 (1%)
Nursing home	3 (0%)	0 (0%)	3 (1%)
Not reported	6 (1%)	2 (1%)	4 (1%)
Country			
United States	166 (26%)	38 (20%)	128 (29%)
China	109 (17%)	27 (14%)	82 (19%)
Italy	48 (8%)	2 (1%)	46 (10%)
France	41 (7%)	5 (3%)	36 (8%)
Spain	41 (7%)	3 (2%)	38 (9%)
India	24 (4%)	16 (8%)	8 (2%)
Iran	21 (3%)	15 (8%)	6 (1%)
United Kingdom	21 (3%)	19 (10%)	2 (0%)
Brazil	17 (3%)	13 (7%)	4 (1%)
Mexico	12 (2%)	6 (3%)	6 (1%)
Turkey	12 (2%)	1 (1%)	11 (3%)
Study duration			
Median duration in days (IQR)	28 (14, 30)	21.5 (14, 28)	28 (20, 35)
Sample size			
Median # participants (IQR)	172 (77, 507)	120 (60, 393)	199 (86, 612)
Study sponsor			
Public	211 (33%)	78 (41%)	133 (30%)
No funding	171 (27%)	22 (12%)	149 (34%)
Private	63 (10%)	51 (27%)	12 (3%)
Public & private	18 (3%)	13 (7%)	5 (1%)
Not reported	167 (27%)	26 (14%)	141 (32%)
Participant characteristics			
Average age (years)			

Study characteristics	Total (n=630)	RCT (n=190)	Non-RCT (n=440)
Median (range)	60 (6, 88)	56 (27, 77)	62 (6, 88)
Average percent of male participants			
Median (IQR)	61 (53, 69)	59 (50, 66)	62 (54, 70)
Diagnosis			
Polymerase chain reaction (PCR) test	450 (71%)	149 (78%)	301 (68%)
PCR and other*	111 (18%)	33 (18%)	78 (18%)
Not specified	69 (11%)	8 (4%)	61 (14%)
Case severity♦			
Severe	166 (26%)	39 (21%)	127 (29%)
Mild or moderate	47 (7%)	24 (13%)	23 (5%)
Moderate or severe	35 (6%)	18 (9%)	17 (4%)
Severe or critical	32 (5%)	7 (4%)	25 (6%)
Moderate	25 (4%)	15 (8%)	10 (2%)
Mild	22 (3%)	15 (8%)	7 (2%)
Mild, moderate or severe	14 (2%)	6 (3%)	8 (2%)
Mild, moderate, severe or critical	8 (1%)	2 (1%)	6 (1%)
Moderate, severe or critical	4 (1%)	1 (1%)	3 (1%)
Special age group**			
Elderly (e.g., ≥65 years of age)	11 (2%)	2 (1%)	9 (2%)
Children (e.g., <16 years of age)	2 (0%)	1 (1%)	1 (0%)
Type of primary outcome			
Death/survival[1]	207 (33%)	20 (11%)	187 (43%)
Clinical status/measures[2]	124 (20%)	73 (38%)	51 (12%)
SARS-CoV-2 virology status/measures[3]	61 (10%)	29 (15%)	32 (7%)
Respiratory status/measures[4]	54 (9%)	19 (10%)	35 (8%)
Safety/adverse events[5]	44 (7%)	9 (5%)	35 (8%)
Composite outcome involving death[6]	43 (7%)	11 (6%)	32 (7%)
Resources measures[7]	20 (3%)	6 (3%)	14 (3%)
Invasive mechanical ventilation	16 (3%)	4 (2%)	12 (3%)
Admission to intensive care unit	11 (2%)	1 (1%)	10 (2%)
Admission to acute care hospital	9 (1%)	3 (2%)	6 (1%)

Study characteristics	Total (n=630)	RCT (n=190)	Non-RCT (n=440)
Inflammatory status/measures[8]	7 (1%)	3 (2%)	4 (1%)
Cardiology status/measures[9]	5 (1%)	2 (1%)	3 (1%)
Emergency room visit	4 (1%)	2 (1%)	2 (0%)
Olfactory status/measures[10]	3 (0%)	2 (1%)	1 (0%)
Other[11]	22 (3%)	6 (3%)	16 (4%)
Number of effect outcomes			
Median # of outcomes (IQR)	4 (2, 6)	6 (4, 9)	3 (2, 6)
Number of harm outcomes			
Median # of outcomes (IQR)	1 (0, 3)	2 (1, 5)	0 (0, 2)

Notes: IQR – interquartile range. *Other diagnostic modality such as lung imaging or suspected Covid-19 cases. ♦Case severity according to the clinical spectrum of SARS-CoV-2 infection by the National Institute of Health(25) **Age group as reported in the included studies. [1]Ddeath/survival or time to death. [2]Clinical status/measures such as improvement/deterioration or time to such events. [3]SARS-CoV-2 virology status/measures such as viral load or duration to Polymerase Chain Reaction negative. [3]Respiratory status/measures such as whole lung lesion volumes or blood oxygen saturation. [5]Safety/adverse events such as other infections than SARS-CoV-2, acute kidney injury or drug tolerance. [6]Composite endpoints involving death such as death and invasive mechanical ventilation or death and admission to intensive care unit. [7]Resources measures such as length of hospital stay. [8]Inflammatory status/measures such as plasma levels of C-reactive protein, or changes in ROX index, the ratio of SpO2/FIO2. [9]Cardiology status/measures such as cardia endpoints with max high-sensitivity cardiac troponin level, and stroke. [10]Olfactory status/measures such as loss of smell and taste.[11]Other primary outcome such as time from Covid-19 symptoms onset to treatment or organ support–free days.

Table 2. Treatment options frequently evaluated in included studies

All individual treatments	Total	RCT	Non-RCT
Total	**828**	**231**	**597**
1. **Tocilizumab**	87 (11%)	12 (5%)	75 (13%)
2. **Hydroxychloroquine**	78 (9%)	22 (10%)	56 (9%)
3. **Convalescent Plasma**	55 (7%)	15 (6%)	40 (7%)
4. **Steroid**	37 (4%)	1 (0%)	36 (6%)
5. **Lopinavir/Ritonavir**	29 (4%)	5 (2%)	24 (4%)
6. **Methylprednisolone**	26 (3%)	3 (1%)	23 (4%)
7. **Remdesivir**	25 (3%)	16 (7%)	9 (2%)
8. **Enoxaparin**	18 (2%)	1 (0%)	17 (3%)
9. **Hydroxychloroquine/Azithromycin**	18 (2%)	2 (1%)	16 (3%)
10. **Anakinra**	16 (2%)	2 (1%)	14 (2%)
Treatment type - Common single treatment	**Total**	**RCT**	**Non-RCT**
All single treatments	**712**	**202**	**510**
1. NS-Immunosuppressant	126 (18%)	27 (13%)	99 (19%)
2. Steroid	110 (15%)	15 (7%)	95 (19%)
3. Antiviral	97 (14%)	40 (20%)	57 (11%)
4. Antimalarial	87 (12%)	25 (12%)	62 (12%)
5. Anticoagulant	66 (5%)	5 (3%)	61 (12%)
Anticoagulant-Therapeutic	17 (2%)	2 (1%)	15 (3%)
Anticoagulant-Prophylactic	14 (2%)	0 (0%)	14 (3%)
6. Convalescent Plasma	56 (8%)	16 (8%)	40 (8%)
7. Antibiotic	29 (4%)	7 (3%)	22 (4%)
8. Anti-Inflammatory	20 (3%)	8 (4%)	12 (2%)
9. Interferon Therapy	16 (2%)	7 (3%)	9 (2%)
10. Anti-parasitic	14 (2%)	12 (6%)	2 (0%)
10. Immunomodulatory	14 (2%)	4 (2%)	10 (2%)
Treatment type – Common combined treatment			
All combined treatment option	**116**	**29**	**87**
1. Antimalarial/Antibiotic	19 (16%)	2 (7%)	17 (20%)
2. Steroid/NS-Immunosuppressant	10 (9%)	0 (0%)	10 (11%)
3. Antimalarial/Antiviral/Antiviral	8 (7%)	1 (3%)	7 (8%)
4. Antiviral/Antiviral	5 (4%)	3 (10%)	2 (2%)
4. Antiviral/Interferon	5 (4%)	0 (0%)	5 (6%)
5. Antimalarial/Antiviral	4 (3%)	0 (0%)	4 (5%)
5. Antimalarial/Antiviral/Antibiotic	4 (3%)	4 (14%)	0 (0%)
5. Anti-parasitic/Antibiotic	4 (3%)	3 (10%)	1 (1%)
5. Antiviral/Antiviral/Antiviral	4 (3%)	0 (0%)	4 (5%)

5. Antiviral/Antiviral/Antiviral/Interferon	4 (3%)	0 (0%)	4 (5%)
5. Antiviral/NS-Immunosuppressant	4 (3%)	3 (10%)	1 (1%)
5. NS-Immunosuppressant/Steroid	4 (3%)	0 (0%)	4 (5%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant.

Table 3. Evidence Synthesis characteristics

	All (n=303)	With protocol (n=89)	Without protocol (n=214)
Review type			
Systematic review with meta-analysis	192 (63%)	67 (75%)	125 (58%)
Systematic review	73 (24%)	15 (17%)	58 (27%)
Meta-analysis	13 (4%)	0 (0%)	13 (6%)
Scoping review	10 (3%)	3 (3%)	7 (3%)
Rapid review	8 (3%)	1 (1%)	7 (3%)
Network meta-analysis	2 (1%)	1 (1%)	1 (0%)
Rapid review with meta-analysis	2 (1%)	1 (1%)	1 (0%)
Systematic review with network meta-analysis	2 (1%)	0 (0%)	2 (1%)
Overview of systematic reviews	1 (0%)	1 (1%)	0 (0%)
Review abstract			
Structured abstract	161 (53%)	47 (53%)	114 (53%)
Abstract with no structure	142 (47%)	42 (47%)	100 (47%)
Eligibility criteria			
Report eligibility criteria	263 (87%)	87 (98%)	176 (82%)
Eligibility criteria are unclear	40 (13%)	2 (2%)	38 (18%)
Include randomized controlled trials			
Include randomized controlled trials only	51 (17%)	18 (20%)	33 (15%)
Include studies of different study designs	252 (83%)	71 (80%)	181 (85%)
Number of data sources			
Median (IQR)	5 (3, 6)	5.5 (4, 7)	4 (3, 6)
Number of included studies			
Median (IQR)	14 (7, 29)	16 (7, 37)	14 (7, 26)
Common country			
1. United States	59 (19%)	13 (15%)	46 (21%)
2. China	41 (14%)	13 (15%)	28 (13%)
3. India	34 (11%)	12 (13%)	22 (10%)
4. Iran	18 (6%)	3 (3%)	15 (7%)
4. United Kingdom	18 (6%)	3 (3%)	15 (7%)
5. Saudi Arabia	13 (4%)	1 (1%)	12 (6%)
6. Canada	12 (4%)	5 (6%)	7 (3%)
7. Italy	12 (4%)	8 (9%)	4 (2%)
8. Indonesia	9 (3%)	2 (2%)	7 (3%)
9. Malaysia	7 (2%)	0 (0%)	7 (3%)
10. France	6 (2%)	4 (4%)	2 (1%)

Table 4. Treatment options evaluated in systematic reviews

All evaluated treatment options	Total (n=540)	With protocol (n=154)	Without protocol (n=386)
Steroid	61 (11%)	14 (9%)	47 (12%)
Hydroxychloroquine	60 (11%)	16 (10%)	44 (11%)
Remdesivir	40 (7%)	11 (7%)	29 (8%)
Tocilizumab	36 (7%)	10 (6%)	26 (7%)
Convalescent plasma	35 (6%)	11 (7%)	24 (6%)
Lopinavir-ritonair	24 (4%)	8 (5%)	16 (4%)
Chloroquine	20 (4%)	6 (4%)	14 (4%)
Antiviral	14 (3%)	4 (3%)	10 (3%)
Anticoagulant	11 (2%)	2 (1%)	9 (2%)
Azithromycin	11 (2%)	3 (2%)	8 (2%)
Hydroxychloroquine/azithromycin	11 (2%)	1 (1%)	10 (3%)
Favipiravir	10 (2%)	1 (1%)	9 (2%)
Intravenous immunoglobulin	10 (2%)	2 (1%)	8 (2%)
Colchicine	9 (2%)	2 (1%)	7 (2%)
Arbidol	7 (1%)	1 (1%)	6 (2%)
Chloroquine/hcq	7 (1%)	1 (1%)	6 (2%)
Invermectin	7 (1%)	3 (2%)	4 (1%)
Anticoagulant therapeutic	6 (1%)	3 (2%)	3 (1%)
Covid-19 treatments	5 (1%)	3 (2%)	2 (1%)
Cell-based therapies	5 (1%)	2 (1%)	3 (1%)
Anakinra	4 (1%)	3 (2%)	1 (0%)
Antibiotics	4 (1%)	1 (1%)	3 (1%)
Famotidine	4 (1%)	1 (1%)	3 (1%)
Hydroxychloroquine/chloroquine	4 (1%)	3 (2%)	1 (0%)
Immunomodulator	4 (1%)	1 (1%)	3 (1%)
Interleukin-6 inhibitors	4 (1%)	2 (1%)	2 (1%)
JAK-inhibitors	4 (1%)	2 (1%)	2 (1%)
Sarilumab	4 (1%)	4 (3%)	0 (0%)

Note: JAK-inhibitors: Janus kinase (JAK) inhibitors

Table 5. Treatment evaluation according to authors' conclusion

Studies evaluating treatment benefits/harms	**All studies**	**RCT**	**Non-RCT**
# of evaluated treatment arms	827	231	596
Favor evaluated treatment	413 (50%)	120 (52%)	293 (49%)
Favor control	63 (8%)	15 (7%)	48 (8%)
Indeterminate/neutral	258 (31%)	90 (39%)	168 (28%)
Reviews evaluating treatment benefits/harms	**All reviews**	**With protocol**	**Without protocol**
# of evaluated treatment arms	540	154	386
Favor evaluated treatment	187 (35%)	50 (32%)	137 (35%)
Favor control	71 (13%)	19 (12%)	52 (13%)
Indeterminate/neutral	182 (34%)	68 (44%)	114 (30%)

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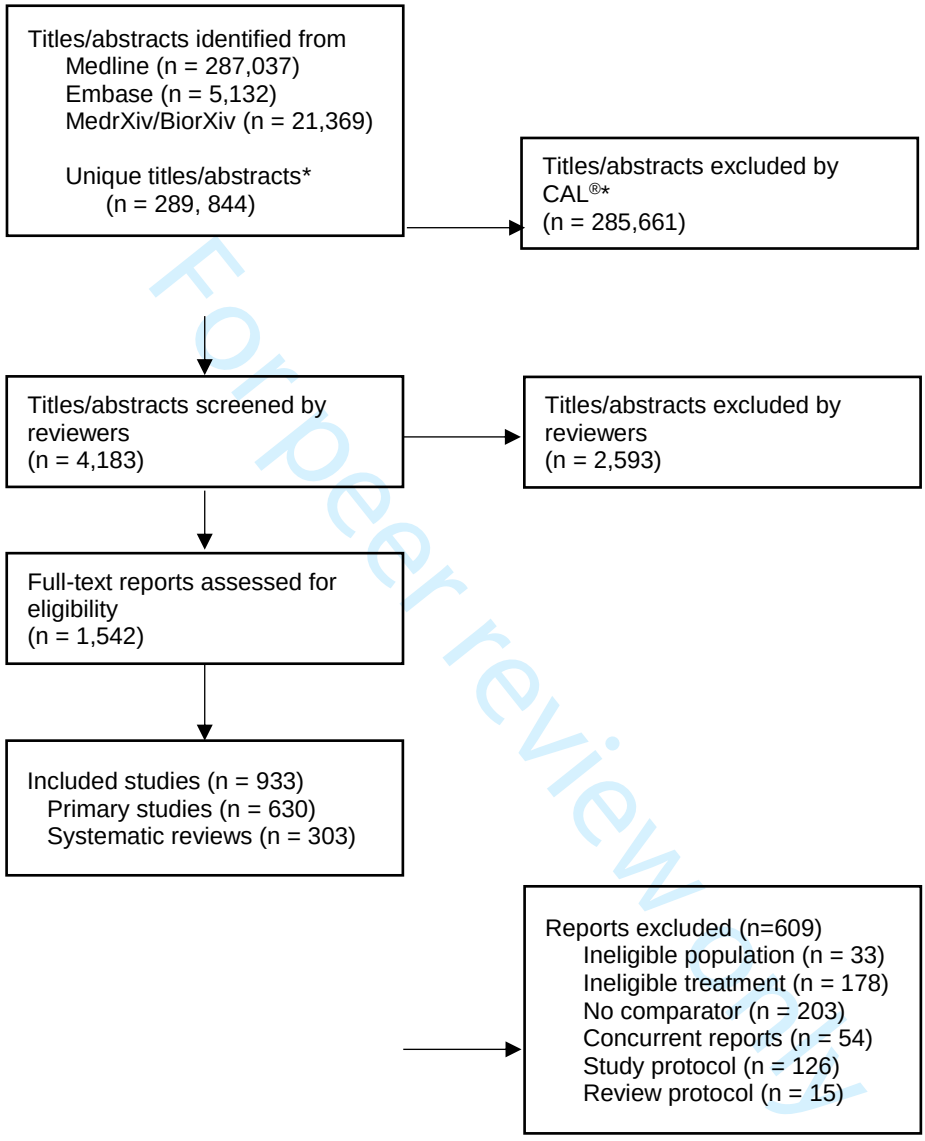
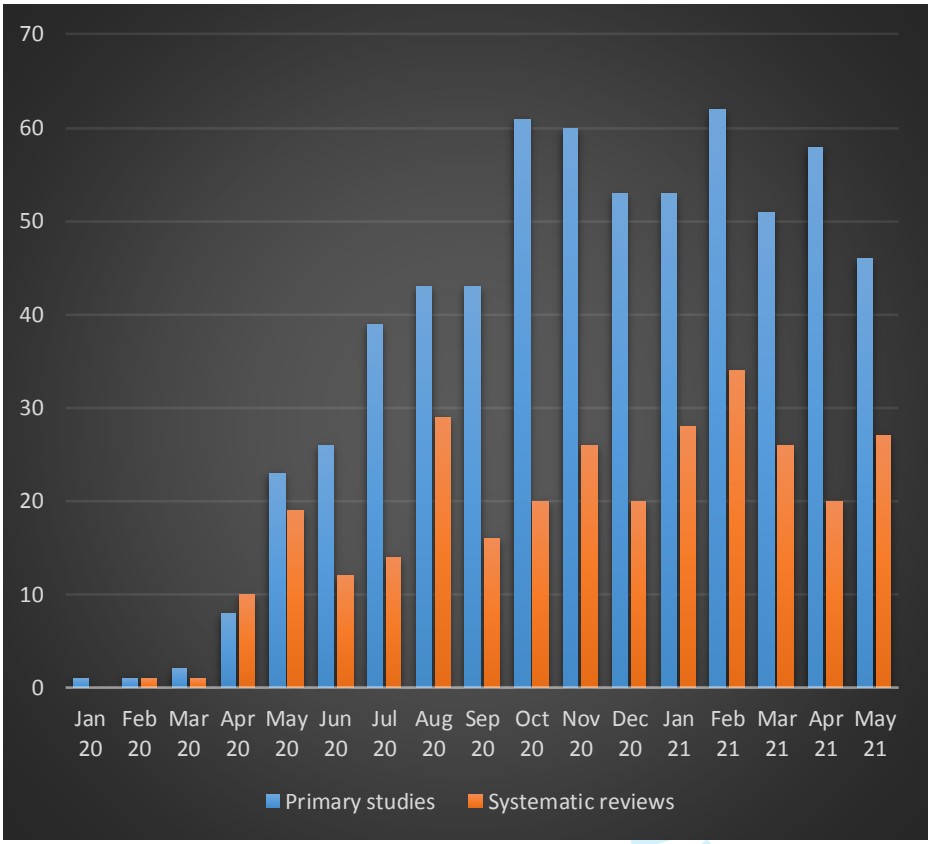
Figure 1. Flow diagram of included studies



Notes: *Estimated number of unique titles/abstracts based upon: Medline (Ovid) includes preprints on Covid-19 from Medrxiv and Biorxiv, and large overlapping records between Medline and Embase. The flowchart was modified from the PRISMA 2020 statement.[25]

Figure 2. Timing of available online of included studies*



Notes: The numbers of primary studies and systematic reviews for May 21 are higher because the literature search ended at May 15, 2021.

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Appendices

Contents

Appendix 1. The Continuous Active Learning (CAL®) tool

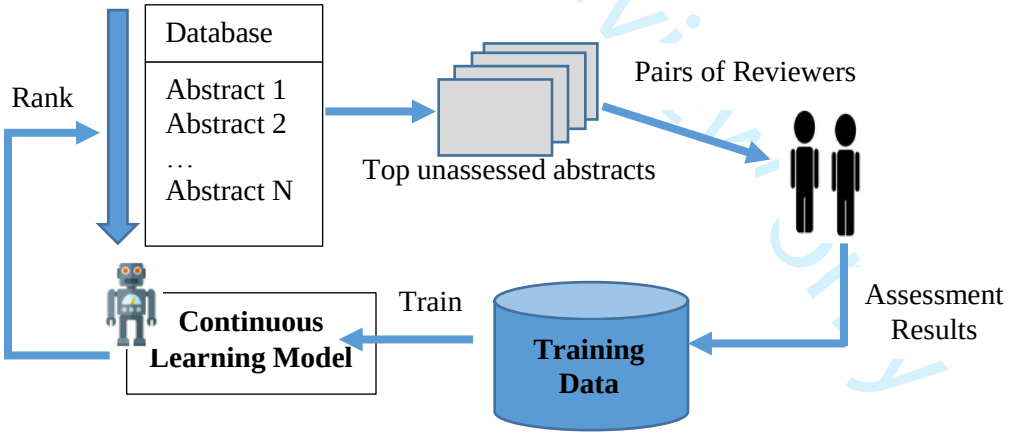

Figure. The algorithm of the CAL® tool

The above figure illustrates the algorithm in the CAL® tool. Text of the review question is used to start training the machine-learning model in the Continuous Active Learning (CAL) method. The CAL model predicts and quantifies the relevance of abstracts from a database. The abstracts are ranked in order of highest to lowest relevance. The top ranked abstracts are presented to a pair of human reviewers for relevance screening. The screening results are used to update the CAL model for better prediction, generating another batch of top ranked abstracts for screening in the next iteration of the feedback loop. The goal is to identify all relevant abstracts with minimum screening effort.

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We selected the CAL® tool because it won multiple international competitions in high-recall information retrieval – the process of retrieving all relevant documents with minimal human effort (Table below)

Table. Summary of evidence on the use of the CAL® tool for knowledge synthesis conduct

International Competition	High-recall tasks	Key findings
Conference and Labs of the Evaluation Forum 2018 (1)	30 systematic reviews of diagnostic test studies	*Task 1:* Without any manual effort to construct literature search strategies, the CAL® tool was the most accurate with 97% recall (sensitivity). *Task 2:* For screening literature search results, CAL® was the most accurate with 99% recall.
Conference and Labs of the Evaluation Forum 2017 (2)	50 systematic reviews of diagnostic test studies	The CAL® tool was a top performer among the 14 tested with 97% to 100% recall at pre-defined stopping threshold.
Text Retrieval Conference Total Recall Tracks 2015/16 (3, 4)	8 legal, clinical, news, email collections	The CAL® tool attained an overall effectiveness not surpassed by any submitted method, manual or automatic.

For archives that could be retrieved in their entirety (e.g., MEDLINE, pre-print servers), the CAL® tool applied broad relevant search terms using the following Posix command:

```
egrep -i 'coronav|corona vir|wuhan|hubei|huanan|[^a-z]ncov|cov2|cov.2|novel.cov|covid|sars-cov'
```

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Appendix 2. EMBASE search strategy

Database:
Embase Classic+Embase <1947 to 2021 July 08>

#	**Query**
1	exp coronaviridae/ or exp Coronaviridae infection/ or exp Coronavirus infection/
2	((wuhan or hubei or huanan) and (severe acute respiratory or pneumonia* or virus*) and outbreak*).mp.
3	(coronavir* or "corona virus*" or "coronavirus pneumonia" or betacoronavir* or COVID or COVID-19).mp.
4	("nCoV" or "cov 2" or cov2 or 2019ncov or 2019-nCoV or "2019 ncov" or "2019-ncov" or "2019 novel cov" or "2019 ncov disease*" or "2019 novel coronavirus*").mp.
5	"wuhan virus*".mp.

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6	or/1-5
7	exp Interferons/ or interleukin-2/ or exp Immunoglobulin/ or anakinra/ or Sarilumab/ or Siltuximab/ or tumor necrosis factor/ or granulocyte macrophage colony stimulating factor/ or beta1a interferon/ or interferon beta serine/
8	(interferon* or "Interferon-alpha" or "Interferon-beta" or "avonex" or "interferon beta-1a" or "Betaseron" or "Extavia" or "betaferon" or "beneseron" or "beta 1-b interferon" or "recombinant interferon beta-1b" or "Rebif" or "Interferon-gamma" or immunoglobulin* or "immuno globulin*" or "immune-globulin*" or anakinra or kineret or Sarilumab or kevzara or regn88 or sar153191 or Siltuximab or sylvant or cnto328 or "cnto 328" or "tumor necrosis factor*" or "tumor necrosis serum*" or cachectin or cachetin or "anti-TNF-alpha" or "TNF alfa" or "TNF alpha" or anti-granulocyte macrophage or anti-GM-CSF or "GM CSF" or gmcsf or Flebogamma or Gamunex or "Globulin-N" or "Globulin N" or Intraglobin Gammagard or Gamimune or Gamimmune or Privigen or Sandoglobulin or Venoglobulin or "Venoglobulin-I" or "Venoglobulin I" or Venimmune or Iveegam or Alphaglobin or Endobulin or "Gamimune N" or "Gamimmune N" or Gammonativ or beriglobin or biggam or carimune or cuvitru or gammagen or gammaplex or gamunex or hizentra or kiovig or norga or panzyga or sandoglobulin* or subcuvia or venogamma or vigam or interleukin-2 or interleukin).tw.
9	umifenovir/ or riamilovir/ or favipiravir/ or sofosbuvir/ or Arbidol/ or Galidesivir/
10	(Favipiravir or Triazavirin or Umifenovir or riamilovir or sofusbivir or sofosbuvir or sovaldi or psi7851 or psi7976 or psi7977 or "EIDD-2801" or "EIDD 2801" or arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.
11	Darunavir/ or Lopinavir/ or Ritonavir/ or danoprevir/ or remdesivir/
12	(ASC09 or Azvudine or Danoprevir or Darunavir or Lopinavir or ritonavir or Remdesivir or "gs 5734" or "gs5734" or prezista or "tmc 114" or tmc114 or "uic 94017" or uic94017 or abt378 or norvir).tw.
13	baloxavir marboxil/ or baloxavir marboxil.tw.
14	exp antimalarial agent/ or exp quinoline derivative/
15	(Amodiaquine or Basoquin or Camoquin or Flavoquine or Chloroquine or Resochin or Dawaquin or Lariago or Aarlen or Hydroxychloroquine or Hydroxy-chloroquine or chloroquinol or hydrochloroquine or hydrocloroquine or oxychloroquine or quensyl or "sn 8137" or ercoquin or Plaquenil or Hydroquin or Axemal or Dolquine or Quensyl or Quinoric or Imiquimiod or Aldara or Vyloma or Zyclara or Primaquine or Jasoprim or Malirid or Neo-Quipenyl or Pimaquin or Pmq or Primachina or Primacin or Primaquina or Primaquine or Primaquine or Remaquin or Tafenoquine or Krinfatel or Kozenis or Arakoda or Krintafel or Pamaquine or Plasmochin or Plasmoquine or Plsamaguine or Neo-Quipenyl or Primachin or Dihydroartemisinin or Mefloquine or lariam or laricam or mefliam or mephaquin* or tropicur or Nitazoxanide or Alinia or colufase or daxon or heliton or "salicylamide acetate" or nodik or "ph 5776" or ph5776 or ambilhar or "ba 32644" or ba32644 or "ciba 32644 ba" or "ciba 32644ba" or ciba32644ba or niradazol* or nitrothiamidazol* or nitrothiazole or "nsc 136947" or nsc136947 or yarocen or Nitrothiazole or Amokin or amokine or anoclor or aralan or aralen or arechin or arechine or

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	arequine or arthrochin or arthrochine or arthroquine or artrichin or artrichine or artriquine or avloclor or bemaphata or bemaphate or bemasulph or bipiquin or cadiquin or chemochin or chemochine or chingamine or chingaminum or chloraquine or chlorochin or chlorochine or chlorofoz or chloroquin or chloroquin* or cidanchin or "clo-kit junior" or clorichina or clorichine or cloriquine or clorochina or delagil or delagyl or dichinalex or diclokin or diquinalex or diroquine or emquin or genocin or gontochin or gontochine or gontoquine or heliopar or imagon or iroquine or klorokin or klorokine or klorokinfosfat or lagaquin or malaquin or malarex or malarivon or malaviron or maliaquine or maquine or mesylith or mexaquin or mirquin or nivachine or nivaquin* or roquine or quinachl or quingamine or repal or resochen* or resochin or resochina or resochine or resochinon resoquina or resoquine or reumachlor or roquine or rp3377 or sanoquin or sanoquine or silbesan or siragan or sirajan or sn7618 or solprina or solprine or tresochin or tresochine or tresoquine or trochin or trochine or troquine).tw.
16	suramin/
17	(Carriomycin or Suramin).tw.
18	exp steroid/ or exp meprednisone/ or exp corticosteroid/ or fingolimod/ or leflunomide/ or thalidomide/
19	(steroid* or methylprednisone or meprednisone or Prednisolone or Fluprednisolone or Corticosteroid* or Fingolimod or Leflunomid* or Thalidomid*).tw.
20	ruxolitinib/
21	(Jakotinib or Ruxolitinib).tw.
22	exp monoclonal antibody/
23	(Ruxolitinib or Tocilizumab or Adalimumab or Camrelizumab or Eculizumab or Mepolizumab or "PD-1 mAb" or Tocilizumab or Adamumab or tozumab or meplazumab or monoclonal antibod*).tw.
24	("SARS-Cov-2 specific neutralizing antibod*" or "SARS-Cov specific neutralizing antibod*" or "MERS-Cov specific neutralizing antibod*" or "Anti C5a monoclonal antibod*").tw.
25	acetylcysteine/ or exp angiotensin receptor antagonist/ or exp angiotensin derivative/ or exp dipeptidyl carboxypeptidase inhibitor/ or citrate potassium/ or glycyrrhizic acid/ or dipyridamole/ or hydrogen peroxide/ or polyinosinic polycytidylic acid/ or thymosin/ or ascorbic acid/
26	(Acetylcysteine or Angiotensin or Angiotensin or "ACE inhibitor*" or ACE-2 or "Angiotensin II receptor blocker*" or ARBs or "potassium citrate" or Bromhexine or "Diammonium glycyrrhizinate" or Glycyrrhizic or Dipyridamole or Ebastine or "Hydrogen peroxide" or Pirfenidone or Polyinosinic-polycytidylic or "Polyinosinic-polycytidylic" or "Poly I-C" or "rhG-CSF" or Thymosin* or Tranilast or "Vitamin C" or "Ascorbic Acid*").tw.
27	("inhal*" adj2 gas*).tw.
28	Cyclosporine/

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29	(Cyclosporin or cequa or "cgc 1072" or "cgc1072" or ciclomulsion or cyclasol or de076 or deximune or implanta or imusporin or neuro-stat or neurostat or opsisporin or "otx 101" or padciclo or papilock or "sp 14019" or verkazia).tw.
30	Fenretinide/
31	(fenretinide or "mcn r 1967" or "4 hydroxyphenylretinamide" or Ifendopril).tw.
32	Dalteparin/ or enoxaparin/ or tinzaparin/ or fondaparinux/ or edoxaban/ or rivaroxaban/ or apixaban/ or betrixaban/ or heparin/ or danaparoid/ or warfarin/ or dabigatran.hw.
33	(dalteparin or fragmin* or "low liquemin" or enoxaparin or clexan or clexane or inhixa or lexane or lovenox or neoparin or neoparin-nx or thorinane or tinzaparin or innohep or logiparin or fondaparinux or quixidar or dabigatran or edoxaban or lixiana or roteas or savaysa or rivaroxaban or xarelto or "bay 59 7939" or apixaban or eliques or eliquis or warfarin or adoisine or carfin or coumadan or coumadin* or marevan or panwarfarin or panwarfin or sofarin or warnerin or betrixaban or bevyxxa or dexxience or heparin or Disebrin or hepalean or lipo-hepin or menaven or multiparin or nevparin or panheparin or panheprin or praecivenin or thrombareduct or thromboliquine or vetren or danaparoid or lomoparan or orgaran).tw.
34	(Azilsartan or candesartan or eprosartan or Irbesartan or telmisartan or valsartan or losartan or olmesartan).hw. or cobicistat/ or losartan/
35	(Azilsartan or Edarbi or "tak 536" or tak536 or candesartan or amcandin or amlodipine or amlopres or camlostar or candam or candeamio or candezek or caramlo or framsyl or unisia or zenicamo or Atacand or eprosartan or epratenz or futuran or naviten or navixen or regulaten or "skf 108566" or "skf108566" or tevesten or tevetan or teveten or tevetenz or Irbesartan or irbertan or Avapro or telmisartan or approvel or aprovel or "arbez lr" or avapro or ifirmasta or irban or irbetan or iretensa or irovel or irvell or karvea or sabervel or Micardis or valsartan or Diovan* or Prexxartan or saval or losartan or Cozaar or entrizen or lavestra or lorista or Olmesartan or Benicar or sarten or entresto or sacubitril or valsartan or byvalson or nebivolol or Aviptadil or Losartan or cozaar or cobicistat or tybost or actelsar or kinzal mono or kinzalmono or micardis or predxal or pritor or pritoral or semintra or telma-20 or tolura or angiosan or cordinate or dalzad ordiovan or diovane or kalpress or miten or nisis or prexxartan or provas or rixil or saval or tareg or tazea or troval or valpression or vals or valsocard or valtan or valtsu or alteis or belsar or benetor or benevas or benicar or cs866 or ixia or laresin or mencord or mesar or olartan or olmeblo or olmec or olmes or Olmesartan or olmetec or olpresor olsar or omesar or openvas or plaunac or rnh6270 or santini or sarten or tensar or tensiol or vivactra or votum or byvalson or cozaar).tw.
36	(benazepril or Captopril or Cilazapril or Enalapril or Fosinopril or Lisinopril or Perindopril Quinapril or Ramipril or Trandolapril).hw.
37	(Benazepril or Lotensin or Captopril or Benace or boncordin or briem or brien or "cgs 148241" or "cgs 14824a" or "cgs148241" or "cgs14824a" or cibace or cibacen* or fortekor or lotensin or tenkuoren or zinadril or ace-bloc or acenorm or acepress or acepril or aceprilex or aceril or aceten or adocor or alopresin or altran or apuzin or asisten or capace or capocard or caposan or capoten* capotril or capril or captace or captensin or capti or captoflux or captohexal or captolane or captomax or capton or captopren or captoprilan or captoril or captral or cardiopril or cardipril or

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	catona or catoplin or catopril or cesplon or cryopril or debax or dexacap or dextro captopril or ecapres or ecaten or epicordin or epsitron or farcopril or farmoten or hiperil or hypopress or hypotensor or insucar or iopril or isopresol or katopil or ketanine or keyerpril or lapril or locap or lopirin or lopril or medepres or midrat or minitent or nolectin or "oltens ge" or petacilon or praten or primace or rilcapton or ropril or smarten or tenofax or tensicap tensiomen or tensiomin or tensobon or tensoprel or tensoril or tenzib or topace or toprilem or typril-ace or vasosta or zapto or orkaptil or Cilazapril or dynorm or inhibace or inibace or initiss or inocar).tw.
38	(justor or vascace or Enalapril or Vasotec or bpnorm or dynacil or eliten or fosenopril or fosinil or fosinonorm or fosinopril or fosinorm or fosipres or fositen or fositens or fovas or fozitec or monopril or newace or sapril or sq28555 or staril or vasopril or acerbon or alapril or alfaken or carace or cipril or coric or dapril or fibsol or inopril or linopril or linvas or lipril or lisi abz orlisibeta or lisigamma or lisihexal or lisinopril dihydrate or lisipril or lisodur or lisopress or lisopril orlisoril or lispril or listril or lysinopril or "mk 0521" or "mk 521" or "mk 522" or "mk0521or mk521" or "mk522" or noperten or novatec or presiten or prinil or prinivil or qbrelis or sinopril or tensopril or tensyn or vivatec or zestomax or zestril or Monopri or Lisinopril or Prinivil or Zestril or Perindopril or Coversyl or Quinapril or Accupril or accuprin or accupro or accupron or acequin or acuitel or acuprel or acupril or asig or "ci906" or conan or ectren or korec or quinalapril or quinaten or quinazi or quinhexal or quinipril or Ramipril or acovil or altace or carasel or cardace or corpril or delix or "hoe 498" or hypren or hytren or lostapres or ramace or ramilich or triatec or tritace or unipril or vesdil or vivace or Altace or Trandolapril or Mavik or gopten or Odace or odric or udrik).tw.
39	Colistin/ or (Teicoplanin or Ivermectin or azithromycin).hw.
40	(Colistin or belcomycin or colimycin* or belcomycin or Colicort or colimycin or colistine or colomycin or coly mycin or colymicin or multimycin or polymyxin or Teicoplanin or planium or tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichoplanin or teichoplanine or teicomid or teicopix or teiplamil or Planium or Tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichomycin or teichoplanin* or teicomid or teicopix or teiplamil or Ivermectin or Avermectin or cardomec or diapec or efacti or epimekor or eqvalan or eqvalenor or ivermectina or ivermectol or ivexterm or ivomec or mectizan or "mk 933" or "mk933" or oramec or quanox or revectina or securo or sklice or soolantra or stromectol or azithromycin or aruzilina or atizor or azadose or azasite or azatril or azenil or azibiot or azimin or azithral or azithromycin or azitrocin or azitromax azitromicin* or aziwok or azomyne or aztrin or azydrop or azyter or azithromycin or bazyt or "cp 62933" or "cp 62993" or "cp62933" or "cp62993" or erythromycin or Forcin or Inedol or infectoazit or "isv 401" or "isv401" or kromicin or macrozit or mezatrin or octavax or ordipha or ribotrex or sumamed or tobyl or tromix or trozocina or ultreon or vinzam or xithrone or "xz 450" or "xz450" or Zaret or Zarom or zetamax or zeto or zibramax or zifin or zimericina or zistic or zithromax or zithrox or zitinn or zitrim or zitrobifan or zitrocin or zitromax or zmax).tw.
41	Tamoxifen.hw. or dasatinib/ or Epirubicin/ or Gemcitabine/ or Homoharringtonin/ or Imatinib/ or toremifene/ or Valrubicin/
42	(dasatinib or Ellence or Epirubicin* or epid or epifil or epiham or epilem or epirubicine or farmorrubicina or farmorubicin or pharmorubicin or Gemcitabine or difluorodeoxycytidine or Gemcite or gemtro or gemzar or infugem or "ly188011" or Homoharringtonine or harringtonine

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	or omacetaxine or ceflatonin or omapro or synribo or Imatinib or "cgp 57148" or "cgp57148b" or gleevac or gleevec or glivec or glivic or ruvise or Tamoxifen or ebefen or kessar or tamoplac or tamoxasta or tamoxifene or toremifene or estrimex or fareston or fc1157a or Valrubicin or valstar or valtaxin).tw.
43	Disulfiram/ or Emetine/ or Clomipramine/ or Loperamide/ or Caspofungin/ or Terconazole/ or Colchicine/ or Promethazine/ or Azelastine/ or Aprepitant/ or Chlorpromazine/ or Icatibant/ or Bepotastine/ or prostacyclin/ or Vapreotide/ or Conivaptan/ or Nitric oxide/ or (Perphenazine or Metformin).hw.
44	(Disulfiram or antabus or Antabuse or esperal or disulfizam or Emetine or Emetin or Clomipramine or Anafranil or anafranilin or anafranyl or clomicalm or hydiphen or Loperamide or immodium or Caspofungin or Cancidas or Terconazole or fungistat or terazol or "r 42470or Colchicine" or colchysat or mitigare or "nsc 757" or Promethazine or allerfen or antiallersin or atosil or fenergan or hiberna or Phenergan or Pipolphen or Prothazine or Romergan or Sayomol or Azelastine or Astelin or "a5610 or afluon" or alerdual or alergodil or allergodrop or allergospray or allespray or allestin or astepro or azedil or azelamed or azelavision or azep or azeptin or carelastin or corifina or "e 0659" or "e0659" or lasticom or lastin or lastinaz or loxin or oculastin or optivar or pollival or proallergodil or radethacin or radethazin or rhinolast or rinelaz or tebarat or visuzel or vividrin or vivispray or Aprepitant or cinvanti or emend or aprepitant or "l754030" or "mk 0869" or "ono7436").tw.
45	(Perphenazine or decentan or etaperazine or ethaperazine or "sch 3940" or thilatazin or tranquisan or trifalon or trilafan or trilafon or trilifan or triliphan or Chlorpromazine or hibernal or contomin or largactil or megaphen or neurazine or plegomazin or promacid or promapar or propaphenin or solidon or sonazine or taroctil or "thor prom" or thorazine or vegetamin or zuledin or Icatibant or firazyr or Metformin or diabetosan or diabex or dianben or diformin or fluamine or flumamine or fortamet or glifage or gliguanid or glucoformin or gluconil or glucophage or glucophage-mite or glucostop or glukophage or glumetza or haurymellin or meguan or merckformin or metforal or metformax or metiguanide or riomet or risidon or siofor or Bepotastine or bepreve or talion or Epoprostenol or prostacyclin or caripul or cycloprostin or epoprostenol or flolan or Vapreotide or docrised or octastatin or Conivaptan or vaprisol or "Nitric oxide" or inomax or noxivent).tw.
46	(convalescence/ and plasma transfusion/) or (Convalesc* adj2 plasma).tw.
47	Natural killer cell/ or exp mesenchymal stem cell/
48	("Recombinant human ACE-2" or "APN0" or "Natural killer cell" or "natural killer cells" or "NK cell" or "NK cells" or mesenchymal).tw.
49	Arbidol/ or Galidesivir/
50	(arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.
51	n methyl dextro aspartic acid receptor blocking agent/
52	("n methyl dextro aspartic acid receptor" or "n methyl d aspartate a" or " NMDA antagonist*" or " NMDA inhibitor*" or " NMDA block*" or " NMDA receptor*").tw.

53	or/7-52
54	6 and 53
55	exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.
56	55 not human/
57	54 not 56
58	limit 57 to dd=20210131-20210518
59	limit 58 to yr="2021"

Search run on July 9, 2021 using the Ovid platform, Embase database. Search was limited by date range, from January 31, 2021 to May 18, 2021, and run in database to update an existing search from May 01, 2020 to January 31, 2021.

Appendix 3. List of drugs from Health Canada and Public Health Agency of Canada

Categories	Drug names/descriptions
ACE Inhibitors	• Benazepril (Lotensin), Captopril (Capoten), Cilazapril (Inhibace), Enalapril (Vasotec), Fosinopril (Monopril), Lisinopril (Prinivil, Zestril), Perindopril (Coversyl), Quinapril (Accupril), Ramipril (Altace), Trandolapril (Mavik)
Angiotensin II Receptor Blocker (ARB)	• Azilsartan (Edarbi), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), telmisartan (Micardis), valsartan (Diovan, Prexxartan), losartan (Cozaar), olmesartan (Benicar), entresto (sacubitril/valsartan), byvalson (nebivolol/valsartan),
Antibiotics/antiparasitic	• Suramin, Carriomycin, Suramin sodium, Colistin, Teicoplanin, Ivermectin, azithromycin
Antibodies	• SARS-Cov-2 specific neutralizing antibodies • Bevicizumab, Ruxolitinib, Tocilizumab, Adalimumab, Camrelizumab, Eculizumab, Mepolizumab, "PD-1 mAb", Tocilizumab, tozumab, abciximab (Reopro), adalimumab (Humira/Amjevita), alefacept (Amevive), alemtuzumab (Campath), basiliximab (Simulect), belimumab (Benlysta), bezlotoxumab (Zinplava), canakinumab (Ilaris), certolizumab (Cimzia), cetuximab (Erbitux), daclizumab (Zenapax/Zinbryta), denosumab (Prolia/Xgeva), efalizumab (Raptiva), golimumab (Simponi), inflectra (Remicade), ipilimumab (Yervoy), ixekizumab (Taltz), natalizumab (Tysabri), nivolumab (Opdivo), olaratumab (Lartruvo), omalizumab (Xolair), palivizumab (Synagis), panitumumab (Vectibix), pembrolizumab (Keytruda), rituximab (Rituxan), tocilizumab

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	(Actemra/ RoActemra), trastuzumab (Herceptin), secukinumab (Cosentyx), ustekinumab (Stelara), Meplazumab
Anticancer/chemotherapy	• Dasatinib, Epirubicin, Gemcitabine hydrochloride, Homoharringtonine, Imatinib mesylate, Tamoxifen, Toremifene, Valrubicin
Anticoagulants	• dalteparin, enoxaparin, tinzaparin, fondaparinux heparin, dabigatran, edoxaban, rivaroxaban, apixaban, warfarin, betrixaban, heparin, danaparoid
Antimalarials	• Amodiaquine, Basoquin, Camoquin, Flavoquine, Chloroquine, Resochin, Dawaquin, Lariago, Aarlen, Hydroxychloroquine, Hydroxy-chloroquine, Plaquenil, Hydroquin, Axemal, Dolquine, Quensyl, Quinoric, Imiquimiod, Aldara, Vyloma,, Zyclara, Primaquine, Jasoprim, Malirid, Neo-Quipenyl, Pimaquin, Pmq, Primachina, Primacin, Primaquina, Primaquine, Primaquine, Remaquin, Tafenoquine, Krinfatel, Kozenis, Arakoda, Krintafel, Pamaquine, Plasmochin, Plasmoquine, Plsamaguine, Neo-Quipenyl, Primachin, Dihydroartemisinin, mefloquine, Nitazoxanide, Nitrothiazole
Antiviral – Direct acting	• Protease inhibitors: boceprevir, telaprevir, lopinavir, ritonavir, lopinavir/ritonavir (Kaletra), darunavir/cobicistat (Prezcobix), indinavir (Crixivan), saquinavir (Invirase) • Integrase inhibitors: raltegravir, elvitegravir, dolutegravir • Entry (fusion) inhibitors: maraviroc (celsentri) • Nucleoside reverse transcriptase inhibitors: abacavir, ziagen, emtricitabine, emtriva, lamivudine, epivir, tenofovir (Viread), zidovudine, azidothymidine, retrovir • Nonnucleoside reverse transcriptase inhibitors : , doravirine, pifeltro, efavirenz, sustiva, etravirine, intelence, nevirapine, viramune, rilpivirine, edurant • Acyclic nucleoside phosphonate analogues: cidofovir diphosphates • Acyclic guanosine analogues: acyclovir • Pyrophosphate analogues: foscarnet, fomivirsen • Oligonucleotides • Nucleotide analog inhibitor: sofusbivir • Nucleoside inhibitor: ribavirin (Ibavyr) • Matrix 2 protein inhibitors: amantadine • RNA polymerase inhibitors: Rimantadine • Neuraminidase inhibitors: oseltamivir (Tamiflu), peramivir (Rapivab), zanamivir (Relenza) • Antiretrovirals: ASC09, Azvudine, Danoprevir, Darunavir, Lopinavir, ritonavir, Remdesivir
Antiviral – Other	• Baloxavir, marboxil, EIDD-2801
Antivirals – Broad spectrum	• Favipiravir, Triazavirin, Umifenovir (arbidol hydrochloride), Galidesivir

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Immune support/modulating	• Convalescent plasma • Recombinant human ACE-2: APN01 • Natural killer (NK) cells • Mesenchymal stem cells • Interferons: Interferon-alpha, Interferon-beta, Interferon-gamma, interferon β – 1b (Betaseron/Extavia), interferon beta – 1a (Rebif) • Intravenous Immunoglobulin: Flebogamma DIF; Gamunex; Globulin-N; Globulin N; Intraglobin; Intraglobin F, Gammagard; Gamimune; Gamimmune, Privigen; Sandoglobulin; Venoglobulin; Venoglobulin-I; Venoglobulin I; Venimmune; Iveegam; Alphaglobin; Endobulin; Gamimune N; Gamimmune N; Gammonativ
Interleukin Inhibitors	• Interleukin (IL)-1 Inhibitor: Anakinra • Interleukin (IL)-6 Inhibitors: Sarilumab (Kevzara); Siltuximab • Anti-Tumor necrosis factor-alpha (anti-TNF-alpha) • Anti-Granulocyte-macrophage colony-stimulating factor (anti-GM-CSF)
Kinase Inhibitors	• Baricitinib, Acalabrutinib (Calquence), Fedratinib, Ruxolitinib, Jakotinib, Ruxolitinib, Sunitinib, Erlotinib
Nonspecific anti-inflammatory and immunosuppressive drugs	• Fingolimod Hydrochloride, Leflunomide, Thalidomide, Methylprednisone, Prednisolone, Fluprednisolone, Corticosteroids, Cyclosporin A, Glycyrrhizic Acid/Glycyrrhizic
Other	• Disulfiram (acetaldehyde dehydrogenase inhibitor), Emetine (alkaloid emetic), Clomipramine (antidepressant), Loperamide (antidiarrheal), Caspofungin (antifungal), Terconazole (antifungal), Colchicine (anti-gout agent), Promethazine hydrochloride (antihistamine), Azelastine (antihistamine), Aprepitant (anti-nausea/antiemetic), Perphenazine (antipsychotic), Chlorpromazine hydrochloride (antipsychotic), Icatibant (Bradykinin B2 Receptor Antagonists), Metformin (diabetes), Bepotastine (histamine 1 antagonist), Epoprostenol (prostaglandin), Vapreotide (somatostatin), Conivaptan (vasopressin inhibitor), Nitric oxide (vasodilator), Acetylcysteine (prodrug), Potassium citrate (alkalinizer), Dipyridamole (vasodilator), Hydrogen peroxide, Cobicistat (Tybost), Bromhexine (mucolytic), Ebastine (H1 receptor agonist), Pirfenidone (antifibrotic), Polyinosinic-polycytidylic (Poly I-C), rhG-CSF, Thymosin, Tranilast, Ascorbic Acid, Aviptadil (neuropeptide), Ifendopril (NMDA inhibitor), fenretinide (synthetic rentinoid), famotidine (H2 receptor antagonist)

Appendix 4. List of included primary studies

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Appendix 5. List of included knowledge syntheses.

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Appendix 6. Additional details for the Results section

Figure A1. Word cloud of description of study participants

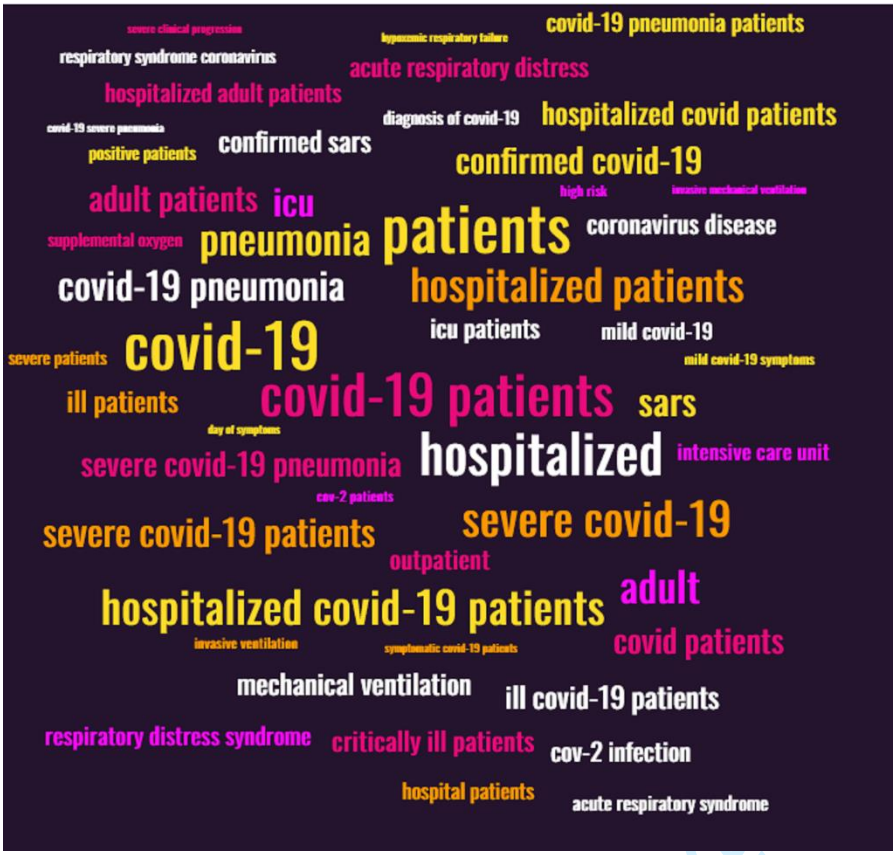

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Table A1. Country of primary study conduct

Country	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
United States	166 (26%)	38 (20%)	128 (29%)
China	109 (17%)	27 (14%)	82 (19%)
Italy	48 (8%)	2 (1%)	46 (10%)
France	41 (7%)	5 (3%)	36 (8%)
Spain	41 (7%)	3 (2%)	38 (9%)
India	24 (4%)	16 (8%)	8 (2%)
Iran	21 (3%)	15 (8%)	6 (1%)
United Kingdom	21 (3%)	19 (10%)	2 (0%)
Brazil	17 (3%)	13 (7%)	4 (1%)
Mexico	12 (2%)	6 (3%)	6 (1%)
Turkey	12 (2%)	1 (1%)	11 (3%)
Argentina	10 (2%)	7 (4%)	3 (1%)
The Netherlands	8 (1%)	2 (1%)	6 (1%)
Greece	6 (1%)	2 (1%)	4 (1%)
Pakistan	6 (1%)	4 (2%)	2 (0%)
Russia	6 (1%)	1 (1%)	5 (1%)
Belgium	5 (1%)	1 (1%)	4 (1%)
Egypt	5 (1%)	4 (2%)	1 (0%)
Saudia Arabia	5 (1%)	0 (0%)	5 (1%)
Bangladesh	4 (1%)	2 (1%)	2 (0%)
Singapore	4 (1%)	0 (0%)	4 (1%)
South Korea	4 (1%)	0 (0%)	4 (1%)
United Arab Emirates	4 (1%)	0 (0%)	4 (1%)
Bahrain	3 (0%)	2 (1%)	1 (0%)
Canada	3 (0%)	3 (2%)	0 (0%)
Cuba	3 (0%)	1 (1%)	2 (0%)
Denmark	3 (0%)	2 (1%)	1 (0%)
Germany	3 (0%)	1 (1%)	2 (0%)
Iraq	3 (0%)	2 (1%)	1 (0%)
Oman	3 (0%)	1 (1%)	2 (0%)
Poland	3 (0%)	0 (0%)	3 (1%)
Austria	2 (0%)	0 (0%)	2 (0%)
Chile	2 (0%)	2 (1%)	0 (0%)
Ireland	2 (0%)	0 (0%)	2 (0%)
Israel	2 (0%)	0 (0%)	2 (0%)
Qatar	2 (0%)	1 (1%)	1 (0%)
Sweden	2 (0%)	0 (0%)	2 (0%)
Australia	1 (0%)	1 (1%)	0 (0%)
Columbia	1 (0%)	1 (1%)	0 (0%)
Hong Kong	1 (0%)	0 (0%)	1 (0%)
Indonesia	1 (0%)	1 (1%)	0 (0%)
Kuwait	1 (0%)	0 (0%)	1 (0%)
Nigeria	1 (0%)	1 (1%)	0 (0%)
Norway	1 (0%)	1 (1%)	0 (0%)
Peru	1 (0%)	0 (0%)	1 (0%)
Philippines	1 (0%)	0 (0%)	1 (0%)
Romania	1 (0%)	0 (0%)	1 (0%)
Suriname	1 (0%)	0 (0%)	1 (0%)
Switzerland	1 (0%)	0 (0%)	1 (0%)
Taiwan	1 (0%)	1 (1%)	0 (0%)

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Country	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Thailand	1 (0%)	0 (0%)	1 (0%)
WHO - 30 countries	1 (0%)	1 (1%)	0 (0%)

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Table A2. Treatment evaluated in primary studies

	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Tocilizumab	87 (14%)	12 (6%)	75 (17%)
Hydroxychloroquine	78 (12%)	22 (12%)	56 (13%)
Convalescent Plasma	55 (9%)	15 (8%)	40 (9%)
Steroid	37 (6%)	1 (1%)	36 (8%)
Lopinavir/Ritonavir	29 (5%)	5 (3%)	24 (5%)
Methylprednisolone	26 (4%)	3 (2%)	23 (5%)
Remdesivir	25 (4%)	16 (8%)	9 (2%)
Enoxaparin	18 (3%)	1 (1%)	17 (4%)
Hydroxychloroquine/Azithromycin	18 (3%)	2 (1%)	16 (4%)
Anakinra	16 (3%)	2 (1%)	14 (3%)
Dexamethasone	16 (3%)	4 (2%)	12 (3%)
Anticoagulant-Therapeutic	15 (2%)	2 (1%)	13 (3%)
Azithromycin	15 (2%)	6 (3%)	9 (2%)
Anticoagulant-Prophylactic	11 (2%)	0 (0%)	11 (3%)
Ivermectin	11 (2%)	9 (5%)	2 (0%)
Heparin	9 (1%)	0 (0%)	9 (2%)
Favipiravir	8 (1%)	6 (3%)	2 (0%)
Sarilumab	8 (1%)	7 (4%)	1 (0%)
Colchicine	7 (1%)	4 (2%)	3 (1%)
Glucocorticoids	7 (1%)	0 (0%)	7 (2%)
Bamlanivimab	6 (1%)	4 (2%)	2 (0%)
Chloroquine	6 (1%)	2 (1%)	4 (1%)
Intravenous Immunoglobulin	6 (1%)	4 (2%)	2 (0%)
Mesenchymal Stem Cells	6 (1%)	4 (2%)	2 (0%)
Steroid	6 (1%)	0 (0%)	6 (1%)
Thymosin-Alpha1	6 (1%)	1 (1%)	5 (1%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Vitamin C	6 (1%)	4 (2%)	2 (0%)
Antiviral	5 (1%)	0 (0%)	5 (1%)
Arbidol	5 (1%)	2 (1%)	3 (1%)
Aspirin	5 (1%)	0 (0%)	5 (1%)
Interferon	5 (1%)	3 (2%)	2 (0%)
Prednisone	5 (1%)	1 (1%)	4 (1%)
Statins	5 (1%)	0 (0%)	5 (1%)
Antibiotic	4 (1%)	0 (0%)	4 (1%)
Anticoagulant	4 (1%)	0 (0%)	4 (1%)
Hydrocortisone	4 (1%)	2 (1%)	2 (0%)
Lopinavir/Ritonavir/Hydroxychloroquine	4 (1%)	0 (0%)	4 (1%)
Ribavirin	4 (1%)	0 (0%)	4 (1%)
Therapeutic Plasma Exchange	4 (1%)	0 (0%)	4 (1%)
Vitamin D	4 (1%)	3 (2%)	1 (0%)
Acei|Arb	3 (0%)	0 (0%)	3 (1%)
Baricitinib	3 (0%)	1 (1%)	2 (0%)
Casirivimab/Imdevimab	3 (0%)	2 (1%)	1 (0%)
Famotidine	3 (0%)	0 (0%)	3 (1%)
Interferon-Alpha-2b	3 (0%)	0 (0%)	3 (1%)
Interferon Alpha-2b	3 (0%)	1 (1%)	2 (0%)
Lenzilumab	3 (0%)	2 (1%)	1 (0%)
Lopinavir/Ritonavir/Interferon-Alpha	3 (0%)	0 (0%)	3 (1%)
Neutralizing Antibody	3 (0%)	1 (1%)	2 (0%)
Zinc Iv	3 (0%)	3 (2%)	0 (0%)
Acei|Arb|Statin	2 (0%)	0 (0%)	2 (0%)
Avifavir	2 (0%)	2 (1%)	0 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Canakinumab	2 (0%)	0 (0%)	2 (0%)
Ceftriaxone	2 (0%)	0 (0%)	2 (0%)
Chlorpromazine	2 (0%)	0 (0%)	2 (0%)
Corticosteroids/Tocilizumab	2 (0%)	0 (0%)	2 (0%)
Darunavir/Cobicistat	2 (0%)	1 (1%)	1 (0%)
Fondaparinux	2 (0%)	0 (0%)	2 (0%)
Functional Inhibition Of Acid Sphingomyelinase	2 (0%)	0 (0%)	2 (0%)
Haloperidol	2 (0%)	0 (0%)	2 (0%)
Heparin-Prophylaxis	2 (0%)	0 (0%)	2 (0%)
Inhaled Budesonide	2 (0%)	2 (1%)	0 (0%)
Interferon Beta-1b	2 (0%)	0 (0%)	2 (0%)
Interferon Kappa/Trefoil Factor 2	2 (0%)	2 (1%)	0 (0%)
Interferon Lambda-1a	2 (0%)	2 (1%)	0 (0%)
Interlukin-6 Inhibitors	2 (0%)	0 (0%)	2 (0%)
Itolizumab	2 (0%)	2 (1%)	0 (0%)
Ivermectin/Doxycycline	2 (0%)	2 (1%)	0 (0%)
Leflunomide	2 (0%)	0 (0%)	2 (0%)
Lopinavir	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Azithromycine	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Doxycline	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Ribavirin/Interferon Beta-1b	2 (0%)	1 (1%)	1 (0%)
Mavrilimumab	2 (0%)	1 (1%)	1 (0%)
Methylprednisolone/Tocilizumab	2 (0%)	0 (0%)	2 (0%)
Neuromuscular Blocking Agents	2 (0%)	0 (0%)	2 (0%)
Nitazoxanide	2 (0%)	2 (1%)	0 (0%)
Oseltamivir	2 (0%)	0 (0%)	2 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Prednisolone	2 (0%)	0 (0%)	2 (0%)
Ribavirin/Interferon-Alpha	2 (0%)	0 (0%)	2 (0%)
Statin	2 (0%)	0 (0%)	2 (0%)
Stem Cell Nebulization	2 (0%)	0 (0%)	2 (0%)
Steroid-Pulse	2 (0%)	0 (0%)	2 (0%)
Tocilizumab/Methylprednisolone	2 (0%)	0 (0%)	2 (0%)
Tocilizumab/Steroid	2 (0%)	0 (0%)	2 (0%)
Umifenovir	2 (0%)	0 (0%)	2 (0%)
Vitamin C/Zinc	2 (0%)	2 (1%)	0 (0%)
Acyclovir	1 (0%)	0 (0%)	1 (0%)
Amantadine	1 (0%)	0 (0%)	1 (0%)
Amoxicillin	1 (0%)	0 (0%)	1 (0%)
Anakinra/Intravenous Immunoglobulin	1 (0%)	0 (0%)	1 (0%)
Anakinra/Methylprednisolone	1 (0%)	0 (0%)	1 (0%)
Antiviral/Antiviral/Antibiotics	1 (0%)	0 (0%)	1 (0%)
Apixaban-Prophylaxis	1 (0%)	0 (0%)	1 (0%)
Apixaban-Therapeutic	1 (0%)	0 (0%)	1 (0%)
Aprepitant	1 (0%)	1 (1%)	0 (0%)
Arbidol/Hydroxycholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Artemisinin-Piperaquine	1 (0%)	0 (0%)	1 (0%)
Auxora	1 (0%)	1 (1%)	0 (0%)
Azithromycin/Hydroxychloroquine	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Prednisolone/Naproxen/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Azvudine	1 (0%)	1 (1%)	0 (0%)
Bacillus Calmette−Guérin Vaccine	1 (0%)	1 (1%)	0 (0%)
Baloxavir Marboxil	1 (0%)	1 (1%)	0 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Bamlanivimab/Etesevimab	1 (0%)	1 (1%)	0 (0%)
Baricitinib/Remdesivir	1 (0%)	1 (1%)	0 (0%)
Berinert	1 (0%)	0 (0%)	1 (0%)
Betamethasone	1 (0%)	1 (1%)	0 (0%)
Bevacizumab	1 (0%)	0 (0%)	1 (0%)
Bromhexine/Hydrochloride	1 (0%)	1 (1%)	0 (0%)
Bromhexine/Hydrochloride/Antiviral	1 (0%)	1 (1%)	0 (0%)
Bromhexine/Spironolactone	1 (0%)	0 (0%)	1 (0%)
Camostat Mesilate	1 (0%)	1 (1%)	0 (0%)
Cerc-002	1 (0%)	1 (1%)	0 (0%)
Choloroquine	1 (0%)	1 (1%)	0 (0%)
Cigb-325	1 (0%)	1 (1%)	0 (0%)
Clarithromycin	1 (0%)	0 (0%)	1 (0%)
Cortecosteroid/Tocilizumab	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Lopinavir/Ritonavir/Interferon Alpha	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Ns-Immunosuppresant	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/Anakinra	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/Baricitinib	1 (0%)	0 (0%)	1 (0%)
Cotrimoxazole	1 (0%)	0 (0%)	1 (0%)
Cyclooxygenase-2	1 (0%)	0 (0%)	1 (0%)
Cyclosporine A	1 (0%)	0 (0%)	1 (0%)
Dexamethasone/Tofacitinib	1 (0%)	0 (0%)	1 (0%)
Diphenhydramine/Ammonium Chloride	1 (0%)	1 (1%)	0 (0%)
Doxycycline	1 (0%)	1 (1%)	0 (0%)
Dutasteride	1 (0%)	1 (1%)	0 (0%)
Eculizumab	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Epoprostenol - Aerosolized	1 (0%)	0 (0%)	1 (0%)
Equine Polyclonal Antibodies	1 (0%)	1 (1%)	0 (0%)
Favipiravir/Chloroquine|Hydroxychloroquine/Lopinavir/ Ritonavir Or Darunavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Chloroquine|Hydroxychloroquine/Lopinavir/ Ritonavir|Darunavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Interferon Beta-1b	1 (0%)	1 (1%)	0 (0%)
Firazyr	1 (0%)	0 (0%)	1 (0%)
Flash Frozen Plasma	1 (0%)	1 (1%)	0 (0%)
Fluticasone Spray/Triamcinolone	1 (0%)	0 (0%)	1 (0%)
Fluvoxamine	1 (0%)	1 (1%)	0 (0%)
Glucocorticoids/Interferon	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine Or Chloroquine	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir/Azithromycin	1 (0%)	1 (1%)	0 (0%)
Hydroxycholoroquine/Favipiravir	1 (0%)	0 (0%)	1 (0%)
Hydroxycholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Hydroxyzine	1 (0%)	0 (0%)	1 (0%)
Inhaled Adenosine	1 (0%)	0 (0%)	1 (0%)
Inhaled Corticosteroid	1 (0%)	0 (0%)	1 (0%)
Inhaled Nitric Oxide	1 (0%)	1 (1%)	0 (0%)
Interferon-B 1a/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b/Arbidol	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Interferon Beta-1a	1 (0%)	1 (1%)	0 (0%)
Itraconazole	1 (0%)	1 (1%)	0 (0%)
Ivermectin/Azithromycin	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Leflunomide/Interferon Alpha 2a	1 (0%)	1 (1%)	0 (0%)
Levamisole	1 (0%)	1 (1%)	0 (0%)
Levofloxacin	1 (0%)	0 (0%)	1 (0%)
Linezolid	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Hydroxychloroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir Or Hydroxycholoroquine+Prednisone	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Chloroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon-Alpha/Abidor|Ribavirin|Cholroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon Beta-2b	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Novaferon	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Novaferon/Interferon	1 (0%)	0 (0%)	1 (0%)
Losartan	1 (0%)	1 (1%)	0 (0%)
Meplazumab	1 (0%)	0 (0%)	1 (0%)
Meropenem	1 (0%)	0 (0%)	1 (0%)
Mesenchymal Stromal Cells	1 (0%)	0 (0%)	1 (0%)
Methylprednisolone/Dexamethasone	1 (0%)	0 (0%)	1 (0%)
Methylprednisolone/Ivig	1 (0%)	1 (1%)	0 (0%)
Multi-Mechanism Approach	1 (0%)	0 (0%)	1 (0%)
Nebulised Interferon Beta-1a	1 (0%)	1 (1%)	0 (0%)
Nitazoxanide/Azithromycin	1 (0%)	1 (1%)	0 (0%)
Nitazoxanide/Doxycycline	1 (0%)	1 (1%)	0 (0%)
Olokizumab	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Opaganib	1 (0%)	0 (0%)	1 (0%)
Otilimab	1 (0%)	1 (1%)	0 (0%)
Pentoxifylline	1 (0%)	1 (1%)	0 (0%)
Pipamperone And Citalopram	1 (0%)	1 (1%)	0 (0%)
Piperacillin	1 (0%)	0 (0%)	1 (0%)
Polymerized-Collagen	1 (0%)	1 (1%)	0 (0%)
Poractant Alfa	1 (0%)	0 (0%)	1 (0%)
Progesterone	1 (0%)	1 (1%)	0 (0%)
Prophylactic Anticoagulant	1 (0%)	0 (0%)	1 (0%)
Proxalutamide	1 (0%)	1 (1%)	0 (0%)
Pyridostigmine	1 (0%)	1 (1%)	0 (0%)
Recombinant Interleukin-2	1 (0%)	0 (0%)	1 (0%)
Remdesivir/Corticosteroid	1 (0%)	0 (0%)	1 (0%)
Ribavarin/Lopinavir/Ritonavir/Interferon-Alpha	1 (0%)	0 (0%)	1 (0%)
Ribavirin/Arbidol/Hydroxicholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Ribavirin/Hydroxicholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Rimantadine	1 (0%)	0 (0%)	1 (0%)
Ruxolitinib	1 (0%)	0 (0%)	1 (0%)
Sofosbuvir/Daclatasvir	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Daclatasvir/Hydroxychloroquine	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Ledipasvir	1 (0%)	1 (1%)	0 (0%)
Soludexide	1 (0%)	1 (1%)	0 (0%)
Sulodexide	1 (0%)	1 (1%)	0 (0%)
Telmisartan	1 (0%)	1 (1%)	0 (0%)
Theophylline/Pentoxifylline	1 (0%)	0 (0%)	1 (0%)
Tocilizumab/Convalescent Plasma	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Tocilizumab/Favipiravir	1 (0%)	1 (1%)	0 (0%)
Toxilizumab/Steroids/Anakinra/Baricitinib	1 (0%)	0 (0%)	1 (0%)
Triazavirin	1 (0%)	1 (1%)	0 (0%)
Vermectin/Doxycycline	1 (0%)	1 (1%)	0 (0%)
Vilobelimab	1 (0%)	1 (1%)	0 (0%)
Vitamin D/Magnesium/Vitamin B12	1 (0%)	0 (0%)	1 (0%)
Vitamins/Dietary Supplements	1 (0%)	0 (0%)	1 (0%)
Zanamivir	1 (0%)	0 (0%)	1 (0%)

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Table A3. Treatment type of single treatment

	Total	RCT	Non-RCT
Total	**712**	**202**	**510**
Non-Steroidal Immunosuppressant	126 (18%)	27 (13%)	99 (19%)
Steroid	110 (15%)	15 (7%)	95 (19%)
Antiviral	97 (14%)	40 (20%)	57 (11%)
Antimalaria	87 (12%)	25 (12%)	62 (12%)
Anticoagulant	66 (5%)	5 (3%)	61 (12%)
Anticoagulant-Therapeutic	17 (2%)	2 (1%)	15 (3%)
Anticoagulant-Prophylactic	14 (2%)	0 (0%)	14 (3%)
Convalescent Plasma	56 (8%)	16 (8%)	40 (8%)
Antibiotic	29 (4%)	7 (3%)	22 (4%)
Anti- Inflammatory	20 (3%)	8 (4%)	12 (2%)
Interferon Therapy	16 (2%)	7 (3%)	9 (2%)
Antiparasitic	14 (2%)	12 (6%)	2 (0%)
Immunomodulator	14 (2%)	4 (2%)	10 (2%)
Neutralizing Antibodies	13 (2%)	7 (3%)	6 (1%)
Mesenchymal Stem Cells	9 (1%)	4 (2%)	5 (1%)
Statin	7 (1%)	0 (0%)	7 (1%)
Intravenous Immunoglobulin	6 (1%)	4 (2%)	2 (0%)
Vitamin C	6 (1%)	4 (2%)	2 (0%)
Antihistamine	4 (1%)	0 (0%)	4 (1%)
Antipsychotic	4 (1%)	0 (0%)	4 (1%)
Vitamin D	4 (1%)	3 (1%)	1 (0%)

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Table A4. Treatment type of combination treatment

	Total	RCT	Non-RCT
Total	**116**	**29**	**87**
Antimalaria/Antibiotic	19 (16%)	2 (7%)	17 (20%)
Steroid/NS-Immunossuppressant	10 (9%)	0 (0%)	10 (11%)
Antimalaria/Antiviral/Antiviral	8 (7%)	1 (3%)	7 (8%)
Antiviral/Antiviral	5 (4%)	3 (10%)	2 (2%)
Antiviral/Interferon	5 (4%)	0 (0%)	5 (6%)
Antimalaria/Antiviral	4 (3%)	0 (0%)	4 (5%)
Antimalaria/Antiviral/Antibiotic	4 (3%)	4 (14%)	0 (0%)
Antiparasitic/Antibiotic	4 (3%)	3 (10%)	1 (1%)
Antiviral/Antiviral/Antiviral	4 (3%)	0 (0%)	4 (5%)
Antiviral/Antiviral/Antiviral/Interferon	4 (3%)	0 (0%)	4 (5%)
Antiviral/NS-Immunosuppressant	4 (3%)	3 (10%)	1 (1%)
NS-Immunosuppressant/Steroid	4 (3%)	0 (0%)	4 (5%)
ACEI/ARB	3 (3%)	0 (0%)	3 (3%)
Antiviral/Antibiotic	3 (3%)	2 (7%)	1 (1%)
Antiviral/Antiviral/Interferon	3 (3%)	1 (3%)	2 (2%)
ACEI/ARB/Statin	2 (2%)	0 (0%)	2 (2%)
Antimalaria/Antiviral/NS-Immunosuppressant	2 (2%)	0 (0%)	2 (2%)
Antiviral/Anti-Inflammatory	2 (2%)	2 (7%)	0 (0%)
Steroid/Steroid	2 (2%)	0 (0%)	2 (2%)
Vitamin C/Zinc	2 (2%)	2 (7%)	0 (0%)
Anticoagulant/Ns-Immunosuppressant	1 (1%)	0 (0%)	1 (1%)
Antihistamine/Disinfectant	1 (1%)	1 (3%)	0 (0%)
Antimalaria/Mucolytic	2 (2%)	1 (3%)	1 (1%)
Antimalaria/Antiviral/Antiviral/Antibiotic	1 (1%)	1 (3%)	0 (0%)
Antimalaria/Antiviral/Antiviral/Antiviral	1 (1%)	0 (0%)	1 (1%)
Antimalaria/Antiviral/Antiviral/Interferon	1 (1%)	0 (0%)	1 (1%)
Antimalaria/Antiviral/Mucolytic	1 (1%)	1 (3%)	0 (0%)
Antiviral/Antiviral/Antibiotic/Anti-Inflammatory/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Antiviral/Antimalaria/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Immunomodulator	1 (1%)	1 (3%)	0 (0%)
Antiviral/Interferon/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Steroid	1 (1%)	0 (0%)	1 (1%)
Bronchodilator/Hemorrheologic Agent	1 (1%)	0 (0%)	1 (1%)
Mucolytic/Diuretic	1 (1%)	0 (0%)	1 (1%)
NS-Immunosuppressant/Convalescent Plasma	1 (1%)	0 (0%)	1 (1%)
NS-Immunosuppressants/IVIG	1 (1%)	0 (0%)	1 (1%)
Steroid/Anti-Inflamatory	1 (1%)	0 (0%)	1 (1%)
Steroid/Interferon	1 (1%)	0 (0%)	1 (1%)
Steroid/IVIG	1 (1%)	1 (3%)	0 (0%)
Vitamin D/Magnesium/Vitamin B12	1 (1%)	0 (0%)	1 (1%)

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	Total	RCT	Non-RCT
Total	**116**	**29**	**87**
Vitamins/Dietary Supplements	1 (1%)	0 (0%)	1 (1%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant. ACEI/ARB: angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). IVIG: Intravenous immune globulin.

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Table A5. Country of knowledge synthesis conduct

	All	With protocol	Without protocol
# reviews	303	89	214
1. United States	59 (19%)	13 (15%)	46 (21%)
2. China	41 (14%)	13 (15%)	28 (13%)
3. India	34 (11%)	12 (13%)	22 (10%)
4. Iran	18 (6%)	3 (3%)	15 (7%)
4. United Kingdom	18 (6%)	3 (3%)	15 (7%)
5. Saudi Arabia	13 (4%)	1 (1%)	12 (6%)
6. Canada	12 (4%)	5 (6%)	7 (3%)
7. Italy	12 (4%)	8 (9%)	4 (2%)
8. Indonesia	9 (3%)	2 (2%)	7 (3%)
9. Malaysia	7 (2%)	0 (0%)	7 (3%)
10. France	6 (2%)	4 (4%)	2 (1%)
Egypt	5 (2%)	2 (2%)	3 (1%)
Peru	5 (2%)	1 (1%)	4 (2%)
Taiwan	5 (2%)	1 (1%)	4 (2%)
Australia	4 (1%)	1 (1%)	3 (1%)
Brazil	4 (1%)	1 (1%)	3 (1%)
Chile	4 (1%)	4 (4%)	0 (0%)
Japan	4 (1%)	2 (2%)	2 (1%)
Nepal	4 (1%)	0 (0%)	4 (2%)
Spain	4 (1%)	1 (1%)	3 (1%)
Bangladesh	3 (1%)	0 (0%)	3 (1%)
Greece	3 (1%)	1 (1%)	2 (1%)
Korea	3 (1%)	1 (1%)	2 (1%)
Pakistan	3 (1%)	0 (0%)	3 (1%)
The Netherlands	3 (1%)	1 (1%)	2 (1%)
Denmark	2 (1%)	1 (1%)	1 (0%)
Germany	2 (1%)	2 (2%)	0 (0%)
Israel	2 (1%)	1 (1%)	1 (0%)
Lebanon	2 (1%)	0 (0%)	2 (1%)
Mexico	2 (1%)	2 (2%)	0 (0%)
Thailand	2 (1%)	2 (2%)	0 (0%)
Switzerland	1 (0%)	0 (0%)	1 (0%)
Tunisia	1 (0%)	0 (0%)	1 (0%)
Nigeria	1 (0%)	1 (1%)	0 (0%)
Portugal	1 (0%)	0 (0%)	1 (0%)
Qatar	1 (0%)	0 (0%)	1 (0%)
Romania	1 (0%)	0 (0%)	1 (0%)
Sweden	1 (0%)	0 (0%)	1 (0%)
Turkey	1 (0%)	0 (0%)	1 (0%)

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Table A6. Treatment evaluated in knowledge syntheses

	Total	With protocol	Without protocol
All Evaluated Treatment Options	**540**	**154**	**386**
Steroid	61 (11%)	14 (9%)	47 (12%)
Hydroxychloroquine	60 (11%)	16 (10%)	44 (11%)
Remdesivir	40 (7%)	11 (7%)	29 (8%)
Tocilizumab	36 (7%)	10 (6%)	26 (7%)
Convalescent Plasma	35 (6%)	11 (7%)	24 (6%)
Lopinavir-Ritonair	24 (4%)	8 (5%)	16 (4%)
Chloroquine	20 (4%)	6 (4%)	14 (4%)
Antiviral	14 (3%)	4 (3%)	10 (3%)
Anticoagulant	11 (2%)	2 (1%)	9 (2%)
Azithromycin	11 (2%)	3 (2%)	8 (2%)
Hydroxychloroquine/Azithromycin	11 (2%)	1 (1%)	10 (3%)
Favipiravir	10 (2%)	1 (1%)	9 (2%)
Ivig	10 (2%)	2 (1%)	8 (2%)
Colchicine	9 (2%)	2 (1%)	7 (2%)
Arbidol	7 (1%)	1 (1%)	6 (2%)
Chloroquine/Hcq	7 (1%)	1 (1%)	6 (2%)
Invermectin	7 (1%)	3 (2%)	4 (1%)
Anticoagulant Therapeutic	6 (1%)	3 (2%)	3 (1%)
Covid-19 Treatments	5 (1%)	3 (2%)	2 (1%)
Cell-Based Therapies	5 (1%)	2 (1%)	3 (1%)
Anakinra	4 (1%)	3 (2%)	1 (0%)
Antibiotics	4 (1%)	1 (1%)	3 (1%)
Famotidine	4 (1%)	1 (1%)	3 (1%)
Hydroxychloroquine/Chloroquine	4 (1%)	3 (2%)	1 (0%)
Immunomodulator	4 (1%)	1 (1%)	3 (1%)
Interleukin- 6 Inhibitors	4 (1%)	2 (1%)	2 (1%)
Jak-Inhibitors	4 (1%)	2 (1%)	2 (1%)
Sarilumab	4 (1%)	4 (3%)	0 (0%)
Antimalaria	3 (1%)	1 (1%)	2 (1%)
Chloroquine/Hcq/Azithromycin	3 (1%)	3 (2%)	0 (0%)
Hydorxychloroquine/Azithromycin	3 (1%)	0 (0%)	3 (1%)
Interferon-Beta	3 (1%)	1 (1%)	2 (1%)
Prophylactic Anticoagulant	3 (1%)	2 (1%)	1 (0%)
Statins	3 (1%)	0 (0%)	3 (1%)
Umifenovir	3 (1%)	0 (0%)	3 (1%)
Vitamin D	3 (1%)	1 (1%)	2 (1%)
Acei	2 (0%)	2 (1%)	0 (0%)
Acei/Arb	2 (0%)	0 (0%)	2 (1%)
Anticoagulant Prophylactic	2 (0%)	2 (1%)	0 (0%)
Antiplatelets	2 (0%)	1 (1%)	1 (0%)
Antivirals/Antibiotics	2 (0%)	2 (1%)	0 (0%)
Arb	2 (0%)	2 (1%)	0 (0%)
Baloxavir Marboxil	2 (0%)	0 (0%)	2 (1%)
Bromhexine	2 (0%)	1 (1%)	1 (0%)
Chloroquine/Azithromycin	2 (0%)	0 (0%)	2 (1%)
Corticosteroids/Iv Immunoglobulin	2 (0%)	1 (1%)	1 (0%)
Interferon	2 (0%)	0 (0%)	2 (1%)

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	Total	With protocol	Without protocol
All Evaluated Treatment Options	**540**	**154**	**386**
Interferon-Beta-1a	2 (0%)	1 (1%)	1 (0%)
Ruxolitinib	2 (0%)	0 (0%)	2 (1%)
Tocilizumab/Sarilumab	2 (0%)	0 (0%)	2 (1%)
Acalabrutinib	1 (0%)	0 (0%)	1 (0%)
Antinflammatory	1 (0%)	0 (0%)	1 (0%)
Antirheumatic	1 (0%)	1 (1%)	0 (0%)
Antitumor	1 (0%)	0 (0%)	1 (0%)
Arbidol/Lopinavir+Ritonavir	1 (0%)	0 (0%)	1 (0%)
Aspirin	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Hcq	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Zinc	1 (0%)	0 (0%)	1 (0%)
Calcifediol	1 (0%)	0 (0%)	1 (0%)
Clazakisumab	1 (0%)	1 (1%)	0 (0%)
Corticosteroid/Antivirals	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/ Tocilizumab/Anakinra/Ivig	1 (0%)	0 (0%)	1 (0%)
Cytokine Therapy	1 (0%)	0 (0%)	1 (0%)
Dpp-4 Inhibitor	1 (0%)	1 (1%)	0 (0%)
Favipiravir/ Baloxavir Marboxil	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Other Antivirals	1 (0%)	0 (0%)	1 (0%)
Galidesivir/Sofosbuvir/Ribavirin	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Antibiotics	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Azithromycin/Ribavirin/Interferon/Interferon Alfa	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Chloroquine/Azithromycin	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Chloroquine/Azithromycin/Or Lopinavir/Ritonavir	1 (0%)	1 (1%)	0 (0%)
Hydroxychloroquine/Lopinavir-Ritonair	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Ribavirin/Interferon/Interferon Alfa	1 (0%)	0 (0%)	1 (0%)
Ibrutinib	1 (0%)	0 (0%)	1 (0%)
Ifn B-1b/ Immunomodulatory/Antivirals	1 (0%)	0 (0%)	1 (0%)
Immune Therapy/Or Antiviral Therapy/Or Both	1 (0%)	0 (0%)	1 (0%)
Immunomodulation/Hcq/Cq	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b	1 (0%)	0 (0%)	1 (0%)
Interferon-Beta/Rbv	1 (0%)	0 (0%)	1 (0%)
Jak-Inhibitor/Type 1 Interferon	1 (0%)	0 (0%)	1 (0%)
Levilimab	1 (0%)	1 (1%)	0 (0%)
Lopinavir	1 (0%)	1 (1%)	0 (0%)
Lopinavir-Ritonair/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Azithromycin	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Remdesivir	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Ribavirin/Interferon Beta	1 (0%)	0 (0%)	1 (0%)
Meplazumab	1 (0%)	0 (0%)	1 (0%)

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	Total	With protocol	Without protocol
All Evaluated Treatment Options	**540**	**154**	**386**
Neutralizing Antibody	1 (0%)	0 (0%)	1 (0%)
Nsaids	1 (0%)	0 (0%)	1 (0%)
Olokizumab	1 (0%)	1 (1%)	0 (0%)
Oseltamivir/Lopinavir/Ritonavir/Arbidol/Ribavirin/ Sfjdc/ Other	1 (0%)	0 (0%)	1 (0%)
Pentoxifylline	1 (0%)	0 (0%)	1 (0%)
Recombinant Human Gcsf	1 (0%)	0 (0%)	1 (0%)
Renal Replacement Therapy/ Glucocorticoids	1 (0%)	0 (0%)	1 (0%)
Ribavirin	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Daclatasvir	1 (0%)	0 (0%)	1 (0%)
Sulodexide	1 (0%)	0 (0%)	1 (0%)
Type I Interferons	1 (0%)	0 (0%)	1 (0%)
Vitamin C	1 (0%)	0 (0%)	1 (0%)
Ritonavir	0 (0%)	0 (0%)	0 (0%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant. ACEI/ARB: angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). IVIG: Intravenous immune globulin.

PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7-8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	7, Appendix 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9

Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	9
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9-10, Figure 1, Appendix 2
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	10-11, Table 1
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	11-12, Table 2, Appendix 3,4,5
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	11-12, Table 5
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	12-15, Table 5
Limitations	20	Discuss the limitations of the scoping review process.	15-16
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	16
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	17

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

BMJ Open

Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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Keywords:	COVID-19, RESPIRATORY MEDICINE (see Thoracic Medicine), Clinical trials < THERAPEUTICS

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Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review

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ABSTRACT

Objectives: The COVID-19 pandemic has stimulated growing research on treatment options. We aim to provide an overview of the characteristics of studies evaluating COVID-19 treatment.

Design: Rapid scoping review

Data sources: Medline, Embase and biorxiv/medrxiv from inception to May 15, 2021

Setting: Hospital and community care

Participants: COVID-19 patients of all ages

Interventions: COVID-19 treatment

Results: The literature search identified 616 relevant primary studies of which 188 were randomized controlled trials and 299 relevant evidence syntheses. The studies and evidence syntheses were conducted in 51 and 39 countries, respectively.

Most studies enrolled patients admitted to acute care hospitals (84%), included on average 169 participants, with an average age of 60 years, study duration of 28 days, number of effect outcomes of four and number of harm outcomes of one. The most common primary outcome was death (32%).

The included studies evaluated 214 treatment options. The most common treatments were tocilizumab (11%), hydroxychloroquine (9%), and convalescent plasma (7%). The most common therapeutic categories were non-steroidal immunosuppressants (18%), steroids (15%), and antivirals (14%). The most common therapeutic categories involving multiple drugs were antimalarials/antibiotics (16%), steroids/non-steroidal immunosuppressants (9%), and antimalarials/antivirals/antivirals (7%). The most common treatments evaluated in systematic reviews were hydroxychloroquine (11%), remdesivir (8%), tocilizumab (7%) and steroids (7%).

The evaluated treatment was in favour 50% and 36% of the evaluations, according to the conclusion of the authors of primary studies and evidence syntheses, respectively.

Conclusions: This scoping review characterized a growing body of comparative-effectiveness primary studies and evidence syntheses. The results suggest future studies should focus on children, elderly ≥65 years of age, patients with mild symptoms, outpatient treatment, multi-mechanism therapies, harms and active comparators. The results also suggest that future living evidence synthesis and network meta-analysis would provide additional information for decision-makers on managing COVID-19.

Keywords: COVID-19; RESPIRATORY MEDICINE; Clinical trials<THERAPEUTICS, scoping review, knowledge synthesis, evidence synthesis

Strengths and limitations of this study

- Broad literature search and study selection yielded 915 study reports, including 616 relevant studies (188 randomized controlled trials) and 299 evidence syntheses.
- Detailed charting of study populations, interventions and outcomes of included studies and reviews were conducted to analyze characteristics and trends in the included literature and to elucidate lessons for future research.
- Practical implications for future research with respect to study design, populations, interventions, comparators, outcomes and methodological approaches were identified.
- Semi-automation approach to study selection, allowing for a very broad literature search and screening approximately 290,000 titles/abstracts in about 40 person-hours over 2.3 weeks.
- This is a scoping review and as such, we did not assess the risk of bias of the included studies and evidence syntheses.

INTRODUCTION

The current global pandemic of Coronavirus Disease 2019 (COVID-19) has resulted in a high burden of disease and mortality worldwide(1, 2). The lack of effective treatments for COVID-19 has resulted in the almost constant production of studies and evidence syntheses evaluating potential treatment options, as illustrated by thousands of study protocols in clinical trial registries and hundreds of review protocols in systematic review registries(3, 4). Attempts to synthesize this evidence thus far have resulted in various scoping reviews focusing on single drugs or isolated drug classes(5-9). Better understanding of the characteristics of study populations, treatments and outcomes of this research is a prerequisite to the design and conduct of future comparative-effectiveness research.

The objective of this rapid scoping review was to provide an overview of the characteristics of studies examining COVID-19 treatment.

METHODS

The conduct of the rapid scoping review was guided by the JBI (formally Joanna Briggs Institute) Guide for scoping reviews, alongside the World Health Organization (WHO) Guide to rapid reviews(10, 11). Compared to a scoping review, we used streamlined methods in this rapid scoping review (e.g., single reviewers conducted study selection). An integrated knowledge translation approach was used to engage with the knowledge users from Health Canada (MK) and Public Health Agency of Canada (MP) throughout the conduct of the rapid scoping review, including during: research question development, literature search, study inclusion, interpretation of results, and draft report. The protocol for the review was registered using the Open Science Framework (https://osf.io/ypz7x). The discussion section includes minor amendments that occurred to the conduct of the review from the original protocol. Reporting of results was guided using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension to Scoping Reviews (PRISMA-ScR) Statement(12).

Our research question was "What evidence exists on the treatments for COVID-19 in primary studies and reviews", which is appropriate for the scoping review methodology(13).

Patient and Public Involvement

Since this work was carried out as part of a rapid response to the COVID-19 pandemic project, timelines did not allow for participation of any patients or members of the public in this scoping review.

Literature search

Comprehensive literature searches and citation screening were used in combination to gather relevant evidence from MEDLINE, EMBASE and pre-print servers (biorxiv/medrxiv)(14). The literature was initially searched from inception to May 21, 2020 and subsequently updated to May 15, 2021. Titles/abstracts were identified for screening using the Continuous Active Learning® (CAL®) tool, which uses supervised machine learning (see Appendix 1 for the description and performance of the tool)(14). For archives that could be retrieved in their entirety (e.g., MEDLINE, pre-print servers), the CAL® tool applied broad relevant search terms (Appendix 1). This search was supplemented by a literature search conducted by an experienced librarian in EMBASE (Appendix 2). The literature search was not restrict by language or publication status.

Eligibility criteria

The eligibility criteria followed the PICOS framework and consisted of:

- Population: Individuals of any age who were clinically and/or laboratory diagnosed with COVID-19.
- Intervention: Any compounds under investigation in human clinical trials as potential COVID-19 therapies (Appendix 3). Chinese medicine and complementary and alternative medicine – either alone or in combination with these medications – were excluded.

- Comparator: Any of the interventions listed above, no intervention or placebo.
- Outcomes: Any reported outcome.
- Study designs: Primary studies of any design with a comparator group. Evidence syntheses of such studies were included, including systematic reviews, scoping reviews, rapid reviews, meta-analysis and overviews of reviews.

Study selection

A streamlined approach to study selection was used for the rapid scoping review. In combination with manual screening by reviewers, the CAL® tool was used to identify and rank the titles and abstracts most likely to meet the inclusion criteria. This process continued iteratively until none of the identified articles met the inclusion criteria. For manual screening, a screening form based on the eligibility criteria was prepared for reviewers to aid in making consistent judgements on article relevance. A pilot-test was conducted using a random sample of 10 titles/abstracts until reviewers reached at least 75% agreement. Subsequently, screening was completed by single reviewers.

Data charting and coding

A charting form was developed and calibrated amongst the entire review team using two randomly selected full-text articles to ensure a standard approach to data collection. Following successful completion of the pilot-test, included studies were charted by single reviewers and verified by a second reviewer to ensure accuracy. Methodological quality or risk of bias appraisal of included studies was not conducted since this is scoping review(10). The items collected included study characteristics (e.g., study duration, study design, country of conduct), patient characteristics (e.g., type of diagnosis, mean age), intervention and comparator details (e.g., type of intervention, dose, frequency, duration) and outcome measures details (e.g., mortality, viral clearance, and hospital admission).

Pharmacological agents were grouped by their therapeutic category(15). Study primary outcomes were grouped together to reflect the clinical, virology, respiratory, inflammatory, cardiology and olfactory status and measures of COVID-19(16, 17). The numbers of effect and harm measures were derived by counting the outcomes from the description of study outcomes. Authors' conclusions were coded into the following categories: favor treatment, favor control, indeterminate and other(18). Pairs of reviewers conducted the data coding independently, with discrepancies reviewed and resolved through discussion by a pair of reviewers.

Synthesis

The charted and coded data were summarized descriptively for all patient population, interventions, comparators, outcomes, and conclusion statements. The data were stratified by study design (randomized controlled trials versus non-RCT) and review type (review conducted according to a review protocol or otherwise).

Data repository

All material related to this review, including EndNote databases, extracted data in MS Excel, coding categories and analysis procedures written in the statistical software R are available at https://knowledgetranslation.net/comparative-effectiveness-research-of-covid-19-treatment-a-rapid-scoping-review-data-repository/.

RESULTS

Literature Search

Figure 1 displays the literature search results. The semi-automation process with CAL® and human reviewers allowed for the screening of approximately 286,000 titles/abstracts in about 40 person-hours over 2.3 weeks. Specifically, CAL® identified 289,844 Covid-19 records and 4,183 potentially relevant titles/abstracts. Title/abstract screening by reviewers resulted in

1,542 potentially relevant reports. Report screening by reviewers resulted in 915 relevant reports, including 616 studies and 299 knowledge syntheses. The list of included primary studies and knowledge syntheses is in Appendix 4 and 5, respectively.

Characteristics of included studies

Figure 2 displays the timing when the studies were available online; on average 48 primary studies per month were published from July 2020 to April 2021. Table 1 displays the characteristics of the 616 included studies of varying design, including randomized controlled trials (188 studies [31%]), retrospective cohort studies (304 [49%]) and prospective cohort studies (70 [11%]), amongst others. The median study duration was 28 days and the median sample size was 169 participants. Public sources provided funding for about a third of the studies; RCTs were funded often by private funding sources (27% relative to 3% for non-RCT). The primary studies were conducted in 51 countries, including the United States (26%), China (17%), Italy (8%), Spain (7%), France (6%), India (4%), Iran (3%), United Kingdom (3%) and Brazil (3%), among others (Table A1, Appendix 6).

Most studies were conducted with participants admitted to acute care hospital (84%). Participants were on average 60 years of age, including 61% male, and mostly with confirmed COVID-19 via PCR test (Table 1). About a third of the included studies enrolled participants with severe or critical COVID-19 conditions. Few studies (0.3%) enrolled children (e.g., <16 years of age) or the elderly (e.g., ≥65 years of age, 2%). Figure A1 displays the cloud of words often used to describe the participants (Appendix 6). Typical words used were COVID-19, COVID-19 patients, hospitalized, severe, pneumonia, ICU, outpatient, respiratory distress, invasive mechanical ventilation, critically ill and supplemental oxygen, among others.

The median number of effect outcomes was four, and the corresponding number of harm outcomes was one (Table 1). Common primary outcomes included death/survival (32% of the

included studies), clinical status/measures (19%), virology status/measures (10%), respiratory status/measures (9%), safety/adverse events excluding death (7%) and composite outcomes involving death (6%, e.g., intubation and death, or intensive care admission and death), among others.

The included studies evaluated 827 treatment arms (711 single-drug and 116 multiple-drug treatment arms) against 616 control arms, of which 106 (17%) control arms involved active comparators (Table 2). The treatment arms consisted of 215 unique treatment options (Table A2, Appendix 6). The most common treatments were tocilizumab (11%), hydroxychloroquine (9%), convalescent plasma (7%), steroid (4%), lopinavir combined with ritonavir (4%), methylprednisolone (3%), remdesivir (3%), enoxaparin (2%), hydroxychloroquine combine with azithromycin (2%), and anakinra (2%), among others. Table 2 also displays the common therapeutic categories of the evaluated treatment. The most common therapeutic categories were non-steroidal immunosuppressant (18%), steroid (15%), antiviral (14%), antimalarial (12%), anticoagulant (5%), convalescent plasma (8%), antibiotic (4%), anti-inflammatory (3%), interferon therapy (2%), anti-parasitic (2%) and immunomodulatory (2%), among others (details in Table A3, Appendix 6). Common therapeutic categories involving multiple drugs were the combination of antimalarial/antibiotic (16%), steroid/non-steroidal immunosuppressant (9%), antimalarial/antiviral/antiviral (7%), 2-antivirals (4%) and antiviral/interferon (4%), among others (Table A4, Appendix 6).

Characteristics of included knowledge syntheses

Figure 2 displays the timing when the knowledge syntheses were available online, on average 22 reviews appeared each month from May 2020 to April 2021. Table 3 displays characteristics of the 299 included knowledge syntheses, including 88 (29%) knowledge syntheses and 211 (71%) knowledge syntheses conducted with and without a review

protocol, respectively. Commonly conducted knowledge syntheses included systematic review with meta-analysis (63%), systematic review (24%), meta-analysis (4%, none mentioned the use of a review protocol), scoping review (3%) and rapid review (3%), among others. Most reviews (83%) included RCT and non-RCT studies. The median number of data sources was five and the median number of included studies was 14. The evidence syntheses were conducted in 39 countries, including the United States (19%), China (14%), India (11%), Iran (6%) and the United Kingdom (6%), among others (Table A5, Appendix 6). The evidence syntheses evaluated 518 treatment arms against 299 control arms (Table 4). The treatment arms consisted of 115 unique treatment options (Table A6, Appendix 6). The most common treatment options were hydroxychloroquine (11%), remdesivir (8%), tocilizumab (7%), steroids (7%), convalescent plasma (6%), and lopinavir/ritonavir (5%), among others (Table 4 and Table A6, Appendix 6).

Treatment evaluation according to authors' conclusion

Table 5 displays the results of the treatment evaluation according to authors' conclusion. Among the included studies and knowledge syntheses, the conclusion was in favour of treatment in 50% and 36% of the evaluated treatment arms, respectively.

DISCUSSION

We completed a rapid scoping review for Health Canada and Public Health Agency of Canada to identify pharmacologic treatments for COVID-19. A comprehensive search of electronic databases, trial registries and other grey literature sources from inception to May 2020 identified 9 controlled trials and 19 cohort studies with approximately 8,000 participants. Updated to May 15, 2021, the search of electronic databases identified 933 relevant reports, including 630 studies with approximately 15.4 million participants, and 303 knowledge syntheses.

With respect to study population, existing studies put much emphasis on adult patients admitted to acute care hospitals. Future studies need to focus on children, older adults aged ≥65 years and patients with mild symptoms in community settings. Future study populations will need to reflect a broader range of age groups as the current pandemic evolves to affect younger age groups(19, 20).

With respect to treatment, many studies and reviews evaluated antimalarial agents. Existing studies emphasised preventing and treating cytokine surge with steroids and non-steroidal immunosuppressants, including interleukin-6 inhibitors (e.g., tocilizumab, sarilumab), interleukin-1 antagonist (e.g., anakinra), anti-IL-1β monoclonal antibody (e.g., canakinumab), TNF-alpha inhibitor (e.g., adalimumab) and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib). Future studies may need to explore treatment for patients not responding to these agents, such as immunomodulators (e.g., thymosin-α1). Existing studies put much emphasis on monotherapy; future studies need to evaluate combination therapy that addresses the multiple aspects of COVID-19, such as virology, respiratory, inflammatory and cardiology. Future studies may also need to explore outpatient treatment for patients with mild symptoms, and treatment options not frequently evaluated in existing studies, such as therapeutic anticoagulants.

With respect to comparators, most existing randomized controlled trials used placebo comparators while most observational studies used standard of care as comparator; future studies may consider active treatment as comparators, especially when evaluating treatments aiming to produce incremental improvement against effective treatments. Methodological issues related to the selection and delineation of comparators in studies evaluating combination therapies deserve attention. For example, a study evaluated multi-mechanism approach with medications targeting early immunomodulation, anticoagulation, and viral suppression to prevent catastrophic cytokine release syndrome encountered large variation in

clinical characteristics of study participants and standard-of-care comparators in the five participant hospitals in two countries, including differences in disease severity and different doses of colchicine and types of steroids used across comparative groups(17).

With respect to outcomes, about a third of the included studies used mortality as the primary outcome. Tracking this outcome may require sufficiently long study duration, perhaps longer than the median duration of less than a month observed among existing studies, especially in patients with prolonged respiratory problems, suggesting longer follow-up duration for future studies. Of note, few existing studies used composite endpoints involving death, including endpoints such as intubation and intensive care admission. This use seems to be particularly suitable to capture the respiratory, immunology and cardiovascular aspects of COVID-19, as well as mortality. Few existing studies focused on harms due to treatment and among those that evaluated benefits and harms, the median number of reported harms was one; future studies need to put more emphasis on harm evaluation. Existing RCTs put much emphasis on the use of clinical status/measures as primary outcome measures. Future trials may consider other primary outcomes that are relevant to patients, such as pneumonia, acute respiratory distress syndrome, multi-organ failure, and septic shock, among others.

With respect to study design, our results showed a breakdown of 30% and 70% for RCTs and observational studies, respectively. Future trials are needed for evaluating combination therapies. Observational studies will remain pertinent in the evaluation of combination therapies, especially when rich data becomes available with their use in practice. Our review excluded qualitative studies, but we wish to emphasize the importance of these studies in elucidating the experience of COVID-19 patients.

With respect to evidence synthesis, we identified a small number of meta-analyses conducted without the associated systematic review and review protocol (n=13). This practice needs to be scrutinized because of the associated high risk of bias in the results, which could be

wrong, but appeared to be convincingly precise(21). Existing knowledge syntheses mostly evaluated monotherapy; future evidence syntheses will need to include data from the evaluation of combination therapy. The number of existing network meta-analyses was low (n=4); future network meta-analyses are needed to identify effective treatment given a plethora of treatment options, as well as to identify effective component treatment options addressing multiple aspects of COVID-19(22). Given the growing literature, there is a definitive need for living knowledge synthesis, in which the synthesis is updated regularly as new studies become available(23). The results suggest that monthly updates may become necessary.

With respect to the growing literature, the use of automation tools like CAL® for study selection will become essential to ensure a highly sensitive yield of relevant studies, responsive timelines for decision-making and reduced workload for reviewers. In this scoping review, we used a continuous active learning approach that integrates machine learning with feedback instructions from reviewers. This approach allowed the screening of approximately 290,000 titles/abstracts in about 40 person-hours over 2.3 weeks. We believe this approach is indispensable for future reviews involving large body of literature. This approach called for slight changes in our review conduct and reporting, of note the reported number of the titles/abstracts excluded by the automation tool in the flowchart (see Figure 1).

There are several limitations of this review. This is a scoping review, and as such, we did not assess the risk of bias in the included studies and reviews. Initially, the review protocol called for a borrowing strength of evidence approach, including studies evaluating treatment for SARS and MERS. The initial literature search in May 2020 included electronic databases, trial registries, Cochrane Library and other grey literature sources. Given the growing literature on COVID-19 by May 2021, the current review was focused only on COVID-19 treatment, with relevant studies identified from MEDLINE, EMBASE and pre-print servers.

In this review, the evaluated treatment options appeared to attain a reasonable chance of being more effective than their comparators, approximately 30% and 50% according to the authors' conclusions from the included studies and reviews, respectively. However, we did not extract outcome data and combined them to verify the authors' conclusions. To provide a broad overview of the comparative effectiveness research on Covid-19 treatment, we included reports from pre-print servers, but these reports had not gone through peer review. Despite these limitations, the methods used in this review were carefully selected to address the needs of our knowledge users from Health Canada and Public Health Agency of Canada. In addition, we made the material from this scoping review available in an online data repository as the data may be useful for conducting systematic reviews of specific therapies or for updating the current review(24).

CONCLUSIONS

This scoping review characterized a growing body of comparative-effectiveness studies and evidence syntheses evaluating hundreds of monotherapy and combination therapy options addressing the multiple sequelae of COVID-19. The results suggest future studies in children, elderly (e.g., ≥65 years of age) and patients with mild symptoms, with additional data on outpatient treatment, multi-mechanism therapy, harms and active comparators. The results also suggest that future living evidence synthesis and network meta-analysis would provide additional information for decision-makers on managing COVID-19.

DECLARATIONS

Ethics approval and consent to participate

Not applicable. This research is exempt from ethics approval because the work is carried out on published documents.

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors have no competing interests to declare.

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Authors' contributions

PR and BP analyzed the data, interpreted the results and drafted the original and revised manuscript, respectively. ACT and SES conceived and designed the study, helped obtain funding, interpreted the results and helped write sections of the manuscript. GVC and MRG provided methodological and technical support and edited the manuscript. AR, ND, JA and FY coordinated the review, screened citations and full-text articles, abstracted data, resolved discrepancies and edited the manuscript. MK, MP and MM helped conceive the study, provided methodological support and content expertise and edited the manuscript. RR and MG provided methodological support, screened citations and full-text articles and assisted with drafting the manuscript. CW, NR, EM and RW screened citations and full-text articles, abstracted data and assisted with data analysis. All authors read and approved the final manuscript.

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Additional File

File Format: Microsoft Word (.docx)

Title of Data: Additional File 1 (Appendices 1-6)

Description of Data: The appendices include the following additional information:

Appendix 1 – The Continuous Active Learning (CAL®) tool

Appendix 2 – EMBASE search strategy

Appendix 3 – List of drugs from Health Canada and Public Health Agency of Canada

Appendix 4 – List of included primary studies

Appendix 5 – List of included knowledge syntheses

Appendix 6 – Additional details for the Results section

FIGURE LEGEND

Figure 1. Flow diagram of included studies

Study Flow Diagram

Figure 2. Timing of available online of included studies*

Online timing chart of included studies

TABLES

Table 1. Study, participant and outcome characteristics

Study characteristics	Total (n=616)	RCT (n=188)	Non-RCT (n=428)
Study design			
RCT	188 (31%)	188	
Retrospective cohort	304 (49%)		304 (71%)
Prospective cohort	70 (11%)		70 (16%)
Case-control	27 (4%)		27 (6%)
Controlled clinical trial	23 (4%)		23 (5%)
Controlled before-after	4 (1%)		4 (1%)
Study setting			
Acute care hospital	515 (84%)	145 (77%)	370 (86%)
Intensive care unit	44 (7%)	4 (2%)	40 (9%)
Community	42 (7%)	34 (18%)	8 (2%)
Community and hospital	6 (1%)	3 (2%)	3 (1%)
Nursing home	3 (0%)	0 (0%)	3 (1%)
Not reported	6 (1%)	2 (1%)	4 (1%)
Country			
United States	161 (26)	37 (20)	124 (29)
China	107 (17)	27 (14)	80 (19)
Italy	47 (8)	2 (1)	45 (11)
Spain	41 (7)	3 (2)	38 (9)
France	39 (6)	5 (3)	34 (8)
India	23 (4)	15 (8)	8 (2)
Iran	21 (3)	15 (8)	6 (1)
United Kingdom	21 (3)	19 (10)	2 (0)
Brazil	17 (3)	13 (7)	4 (1)
Turkey	12 (2)	1 (1)	11 (3)
Mexico	11 (2)	6 (3)	5 (1)
Argentina	10 (2)	7 (4)	3 (1)
Study duration			
Median duration in days (IQR)	28 (14, 30)	21.5 (14, 28)	28 (20, 35)
Sample size			
Median # participants (IQR)	169 (74, 475)	120 (60, 394)	194 (82, 592)
Study sponsor			
Public	206 (33%)	78 (41%)	128 (30%)
No funding	165 (27%)	21 (11%)	144 (34%)
Private	63 (10%)	50 (27%)	13 (3%)
Public & private	18 (3%)	13 (7%)	5 (1%)
Not reported	164 (27%)	26 (14%)	138 (33%)
Participant characteristics			

Study characteristics	Total (n=616)	RCT (n=188)	Non-RCT (n=428)
Average age (years)			
Median (range)	60 (6, 88)	56 (27, 77)	62 (6, 88)
Average percent of male participants			
Median (IQR)	61 (53, 69)	59 (50, 66)	62 (54, 70)
SARS-CoV-2 diagnosis			
Polymerase chain reaction (PCR) test	436 (71%)	146 (78%)	290 (68%)
PCR and other*	105 (17%)	33 (18%)	72 (17%)
Not specified	75 (12%)	9 (5%)	66 (15%)
Case severity♦			
Severe	163 (26%)	39 (21%)	124 (29%)
Mild or moderate	46 (7%)	25 (13%)	21 (5%)
Moderate or severe	33 (6%)	17 (9%)	16 (4%)
Severe or critical	30 (5%)	7 (4%)	23 (5%)
Moderate	24 (4%)	14 (8%)	10 (2%)
Mild	22 (3%)	16 (9%)	6 (1%)
Mild, moderate or severe	14 (2%)	6 (3%)	8 (2%)
Mild, moderate, severe or critical	8 (1%)	2 (1%)	6 (1%)
Moderate, severe or critical	4 (1%)	1 (1%)	3 (1%)
Not specified	117 (19%)	34 (19%)	83 (19%)
Special age group**			
Elderly (e.g., ≥65 years of age)	11 (2%)	2 (1%)	9 (2%)
Children (e.g., <16 years of age)	2 (0%)	1 (1%)	1 (0%)
Type of primary outcome			
Death/survival[1]	198 (32%)	20 (11%)	178 (42%)
Clinical status/measures[2]	119 (19%)	71 (38%)	48 (11%)
SARS-CoV-2 virology status/measures[3]	61 (10%)	29 (15%)	32 (7%)
Respiratory status/measures[4]	53 (9%)	19 (10%)	34 (8%)
Safety/adverse events[5]	43 (7%)	9 (5%)	34 (8%)
Composite outcome involving death[6]	39 (6%)	10 (5%)	29 (7%)
Resources measures[7]	20 (3%)	6 (3%)	14 (3%)
Invasive mechanical ventilation	15 (2%)	4 (2%)	11 (3%)
Admission to intensive care unit	11 (2%)	1 (1%)	10 (2%)

Study characteristics	Total (n=616)	RCT (n=188)	Non-RCT (n=428)
Admission to acute care hospital	9 (1%)	3 (2%)	6 (1%)
Inflammatory status/measures[8]	9 (1%)	4 (2%)	5 (1%)
Emergency room visit	4 (1%)	2 (1%)	2 (0%)
Cardiology status/measures[9]	3 (1%)	1 (1%)	2 (1%)
Olfactory status/measures[10]	3 (0%)	2 (1%)	1 (0%)
Hospital discharge	2 (0%)	1 (0%)	1 (0%)
Other status/measures[11]	9 (1%)	2 (1%)	7 (2%)
Not reported	18 (3%)	4 (2%)	14 (3%)
Number of effect outcomes			
Median # of outcomes (IQR)	4 (2, 7)	6 (4, 9)	3 (2, 6)
Number of harm outcomes			
Median # of outcomes (IQR)	1 (0, 3)	2 (1, 5)	0 (0, 2)

Notes: IQR – interquartile range. *Other diagnostic modality such as lung imaging or suspected Covid-19 cases. ♦Case severity according to the clinical spectrum of SARS-CoV-2 infection by the National Institute of Health(25) **Age group as reported in the included studies. [1]Ddeath/survival or time to death. [2]Clinical status/measures such as improvement/deterioration or time to such events. [3]SARS-CoV-2 virology status/measures such as viral load or duration to Polymerase Chain Reaction negative. [3]Respiratory status/measures such as whole lung lesion volumes or blood oxygen saturation. [5]Safety/adverse events such as other infections than SARS-CoV-2, acute kidney injury or drug tolerance. [6]Composite endpoints involving death such as death and invasive mechanical ventilation or death and admission to intensive care unit. [7]Resources measures such as length of hospital stay. [8]Inflammatory status/measures such as plasma levels of C-reactive protein, or changes in ROX index, the ratio of SpO2/FIO2. [9]Cardiology status/measures such as cardia endpoints with max high-sensitivity cardiac troponin level, and stroke. [10]Olfactory status/measures such as loss of smell and taste.[11]Other primary outcome such as time from Covid-19 symptoms onset to treatment or organ support–free days.

Table 2. Treatment options frequently evaluated in included studies

All individual treatments	Total	RCT	Non-RCT
Total	**827**	**231**	**596**
1. **Tocilizumab**	87 (11%)	12 (5%)	75 (13%)
2. **Hydroxychloroquine**	78 (9%)	22 (10%)	56 (9%)
3. **Convalescent Plasma**	55 (7%)	15 (6%)	40 (7%)
4. **Steroid**	37 (4%)	1 (0%)	36 (6%)
5. **Lopinavir/Ritonavir**	29 (4%)	5 (2%)	24 (4%)
6. **Methylprednisolone**	26 (3%)	3 (1%)	23 (4%)
7. **Remdesivir**	25 (3%)	16 (7%)	9 (2%)
8. **Enoxaparin**	18 (2%)	1 (0%)	17 (3%)
9. **Hydroxychloroquine/Azithromycin**	18 (2%)	2 (1%)	16 (3%)
10. **Anakinra**	16 (2%)	2 (1%)	14 (2%)
Treatment type - Common single treatment	**Total**	**RCT**	**Non-RCT**
All single treatments	**711**	**202**	**509**
1. NS-Immunosuppressant	126 (18%)	27 (13%)	99 (19%)
2. Steroid	110 (15%)	15 (7%)	95 (19%)
3. Antiviral	97 (14%)	40 (20%)	57 (11%)
4. Antimalarial	87 (12%)	25 (12%)	62 (12%)
5. Anticoagulant	66 (5%)	5 (3%)	61 (12%)
Anticoagulant-Therapeutic	17 (2%)	2 (1%)	15 (3%)
Anticoagulant-Prophylactic	14 (2%)	0 (0%)	14 (3%)
6. Convalescent Plasma	56 (8%)	16 (8%)	40 (8%)
7. Antibiotic	29 (4%)	7 (3%)	22 (4%)
8. Anti-Inflammatory	20 (3%)	8 (4%)	12 (2%)
9. Interferon Therapy	16 (2%)	7 (3%)	9 (2%)
10. Anti-parasitic	14 (2%)	12 (6%)	2 (0%)
10. Immunomodulatory	14 (2%)	4 (2%)	10 (2%)
Treatment type – Common combined treatment			
All combined treatment option	**116**	**29**	**87**
1. Antimalarial/Antibiotic	19 (16%)	2 (7%)	17 (20%)
2. Steroid/NS-Immunosuppressant	10 (9%)	0 (0%)	10 (11%)
3. Antimalarial/Antiviral/Antiviral	8 (7%)	1 (3%)	7 (8%)
4. Antiviral/Antiviral	5 (4%)	3 (10%)	2 (2%)
4. Antiviral/Interferon	5 (4%)	0 (0%)	5 (6%)
5. Antimalarial/Antiviral	4 (3%)	0 (0%)	4 (5%)
5. Antimalarial/Antiviral/Antibiotic	4 (3%)	4 (14%)	0 (0%)
5. Anti-parasitic/Antibiotic	4 (3%)	3 (10%)	1 (1%)
5. Antiviral/Antiviral/Antiviral	4 (3%)	0 (0%)	4 (5%)

5. Antiviral/Antiviral/Antiviral/Interferon	4 (3%)	0 (0%)	4 (5%)
5. Antiviral/NS-Immunosuppressant	4 (3%)	3 (10%)	1 (1%)
5. NS-Immunosuppressant/Steroid	4 (3%)	0 (0%)	4 (5%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant.

Table 3. Evidence Synthesis characteristics

	All (n=299)	With protocol (n=88)	Without protocol (n=211)
Review type			
Systematic review with meta-analysis	189 (63%)	66 (75%)	123 (58%)
Systematic review	73 (24%)	15 (17%)	58 (27%)
Meta-analysis	12 (4%)	0 (0%)	12 (6%)
Scoping review	10 (3%)	3 (3%)	7 (3%)
Rapid review	8 (3%)	1 (1%)	7 (3%)
Network meta-analysis	2 (1%)	1 (1%)	1 (0%)
Rapid review with meta-analysis	2 (1%)	1 (1%)	1 (0%)
Systematic review with network meta-analysis	2 (1%)	0 (0%)	2 (1%)
Overview of systematic reviews	1 (0%)	1 (1%)	0 (0%)
Review abstract			
Structured abstract	159 (53%)	47 (53%)	112 (53%)
Abstract with no structure	140 (47%)	41 (47%)	99 (47%)
Eligibility criteria			
Report eligibility criteria	259 (87%)	86 (98%)	173 (82%)
Eligibility criteria are unclear	40 (13%)	2 (2%)	38 (18%)
Include randomized controlled trials			
Include RCTs only	51 (17%)	19 (22%)	32 (15%)
Include different study designs	248 (83%)	69 (78%)	179 (85%)
Number of data sources			
Median (IQR)	5 (3, 6)	6 (4, 7)	4 (3, 6)
Number of included studies			
Median (IQR)	14 (7, 28)	17 (7, 38)	14 (7, 25)
Common country			
1. United States	57 (19%)	13 (15%)	44 (21%)
2. China	40 (14%)	13 (15%)	27 (13%)
3. India	34 (11%)	12 (13%)	22 (10%)
4. Iran	18 (6%)	3 (3%)	15 (7%)
4. United Kingdom	18 (6%)	3 (3%)	15 (7%)
5. Saudi Arabia	13 (4%)	1 (1%)	12 (6%)
6. Canada	12 (4%)	5 (6%)	7 (3%)
7. Italy	12 (4%)	8 (9%)	4 (2%)
8. Indonesia	9 (3%)	2 (2%)	7 (3%)
9. Malaysia	7 (2%)	0 (0%)	7 (3%)
10. Egypt	5 (2%)	2 (2%)	3 (1%)
10. France	5 (2%)	3 (3%)	2 (1%)
10. Peru	5 (2%)	1 (1%)	4 (2%)
10. Taiwan	5 (2%)	1 (1%)	4 (2%)

Note: RCT: randomized controlled trial. IQR: inter-quartile range.

Table 4. Treatment options evaluated in systematic reviews

Treatment option	Total (n=518)	With protocol (n=152)	Without protocol (n=366)
Hydroxychloroquine	58 (11%)	15 (10%)	43 (12%)
Remdesivir	39 (8%)	11 (7%)	28 (8%)
Tocilizumab	35 (7%)	10 (7%)	25 (7%)
Corticosteroid	35 (7%)	10 (7%)	25 (7%)
Convalescent Plasma	33 (6%)	10 (7%)	23 (6%)
Lopinavir-Ritonair	24 (5%)	8 (5%)	16 (4%)
Chloroquine	19 (4%)	6 (4%)	13 (4%)
Hydroxychloroquine/Azithromycin	14 (3%)	1 (1%)	13 (4%)
Antivirals	12 (2%)	4 (3%)	8 (2%)
Anticoagulant	11 (2%)	2 (1%)	9 (2%)
Azithromycin	11 (2%)	3 (2%)	8 (2%)
Favipiravir	10 (2%)	1 (1%)	9 (2%)
Hydroxychloroquine/Chloroquine	10 (2%)	4 (3%)	6 (2%)
Colchicine	9 (2%)	2 (1%)	7 (2%)
Dexamethasone	9 (2%)	1 (1%)	8 (2%)
Arbidol	7 (1%)	1 (1%)	6 (2%)
Invermectin	7 (1%)	3 (2%)	4 (1%)
Glucocorticoid	7 (1%)	3 (2%)	4 (1%)
ACEI/ARB	6 (1%)	4 (3%)	2 (1%)
Therapeutic Anticoagulant	5 (1%)	2 (1%)	3 (1%)
Prophylactic Anticoagulant	4 (1%)	3 (2%)	1 (0%)
Anakinra	4 (1%)	3 (2%)	1 (0%)
Famotidine	4 (1%)	1 (1%)	3 (1%)
JAK-Inhibitors	4 (1%)	2 (1%)	2 (1%)
Sarilumab	4 (1%)	4 (3%)	0 (0%)

Note: JAK-inhibitors: Janus kinase (JAK) inhibitors. HCQ: Hydroxychloroquine.
ACEI/ARB: Angiotensin Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers

Table 5. Treatment evaluation according to authors' conclusion

Studies evaluating treatment benefits/harms	**All studies**	**RCT**	**Non-RCT**
# of evaluated treatment arms	827	231	596
Favor evaluated treatment	413 (50%)	120 (52%)	293 (49%)
Favor control	63 (8%)	15 (7%)	48 (8%)
Indeterminate/neutral	258 (31%)	90 (39%)	168 (28%)
Reviews evaluating treatment benefits/harms	**All reviews**	**With protocol**	**Without protocol**
# of evaluated treatment arms	518	152	366
Favor evaluated treatment	185 (36%)	50 (33%)	135 (37%)
Favor control	64 (12%)	18 (12%)	46 (13%)
Indeterminate/neutral	182 (35%)	68 (45%)	114 (31%)

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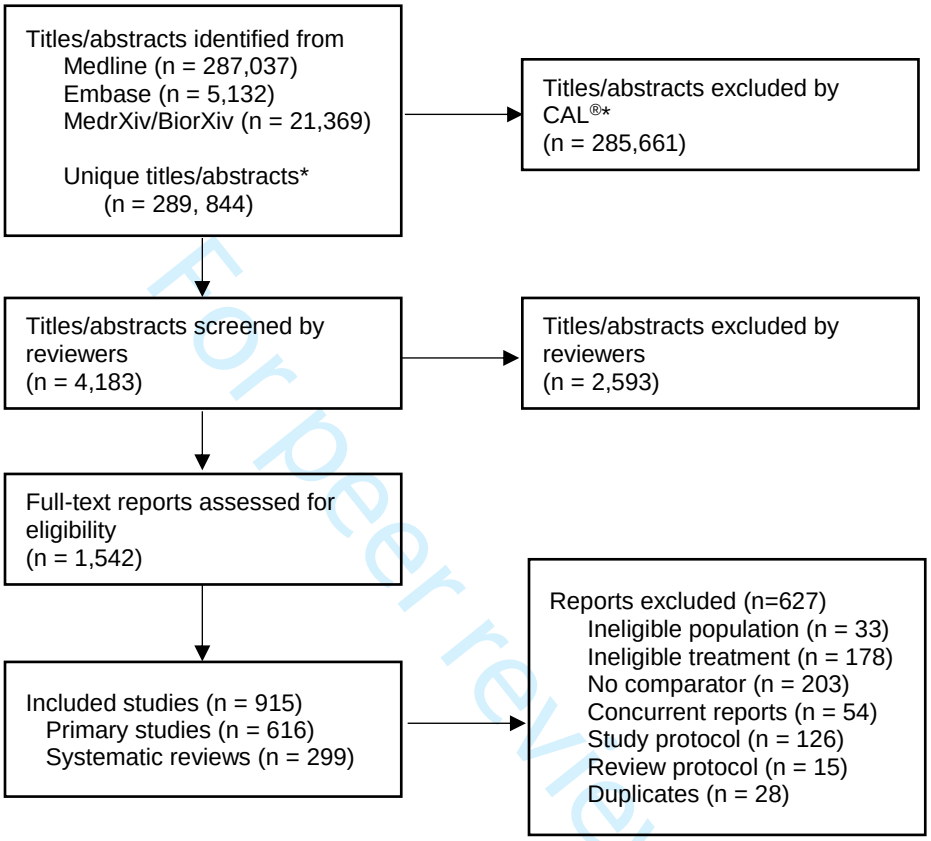
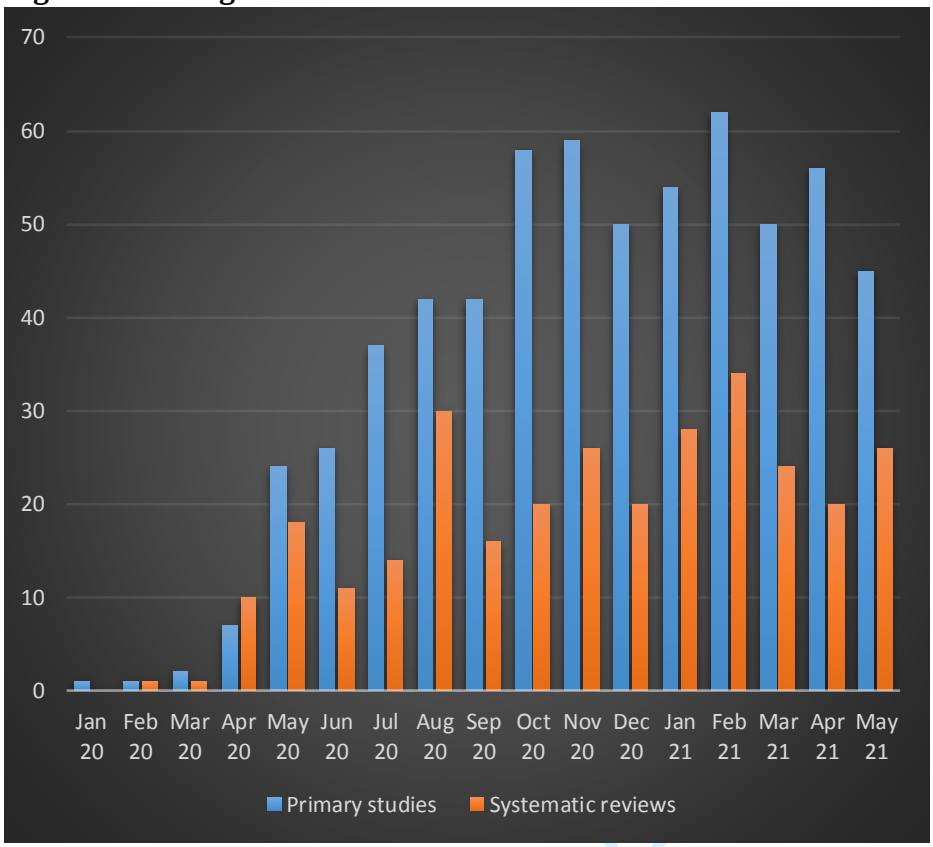
Figure 1. Flow diagram of included studies



Notes: *Estimated number of unique titles/abstracts based upon: Medline (Ovid) includes preprints on Covid-19 from Medrxiv and Biorxiv, and large overlapping records between Medline and Embase. The flowchart was modified from the PRISMA 2020 statement.[25]

Figure 2. Timing of available online of included studies*



Notes: The numbers of primary studies and systematic reviews for May 21 are higher because the literature search ended at May 15, 2021.

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Appendices

Contents

Appendix 1. The Continuous Active Learning (CAL®) tool

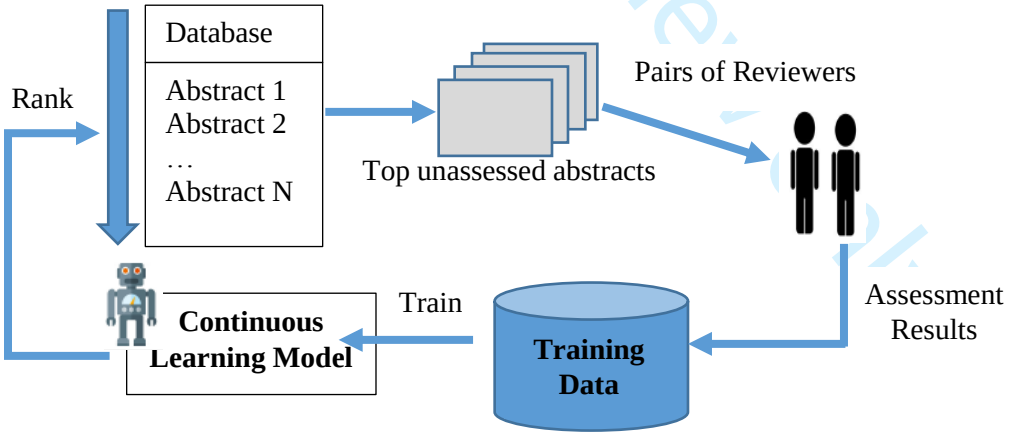

Figure. The algorithm of the CAL® tool

The above figure illustrates the algorithm in the CAL® tool. Text of the review question is used to start training the machine-learning model in the Continuous Active Learning (CAL) method. The CAL model predicts and quantifies the relevance of abstracts from a database. The abstracts are ranked in order of highest to lowest relevance. The top ranked abstracts are presented to a pair of human reviewers for relevance screening. The screening results are used to update the CAL model for better prediction, generating another batch of top ranked abstracts for screening in the next iteration of the feedback loop. The goal is to identify all relevant abstracts with minimum screening effort.

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We selected the CAL® tool because it won multiple international competitions in high-recall information retrieval – the process of retrieving all relevant documents with minimal human effort (Table below)

Table. Summary of evidence on the use of the CAL® tool for knowledge synthesis conduct

International Competition	High-recall tasks	Key findings
Conference and Labs of the Evaluation Forum 2018 (1)	30 systematic reviews of diagnostic test studies	*Task 1:* Without any manual effort to construct literature search strategies, the CAL® tool was the most accurate with 97% recall (sensitivity). *Task 2:* For screening literature search results, CAL® was the most accurate with 99% recall.
Conference and Labs of the Evaluation Forum 2017 (2)	50 systematic reviews of diagnostic test studies	The CAL® tool was a top performer among the 14 tested with 97% to 100% recall at pre-defined stopping threshold.
Text Retrieval Conference Total Recall Tracks 2015/16 (3, 4)	8 legal, clinical, news, email collections	The CAL® tool attained an overall effectiveness not surpassed by any submitted method, manual or automatic.

For archives that could be retrieved in their entirety (e.g., MEDLINE, pre-print servers), the CAL® tool applied broad relevant search terms using the following Posix command:

```
egrep -i 'coronav|corona vir|wuhan|hubei|huanan|[^a-z]ncov|cov2|cov.2|novel.cov|covid|sars-cov'
```

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3. Roegiest A, Cormack G, Grossman M, et al. TREC 2015 Total Recall track overview TREC. 2015.
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Appendix 2. EMBASE search strategy

Database:
Embase Classic+Embase <1947 to 2021 July 08>

#	**Query**
1	exp coronaviridae/ or exp Coronaviridae infection/ or exp Coronavirus infection/
2	((wuhan or hubei or huanan) and (severe acute respiratory or pneumonia* or virus*) and outbreak*).mp.
3	(coronavir* or "corona virus*" or "coronavirus pneumonia" or betacoronavir* or COVID or COVID-19).mp.
4	("nCoV" or "cov 2" or cov2 or 2019ncov or 2019-nCoV or "2019 ncov" or "2019-ncov" or "2019 novel cov" or "2019 ncov disease*" or "2019 novel coronavirus*").mp.
5	"wuhan virus*".mp.

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6	or/1-5
7	exp Interferons/ or interleukin-2/ or exp Immunoglobulin/ or anakinra/ or Sarilumab/ or Siltuximab/ or tumor necrosis factor/ or granulocyte macrophage colony stimulating factor/ or beta1a interferon/ or interferon beta serine/
8	(interferon* or "Interferon-alpha" or "Interferon-beta" or "avonex" or "interferon beta-1a" or "Betaseron" or "Extavia" or "betaferon" or "beneseron" or "beta 1-b interferon" or "recombinant interferon beta-1b" or "Rebif" or "Interferon-gamma" or immunoglobulin* or "immuno globulin*" or "immune-globulin*" or anakinra or kineret or Sarilumab or kevzara or regn88 or sar153191 or Siltuximab or sylvant or cnto328 or "cnto 328" or "tumor necrosis factor*" or "tumor necrosis serum*" or cachectin or cachetin or "anti-TNF-alpha" or "TNF alfa" or "TNF alpha" or anti-granulocyte macrophage or anti-GM-CSF or "GM CSF" or gmcsf or Flebogamma or Gamunex or "Globulin-N" or "Globulin N" or Intraglobin Gammagard or Gamimune or Gamimmune or Privigen or Sandoglobulin or Venoglobulin or "Venoglobulin-I" or "Venoglobulin I" or Venimmune or Iveegam or Alphaglobin or Endobulin or "Gamimune N" or "Gamimmune N" or Gammonativ or beriglobin or biggam or carimune or cuvitru or gammagen or gammaplex or gamunex or hizentra or kiovig or norga or panzyga or sandoglobulin* or subcuvia or venogamma or vigam or interleukin-2 or interleukin).tw.
9	umifenovir/ or riamilovir/ or favipiravir/ or sofosbuvir/ or Arbidol/ or Galidesivir/
10	(Favipiravir or Triazavirin or Umifenovir or riamilovir or sofusbivir or sofosbuvir or sovaldi or psi7851 or psi7976 or psi7977 or "EIDD-2801" or "EIDD 2801" or arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.
11	Darunavir/ or Lopinavir/ or Ritonavir/ or danoprevir/ or remdesivir/
12	(ASC09 or Azvudine or Danoprevir or Darunavir or Lopinavir or ritonavir or Remdesivir or "gs 5734" or "gs5734" or prezista or "tmc 114" or tmc114 or "uic 94017" or uic94017 or abt378 or norvir).tw.
13	baloxavir marboxil/ or baloxavir marboxil.tw.
14	exp antimalarial agent/ or exp quinoline derivative/
15	(Amodiaquine or Basoquin or Camoquin or Flavoquine or Chloroquine or Resochin or Dawaquin or Lariago or Aarlen or Hydroxychloroquine or Hydroxy-chloroquine or chloroquinol or hydrochloroquine or hydrocloroquine or oxychloroquine or quensyl or "sn 8137" or ercoquin or Plaquenil or Hydroquin or Axemal or Dolquine or Quensyl or Quinoric or Imiquimiod or Aldara or Vyloma or Zyclara or Primaquine or Jasoprim or Malirid or Neo-Quipenyl or Pimaquin or Pmq or Primachina or Primacin or Primaquina or Primaquine or Primaquine or Remaquin or Tafenoquine or Krinfatel or Kozenis or Arakoda or Krintafel or Pamaquine or Plasmochin or Plasmoquine or Plsamaguine or Neo-Quipenyl or Primachin or Dihydroartemisinin or Mefloquine or lariam or laricam or mefliam or mephaquin* or tropicur or Nitazoxanide or Alinia or colufase or daxon or heliton or "salicylamide acetate" or nodik or "ph 5776" or ph5776 or ambilhar or "ba 32644" or ba32644 or "ciba 32644 ba" or "ciba 32644ba" or ciba32644ba or niradazol* or nitrothiamidazol* or nitrothiazole or "nsc 136947" or nsc136947 or yarocen or Nitrothiazole or Amokin or amokine or anoclor or aralan or aralen or arechin or arechine or

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	arequine or arthrochin or arthrochine or arthroquine or artrichin or artrichine or artriquine or avloclor or bemaphata or bemaphate or bemasulph or bipiquin or cadiquin or chemochin or chemochine or chingamine or chingaminum or chloraquine or chlorochin or chlorochine or chlorofoz or chloroquin or chloroquin* or cidanchin or "clo-kit junior" or clorichina or clorichine or cloriquine or clorochina or delagil or delagyl or dichinalex or diclokin or diquinalex or diroquine or emquin or genocin or gontochin or gontochine or gontoquine or heliopar or imagon or iroquine or klorokin or klorokine or klorokinfosfat or lagaquin or malaquin or malarex or malarivon or malaviron or maliaquine or maquine or mesylith or mexaquin or mirquin or nivachine or nivaquin* or roquine or quinachl or quingamine or repal or resochen* or resochin or resochina or resochine or resochinon resoquina or resoquine or reumachlor or roquine or rp3377 or sanoquin or sanoquine or silbesan or siragan or sirajan or sn7618 or solprina or solprine or tresochin or tresochine or tresoquine or trochin or trochine or troquine).tw.
16	suramin/
17	(Carriomycin or Suramin).tw.
18	exp steroid/ or exp meprednisone/ or exp corticosteroid/ or fingolimod/ or leflunomide/ or thalidomide/
19	(steroid* or methylprednisone or meprednisone or Prednisolone or Fluprednisolone or Corticosteroid* or Fingolimod or Leflunomid* or Thalidomid*).tw.
20	ruxolitinib/
21	(Jakotinib or Ruxolitinib).tw.
22	exp monoclonal antibody/
23	(Ruxolitinib or Tocilizumab or Adalimumab or Camrelizumab or Eculizumab or Mepolizumab or "PD-1 mAb" or Tocilizumab or Adamumab or tozumab or meplazumab or monoclonal antibod*).tw.
24	("SARS-Cov-2 specific neutralizing antibod*" or "SARS-Cov specific neutralizing antibod*" or "MERS-Cov specific neutralizing antibod*" or "Anti C5a monoclonal antibod*").tw.
25	acetylcysteine/ or exp angiotensin receptor antagonist/ or exp angiotensin derivative/ or exp dipeptidyl carboxypeptidase inhibitor/ or citrate potassium/ or glycyrrhizic acid/ or dipyridamole/ or hydrogen peroxide/ or polyinosinic polycytidylic acid/ or thymosin/ or ascorbic acid/
26	(Acetylcysteine or Angiotensin or Angiotensin or "ACE inhibitor*" or ACE-2 or "Angiotensin II receptor blocker*" or ARBs or "potassium citrate" or Bromhexine or "Diammonium glycyrrhizinate" or Glycyrrhizic or Dipyridamole or Ebastine or "Hydrogen peroxide" or Pirfenidone or Polyinosinic-polycytidylic or "Polyinosinic-polycytidylic" or "Poly I-C" or "rhG-CSF" or Thymosin* or Tranilast or "Vitamin C" or "Ascorbic Acid*").tw.
27	("inhal*" adj2 gas*).tw.
28	Cyclosporine/

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29	(Cyclosporin or cequa or "cgc 1072" or "cgc1072" or ciclomulsion or cyclasol or de076 or deximune or implanta or imusporin or neuro-stat or neurostat or opsisporin or "otx 101" or padciclo or papilock or "sp 14019" or verkazia).tw.
30	Fenretinide/
31	(fenretinide or "mcn r 1967" or "4 hydroxyphenylretinamide" or Ifendopril).tw.
32	Dalteparin/ or enoxaparin/ or tinzaparin/ or fondaparinux/ or edoxaban/ or rivaroxaban/ or apixaban/ or betrixaban/ or heparin/ or danaparoid/ or warfarin/ or dabigatran.hw.
33	(dalteparin or fragmin* or "low liquemin" or enoxaparin or clexan or clexane or inhixa or lexane or lovenox or neoparin or neoparin-nx or thorinane or tinzaparin or innohep or logiparin or fondaparinux or quixidar or dabigatran or edoxaban or lixiana or roteas or savaysa or rivaroxaban or xarelto or "bay 59 7939" or apixaban or eliques or eliquis or warfarin or adoisine or carfin or coumadan or coumadin* or marevan or panwarfarin or panwarfin or sofarin or warnerin or betrixaban or bevyxxa or dexxience or heparin or Disebrin or hepalean or lipo-hepin or menaven or multiparin or nevparin or panheparin or panheprin or praecivenin or thrombareduct or thromboliquine or vetren or danaparoid or lomoparan or orgaran).tw.
34	(Azilsartan or candesartan or eprosartan or Irbesartan or telmisartan or valsartan or losartan or olmesartan).hw. or cobicistat/ or losartan/
35	(Azilsartan or Edarbi or "tak 536" or tak536 or candesartan or amcandin or amlodipine or amlopres or camlostar or candam or candeamio or candezek or caramlo or framsyl or unisia or zenicamo or Atacand or eprosartan or epratenz or futuran or naviten or navixen or regulaten or "skf 108566" or "skf108566" or tevesten or tevetan or teveten or tevetenz or Irbesartan or irbertan or Avapro or telmisartan or approvel or aprovel or "arbez lr" or avapro or ifirmasta or irban or irbetan or iretensa or irovel or irvell or karvea or sabervel or Micardis or valsartan or Diovan* or Prexxartan or saval or losartan or Cozaar or entrizen or lavestra or lorista or Olmesartan or Benicar or sarten or entresto or sacubitril or valsartan or byvalson or nebivolol or Aviptadil or Losartan or cozaar or cobicistat or tybost or actelsar or kinzal mono or kinzalmono or micardis or predxal or pritor or pritoral or semintra or telma-20 or tolura or angiosan or cordinate or dalzad ordiovan or diovane or kalpress or miten or nisis or prexxartan or provas or rixil or saval or tareg or tazea or troval or valpression or vals or valsocard or valtan or valtsu or alteis or belsar or benetor or benevas or benicar or cs866 or ixia or laresin or mencord or mesar or olartan or olmeblo or olmec or olmes or Olmesartan or olmetec or olpresor olsar or omesar or openvas or plaunac or rnh6270 or santini or sarten or tensar or tensiol or vivactra or votum or byvalson or cozaar).tw.
36	(benazepril or Captopril or Cilazapril or Enalapril or Fosinopril or Lisinopril or Perindopril Quinapril or Ramipril or Trandolapril).hw.
37	(Benazepril or Lotensin or Captopril or Benace or boncordin or briem or brien or "cgs 148241" or "cgs 14824a" or "cgs148241" or "cgs14824a" or cibace or cibacen* or fortekor or lotensin or tenkuoren or zinadril or ace-bloc or acenorm or acepress or acepril or aceprilex or aceril or aceten or adocor or alopresin or altran or apuzin or asisten or capace or capocard or caposan or capoten* capotril or capril or captace or captensin or capti or captoflux or captohexal or captolane or captomax or capton or captopren or captoprilan or captoril or captral or cardiopril or cardipril or

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	catona or catoplin or catopril or cesplon or cryopril or debax or dexacap or dextro captopril or ecapres or ecaten or epicordin or epsitron or farcopril or farmoten or hiperil or hypopress or hypotensor or insucar or iopril or isopresol or katopil or ketanine or keyerpril or lapril or locap or lopirin or lopril or medepres or midrat or minitent or nolectin or "oltens ge" or petacilon or praten or primace or rilcapton or ropril or smarten or tenofax or tensicap tensiomen or tensiomin or tensobon or tensoprel or tensoril or tenzib or topace or toprilem or typril-ace or vasosta or zapto or orkaptil or Cilazapril or dynorm or inhibace or inibace or initiss or inocar).tw.
38	(justor or vascace or Enalapril or Vasotec or bpnorm or dynacil or eliten or fosenopril or fosinil or fosinonorm or fosinopril or fosinorm or fosipres or fositen or fositens or fovas or fozitec or monopril or newace or sapril or sq28555 or staril or vasopril or acerbon or alapril or alfaken or carace or cipril or coric or dapril or fibsol or inopril or linopril or linvas or lipril or lisi abz orlisibeta or lisigamma or lisihexal or lisinopril dihydrate or lisipril or lisodur or lisopress or lisopril orlisoril or lispril or listril or lysinopril or "mk 0521" or "mk 521" or "mk 522" or "mk0521or mk521" or "mk522" or noperten or novatec or presiten or prinil or prinivil or qbrelis or sinopril or tensopril or tensyn or vivatec or zestomax or zestril or Monopri or Lisinopril or Prinivil or Zestril or Perindopril or Coversyl or Quinapril or Accupril or accuprin or accupro or accupron or acequin or acuitel or acuprel or acupril or asig or "ci906" or conan or ectren or korec or quinalapril or quinaten or quinazi or quinhexal or quinipril or Ramipril or acovil or altace or carasel or cardace or corpril or delix or "hoe 498" or hypren or hytren or lostapres or ramace or ramilich or triatec or tritace or unipril or vesdil or vivace or Altace or Trandolapril or Mavik or gopten or Odace or odric or udrik).tw.
39	Colistin/ or (Teicoplanin or Ivermectin or azithromycin).hw.
40	(Colistin or belcomycin or colimycin* or belcomycin or Colicort or colimycin or colistine or colomycin or coly mycin or colymicin or multimycin or polymyxin or Teicoplanin or planium or tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichoplanin or teichoplanine or teicomid or teicopix or teiplamil or Planium or Tagocid or talinac or tapocin or targocid or targoplanin or targosid or teichomycin or teichomycin or teichoplanin* or teicomid or teicopix or teiplamil or Ivermectin or Avermectin or cardomec or diapec or efacti or epimekor or eqvalan or eqvalenor or ivermectina or ivermectol or ivexterm or ivomec or mectizan or "mk 933" or "mk933" or oramec or quanox or revectina or securo or sklice or soolantra or stromectol or azithromycin or aruzilina or atizor or azadose or azasite or azatril or azenil or azibiot or azimin or azithral or azithromycin or azitrocin or azitromax azitromicin* or aziwok or azomyne or aztrin or azydrop or azyter or azithromycin or bazyt or "cp 62933" or "cp 62993" or "cp62933" or "cp62993" or erythromycin or Forcin or Inedol or infectoazit or "isv 401" or "isv401" or kromicin or macrozit or mezatrin or octavax or ordipha or ribotrex or sumamed or tobyl or tromix or trozocina or ultreon or vinzam or xithrone or "xz 450" or "xz450" or Zaret or Zarom or zetamax or zeto or zibramax or zifin or zimericina or zistic or zithromax or zithrox or zitinn or zitrim or zitrobifan or zitrocin or zitromax or zmax).tw.
41	Tamoxifen.hw. or dasatinib/ or Epirubicin/ or Gemcitabine/ or Homoharringtonin/ or Imatinib/ or toremifene/ or Valrubicin/
42	(dasatinib or Ellence or Epirubicin* or epid or epifil or epiham or epilem or epirubicine or farmorrubicina or farmorubicin or pharmorubicin or Gemcitabine or difluorodeoxycytidine or Gemcite or gemtro or gemzar or infugem or "ly188011" or Homoharringtonine or harringtonine

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	or omacetaxine or ceflatonin or omapro or synribo or Imatinib or "cgp 57148" or "cgp57148b" or gleevac or gleevec or glivec or glivic or ruvise or Tamoxifen or ebefen or kessar or tamoplac or tamoxasta or tamoxifene or toremifene or estrimex or fareston or fc1157a or Valrubicin or valstar or valtaxin).tw.
43	Disulfiram/ or Emetine/ or Clomipramine/ or Loperamide/ or Caspofungin/ or Terconazole/ or Colchicine/ or Promethazine/ or Azelastine/ or Aprepitant/ or Chlorpromazine/ or Icatibant/ or Bepotastine/ or prostacyclin/ or Vapreotide/ or Conivaptan/ or Nitric oxide/ or (Perphenazine or Metformin).hw.
44	(Disulfiram or antabus or Antabuse or esperal or disulfizam or Emetine or Emetin or Clomipramine or Anafranil or anafranilin or anafranyl or clomicalm or hydiphen or Loperamide or immodium or Caspofungin or Cancidas or Terconazole or fungistat or terazol or "r 42470or Colchicine" or colchysat or mitigare or "nsc 757" or Promethazine or allerfen or antiallersin or atosil or fenergan or hiberna or Phenergan or Pipolphen or Prothazine or Romergan or Sayomol or Azelastine or Astelin or "a5610 or afluon" or alerdual or alergodil or allergodrop or allergospray or allespray or allestin or astepro or azedil or azelamed or azelavision or azep or azeptin or carelastin or corifina or "e 0659" or "e0659" or lasticom or lastin or lastinaz or loxin or oculastin or optivar or pollival or proallergodil or radethacin or radethazin or rhinolast or rinelaz or tebarat or visuzel or vividrin or vivispray or Aprepitant or cinvanti or emend or aprepitant or "l754030" or "mk 0869" or "ono7436").tw.
45	(Perphenazine or decentan or etaperazine or ethaperazine or "sch 3940" or thilatazin or tranquisan or trifalon or trilafan or trilafon or trilifan or triliphan or Chlorpromazine or hibernal or contomin or largactil or megaphen or neurazine or plegomazin or promacid or promapar or propaphenin or solidon or sonazine or taroctil or "thor prom" or thorazine or vegetamin or zuledin or Icatibant or firazyr or Metformin or diabetosan or diabex or dianben or diformin or fluamine or flumamine or fortamet or glifage or gliguanid or glucoformin or gluconil or glucophage or glucophage-mite or glucostop or glukophage or glumetza or haurymellin or meguan or merckformin or metforal or metformax or metiguanide or riomet or risidon or siofor or Bepotastine or bepreve or talion or Epoprostenol or prostacyclin or caripul or cycloprostin or epoprostenol or flolan or Vapreotide or docrised or octastatin or Conivaptan or vaprisol or "Nitric oxide" or inomax or noxivent).tw.
46	(convalescence/ and plasma transfusion/) or (Convalesc* adj2 plasma).tw.
47	Natural killer cell/ or exp mesenchymal stem cell/
48	("Recombinant human ACE-2" or "APN0" or "Natural killer cell" or "natural killer cells" or "NK cell" or "NK cells" or mesenchymal).tw.
49	Arbidol/ or Galidesivir/
50	(arbidol or Galidesivir or "immucillin A bcx4430" or "bcx 4430").tw.
51	n methyl dextro aspartic acid receptor blocking agent/
52	("n methyl dextro aspartic acid receptor" or "n methyl d aspartate a" or " NMDA antagonist*" or " NMDA inhibitor*" or " NMDA block*" or " NMDA receptor*").tw.

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53	or/7-52
54	6 and 53
55	exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.
56	55 not human/
57	54 not 56
58	limit 57 to dd=20210131-20210518
59	limit 58 to yr="2021"

Search run on July 9, 2021 using the Ovid platform, Embase database. Search was limited by date range, from January 31, 2021 to May 18, 2021, and run in database to update an existing search from May 01, 2020 to January 31, 2021.

Appendix 3. List of drugs from Health Canada and Public Health Agency of Canada

Categories	Drug names/descriptions
ACE Inhibitors	• Benazepril (Lotensin), Captopril (Capoten), Cilazapril (Inhibace), Enalapril (Vasotec), Fosinopril (Monopril), Lisinopril (Prinivil, Zestril), Perindopril (Coversyl), Quinapril (Accupril), Ramipril (Altace), Trandolapril (Mavik)
Angiotensin II Receptor Blocker (ARB)	• Azilsartan (Edarbi), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), telmisartan (Micardis), valsartan (Diovan, Prexxartan), losartan (Cozaar), olmesartan (Benicar), entresto (sacubitril/valsartan), byvalson (nebivolol/valsartan),
Antibiotics/antiparasitic	• Suramin, Carriomycin, Suramin sodium, Colistin, Teicoplanin, Ivermectin, azithromycin
Antibodies	• SARS-Cov-2 specific neutralizing antibodies • Bevicizumab, Ruxolitinib, Tocilizumab, Adalimumab, Camrelizumab, Eculizumab, Mepolizumab, "PD-1 mAb", Tocilizumab, tozumab, abciximab (Reopro), adalimumab (Humira/Amjevita), alefacept (Amevive), alemtuzumab (Campath), basiliximab (Simulect), belimumab (Benlysta), bezlotoxumab (Zinplava), canakinumab (Ilaris), certolizumab (Cimzia), cetuximab (Erbitux), daclizumab (Zenapax/Zinbryta), denosumab (Prolia/Xgeva), efalizumab (Raptiva), golimumab (Simponi), inflectra (Remicade), ipilimumab (Yervoy), ixekizumab (Taltz), natalizumab (Tysabri), nivolumab (Opdivo), olaratumab (Lartruvo), omalizumab (Xolair), palivizumab (Synagis), panitumumab (Vectibix), pembrolizumab (Keytruda), rituximab (Rituxan), tocilizumab

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	(Actemra/ RoActemra), trastuzumab (Herceptin), secukinumab (Cosentyx), ustekinumab (Stelara), Meplazumab
Anticancer/chemotherapy	• Dasatinib, Epirubicin, Gemcitabine hydrochloride, Homoharringtonine, Imatinib mesylate, Tamoxifen, Toremifene, Valrubicin
Anticoagulants	• dalteparin, enoxaparin, tinzaparin, fondaparinux heparin, dabigatran, edoxaban, rivaroxaban, apixaban, warfarin, betrixaban, heparin, danaparoid
Antimalarials	• Amodiaquine, Basoquin, Camoquin, Flavoquine, Chloroquine, Resochin, Dawaquin, Lariago, Aarlen, Hydroxychloroquine, Hydroxy-chloroquine, Plaquenil, Hydroquin, Axemal, Dolquine, Quensyl, Quinoric, Imiquimiod, Aldara, Vyloma,, Zyclara, Primaquine, Jasoprim, Malirid, Neo-Quipenyl, Pimaquin, Pmq, Primachina, Primacin, Primaquina, Primaquine, Primaquine, Remaquin, Tafenoquine, Krinfatel, Kozenis, Arakoda, Krintafel, Pamaquine, Plasmochin, Plasmoquine, Plsamaguine, Neo-Quipenyl, Primachin, Dihydroartemisinin, mefloquine, Nitazoxanide, Nitrothiazole
Antiviral – Direct acting	• Protease inhibitors: boceprevir, telaprevir, lopinavir, ritonavir, lopinavir/ritonavir (Kaletra), darunavir/cobicistat (Prezcobix), indinavir (Crixivan), saquinavir (Invirase) • Integrase inhibitors: raltegravir, elvitegravir, dolutegravir • Entry (fusion) inhibitors: maraviroc (celsentri) • Nucleoside reverse transcriptase inhibitors: abacavir, ziagen, emtricitabine, emtriva, lamivudine, epivir, tenofovir (Viread), zidovudine, azidothymidine, retrovir • Nonnucleoside reverse transcriptase inhibitors : , doravirine, pifeltro, efavirenz, sustiva, etravirine, intelence, nevirapine, viramune, rilpivirine, edurant • Acyclic nucleoside phosphonate analogues: cidofovir diphosphates • Acyclic guanosine analogues: acyclovir • Pyrophosphate analogues: foscarnet, fomivirsen • Oligonucleotides • Nucleotide analog inhibitor: sofusbivir • Nucleoside inhibitor: ribavirin (Ibavyr) • Matrix 2 protein inhibitors: amantadine • RNA polymerase inhibitors: Rimantadine • Neuraminidase inhibitors: oseltamivir (Tamiflu), peramivir (Rapivab), zanamivir (Relenza) • Antiretrovirals: ASC09, Azvudine, Danoprevir, Darunavir, Lopinavir, ritonavir, Remdesivir
Antiviral – Other	• Baloxavir, marboxil, EIDD-2801
Antivirals – Broad spectrum	• Favipiravir, Triazavirin, Umifenovir (arbidol hydrochloride), Galidesivir

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Immune support/modulating	• Convalescent plasma • Recombinant human ACE-2: APN01 • Natural killer (NK) cells • Mesenchymal stem cells • Interferons: Interferon-alpha, Interferon-beta, Interferon-gamma, interferon β – 1b (Betaseron/Extavia), interferon beta – 1a (Rebif) • Intravenous Immunoglobulin: Flebogamma DIF; Gamunex; Globulin-N; Globulin N; Intraglobin; Intraglobin F, Gammagard; Gamimune; Gamimmune, Privigen; Sandoglobulin; Venoglobulin; Venoglobulin-I; Venoglobulin I; Venimmune; Iveegam; Alphaglobin; Endobulin; Gamimune N; Gamimmune N; Gammonativ
Interleukin Inhibitors	• Interleukin (IL)-1 Inhibitor: Anakinra • Interleukin (IL)-6 Inhibitors: Sarilumab (Kevzara); Siltuximab • Anti-Tumor necrosis factor-alpha (anti-TNF-alpha) • Anti-Granulocyte-macrophage colony-stimulating factor (anti-GM-CSF)
Kinase Inhibitors	• Baricitinib, Acalabrutinib (Calquence), Fedratinib, Ruxolitinib, Jakotinib, Ruxolitinib, Sunitinib, Erlotinib
Nonspecific anti-inflammatory and immunosuppressive drugs	• Fingolimod Hydrochloride, Leflunomide, Thalidomide, Methylprednisone, Prednisolone, Fluprednisolone, Corticosteroids, Cyclosporin A, Glycyrrhizic Acid/Glycyrrhizic
Other	• Disulfiram (acetaldehyde dehydrogenase inhibitor), Emetine (alkaloid emetic), Clomipramine (antidepressant), Loperamide (antidiarrheal), Caspofungin (antifungal), Terconazole (antifungal), Colchicine (anti-gout agent), Promethazine hydrochloride (antihistamine), Azelastine (antihistamine), Aprepitant (anti-nausea/antiemetic), Perphenazine (antipsychotic), Chlorpromazine hydrochloride (antipsychotic), Icatibant (Bradykinin B2 Receptor Antagonists), Metformin (diabetes), Bepotastine (histamine 1 antagonist), Epoprostenol (prostaglandin), Vapreotide (somatostatin), Conivaptan (vasopressin inhibitor), Nitric oxide (vasodilator), Acetylcysteine (prodrug), Potassium citrate (alkalinizer), Dipyridamole (vasodilator), Hydrogen peroxide, Cobicistat (Tybost), Bromhexine (mucolytic), Ebastine (H1 receptor agonist), Pirfenidone (antifibrotic), Polyinosinic-polycytidylic (Poly I-C), rhG-CSF, Thymosin, Tranilast, Ascorbic Acid, Aviptadil (neuropeptide), Ifendopril (NMDA inhibitor), fenretinide (synthetic rentinoid), famotidine (H2 receptor antagonist)

Appendix 4. List of included primary studies

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Appendix 5. List of included knowledge syntheses.

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Appendix 6. Additional details for the Results section

Figure A1. Word cloud of description of study participants

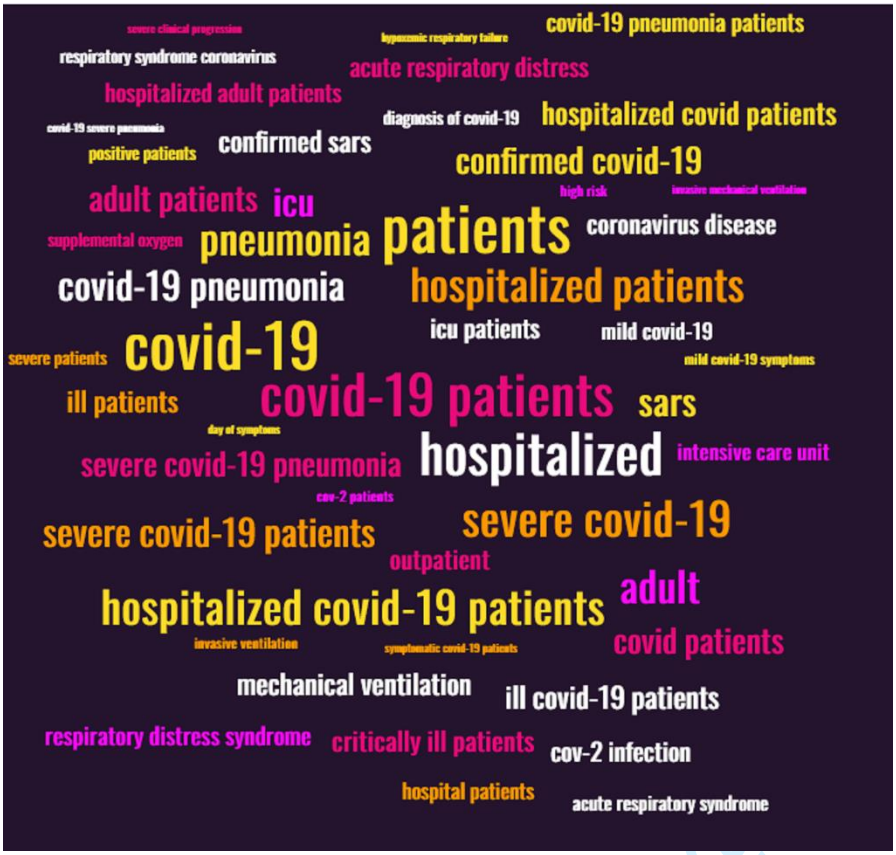

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Table A1. Country of primary study conduct

Country	Total	RCT	Non-RCT
Total	**616**	**188**	**428**
USA	161 (26)	37 (20)	124 (29)
China	107 (17)	27 (14)	80 (19)
Italy	47 (8)	2 (1)	45 (11)
Spain	41 (7)	3 (2)	38 (9)
France	39 (6)	5 (3)	34 (8)
India	23 (4)	15 (8)	8 (2)
Iran	21 (3)	15 (8)	6 (1)
United Kingdom	21 (3)	19 (10)	2 (0)
Brazil	17 (3)	13 (7)	4 (1)
Turkey	12 (2)	1 (1)	11 (3)
Mexico	11 (2)	6 (3)	5 (1)
Argentina	10 (2)	7 (4)	3 (1)
The Netherlands	8 (1)	2 (1)	6 (1)
Greece	6 (1)	2 (1)	4 (1)
Pakistan	6 (1)	4 (2)	2 (0)
Russia	6 (1)	1 (1)	5 (1)
Belgium	5 (1)	1 (1)	4 (1)
Egypt	5 (1)	4 (2)	1 (0)
Saudi Arabia	5 (1)	0 (0)	5 (1)
Bangladesh	4 (1)	2 (1)	2 (0)
Singapore	4 (1)	0 (0)	4 (1)
South Korea	4 (1)	0 (0)	4 (1)
Bahrain	3 (0)	2 (1)	1 (0)
Canada	3 (0)	3 (2)	0 (0)
Denmark	3 (0)	2 (1)	1 (0)
Germany	3 (0)	1 (1)	2 (0)
Iraq	3 (0)	2 (1)	1 (0)
Oman	3 (0)	1 (1)	2 (0)
Poland	3 (0)	0 (0)	3 (1)
United Arab Emirates	3 (0)	0 (0)	3 (1)
Austria	2 (0)	0 (0)	2 (0)
Chile	2 (0)	2 (1)	0 (0)
Cuba	2 (0)	1 (1)	1 (0)
Ireland	2 (0)	0 (0)	2 (0)
Israel	2 (0)	0 (0)	2 (0)
Qatar	2 (0)	1 (1)	1 (0)
Sweden	2 (0)	0 (0)	2 (0)
Australia	1 (0)	1 (1)	0 (0)
Columbia	1 (0)	1 (1)	0 (0)
Hong Kong	1 (0)	0 (0)	1 (0)
Indonesia	1 (0)	1 (1)	0 (0)
Kuwait	1 (0)	0 (0)	1 (0)
Nigeria	1 (0)	1 (1)	0 (0)

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Country	Total	RCT	Non-RCT
Total	**616**	**188**	**428**
Norway	1 (0)	1 (1)	0 (0)
Peru	1 (0)	0 (0)	1 (0)
Philippines	1 (0)	0 (0)	1 (0)
Romania	1 (0)	0 (0)	1 (0)
Suriname	1 (0)	0 (0)	1 (0)
Switzerland	1 (0)	0 (0)	1 (0)
Taiwan	1 (0)	1 (1)	0 (0)
Thailand	1 (0)	0 (0)	1 (0)
WHO - 30 countries	1 (0)	1 (1)	0 (0)

Notes: Values are numbers of primary studies and related percentages.

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Table A2. Treatment evaluated in primary studies

	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Tocilizumab	87 (14%)	12 (6%)	75 (17%)
Hydroxychloroquine	78 (12%)	22 (12%)	56 (13%)
Convalescent Plasma	55 (9%)	15 (8%)	40 (9%)
Steroid	37 (6%)	1 (1%)	36 (8%)
Lopinavir/Ritonavir	29 (5%)	5 (3%)	24 (5%)
Methylprednisolone	26 (4%)	3 (2%)	23 (5%)
Remdesivir	25 (4%)	16 (8%)	9 (2%)
Enoxaparin	18 (3%)	1 (1%)	17 (4%)
Hydroxychloroquine/Azithromycin	18 (3%)	2 (1%)	16 (4%)
Anakinra	16 (3%)	2 (1%)	14 (3%)
Dexamethasone	16 (3%)	4 (2%)	12 (3%)
Anticoagulant-Therapeutic	15 (2%)	2 (1%)	13 (3%)
Azithromycin	15 (2%)	6 (3%)	9 (2%)
Anticoagulant-Prophylactic	11 (2%)	0 (0%)	11 (3%)
Ivermectin	11 (2%)	9 (5%)	2 (0%)
Heparin	9 (1%)	0 (0%)	9 (2%)
Favipiravir	8 (1%)	6 (3%)	2 (0%)
Sarilumab	8 (1%)	7 (4%)	1 (0%)
Colchicine	7 (1%)	4 (2%)	3 (1%)
Glucocorticoids	7 (1%)	0 (0%)	7 (2%)
Bamlanivimab	6 (1%)	4 (2%)	2 (0%)
Chloroquine	6 (1%)	2 (1%)	4 (1%)
Intravenous Immunoglobulin	6 (1%)	4 (2%)	2 (0%)
Mesenchymal Stem Cells	6 (1%)	4 (2%)	2 (0%)
Steroid	6 (1%)	0 (0%)	6 (1%)
Thymosin-Alpha1	6 (1%)	1 (1%)	5 (1%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Vitamin C	6 (1%)	4 (2%)	2 (0%)
Antiviral	5 (1%)	0 (0%)	5 (1%)
Arbidol	5 (1%)	2 (1%)	3 (1%)
Aspirin	5 (1%)	0 (0%)	5 (1%)
Interferon	5 (1%)	3 (2%)	2 (0%)
Prednisone	5 (1%)	1 (1%)	4 (1%)
Statins	5 (1%)	0 (0%)	5 (1%)
Antibiotic	4 (1%)	0 (0%)	4 (1%)
Anticoagulant	4 (1%)	0 (0%)	4 (1%)
Hydrocortisone	4 (1%)	2 (1%)	2 (0%)
Lopinavir/Ritonavir/Hydroxychloroquine	4 (1%)	0 (0%)	4 (1%)
Ribavirin	4 (1%)	0 (0%)	4 (1%)
Therapeutic Plasma Exchange	4 (1%)	0 (0%)	4 (1%)
Vitamin D	4 (1%)	3 (2%)	1 (0%)
Acei|Arb	3 (0%)	0 (0%)	3 (1%)
Baricitinib	3 (0%)	1 (1%)	2 (0%)
Casirivimab/Imdevimab	3 (0%)	2 (1%)	1 (0%)
Famotidine	3 (0%)	0 (0%)	3 (1%)
Interferon-Alpha-2b	3 (0%)	0 (0%)	3 (1%)
Interferon Alpha-2b	3 (0%)	1 (1%)	2 (0%)
Lenzilumab	3 (0%)	2 (1%)	1 (0%)
Lopinavir/Ritonavir/Interferon-Alpha	3 (0%)	0 (0%)	3 (1%)
Neutralizing Antibody	3 (0%)	1 (1%)	2 (0%)
Zinc Iv	3 (0%)	3 (2%)	0 (0%)
Acei|Arb|Statin	2 (0%)	0 (0%)	2 (0%)
Avifavir	2 (0%)	2 (1%)	0 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Canakinumab	2 (0%)	0 (0%)	2 (0%)
Ceftriaxone	2 (0%)	0 (0%)	2 (0%)
Chlorpromazine	2 (0%)	0 (0%)	2 (0%)
Corticosteroids/Tocilizumab	2 (0%)	0 (0%)	2 (0%)
Darunavir/Cobicistat	2 (0%)	1 (1%)	1 (0%)
Fondaparinux	2 (0%)	0 (0%)	2 (0%)
Functional Inhibition Of Acid Sphingomyelinase	2 (0%)	0 (0%)	2 (0%)
Haloperidol	2 (0%)	0 (0%)	2 (0%)
Heparin-Prophylaxis	2 (0%)	0 (0%)	2 (0%)
Inhaled Budesonide	2 (0%)	2 (1%)	0 (0%)
Interferon Beta-1b	2 (0%)	0 (0%)	2 (0%)
Interferon Kappa/Trefoil Factor 2	2 (0%)	2 (1%)	0 (0%)
Interferon Lambda-1a	2 (0%)	2 (1%)	0 (0%)
Interlukin-6 Inhibitors	2 (0%)	0 (0%)	2 (0%)
Itolizumab	2 (0%)	2 (1%)	0 (0%)
Ivermectin/Doxycycline	2 (0%)	2 (1%)	0 (0%)
Leflunomide	2 (0%)	0 (0%)	2 (0%)
Lopinavir	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Azithromycine	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Doxycline	2 (0%)	2 (1%)	0 (0%)
Lopinavir/Ritonavir/Ribavirin/Interferon Beta-1b	2 (0%)	1 (1%)	1 (0%)
Mavrilimumab	2 (0%)	1 (1%)	1 (0%)
Methylprednisolone/Tocilizumab	2 (0%)	0 (0%)	2 (0%)
Neuromuscular Blocking Agents	2 (0%)	0 (0%)	2 (0%)
Nitazoxanide	2 (0%)	2 (1%)	0 (0%)
Oseltamivir	2 (0%)	0 (0%)	2 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Prednisolone	2 (0%)	0 (0%)	2 (0%)
Ribavirin/Interferon-Alpha	2 (0%)	0 (0%)	2 (0%)
Statin	2 (0%)	0 (0%)	2 (0%)
Stem Cell Nebulization	2 (0%)	0 (0%)	2 (0%)
Steroid-Pulse	2 (0%)	0 (0%)	2 (0%)
Tocilizumab/Methylprednisolone	2 (0%)	0 (0%)	2 (0%)
Tocilizumab/Steroid	2 (0%)	0 (0%)	2 (0%)
Umifenovir	2 (0%)	0 (0%)	2 (0%)
Vitamin C/Zinc	2 (0%)	2 (1%)	0 (0%)
Acyclovir	1 (0%)	0 (0%)	1 (0%)
Amantadine	1 (0%)	0 (0%)	1 (0%)
Amoxicillin	1 (0%)	0 (0%)	1 (0%)
Anakinra/Intravenous Immunoglobulin	1 (0%)	0 (0%)	1 (0%)
Anakinra/Methylprednisolone	1 (0%)	0 (0%)	1 (0%)
Antiviral/Antiviral/Antibiotics	1 (0%)	0 (0%)	1 (0%)
Apixaban-Prophylaxis	1 (0%)	0 (0%)	1 (0%)
Apixaban-Therapeutic	1 (0%)	0 (0%)	1 (0%)
Aprepitant	1 (0%)	1 (1%)	0 (0%)
Arbidol/Hydroxycholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Artemisinin-Piperaquine	1 (0%)	0 (0%)	1 (0%)
Auxora	1 (0%)	1 (1%)	0 (0%)
Azithromycin/Hydroxychloroquine	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Prednisolone/Naproxen/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Azvudine	1 (0%)	1 (1%)	0 (0%)
Bacillus Calmette–Guérin Vaccine	1 (0%)	1 (1%)	0 (0%)
Baloxavir Marboxil	1 (0%)	1 (1%)	0 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Bamlanivimab/Etesevimab	1 (0%)	1 (1%)	0 (0%)
Baricitinib/Remdesivir	1 (0%)	1 (1%)	0 (0%)
Berinert	1 (0%)	0 (0%)	1 (0%)
Betamethasone	1 (0%)	1 (1%)	0 (0%)
Bevacizumab	1 (0%)	0 (0%)	1 (0%)
Bromhexine/Hydrochloride	1 (0%)	1 (1%)	0 (0%)
Bromhexine/Hydrochloride/Antiviral	1 (0%)	1 (1%)	0 (0%)
Bromhexine/Spironolactone	1 (0%)	0 (0%)	1 (0%)
Camostat Mesilate	1 (0%)	1 (1%)	0 (0%)
Cerc-002	1 (0%)	1 (1%)	0 (0%)
Choloroquine	1 (0%)	1 (1%)	0 (0%)
Cigb-325	1 (0%)	1 (1%)	0 (0%)
Clarithromycin	1 (0%)	0 (0%)	1 (0%)
Cortecosteroid/Tocilizumab	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Lopinavir/Ritonavir/Interferon Alpha	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Ns-Immunosuppresant	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/Anakinra	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/Baricitinib	1 (0%)	0 (0%)	1 (0%)
Cotrimoxazole	1 (0%)	0 (0%)	1 (0%)
Cyclooxygenase-2	1 (0%)	0 (0%)	1 (0%)
Cyclosporine A	1 (0%)	0 (0%)	1 (0%)
Dexamethasone/Tofacitinib	1 (0%)	0 (0%)	1 (0%)
Diphenhydramine/Ammonium Chloride	1 (0%)	1 (1%)	0 (0%)
Doxycycline	1 (0%)	1 (1%)	0 (0%)
Dutasteride	1 (0%)	1 (1%)	0 (0%)
Eculizumab	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Epoprostenol - Aerosolized	1 (0%)	0 (0%)	1 (0%)
Equine Polyclonal Antibodies	1 (0%)	1 (1%)	0 (0%)
Favipiravir/Chloroquine|Hydroxychloroquine/Lopinavir/ Ritonavir Or Darunavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Chloroquine|Hydroxychloroquine/Lopinavir/ Ritonavir|Darunavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Interferon Beta-1b	1 (0%)	1 (1%)	0 (0%)
Firazyr	1 (0%)	0 (0%)	1 (0%)
Flash Frozen Plasma	1 (0%)	1 (1%)	0 (0%)
Fluticasone Spray/Triamcinolone	1 (0%)	0 (0%)	1 (0%)
Fluvoxamine	1 (0%)	1 (1%)	0 (0%)
Glucocorticoids/Interferon	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine Or Chloroquine	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Lopinavir/Ritonavir/Azithromycin	1 (0%)	1 (1%)	0 (0%)
Hydroxycholoroquine/Favipiravir	1 (0%)	0 (0%)	1 (0%)
Hydroxycholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Hydroxyzine	1 (0%)	0 (0%)	1 (0%)
Inhaled Adenosine	1 (0%)	0 (0%)	1 (0%)
Inhaled Corticosteroid	1 (0%)	0 (0%)	1 (0%)
Inhaled Nitric Oxide	1 (0%)	1 (1%)	0 (0%)
Interferon-B 1a/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b/Arbidol	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Interferon Beta-1a	1 (0%)	1 (1%)	0 (0%)
Itraconazole	1 (0%)	1 (1%)	0 (0%)
Ivermectin/Azithromycin	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Leflunomide/Interferon Alpha 2a	1 (0%)	1 (1%)	0 (0%)
Levamisole	1 (0%)	1 (1%)	0 (0%)
Levofloxacin	1 (0%)	0 (0%)	1 (0%)
Linezolid	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Hydroxychloroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir Or Hydroxycholoroquine+Prednisone	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Chloroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon-Alpha/Abidor|Ribavirin|Cholroquine	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon Beta-2b	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Interferon/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Novaferon	1 (0%)	0 (0%)	1 (0%)
Lopinavir/Ritonavir/Novaferon/Interferon	1 (0%)	0 (0%)	1 (0%)
Losartan	1 (0%)	1 (1%)	0 (0%)
Meplazumab	1 (0%)	0 (0%)	1 (0%)
Meropenem	1 (0%)	0 (0%)	1 (0%)
Mesenchymal Stromal Cells	1 (0%)	0 (0%)	1 (0%)
Methylprednisolone/Dexamethasone	1 (0%)	0 (0%)	1 (0%)
Methylprednisolone/Ivig	1 (0%)	1 (1%)	0 (0%)
Multi-Mechanism Approach	1 (0%)	0 (0%)	1 (0%)
Nebulised Interferon Beta-1a	1 (0%)	1 (1%)	0 (0%)
Nitazoxanide/Azithromycin	1 (0%)	1 (1%)	0 (0%)
Nitazoxanide/Doxycycline	1 (0%)	1 (1%)	0 (0%)
Olokizumab	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Opaganib	1 (0%)	0 (0%)	1 (0%)
Otilimab	1 (0%)	1 (1%)	0 (0%)
Pentoxifylline	1 (0%)	1 (1%)	0 (0%)
Pipamperone And Citalopram	1 (0%)	1 (1%)	0 (0%)
Piperacillin	1 (0%)	0 (0%)	1 (0%)
Polymerized-Collagen	1 (0%)	1 (1%)	0 (0%)
Poractant Alfa	1 (0%)	0 (0%)	1 (0%)
Progesterone	1 (0%)	1 (1%)	0 (0%)
Prophylactic Anticoagulant	1 (0%)	0 (0%)	1 (0%)
Proxalutamide	1 (0%)	1 (1%)	0 (0%)
Pyridostigmine	1 (0%)	1 (1%)	0 (0%)
Recombinant Interleukin-2	1 (0%)	0 (0%)	1 (0%)
Remdesivir/Corticosteroid	1 (0%)	0 (0%)	1 (0%)
Ribavarin/Lopinavir/Ritonavir/Interferon-Alpha	1 (0%)	0 (0%)	1 (0%)
Ribavirin/Arbidol/Hydroxicholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Ribavirin/Hydroxicholoroquine/Lopinavir/Ritonavir	1 (0%)	0 (0%)	1 (0%)
Rimantadine	1 (0%)	0 (0%)	1 (0%)
Ruxolitinib	1 (0%)	0 (0%)	1 (0%)
Sofosbuvir/Daclatasvir	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Daclatasvir/Hydroxychloroquine	1 (0%)	1 (1%)	0 (0%)
Sofosbuvir/Ledipasvir	1 (0%)	1 (1%)	0 (0%)
Soludexide	1 (0%)	1 (1%)	0 (0%)
Sulodexide	1 (0%)	1 (1%)	0 (0%)
Telmisartan	1 (0%)	1 (1%)	0 (0%)
Theophylline/Pentoxifylline	1 (0%)	0 (0%)	1 (0%)
Tocilizumab/Convalescent Plasma	1 (0%)	0 (0%)	1 (0%)

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	Total	RCT	Non-RCT
Total	**630**	**190**	**440**
Tocilizumab/Favipiravir	1 (0%)	1 (1%)	0 (0%)
Toxilizumab/Steroids/Anakinra/Baricitinib	1 (0%)	0 (0%)	1 (0%)
Triazavirin	1 (0%)	1 (1%)	0 (0%)
Vermectin/Doxycycline	1 (0%)	1 (1%)	0 (0%)
Vilobelimab	1 (0%)	1 (1%)	0 (0%)
Vitamin D/Magnesium/Vitamin B12	1 (0%)	0 (0%)	1 (0%)
Vitamins/Dietary Supplements	1 (0%)	0 (0%)	1 (0%)
Zanamivir	1 (0%)	0 (0%)	1 (0%)

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Table A3. Treatment type of single treatment

	Total	RCT	Non-RCT
Total	**711**	**202**	**509**
Non-Steroidal Immunosuppressant	126 (18%)	27 (13%)	99 (19%)
Steroid	110 (15%)	15 (7%)	95 (19%)
Antiviral	97 (14%)	40 (20%)	57 (11%)
Antimalaria	87 (12%)	25 (12%)	62 (12%)
Anticoagulant	66 (5%)	5 (3%)	61 (12%)
Anticoagulant-Therapeutic	17 (2%)	2 (1%)	15 (3%)
Anticoagulant-Prophylactic	14 (2%)	0 (0%)	14 (3%)
Convalescent Plasma	56 (8%)	16 (8%)	40 (8%)
Antibiotic	29 (4%)	7 (3%)	22 (4%)
Anti- Inflammatory	20 (3%)	8 (4%)	12 (2%)
Interferon Therapy	16 (2%)	7 (3%)	9 (2%)
Antiparasitic	14 (2%)	12 (6%)	2 (0%)
Immunomodulator	14 (2%)	4 (2%)	10 (2%)
Neutralizing Antibodies	13 (2%)	7 (3%)	6 (1%)
Mesenchymal Stem Cells	9 (1%)	4 (2%)	5 (1%)
Statin	7 (1%)	0 (0%)	7 (1%)
Intravenous Immunoglobulin	6 (1%)	4 (2%)	2 (0%)
Vitamin C	6 (1%)	4 (2%)	2 (0%)
Antihistamine	4 (1%)	0 (0%)	4 (1%)
Antipsychotic	4 (1%)	0 (0%)	4 (1%)
Vitamin D	4 (1%)	3 (1%)	1 (0%)

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Table A4. Treatment type of combination treatment

	Total	RCT	Non-RCT
Total	**116**	**29**	**87**
Antimalaria/Antibiotic	19 (16%)	2 (7%)	17 (20%)
Steroid/NS-Immunossuppressant	10 (9%)	0 (0%)	10 (11%)
Antimalaria/Antiviral/Antiviral	8 (7%)	1 (3%)	7 (8%)
Antiviral/Antiviral	5 (4%)	3 (10%)	2 (2%)
Antiviral/Interferon	5 (4%)	0 (0%)	5 (6%)
Antimalaria/Antiviral	4 (3%)	0 (0%)	4 (5%)
Antimalaria/Antiviral/Antibiotic	4 (3%)	4 (14%)	0 (0%)
Antiparasitic/Antibiotic	4 (3%)	3 (10%)	1 (1%)
Antiviral/Antiviral/Antiviral	4 (3%)	0 (0%)	4 (5%)
Antiviral/Antiviral/Antiviral/Interferon	4 (3%)	0 (0%)	4 (5%)
Antiviral/NS-Immunosuppressant	4 (3%)	3 (10%)	1 (1%)
NS-Immunosuppressant/Steroid	4 (3%)	0 (0%)	4 (5%)
ACEI/ARB	3 (3%)	0 (0%)	3 (3%)
Antiviral/Antibiotic	3 (3%)	2 (7%)	1 (1%)
Antiviral/Antiviral/Interferon	3 (3%)	1 (3%)	2 (2%)
ACEI/ARB/Statin	2 (2%)	0 (0%)	2 (2%)
Antimalaria/Antiviral/NS-Immunosuppressant	2 (2%)	0 (0%)	2 (2%)
Antiviral/Anti-Inflammatory	2 (2%)	2 (7%)	0 (0%)
Steroid/Steroid	2 (2%)	0 (0%)	2 (2%)
Vitamin C/Zinc	2 (2%)	2 (7%)	0 (0%)
Anticoagulant/Ns-Immunosuppressant	1 (1%)	0 (0%)	1 (1%)
Antihistamine/Disinfectant	1 (1%)	1 (3%)	0 (0%)
Antimalaria/Mucolytic	2 (2%)	1 (3%)	1 (1%)
Antimalaria/Antiviral/Antiviral/Antibiotic	1 (1%)	1 (3%)	0 (0%)
Antimalaria/Antiviral/Antiviral/Antiviral	1 (1%)	0 (0%)	1 (1%)
Antimalaria/Antiviral/Antiviral/Interferon	1 (1%)	0 (0%)	1 (1%)
Antimalaria/Antiviral/Mucolytic	1 (1%)	1 (3%)	0 (0%)
Antiviral/Antiviral/Antibiotic/Anti-Inflammatory/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Antiviral/Antimalaria/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Immunomodulator	1 (1%)	1 (3%)	0 (0%)
Antiviral/Interferon/Steroid	1 (1%)	0 (0%)	1 (1%)
Antiviral/Steroid	1 (1%)	0 (0%)	1 (1%)
Bronchodilator/Hemorrheologic Agent	1 (1%)	0 (0%)	1 (1%)
Mucolytic/Diuretic	1 (1%)	0 (0%)	1 (1%)
NS-Immunosuppressant/Convalescent Plasma	1 (1%)	0 (0%)	1 (1%)
NS-Immunosuppressants/IVIG	1 (1%)	0 (0%)	1 (1%)
Steroid/Anti-Inflamatory	1 (1%)	0 (0%)	1 (1%)
Steroid/Interferon	1 (1%)	0 (0%)	1 (1%)
Steroid/IVIG	1 (1%)	1 (3%)	0 (0%)
Vitamin D/Magnesium/Vitamin B12	1 (1%)	0 (0%)	1 (1%)

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	Total	RCT	Non-RCT
Total	**116**	**29**	**87**
Vitamins/Dietary Supplements	1 (1%)	0 (0%)	1 (1%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant. ACEI/ARB: angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). IVIG: Intravenous immune globulin.

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Table A5. Country of knowledge synthesis conduct

	Total (n = 299)	With protocol (n = 88)	Without protocol (n = 211)
United States	57 (19%)	13 (15%)	44 (21%)
China	40 (13%)	13 (15%)	27 (13%)
India	34 (11%)	12 (14%)	22 (10%)
Iran	18 (6%)	3 (3%)	15 (7%)
United Kingdom	18 (6%)	3 (3%)	15 (7%)
Saudi Arabia	13 (4%)	1 (1%)	12 (6%)
Canada	12 (4%)	5 (6%)	7 (3%)
Italy	12 (4%)	8 (9%)	4 (2%)
Indonesia	9 (3%)	2 (2%)	7 (3%)
Malaysia	7 (2%)	0 (0%)	7 (3%)
Egypt	5 (2%)	2 (2%)	3 (1%)
France	5 (2%)	3 (3%)	2 (1%)
Peru	5 (2%)	1 (1%)	4 (2%)
Taiwan	5 (2%)	1 (1%)	4 (2%)
Australia	4 (1%)	1 (1%)	3 (1%)
Brazil	4 (1%)	1 (1%)	3 (1%)
Chile	4 (1%)	4 (5%)	0 (0%)
Japan	4 (1%)	2 (2%)	2 (1%)
Nepal	4 (1%)	0 (0%)	4 (2%)
Spain	4 (1%)	1 (1%)	3 (1%)
Bangladesh	3 (1%)	0 (0%)	3 (1%)
Greece	3 (1%)	1 (1%)	2 (1%)
Korea	3 (1%)	1 (1%)	2 (1%)
Pakistan	3 (1%)	0 (0%)	3 (1%)
The Netherlands	3 (1%)	1 (1%)	2 (1%)
Denmark	2 (1%)	1 (1%)	1 (0%)
Germany	2 (1%)	2 (2%)	0 (0%)
Israel	2 (1%)	1 (1%)	1 (0%)
Lebanon	2 (1%)	0 (0%)	2 (1%)
Mexico	2 (1%)	2 (2%)	0 (0%)
Thailand	2 (1%)	2 (2%)	0 (0%)
Switzerland	1 (0%)	0 (0%)	1 (0%)
Tunisia	1 (0%)	0 (0%)	1 (0%)
Nigeria	1 (0%)	1 (1%)	0 (0%)
Portugal	1 (0%)	0 (0%)	1 (0%)
Qatar	1 (0%)	0 (0%)	1 (0%)
Romania	1 (0%)	0 (0%)	1 (0%)
Sweden	1 (0%)	0 (0%)	1 (0%)
Turkey	1 (0%)	0 (0%)	1 (0%)

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Table A6. Treatment evaluated in knowledge syntheses

	Total (n = 518)	With Protocol (n = 152)	Without Protocol (n = 366)
Hydroxychloroquine	58 (11%)	15 (10%)	43 (12%)
Remdesivir	39 (8%)	11 (7%)	28 (8%)
Tocilizumab	35 (7%)	10 (7%)	25 (7%)
Corticosteroid	35 (7%)	10 (7%)	25 (7%)
Convalescent Plasma	33 (6%)	10 (7%)	23 (6%)
Lopinavir-Ritonair	24 (5%)	8 (5%)	16 (4%)
Chloroquine	19 (4%)	6 (4%)	13 (4%)
Hydroxychloroquine/Azithromycin	14 (3%)	1 (1%)	13 (4%)
Antivirals	12 (2%)	4 (3%)	8 (2%)
Anticoagulant	11 (2%)	2 (1%)	9 (2%)
Azithromycin	11 (2%)	3 (2%)	8 (2%)
Favipiravir	10 (2%)	1 (1%)	9 (2%)
Hydroxychloroquine/Chloroquine	10 (2%)	4 (3%)	6 (2%)
Colchicine	9 (2%)	2 (1%)	7 (2%)
Dexamethasone	9 (2%)	1 (1%)	8 (2%)
Arbidol	7 (1%)	1 (1%)	6 (2%)
Invermectin	7 (1%)	3 (2%)	4 (1%)
Glucocorticoid	7 (1%)	3 (2%)	4 (1%)
Acei/Arb	6 (1%)	4 (3%)	2 (1%)
Therapeutic Anticoagulant	5 (1%)	2 (1%)	3 (1%)
Prophylactic Anticoagulant	4 (1%)	3 (2%)	1 (0%)
Anakinra	4 (1%)	3 (2%)	1 (0%)
Famotidine	4 (1%)	1 (1%)	3 (1%)
Jak-Inhibitors	4 (1%)	2 (1%)	2 (1%)
Sarilumab	4 (1%)	4 (3%)	0 (0%)
Antibiotics	3 (1%)	1 (1%)	2 (1%)
Antimalaria	3 (1%)	1 (1%)	2 (1%)
Chloroquine/Hcq/Azithromycin	3 (1%)	3 (2%)	0 (0%)
Immunomodulation Treatment	3 (1%)	1 (1%)	2 (1%)
Interferon-Beta	3 (1%)	1 (1%)	2 (1%)
Intravenous Immunoglobin	3 (1%)	1 (1%)	2 (1%)
Methylprednisolone	3 (1%)	0 (0%)	3 (1%)
Statins	3 (1%)	0 (0%)	3 (1%)
Umifenovir	3 (1%)	0 (0%)	3 (1%)
Vitamin D	3 (1%)	1 (1%)	2 (1%)
Antiplatelets	2 (0%)	1 (1%)	1 (0%)
Antivirals/Antibiotics	2 (0%)	2 (1%)	0 (0%)
Baloxavir Marboxil	2 (0%)	0 (0%)	2 (1%)
Bromhexine	2 (0%)	1 (1%)	1 (0%)
Cell-Based Therapies	2 (0%)	1 (1%)	1 (0%)
Chloroquine/Azithromycin	2 (0%)	0 (0%)	2 (1%)
Corticosteroids/Iv Immunoglobulin/ Or Siltuximab/Tocilizumab	2 (0%)	1 (1%)	1 (0%)
Hydrocortisone	2 (0%)	0 (0%)	2 (1%)
Hyperimmune Immunoglobulin	2 (0%)	1 (1%)	1 (0%)
Immunoglobins	2 (0%)	0 (0%)	2 (1%)

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	Total (n = 518)	With Protocol (n = 152)	Without Protocol (n = 366)
Interferon-Beta-1a	2 (0%)	1 (1%)	1 (0%)
Interleukin- 6 Inhibitors	2 (0%)	0 (0%)	2 (1%)
Mesenchymal Stem Cells	2 (0%)	1 (1%)	1 (0%)
Ruxolitinib	2 (0%)	0 (0%)	2 (1%)
Tocilizumab/Sarilumab	2 (0%)	0 (0%)	2 (1%)
Acalabrutinib	1 (0%)	0 (0%)	1 (0%)
All Pharmacologicals	1 (0%)	1 (1%)	0 (0%)
Anticoagulant Therapeutic	1 (0%)	1 (1%)	0 (0%)
Antinflammatories	1 (0%)	0 (0%)	1 (0%)
Antiretroviral	1 (0%)	0 (0%)	1 (0%)
Antirheumatic	1 (0%)	1 (1%)	0 (0%)
Antitumor	1 (0%)	0 (0%)	1 (0%)
Arbidol/Lopinavir+Ritonavir	1 (0%)	0 (0%)	1 (0%)
Aspirin	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Hcq	1 (0%)	0 (0%)	1 (0%)
Azithromycin/Zinc	1 (0%)	0 (0%)	1 (0%)
Calcifediol	1 (0%)	0 (0%)	1 (0%)
Clazakisumab	1 (0%)	1 (1%)	0 (0%)
Convalescent Plasma Or Hyperimmune Plasma	1 (0%)	0 (0%)	1 (0%)
Corticosteroid/Antivirals	1 (0%)	0 (0%)	1 (0%)
Corticosteroids/ Tocilizumab/Anakinra/Ivig	1 (0%)	0 (0%)	1 (0%)
Cytokine Therapy	1 (0%)	0 (0%)	1 (0%)
Dpp-4 Inhibitor	1 (0%)	1 (1%)	0 (0%)
Favipiravir/ Baloxavir Marboxil	1 (0%)	0 (0%)	1 (0%)
Favipiravir/Other Antivirals	1 (0%)	0 (0%)	1 (0%)
Galidesivir/Sofosbuvir/Ribavirin	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Antibiotics	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Azithromycin/Ribavirin/Interferon/Interferon Alfa	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Chloroquine/Azithromycin	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Chloroquine/Azithromycin/Or Lopinavir/Ritonavir	1 (0%)	1 (1%)	0 (0%)
Hydroxychloroquine/Lopinavir-Ritonair	1 (0%)	0 (0%)	1 (0%)
Hydroxychloroquine/Ribavirin/Interferon/Interferon Alfa	1 (0%)	0 (0%)	1 (0%)
Hyrdocortisone	1 (0%)	0 (0%)	1 (0%)
Ibrutinib	1 (0%)	0 (0%)	1 (0%)
Ifn B-1b/ Immunomodulatory/Antivirals	1 (0%)	0 (0%)	1 (0%)
Immune Modulation Drugs	1 (0%)	0 (0%)	1 (0%)
Immune Therapy/Or Antiviral Therapy/Or Both	1 (0%)	0 (0%)	1 (0%)
Immunoglobin	1 (0%)	0 (0%)	1 (0%)
Immunomodulation/Hcq/Cq	1 (0%)	0 (0%)	1 (0%)
Prophylaxis Coagulant	1 (0%)	1 (1%)	0 (0%)
Interferon-Beta/Rbv	1 (0%)	0 (0%)	1 (0%)
Interferon Alpha-2b	1 (0%)	0 (0%)	1 (0%)
Interferons	1 (0%)	0 (0%)	1 (0%)
Interleukin-6 Inhibitors	1 (0%)	1 (1%)	0 (0%)
Interleukin-6/Tocilizumab	1 (0%)	1 (1%)	0 (0%)

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	Total (n = 518)	With Protocol (n = 152)	Without Protocol (n = 366)
Intravenous Steroids	1 (0%)	0 (0%)	1 (0%)
Jak-Inhibitor/Type I Interferon	1 (0%)	0 (0%)	1 (0%)
Levilimab	1 (0%)	1 (1%)	0 (0%)
Lopinavir	1 (0%)	1 (1%)	0 (0%)
Lopinavir-Ritonair/Arbidol	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Azithromycin	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Remdesivir	1 (0%)	0 (0%)	1 (0%)
Lopinavir-Ritonair/Ribavirin/Interferon Beta	1 (0%)	0 (0%)	1 (0%)
Meplazumab	1 (0%)	0 (0%)	1 (0%)
Methlyprednisone	1 (0%)	0 (0%)	1 (0%)
Neutralizing Antibody	1 (0%)	0 (0%)	1 (0%)
Nsaids	1 (0%)	0 (0%)	1 (0%)
Olokizumab	1 (0%)	1 (1%)	0 (0%)
Oseltamivir/Lopinavir/Ritonavir/Arbidol/Ribavirin/ Sfjdc/ Other	1 (0%)	0 (0%)	1 (0%)
Pentoxifylline	1 (0%)	0 (0%)	1 (0%)
Recombinant Human Gcsf	1 (0%)	0 (0%)	1 (0%)
Renal Replacement Therapy/ Glucocorticoids	1 (0%)	0 (0%)	1 (0%)
Repurposed Pharmacological Agents	1 (0%)	1 (1%)	0 (0%)
Ribavirin	1 (0%)	1 (1%)	0 (0%)
Rna-Dependent Rna Polymerase	1 (0%)	0 (0%)	1 (0%)
Sofosbuvir/Daclatasvir	1 (0%)	0 (0%)	1 (0%)
Stem Cell Therapy	1 (0%)	0 (0%)	1 (0%)
Sulodexide	1 (0%)	0 (0%)	1 (0%)
Type I Interferons	1 (0%)	0 (0%)	1 (0%)
Vitamin C	1 (0%)	0 (0%)	1 (0%)

Note: NS-immunosuppressant: non-steroidal immunosuppressant. ACEI/ARB: angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB). IVIG: Intravenous immune globulin.

PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7-8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	7, Appendix 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9

Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	9
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9-10, Figure 1, Appendix 4
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	10-11, Table 1, Appendix 3
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	11-12, Table 2, Appendix 5
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	11-12, Table 5
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	12-15, Table 5
Limitations	20	Discuss the limitations of the scoping review process.	15-16
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	16
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	17

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).