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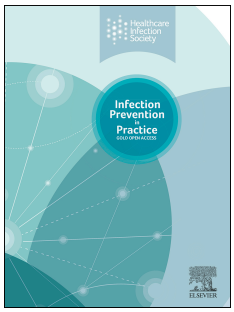

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Mansour Tobaiqy, Mohammed Qashqary, Shrooq Al-Dahery, Alaa Mujallad, Almonther Abdullah Hershan, Mohammad Azhar Kamal, Nawal Helmi

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Therapeutic Management of COVID-19 Patients: A systematic review

Mansour Tobaiqy[1], Mohammed Qashqary[2], Shrooq Al-Dahery[3], Alaa Mujallad[4], Almonther Abdullah Hershan[5], Mohammad Azhar Kamal[6,7], Nawal Helmi[6,8]

[1] Department of Pharmacology, College of Medicine, University of Jeddah, Jeddah, Kingdom of Saudi Arabia

[2] Department of Family Medicine, College of Medicine, University of Jeddah

[3] Department of Applied Radiologic Technology, College of Applied Medical Sciences, University of Jeddah

[4] Department of Nursing, College of Applied Medical Sciences, University of Jeddah

[5] Department of Medical Microbiology and Parasitology, College of Medicine, University of Jeddah

[6] Department of Biochemistry, College of Science, University of Jeddah, Jeddah, Saudi Arabia

[7] Centre for Science and Medical Research (UJC-SMR), University of Jeddah, Jeddah, Saudi Arabia

[8] Department of Medical Laboratory Technology, College of Applied Medical Sciences, University of Jeddah

Corresponding Author

Dr. Mansour Tobaiqy
BSc, MSc, Clin. Pharmacol, PhD, PgCert
Assistant Professor
Department of Pharmacology
College of Medicine
University of Jeddah
Jeddah, Kingdom of Saudi Arabia

P.O. Box 45311 Jeddah 21512
ORCID: https://orcid.org/0000-0002-4292-0900
E-mail mtobaiqy@uj.edu.sa

Abstract

Background: SARS-CoV-2 is the causative agent of COVID-19; that has been declared a global pandemic by the WHO in 2020. The COVID-19 treatment guidelines vary in each country, and yet there is no approved therapeutic for COVID-19.

Aims of the study: this review aimed to report any evidence of therapeutics used for the management of COVID-19 patients in clinical practice since the emergence of the virus.

Methods: A systematic review protocol was developed based on PRISMA Statement. Articles for review were selected from electronic databases (Embase, Medline and Google Scholar). Readily accessible peer-reviewed, full articles in English published from December 1st , 2019 to March 26th , 2020 were included. The search terms included combinations of: COVID, SARS-COV-2, glucocorticoids, convalescent plasma, antiviral and antibacterial. There were no restrictions on the type of study design eligible for inclusion.

Results: As of March 26th, 2020, of the initial manuscripts identified (n=449); forty-one studies were included. These consisted of clinical trials (n=3), case reports (n=7), case series (n=10), retrospective (n=11) and prospective (n=10) observational studies. Thirty-six studies were conducted in China (88%).

The most commonly reported medicine in this systematic review was corticosteroids (n=25), followed by Lopinavir (n=21) and Oseltamivir (n=16).

Conclusions: This is the first systematic review to date related to the therapeutics used in COVID-19 patients. Only 41 research articles on COVID-19 and therapeutics were found eligible to be included, most conducted in China. Corticosteroid therapy was found to be the most studied medicine in the literature.

Key word:

SARS-CoV-2, COVID-19, Hydroxychloroquine, Arbidol hydrochloride, Corticosteroids, Convalescent Plasma Therapy

Introduction

Severe acute respiratory syndrome coronavirus SARS-CoV-2 is the cause of the coronavirus disease 2019 (COVID-19) that has been declared a global pandemic by the World Health Organization (WHO) in 2020. SARS-CoV-2 was discovered in December 2019, in Wuhan City (the capital of Hubei province), China. The origin of the virus is unknown, but initially newly diagnosed cases were linked to the Huanan Seafood Wholesale Market where people can buy wild animals, such as bats [(1)]. SARS-CoV-2 has phylogenetic similarity to SARS-CoV and MERS- CoV. The virus was identified as a novel enveloped RNA betacoronavirus that has been named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [(2)].

One of the characteristics of COVID-19 is that it is highly contagious; many countries were affected, including China and 164 other countries in less than three months. Despite China reaching 81,151 confirmed cases with 3,242 deaths, the country reported only one new domestic case as of March 18th, 2020. As of that date, the total worldwide confirmed cases are 193,475 with 7,864 deaths (WHO). Although protective measures have been implemented in China (such as isolation from confirmed and suspected cases) to reduce the spread of the virus, the need for effective treatment is imperative to stop the outbreak and reduce the morbidity and mortality of COVID-19[(1)].

Since onset of the outbreak, researchers have proposed many agents that could have efficacy against COVID-19. Different antiviral agents were included in the latest guidelines from the National Health Commission (NHC) including Interferon, Lopinavir/Ritonavir, Chloroquine Phosphate, Ribavirin, and Arbidol[(3)]. Angiotensin receptor blockers, such as Losartan, are another suggestion to treat COVID-19[(4)].

COVID-19 treatment guidelines vary in each country. The WHO guidelines are very general, to manage only the symptoms and advise to be cautious with paediatric patients, pregnant, and patients with underlying co-morbidities. There is no approved treatment for COVID-19; the care advised is to give supportive management according to each patient's need; Such as antipyretics for fever and oxygen therapy for patients with respiratory distress. Moreover, WHO recommendations for severe cases are to give empiric antimicrobial therapy and implement mechanical ventilation depending on the patient's clinical condition. Some of the Asian guidelines were not easy to interpret because they are not yet translated to English, such as the Japanese guidelines. The treatment protocols across countries are similar. They are using Hydroxychloroquine, Chloroquine phosphate, Remedesivir, and Lopinavir/Ritonavir[(5-7)]. There are slight differences between some countries treatment guidelines which will be represented in the Table 1[(8-11)].

In light of limited and scarce evidence around therapeutics for COVID-19 in the literature, this review aims to retrospectively evaluate the therapeutic management that was given to COVID-19 patients since the emergence of the virus.

Methods

A systematic review protocol was developed based on PRISMA-P and the PRISMA statement. Articles for review were selected from electronic databases (Embase, Medline and Google Scholar). Readily accessible peer-reviewed, full articles in English, published from December 1st, 2019 to March 26th, 2020 were included. The search terms included combinations of: COVID-19, SARS-COV-2, Glucocorticoids, Chloroquine, convalescent plasma, antiviral, antibacterial, Oseltamivir, Hydroxychloroquine, Chloroquine phosphate and monoclonal antibodies. There were no restrictions on the type of study design eligible for inclusion; however, these were likely to be quantitative and RCT studies. The focus of the review was therapeutics for use of the management of COVID-19 patients. Primary outcomes were:

(1) the evidence of therapeutics used for the management of COVID-19 patients in clinical practice, irrespective of patient characteristics, setting and outcome measures to discuss the most common reported medicines in this review.

(2) the clinical outcome of the therapeutic treatment (recovery, mortality) in COVID-19 patients. The secondary outcome was adverse events associated with the treatment.

Duplicate articles were removed. Titles were independently screened by both reviewers with abstracts followed by full articles reviewed where any doubt remained. Inclusions and exclusions were recorded following PRISMA guidelines presented in the form of a PRISMA flow diagram and detailed reasons recorded for exclusion. Critical appraisal checklists appropriate to each study design were applied and checked by a second team member. Any bias or quality issues identified were considered prior to a quantitative meta-analysis and meta-narrative. CASP appraisal checklist tools were used for quality assessments. A data extraction tool was designed to capture focus of interest, population, geographical location, methodology, specific mention of therapeutic treatment and adverse events, key findings and further research. Ethical approval was not required for this review of existing peer reviewed literature.

Results

As of March 26th, 2020, the initial manuscripts identified 449 articles. Inclusions and exclusions are reported following PRISMA guidelines presented in the form of a PRISMA flow diagram (Figure 1) with reasons for exclusion recorded (Table 2) as follows: duplicates removed (n=213), 28 records were excluded of which 18 were excluded due to language (9 Chinese, 2 Dutch, 1 Vietnamese, 1Spanish, 1 Italian, 1 Russian, 1 Portuguese, 1 Iranian and 1 German). Ten articles were excluded for other reasons, including incomplete and irrelevant articles.

Consensus on final inclusion of studies (n=41) (negotiated without the need for a third reviewer) is presented in Table 3.

Forty-one studies were included, of which clinical trials (n=3), case reports (n=7), case series (n=10), retrospective (n=11) and prospective (n=10) observational studies. Thirty-six studies were conducted in China, and one in each of; Korea, USA, France, Singapore and Macau .

Patient Characteristics

Total number of patients reported in these studies were 8,806. The mean of age was 50.8 years in 39 studies; the age was not specified in other studies.

Reported therapeutics

The most commonly reported therapeutic in this systematic review was the anti-inflammatory medication, Corticosteroid (n=25) with different names and product characteristics, (Corticosteroid n=21, Methylprednisolone n=3, Dexamethasone n=1). This was followed by the antiviral HIV medication Lopinavir (n=21), as combination Lopinavir/Ritonavir (n=18), alone (n=3), followed by the Oseltamivir (n=16) and Arbidol Hydrochloride (n=8).

In terms of antibacterial medicines, Moxifloxacin (n=4) and Tigecycline were the most reported.

Convalescent plasma therapy was reported in one multi center retrospective observational study of six patients.

The outcome of the treatment

The outcome measures recorded vary between patients discharge and recovery, ongoing hospitalization, and mortality. Available data concerning this issue is shown in Table 3.

Discussion

This is the first up to date review related the therapeutics used in COVID-19 patients in a systematic manner. As of March 26th, 2020 (since the emergence of COVID-19) only 41 eligible research articles on COVID-19 and therapeutics were found to be included in the current systematic review[2,5,12-49]. Only three were clinical trials; most were either case reports, case series or prospective and retrospective observational studies. Systemic Corticosteroid of different names and formulation was the most commonly reported, medication, followed by the antivirals Lopinavir , Oseltamivir and Arbidol hydrochloride. Convalescent plasma therapy was mentioned in one multi-center retrospective observational study and was administered to six patients.

Although quality assessment was applied to the included research articles, there was insufficient evidence from the articles identified in this review to conduct a meta-analysis. Nor was a subgroup analysis (adults and children, different formulations, dosages and duration) appropriate.

Most reported articles in this review are low quality; the design and outcome of the studies are incomplete or inconsistent, hence difficult to interpret the therapeutics in terms of efficacy and safety.

Despite these limitations, this is the first systematic review linked the therapeutics used in COVID-19 patients. Furthermore, the review provided up-to-date insight on the current therapeutics' guidelines for the management of COVID-19 patients; most of reported medicines in this review were already in place in the USA, Saudi Arabia, Europe, and Egypt (Table 1).

Corticosteroids were the most commonly reported and used medicine in this review, however, they are not recommended in any of the mentioned guidelines. The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC), in the absence of conclusive scientific evidence, recommended that Corticosteroids should not be routinely used in patients with COVID-19 for treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) unless indicated for other conditions, such as asthma or chronic obstructive pulmonary disease (COPD) exacerbation, or septic shock[5,50-51]. Careful use of Corticosteroids with low-to-moderate doses in short courses is advised. Hyperglycemia, hypernatremia and hypokalemia are the most common adverse effects associated with Corticosteroid use and should be routinely monitored[5,51].

Lopinavir/Ritonavir is available as the brand name Kaletra and was the second most reported medicine in this review. In their RCT, Cao B et al reported negative outcomes of this HIV treatment for COVID-19 patients (Table 2) [30,52-54]. No benefit was observed with Lopinavir/Ritonavir treatment beyond standard care in this study, 19 patients who received the intervention died. However, some limitations were observed in the study, including the lack of blinding. RCT NCT04252885 and SOLIDARITY trial are ongoing to determine the efficacy in Lopinavir/Ritonavir COVID-19 patients[52].

Oseltamivir was the third most reported therapeutic in this review, and sold under the brand name Tamiflu, it is used to treat influenza A and influenza B. Oseltamivir was recommended by WHO for people at high risk of infection for prevention of pandemic influenza. Guan W and colleagues in their retrospective observational study reported the use of Oseltamivir in 1,099 patients; however, the study was not able to provide any solid data on the effectiveness of Oseltamivir in the prevention or treatment of COVID-19 patients. Study limitations included incomplete documentation of patients' data and recall bias[55-56].

Arbidol hydrochloride was the fourth most reported medicine in this review; it is a broad-spectrum inhibitor of influenza A and B virus, parainfluenza virus, and other viruses, including hepatitis C virus. It is used in Russia and China, yet not approved for use in other countries[52]. However, no conclusive evidence of its efficacy in COVID-19 was reported. In this review, it was reported together with Favipiravir, which was approved recently for treatment of novel influenza on February 15th, 2020 in China[52].

Chloroquine phosphate and **Hydroxychloroquine** were reported in this review and showed favorable outcomes in the recovery of COVID-19 patients[6-7,57-60]. The mechanism of action on viruses for these two medicines is likely the same effect. Chloroquine has been used for a long time to treat malaria and showed positive outcomes in patients. Furthermore, Hydroxychloroquine showed a significant effectiveness to kill intracellar pathogens such as *Coxiella burnetii*, the agent of Q fever[22]. The French open label, non- randomized clinical trial was promising and the first clinical trial of these medications in COVID-19 patients. The effect of Hydroxychloroquine was significant because it showed reduction in the viral load when it compared with the control group[22]. Moreover, the effect of Hydroxychloroquine was significantly more potent when Azithromycin was added to the patients according to their clinical need. However, clinical follow-up and occurrence of adverse effects were not discussed in the paper; further work should be done on these medicines with the aim of reducing the morbidity and mortality of COVID-19 [57-59]. Although these two medicines have shown promising activity against SARSCoV-2, there is a risk of arrhythmia associated with their administration. Therefore caution is required for use at higher cumulative dosages. It is recommended that their use in suspected/confirmed COVID-19 is to be restricted to hospitalized patients. On March 30th, 2020 the U.S Food and Drug Administration (US FDA) has issued an emergency use authorization (EUA) for Chloroquine and Hydroxychloroquine to treat patients hospitalized with Covid-19 [60].

Convalescent plasma treatment was mentioned once in this review, in a multi-centre cohort research trial of 45 critically ill COVID-19 patients admitted to ICU in Wuhan. The findings showed that convalescent plasma was administered to six patients and no transfusion reactions occurred; however, the study could not provide adequate information about the efficacy of convalescent plasma, due to limited sample sizes and lack of randomized control group[61-62].

In fact, convalescent plasma therapy could be a promising method of treatment for COVID-19 patients. A very recent case series reported from China, showed that five critically ill patients with laboratory confirmed COVID-19 (who had ARDS) improved. After receiving plasma transfusion, their body temperature normalized within 3 days (in 4 of 5 patients), their viral loads became undetectable within 12 days and 3 of 5 patients

were discharged from the hospital and were in stable condition at 37 days post transfusion[63].

On March 24th, 2020 the US FDA has approved convalescent plasma treatment for investigational use under the traditional Investigational New Drug Applications (IND) regulatory pathway, and for **e**ligible patients who have confirmed COVID-19 and severe or immediately life-threatening conditions such as respiratory failure, septic shock, and/or multiple organ dysfunction or failure[64-65].

Notably there are some potential risks and ethical issues associated with their use, including increased thrombotic event risk (0.04 to 14.9%), lack of high quality research in this particular area and the selection of donors with high neutralizing antibody titers[65].

Conclusions

This is the first up to date systematic review of therapeutics used in COVID-19 patients. Only 41 research articles on COVID-19 and therapeutics were found eligible to be included, most conducted in China, of which only three were clinical trials.

The anti-inflammatory medication Corticosteroid was found to be the most mentioned and widely used medicine in these studies, despite the safety alert issued by WHO and CDC, followed by antiviral medication Lopinavir, Oseltamivir and Arbidol hydrochloride.

Although further research is warranted as the amount of the evidence increases, this study presents the current picture of treatment modalities used for COVID-19. Efficacy and safety profiles of treatments for COVID-19 will need to be characterized in future studies.

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Table 1: *Comparison between the Treatment Guidelines for COVID-19 in Saudi Arabia, USA, Europe, and Egypt*

	Ministry of Health **M.O. H** **Saudi Arabia**	**USA** **Massachusetts General Hospital**	**Europe** **Ireland**	**Egypt**
Mild to moderate disease	-Hydroxychloroquine -Chloroquine -chloroquine phosphate	-Clinical trial of Remdesivir	-Chloroquine (oral) -Hydroxychloroquine (oral) -Lopinavir/ritonavir (oral) -Remdesivir (intravenous)	-Oseltamivir -Hydroxy Chloroquine -Chloroquine phosphate
Severe COVID-19	-Hydroxychloroquine -Chloroquine -Chloroquine phosphate -Combination therapy (Lopinavir/Ritonavir)	-Hydroxychloroquine -Chloroquine -Lopinavir/ritonavir darunavir/cobicistat		-Oseltamivir -Hydroxychloroquine -Chloroquine phosphate -Lopinavir/Ritonavir -Serum ferritin, D-Dimer
Critical	-Combination therapy (Lopinavir/Ritonavir) -hydroxychloroquine -remdesivir	-With ID approval, Interferon beta B1 (Betaseron)		-Antibiotics -Oseltamivir -Hydroxy Chloroquine (or _Chloroquine phosphate) -Azithromycin (Hydrocortisone (anticoagulants if -D-Dimer Invasive

Ref.:8, 9, 10, and 11.

Table 2. List of excluded papers and reasons for exclusion:

No.#	Authors	Title	Covid-19 Yes / No	Reason for Exclusion
1	Chughtai A. et al, 2020	Policies on the use of respiratory protection for hospital health workers to protect from coronavirus disease (covid-19).	Yes	No details on therapeutics/commentary
2	Gurwitz D. 2020	Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics	Yes	Commentary
3	Wang M., et al, 2020	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro	Yes	Commentary
4	Colson P., et al, 2020	Chloroquine and hydroxychloroquine as available weapons to fight COVID-19	Yes	Commentary
5	Liu Y., Chen H., Tang K., Guo Y., 2020	Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy	Yes	No details on therapeutics/commentary
6	Baron S., et al., 2020	Teicoplanin: an alternative drug for the treatment of coronavirus COVID-19?	Yes	Commentary
7	Mitja O., & Clotet B., 2020	Use of antiviral drugs to reduce COVID-19 transmission	Yes	Commentary
8	Colson P., Rolain JM., & Raoult D., 2020	Chloroquine for the 2019 novel coronavirus SARS-CoV-2	Yes	Commentary
9	Morse J., et al, 2020	Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV	Yes	Commentary
10	Thevarajan I. et al., 2020	Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19	Yes	Commentary
11	Elfiky A., 2020	Anti-HCV, nucleotide inhibitors, repurposing against COVID-19	Yes	Commentary
12	Ung C., 2020	Community pharmacist in public health emergencies: Quick to action against the coronavirus 2019-nCoV outbreak	Yes	Commentary
13	Gupta R., 2020	Clinical considerations for patients with diabetes in times of COVID-19 epidemic	Yes	Commentary
14	Dong L., Hu S., and Gao J., 2020	Discovering drugs to treat coronavirus disease 2019 (COVID-19)	Yes	Commentary
15	Zhang C., Shi L., and Wang FS., 2020	Liver injury in COVID-19: management and challenges	Yes	Commentary
16	Cunningham A., Goh H., and Koh D., 2020	Treatment of COVID-19: old tricks for new challenges	Yes	Commentary
17	Ko WC., et al., 2020	Arguments in favour of remdesivir for treating SARS-CoV-2 infections	Yes	Commentary
18	Arabi Y., Murthy S., and Webb S., 2020	COVID-19: a novel coronavirus and a novel challenge for critical care	Yes	Commentary
19	Wang J., and Shi Y., 2020	Managing neonates with respiratory failure due to SARS-CoV-2	Yes	Commentary
20	Stebbing J., et al.,	COVID-19: combining antiviral and anti-in	Yes	Commentary

	2020	ammatory treatments		
21	Touret F., and Lamballerie X., 2020	Of chloroquine and COVID-19	Yes	Commentary
22	Porcheddu R., et al., 2020	Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China	Yes	No therapeutic data/commentary
23	Zhang J., et al 2020	Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics	Yes	Commentary
24	Baden L., and Rubin E. 2020	Covid-19 — The Search for Effective Therapy	Yes	Commentary
25	Baud D., et al. 2020	COVID-19 in pregnant women	Yes	No therapeutic data/commentary
26	Ortega J., et al., 2020	Unrevealing sequence and structural features of novel coronavirus using in silico approaches: the main protease as molecular target	Yes	No therapeutic data
27	Ma Y., et al. 2020	2019 novel coronavirus disease in hemodialysis (HD) patients: Report from one HD center in Wuhan, China	Yes	No therapeutic data
28	Columbus C, Brust K., and Arroliga A., 2020	2019 novel coronavirus: an emerging global threat	Yes	Commentary
29	Barry M., Amri M., and Memish. 2020	COVID-19 in the Shadows of MERS-CoV in the Kingdom of Saudi Arabia	Yes	Commentary
30	Wang M., et al., 2020	A precision medicine approach to managing 2019 novel coronavirus pneumonia	Yes	No therapeutic data/commentary
31	Singhal T., 2020	A Review of Coronavirus Disease-2019 (COVID-19)	Yes	Review article
32	Li Q., et al. 2020	A simple laboratory parameter facilitates early identification of COVID-19 patients	Yes	Retrospective case-negative control study
33	Guo W., et al. 2020	A Survey for COVID-19 among HIV/AIDS Patients in Two Districts of Wuhan, China	Yes	No therapeutic data
34	Gao J., Tian Z., and Yang X. 2020	Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies	Yes	Commentary
35	Deng L., et al. 2020	Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study	Yes	Retrospective control study
36	Murthy S., Gomersall C., and Fowler R. 2020	Care for Critically Ill Patients With COVID-19	Yes	Commentary
37	Deng SQ., and Peng HJ. 2020	Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China	Yes	Review
38	Wang Z., et al. 2020	Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China	Yes	No therapeutic data
39	Xiong Y., et al. 2020	Clinical and High-Resolution CT Features of	Yes	No therapeutic data

		the COVID-19 Infection: Comparison of the Initial and Follow-up Changes		
40	Chen G., et al. 2020	Clinical and immunologic features in severe and moderate forms of Coronavirus Disease 2019	Yes	No therapeutic data
41	Chen H., et al. 2020	Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	Yes	No therapeutic data
42	Hong H., et al. 2020	Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children	Yes	Perspectives / No therapeutic data
43	Ye G., et al. 2020	Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation	Yes	No therapeutic data
44	Anderson D., et al. 2020	Clinical management of suspected or confirmed COVID-19 disease	Yes	Review
45	Zhang T., et al. 2020	Clinical trials for the treatment of coronavirus disease 2019 (COVID-19): A rapid response to urgent need	Yes	Commentary
46	Chen L., et al. 2020	Convalescent plasma as a potential therapy for COVID-19	Yes	Commentary
47	Yang P., et al. 2020	Corona Virus Disease 2019, a growing threat to children?	Yes	Commentary / No therapeutic data
48	Kooraki S., et al. 2020	Coronavirus (COVID-19) Outbreak: What the Department of Radiology Should Know	Yes	Commentary / No therapeutic data
49	Rasmussen S., et al., 2020	Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know	Yes	Commentary / No therapeutic data
50	Liu W., et al. 2020	Coronavirus disease 2019 (COVID-19) during pregnancy: a case series	Yes	No therapeutic data
51	Mclntosh K., Hirsch M., and Bloom. 2020	Coronavirus disease 2019 (COVID-19)	Yes	Review
52	He F., and Li W. 2020	Coronavirus Disease 2019 (COVID-19): What we know?	Yes	Review
53	Xiong TY., et al. 2020	Coronaviruses and the cardiovascular system: acute and long-term implications	Yes	Commentary
54	Gong J., et al. 2020	Correlation Analysis Between Disease Severity and Inflammation-related Parameters in Patients with COVID-19 Pneumonia	Yes	No therapeutic data
55	Dong Y., et al. 2020	Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China	Yes	No therapeutic data
56	Shereen M., et al. 2020	COVID-19 infection: origin, transmission, and characteristics of human coronaviruses	Yes	Review
57	Rio C., and Malani P. 2020	COVID-19—New Insights on a Rapidly Changing Epidemic	Yes	Review
58	Yi Y., et al., 2020	COVID-19: what has been learned and to be learned about the novel coronavirus disease	Yes	Review
59	Rezaeetalab F., et al.	COVID-19: A New Virus as a Potential	Yes	Review

	2020	Rapidly Spreading in the Worldwide		
60	Shaker M., et al. 2020	COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic	Yes	No therapeutic data
61	Aslam S., and Mehra M. 2020	COVID-19: Yet Another Coronavirus Challenge in Transplantation	Yes	Commentary
62	Padmanabhan S. 2020	Potential dual therapeutic approach against SARS-CoV-2/COVID-19 with Nitazoxanide and Hydroxychloroquine	Yes	Commentary
63	Hick J., et al, 2020	Duty to Plan: Health Care, Crisis Standards of Care, and Novel Coronavirus SARS-CoV-2	Yes	Discussion
64	Yang P., et al. 2020	Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China	Yes	No therapeutic data
65	Khan N. 2020	Epidemiology of corona virus in the world and its effects on the China economy	Yes	Review
66	Hoehl S., et al. 2020	Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China	Yes	Commentary
67	Yang Y., et al. 2020	Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome	Yes	Review
68	Cascella M., et al. 2020	Features, Evaluation and Treatment Coronavirus (COVID-19)	Yes	Review
69	Erol A. 2020	High-dose intravenous vitamin C treatment for COVID-19 (a mechanistic approach)	Yes	Review
70	Liu F., et al. 2020	Highly ACE2 Expression in Pancreas May Cause Pancreas Damage After SARS-CoV-2 Infection	Yes	Commentary
71	Zhang B. et al. 2020	Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19	Yes	No therapeutic data
72	Mao R., et al. 2020	Implications of COVID-19 for patients with pre-existing digestive diseases	Yes	Commentary
73	Ferguson N. et al. 2020	Impact of non-pharmaceutical interventions (NPIs) to reduce COVID- 19 mortality and healthcare demand	Yes	No therapeutic data
74	Qiu H., et al. 2020	Intensive care during the coronavirus epidemic	Yes	Commentary
75	Poon L. et al. 2020	ISUOG Interim Guidance on 2019 novel coronavirus infection during pregnancy and puerperium: information for healthcare professionals	Yes	Review
76	Khan S., et al. 2020	The emergence of a novel coronavirus (SARS-CoV-2), their biology and therapeutic options	Yes	Discussion
77	Sun Q., et al. 2020	Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province	Yes	Commentary
78	Guzzi P., et al. 2020	Master Regulator Analysis of the SARS-CoV-	Yes	No therapeutic data

		2/Human interactome		
79	Memish Z. et al. 2020	Middle East respiratory syndrome	No	Review
80	Nicastri E., 2020	National Institute for the Infectious Diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management	Yes	Commentary
81	Li X., et al. 2020	Network bioinformatics analysis provides insight into drug repurposing for COVID-2019	Yes	No therapeutic data
82	Xiong R., et al. 2020	Novel and potent inhibitors targeting DHODH, a rate-limiting enzymein de novo pyrimidine biosynthesis, are broad-spectrum antiviral against RNA viruses including newly emerged coronavirus SARS-CoV-2	Yes	No therapeutic data
83	Rezabakhsh A., Ala A., and Khodaei S. 2020	Novel Coronavirus (COVID-19): A New Emerging Pandemic Threat	Yes	Survey/ No therapeutic data
84	Ai JW., et al. 2020	Optimizing diagnostic strategy for novel coronavirus pneumonia, a multi-center study in Eastern China	Yes	No therapeutic data
85	Qiu R., et al. 2020	Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review	Yes	No therapeutic data
86	Bajema K., et al. 2020	Persons Evaluated for 2019 Novel Coronavirus — United States, January 2020	Yes	Commentary
87	Shanmugaraj B., et al. 2020	Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19)	Yes	Review
88	Zhou G., and Zhao Q., 2020	Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2	Yes	Review
89	Hoffmann M., et al. 2020	SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor	Yes	No therapeutic data
90	Zhang L., and Liu Y. 2020	Potential interventions for novel coronavirus in China: A systematic review	Yes	Review
91	Vasylyeva O. 2020	Pregnancy and COVID-19: a brief review	Yes	Review
92	Alamri M., Qamar M., and Alqahtani S. 2020	Pharmacoinformatics and molecular dynamic simulation studies reveal potential inhibitors of SARS-CoV-2 main protease $3CL^{pro}$	Yes	No therapeutic data
93	Fisher d., and Heymann d. 2020	Q&A: The novel coronavirus outbreak causing COVID-19	Yes	Commentary
94	Goh K., et al. 2020	Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from COVID-19 Infection	Yes	No therapeutic data
95	Chen X., et al. 2020	Restoration of leukomonocyte counts is associated with viral clearance in COVID-19 hospitalized patients	Yes	No therapeutic data
96	Bouadma L., et al. 2020	Severe SARS-CoV-2 infections: practical considerations and management strategy for	Yes	Review

		intensivists		
97	Zhu R., et al. 2020	Systematic Review of the Registered Clinical Trials of Coronavirus Disease2019 (COVID-19)	Yes	Review
98	Yang Y. et al. 2020	The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China	Yes	Review
99	Li YS., Bai WZ., and Hashikawa T. 2020	The neuroinvasive potential of SARS CoV2 may play a role in the respiratory failure of COVID 19 patients	Yes	Review
100	Naicker S., et al. 2020	The Novel Coronavirus 2019 epidemic and kidneys	Yes	Review
101	Fang Y., Nie Y., and Penny. M., 2020	Transmission dynamics of the COVID 19 outbreak and effectiveness of government interventions: A data driven analysis	Yes	No therapeutic data
102	Sun P., et al. 2020	Understanding of COVID 19 based on current evidence	Yes	Review
103	Wang Y., et al. 2020	Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures	Yes	Review
104	Maoujoud O., Asserraji M., and Belarbi M. 2020	What nephrologist should know about COVID-19 outbreak?	Yes	Commentary
105	Cortegiani a., et al., 2020	A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19	Yes	Review
106	Ryu S., et al. 2020	An interim review of the epidemiological characteristics of 2019 novel coronavirus	Yes	Review
107	Yang N., and Shen HM. 2020	Targeting the Endocytic Pathway and Autophagy Process as A Novel Therapeutic Strategy In COVID-19	Yes	Review
108	Fan Y., et al. 2020	Bat Coronaviruses in China	Yes	Review
109	Russell C., Millar j., and Bailliek. 2020	Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury	Yes	Commentary
110	Liang B., et al 2020	Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells	Yes	No therapeutic data/commentary
111	Wu. X., et al. 2020	Co-infection with SARS-CoV-2 and Influenza A Virus in Patient with Pneumonia, China	Yes	Commentary
112	Martinez M., et al. 2020	Compounds with therapeutic potential against novel respiratory 2019 coronavirus	Yes	Commentary
113	Tang B., et al. 2020	Coronavirus Disease 2019 (COVID-19) Pneumonia in a Hemodialysis Patient	Yes	No therapeutic data
114	Chang L., Yan Y., and Wang L. 2020	Coronavirus Disease 2019: Coronaviruses and Blood Safety	Yes	Review
115	Walker L. 2020	COVID-19, Australia: Epidemiology Report 2	Yes	Commentary
116	Lu H., 2020	Drug treatment options for the 2019-new	Yes	Commentary

		coronavirus (2019- nCoV)		
117	Hellewell J., et al. 2020	Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts	Yes	No therapeutic data
118	Prompetchara E. Ketloy C., and Palaga T., 2020	Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic	Yes	Review
119	Ashour H., et al. 2020	Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks	Yes	Review
120	Zhou Y., et al. 2020	Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2	Yes	No therapeutic data
121	Devaux C., et al. 2020	New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?	Yes	Review
122	Cauchi S., and Locht C. 2020	Non-specific Effects of Live Attenuated Pertussis Vaccine Against Heterologous Infectious and Inflammatory Diseases	Yes	Review
123	Chang YC., et al. 2020	Potential therapeutic agents for COVID-19 based on the analysis of protease and RNA polymerase docking	Yes	No therapeutic data
124	Pang J., et al. 2020	Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review	Yes	Review
125	Chen D., et al. 2020	Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report	Yes	Commentary
126	Liu C., et al. 2020	Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases	Yes	Review
127	Gralinski L., and Menachery V. 2020	Return of the Coronavirus: 2019-nCoV Return of the Coronavirus: 2019-nCoV	Yes	Commentary
128	Cao Q., et al. 2020	SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics	Yes	Commentary
129	Walls A., et al. 2020	Structure, Function, and Antigenicity of the SARS- CoV-2 Spike Glycoprotein	Yes	Commentary
130	Xu J., et al. 2020	Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV	Yes	Review
131	Garrett L. 2020	The art of medicine COVID-19: the medium is the message	Yes	Commentary
132	Habibzadeh P., and Stoneman E.	The Novel Coronavirus: A Bird's Eye View	Yes	Review
133	Wu D., et al. 2020	The SARS-CoV-2 Outbreak: What We Know	Yes	Review
134	Nezhad F., et al. 2020	Therapeutic approaches for COVID-19 based on the dynamics of interferon- mediated immune responses	Yes	No therapeutic data
135	Lu S. 2020	Timely development of vaccines against SARS- CoV-2	Yes	Commentary
136	Kim J., et al. 2020	Viral Load Kinetics of SARS-CoV-2 Infection in First Two Patients in Korea	Yes	Commentary

137	Sekhar T. 2020	Virtual screening bades prediction of potential drugs for COVID-19	Yes	No therapeutic data
138	Park W., et al. 2020	Virus Isolation from the First Patient with SARS-CoV-2 in Korea	Yes	Commentary
139	Lake M., 2020	What we know so far: COVID-19 current clinical knowledge and research	Yes	Review
140	Ralph R., et al. 2020	2019-nCoV (Wuhan virus), a novel Coronavirus: human-to-human transmission, travel-related cases, and vaccine rea	Yes	Review
141	Jin YH., 2020	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)	Yes	Review
142	Liu R., et al. 2020	Association of Cardiovascular Manifestations with In-hospital Outcomes in Patients with COVID-19: A Hospital Staff Data	Yes	No therapeutic data
143	Lai CC., et al. 2020	Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths	Yes	Review
144	Bordi L., et al. 2020	Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2), Italy, February 2020	Yes	Commentary
145	Li T. 2020	Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS- CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0)	Yes	Review
146	Song P., and Karako T. 2020	COVID-19: Real-time dissemination of scientific information to fight a public health emergency of international concern	Yes	Commentary
147	Vankadari N., and Wilce J. 2020	Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26	Yes	Review
148	Hsih WH., et al. 2020	Featuring COVID-19 cases via screening symptomatic patients with epidemiologic link during flu season in a medical center of central Taiwan	Yes	No therapeutic data
149	Stoecklin S., et al. 2020	First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020	Yes	No therapeutic data
150	Chan J., et al. 2020	Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan	Yes	No therapeutic data
151	Boulos M., and Geraghty E. 2020	Geographical tracking and mapping of coronavirus disease COVID-19/severe acute respiratory syndrome coronavirus 2	Yes	No therapeutic data

		(SARS-CoV-2) epidemic and associated events around the world: how 21st century GIS technologies are supporting the global fight against outbreaks and epidemics		
152	Zeng Q., et al. 2020	Mortality of COVID-19 is Associated with Cellular Immune Function Compared to Immune Function in Chinese Han Population	Yes	No therapeutic data
153	Ahmed S., et al. 2020	Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies	Yes	No therapeutic data
154	Lai CC. et al. 2020	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges	Yes	Review
155	Alhazzani W., et al. 2020	Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)	Yes	No therapeutic data
156	Guo YR., et al. 2020	The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status	Yes	Review
157	Yang Y., et al. 2020	Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective	Yes	Review
158	Liu X., et al. 2020	Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction	Yes	No therapeutic data
159	WHO. 2020	Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected	Yes	Guidelines
160	Li Z., et al. 2020	Development and Clinical Application of a Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis	Yes	No therapeutic data
161	Mao Y., et al. 2020	Clinical and pathological characteristics of 2019 novel coronavirus disease (COVID-19): a systematic reviews	Yes	Review
162	Cui P., et al. 2020	Clinical features and sexual transmission potential of SARS-CoV-2 infected female patients: a descriptive study in Wuhan, China	Yes	No therapeutic data
163	Saw Swee Hock School of Public Health, 2020	COVID-19 Science Report: Therapeutics	Yes	Report
164	Yao X., 2020	In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	Yes	Commentary

165	Pongpirul W., et al. 2020	Journey of a Thai Taxi Driver and Novel Coronavirus	Yes	No therapeutic data
166	Liu YC., et al. 2020	A Locally Transmitted Case of SARS-CoV-2 Infection in Taiwan	Yes	No therapeutic data
167	Velavan T., and Meyer C. 2020	The COVID-19 epidemic	Yes	Commentary

	Author/Title/DOI	Sample size	Age (mean)	Gender	Type of study	Therapeutic treatment	Type/number%	Outcomes (recovery/mortality)	Adverse events	Quality assessment (applicable/inapplicable)
1	Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020. doi:https://doi.org/10.1056/NEJMoa2001282	199	58 Y	120 M 79 F	Randomised Clinical Trial RCT	Lopinavir & ritonavir	Lopinavir & ritonavir / 50% Standard care / 50%	- In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. - 19 patients from whom received the intervention died.	14% of lopinavir–ritonavir developed gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both acute gastritis. Two recipients had self-limited skin eruptions.	The study addressed a focused issue. Randomization done with intention to treat analysis. The population who entered the study are properly accounted for its conclusion. Blindness not done. The 2 groups who enter the study were similar together and treated equally. The primary outcome clearly specified.
2	Cao J, Hu X, Cheng W, Yu L, Tu W, Liu Q. Clinical features and short-term outcomes of 18 patients with corona virus disease 2019 in intensive care unit. Intensive Care Med. 2020:1-3. doi:https://doi.org/10.1007/s00134-020-05987-7	41	49 Y	30 M 11 F	Prospective	Antibiotics and oseltamivir (orally 75 mg twice daily) Corticosteroid therapy was given as a combined regimen if severe community-acquired pneumonia was diagnosed by physicians at the designated hospital.	All patients were administered with empirical antibiotic treatment, 38 (93%) patients received antiviral therapy (oseltamivir). 9 (22%) patients were given systematic corticosteroids.	-Antiviral: 12 ICU admission (92%) - Antibiotics: 13 ICU admission (100%) -Corticosteroids: 6 ICU admission (46%)	Not reported	Adverse events not reported. Treatment given not specified. Types of antibiotics given not mentioned.
3	Chen C, Huang J,	236	56 (25-	Favipirav	Randomised	Favipiravir Arbidol	Antiviral /116	71 Recovery	LFT abnormal,	There is no effective antiviral drug

	Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.17.200	adults	86)	ir group 59 M 57 F Arbidol group 51 M 69 F	Controlled Trial		Antiviral /120		Raised serum uric acid, Psychiatric symptom reactions, and Digestive tract reactions.	was reported, and the drugs mentioned were based on in the sixth edition of the guidelines.
4	Chen C, Qi F, Shi K, et al. Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19 Pneumonia. 2020.	1	45 Y	F	Case report	A case report of a 45-year-old Covid_19 Pneumonia female patient was treated with thalidomide and low-dose glucocorticoid. She was first treated with oral administration of ofloxacin and oseltamivir, but the condition deteriorated. And then treated with lopinavir/ritonavir		Thalidomide inhibit cytokine surge and regulate immune functions, also it could be used to calm patients down to reduce oxygen consumption and relieve digestive symptoms in COVID-19 patients.	Not reported	Need randomized control trials to be done.
5	Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. Engineering. 2020. doi:https://doi.org/10.1016/j.eng.2020.02.006	61	62 Y	Not mentioned	Open labelled clinical trail	Oseltamivir or peramivir according to the standard therapy, and antibiotics were given based on positive results from blood test.	Not mentioned	17.6% died in the experimental group while 54.5% died in the control group.	Not reported	With only 17 patients using MSC, cannot guarantee that every step was perfect during the phase with only a one-time clinical trial. Some patients refused to attend, and some did not complete follow-up. Thus, they are still concerned about the long-term safety of MSC transplantation for treating H7N9-induced ARDS, despite the lack of side effects observed in this clinical trial. The study done on H7N9 patients not COVID-19 patients.
6	Chen J, Fan H, Zhang L, et al. Retrospective	101	65.46 Y	64 M 37 F	single centre and	- Antiviral drugs, including	61 (60.40%) patients were	101 Death	Not reported	Only the critical death patients are

	Analysis of Clinical Features in 101 Death Cases with COVID-19. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.09.20033068				observational study (retrospective).	Oseltamivir, Ribavirin, Lopinavir, Ritonavir, Ganciclovir, or Interferon, etc.; Glucocorticoids, intravenous immunoglobulins, and thymosin preparations antibiotic treatment, including cephalosporins and quinolones & carbapenems, linezolid, tigecycline, etc.	given antiviral drugs, 59 (58.42%), received glucocorticoids, 63.37% were given intravenous immunoglobulins, and 44.55% were treated with thymosin preparations. All patients received antibiotic treatment, 63(62.38%) were given restricted antibiotics, 23(22.78%) were administrated to antifungal drugs.			included. No comparison was made between the improvement groups.
7	Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020. doi:https://doi.org/10.1016/j.jinf.2020.03.004	249	51 Y	126 M 123 F	retrospective, single-centre study.	Antiviral drugs (e.g., lopinavir/ritonavir, arbidol) were used in small proportion of patients. Corticosteroid was not used unless a panel discussion by experts considered necessary (e.g., ARDS).	Not mentioned	2 patients died (0.8%). 22 patients admitted to ICU (8.8%) 8 patients developed ARDS (3.2%) 215 patients discharged (86.3%).	Not reported	A small proportion the patients were still hospitalized at the time of manuscript submission. Therefore, clinical outcomes in these patients were not available and continued observations are still needed. They did not test SARS-CoV-2 daily for everybody. Hence, the actual duration to viral clearance should be shorter than the estimated one.
8	Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507-	99	55.5 Y	67 M 32 F	retrospective, single Centre descriptive study.	Antibiotic: cephalosporins, quinolones, carbapenems, tigecycline against methicillin resistant *Staphylococcus aureus*, linezolid,	Antibiotic treatment 70 (71%) Antifungal treatment 15 (15%) Antiviral treatment:	11 (11%) patients had died	Not reported or NA	Suspected but undiagnosed cases were ruled out in the analyses. More detailed patient information, particularly regarding clinical outcomes, was unavailable at the time of analysis.

	513. doi:https://doi.org/10.1016/S0140-6736(20)30211-7					Antifungal Antiviral treatment: Oseltamivir – ganciclovir – lopinavir & ritonavir Glucocorticoids: methylprednisolone sodium succinate, methylprednisolone, and dexamethasone Immunoglobulin	(75 (76%) patients received antiviral treatment, including oseltamivir (75 mg every 12 h, orally), ganciclovir (0·25 g every 12 h, intravenously), and lopinavir and ritonavir tablets (500 mg twice daily, orally). The duration of antiviral treatment was 3–14 days). Glucocorticoids 19 (19%) Intravenous immunoglobulin therapy 27 (27%)			
9	Chen X, Zheng F, Qing Y, et al. Epidemiological and clinical features of 291 cases with coronavirus disease 2019 in areas adjacent to Hubei, China: a double-center observational study. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.03.20030353	291	46 Y	145 M 146 F	double-center observational study	antiviral therapy including lopinavir and ritonavir tablet Recombinant human interferon α2b Recombinant cytokine gene derived protein Arbidol hydrochloride capsules Chinese Medicine.	285 (97.9%) patients received antiviral therapy: lopinavir and ritonavir tablets (75.9%), recombinant human interferon α2b (45.4%), recombinant cytokine gene derived protein (18.9%) and arbidol hydrochloride capsules (17.2%). 281 (96.6%) patients were treated with Chinese Medicine.	2 (0.7%) patients have died	Not reported	Due to the limitations of the retrospective study, laboratory examinations were performed according to the clinical care needs of the patient, thus some patients' laboratory exam results were uncompleted. Given the short observation period nearly half of our patients were still receiving treatment in hospital at the end of the follow-up and they could not decide the mortality and prognosis of the whole case series.

10	Cui Y, Tian M, Huang D, et al. A 55-Day-Old Female Infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage. J Infect Dis. 2020. doi:https://doi.org/10.1093/infdis/jiaa113	1	55 Day old female infant	NA	Case report	inhaled interferon α-1b (15μg, bid); amoxicillin potassium clavulanate (30mg/kg, Q8H, ivgtt).	NA	NA	NA	Case report for infant patient. Adverse events & outcomes not reported.
11	Du Y, Tu L, Zhu P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. 2020. doi:https://ssrn.com/abstract=3546088	191	56 Y	119 M 72 F	Retrospective, multicenter cohort study.	Antibiotics Antivirals (lopinavir and ritonavir) Corticosteroids IV immunoglobulin	Antibiotics 181 (95%) Antivirals (lopinavir and ritonavir) 41 (21%) Corticosteroids 57 (30%) IV immunoglobulin 46 (24%)	Patients received antibiotics 181 (95%), non-survivor 53 (98%), survivor 128 (93%) P. value 0·15. Antiviral treatment 41 (21%), non-survivor 12 (22%), survivor 29 (21%), P. value 0·87 Corticosteroids 57 (30%) non-survivor 26 (48%) survivor 31 (23%), P. value 0·0005. IVIG: 46 (24%) Non-survivor 36 (67%) survivor 10 (7%) p value < 0.0001 54 died in hospital.	Not reported	Lack of effective antivirals, inadequate adherence to standard supportive therapy, and high-dose corticosteroid use might have also contributed to the poor clinical outcomes in some patients.
12	Gautret P, Lagier J, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020:105949. . doi:https://doi.org/10.1016/j.ijantimicag.2020.105949	Treated 20 Control 16 Total 36	45.1	15 M other= 21	Open label non-randomized clinical trail.	Hydroxychloroquin and azithromycin	hydroxychloroquine sulfate 200 mg, 3 times per day during 10 days	At day 6 post-inclusion, 100% of patients treated with hydroxychloroquine and azithromycin combination were virologicaly cured comparing with 57.1% in patients treated with hydroxychloroquine only, and 12.5% in the control group.	One patient stopped the treatment on day3 post-inclusion because of nausea.	Clinical follow-up and occurrence of side-effects were not discussed in the paper.
13	Guan W, Ni Z, Hu Y, et al. Clinical	1099	47.9	F= 41.1% Other=	Retrospective observational	Intravenous antibiotics	637 patients (58%)	5.0% who were admitted to the ICU, 2.3% who	Not reported	The study did not include the drugs' doses, frequency, and duration.

	characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. doi:https://doi.org/10.1056/NEJMoa2002032				study	Oseltamivir Antifungal Systemic Glucocorticoids	393 patients (35.8%) 31 patients (2.8%) 204 patients (18.6%)	underwent invasive mechanical ventilation, and 1.4% who died. Among the 173 patients with severe disease.		
14	Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020. doi: https://doi.org/10.1056/NEJMoa2001191	1	35	M	Case report	antipyretic therapy consisting of guaifenesin	650 mg 600 mg	Discharged with no symptoms	Not reported	It is only one case study and it does not represent the whole population. It is a case report, we cannot assure the positive impact on the patient's health is due to the medication that he has taken. Need randomized control trials to be done.
15	. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506. :https://doi.org/10.1016/S0140-6736(20)30183-5	41	49	M= 30 (73%) F= 11(27%)	Prospective collection and analysed data for pneumonia patients	Antiviral therapy 38 (93%) Antibiotic therapy 41 (100%) Corticosteroid 9 (22%)	Not mentioned	1 patient was admitted to ICU 6 patients died.	Not reported	Since the causative pathogen has just been identified, kinetics of viral load and antibody titres were not available at the time of the study.
16	Huang M, Yang Y, Shang F, et al. Early and Critical Care in Severe Patients with COVID-19 in Jiangsu Province, China: A Descriptive Study. 2020. doi:https://doi.org/10.21203/rs.3.rs-17397/v1	60 are severe cases	57	M= 58.3% Other= 42.8%	multicentre retrospective cohort study was conducted to extract and analyse epidemiological, clinical, laboratory data and treatment of 60 severe cases	Antiviral therapy 60 (100%) Abidor 50 (83.3) Lopinavir and Ritonavir Tablets 41 (68.3) Interferon 12 (20.0) Ribavirin 7 (11.7) Oseltamivir 2 (3.3) fluoroquinolones (61.7%)	. 34 patients (56.7%) received intravenous glucocorticoid administration at doses ranging from 40 to 80 mg/d. 28 patients (46.7%) received immunoglobulin (IgG enriched) injections for a period of 5 to 9 days immunoregulation	50 patients had significantly improved, 2 patients had been discharged, 8 patients were still in serious conditions	4 patients who developed secondary infections were received glucocorticoids,	The study did not include most of the drugs' doses, frequency, and duration. In the study, the effect of glucocorticoids was not significant

17	. Huang Y, Zhou H, Yang R, Xu Y, Feng X, Gong P. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. medRxiv. 2020. doi:https://doi.org/10.1101/2020.02.27.20029009	36	69.22	M= 25(69.44 %) F= 11(30.56 %)	retrospective, single-centre study	Antibiotic treatment 36 (100%) Antiviral treatment 35 (97.22%) Glucocorticoids 25 (69.44%)	Not mentioned	All the patients died	All the patients died.	The study did not include the drugs doses, frequency, and duration)
18	. Jian-ya G. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. medRxiv. 2020. doi:https://doi.org/10.1101/2020.02.20.20025536	51	45	M=32(62 .7%) F= 19 (37.3%)	Retrospective , single-centre case series	Oseltamivir (po) 7(13.7) Interferon (po) 51(100) Kaletra (po) 51 (100) Thymopentin (im) 48(94.1) Traditional Chinese medicine decoction (po) 28(54.9) Reduling(iv) 30(58.8) Xuebijing（iv） 2(3.9)	Not mentioned	1 patient died with shock complications .	6 patients had obvious appetite decline	The study did not include the drugs' doses, frequency, and duration).
19	Liang B, Zhao Y, Zhang X, Lu J, Gu N. Clinical Characteristics of 457 Cases with Coronavirus Disease 2019. Available at SSRN 3543581. 2020. doi:http://dx.doi.org/10.2139/ssrn.3543581	457	It varies	M= 267 (58%) Pregnant women= 9 (2%)	Systematic Review	Antiviral therapy 352(77%) Antibacterial therapy 258(56%) Glucocorticoids 130(28%)	Not mentioned	195 in improved and discharged	35 death	The study did not include the drugs' doses, frequency, and duration)
20	Liao J, Fan S, Chen J, et al. Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.10.20032136	46	Not mentio ned becaus e they were two groups	M= 17(53.1) F = 15(46.9)	Retrospective Case series data	Antiviral therapy 46 (100.0) Antifungal treatment 5 (10.9) glucocorticoid therapy	Not mentioned	(78.3%) were discharged	Three patients developed acute kidney injury during treatment	At the end date of this study, nearly 20% of the patients still hospitalized.

21	Lim J, Jeon S, Shin H, et al. Case of the index patient who caused tertiary transmission of Coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020;35(6). doi:https://doi.org/10.3346/jkms.2020.35.e79	1	54	M	Case Report	Lopinavir ritonavir	200 mg 50 mg (2 tablets bid)	Reduced viral loads and improved clinical symptoms	The patient also complained of psychiatric symptoms such as depression, insomnia and suicidal thoughts after isolation	It is only one case and does not represent the whole population. Need randomized control trials to be done.
22	. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. International Journal of Infectious Diseases. 2020. doi:https://doi.org/10.1016/j.ijid.2020.03.013	10	42	6 F Other=4	retrospective observational single-center study	lopinavir, LPV, interferon α2b atomization inhalation,	400 mg every twelve 5 million U twice daily hours	Eosinophil counts presented potentiality as predictor on the development process of COVID-19 in this study Seven discharged Three patients stopped lopinavir Two of them deteriorated, one hospitalized longer than others who with sustained lopinavir using	Digestive adverse effect and hypokalemia	Small sample size
23	Liu J, Ouyang L, Guo P, et al. Epidemiological, Clinical Characteristics and Outcome of Medical Staff Infected with COVID-19 in Wuhan, China: A Retrospective Case Series Analysis. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.09.20033118	64 medical staff	35 (29-43)	23 M 41 F	Single centre-Retrospective – observational study	Immune globulin Thymosin Corticosteroids	Antibody / 23 Hormone / 33 Steroid hormone / 7	34 discharged 30 hospitalised	Not reported	Preliminary insight into epidemiological features and clinical outcomes. Single center.
24	Liu W, Zhang Q, Chen J, et al. Detection of	6	3 (1-7)	2 M 4 F	Retrospective Case Series	Ribavirin.	Antiviral /2	6 recovery	Not reported	Small sample size

	Covid-19 in Children in Early January 2020 in Wuhan, China. N Engl J Med. 2020. doi:https://doi.org/10.1056/NEJMc2003717	children			Analysis	Oseltamivir. Glucocorticoiuds. Intravenous immune globulin.	Antiviral /6 Steroid hormone /4 Antibody /1.			
25	Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv. 2020. doi:https://doi.org/10.1101/2020.02.17.20024166	109 patients	55	59 M 50 F	Retrospective Case Series Analysis	Glucocorticoid. Intravenous immunoglobulin therapies	Steroid hormone /43 Antibody / 32 Antibiotics /105 Antivirus /105	31 deaths	Not reported	This study did not mention the names of the therapeutic treatment used among ARDS patients.
26	Lo IL, Lio CF, Cheong HH, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. Int J Biol Sci. 2020;16(10):1698-1707. doi:https://doi.org/10.7150/ijbs.45357	10 patients	54 (27-64)	3 M 1 teenager 6 others	Retrospective Case Series Analysis	Lopinavir Ritonavir	Antiviral / 10	5 discharged 5 hospitalised	Not reported	Small sample size, so it is hard to draw a definite conclusion. Single center. Half of the enrolled patients are still hospitalized at the time of the submission of this paper. Therefore, there may have been bias regarding the prognosis of the patients.
27	Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clinical Infectious Diseases. 2020. doi:https://doi.org/10.1093/cid/ciaa270	155 patients	54 (42-66)	86 M 69 others	Single-centre, Retrospective Case Series Analysis	Arbidol lopinavir and ritonavir; interferon inhalation Immune enhancer	Antiviral /31 Antiviral /27 Antiviral /30 14	22 deaths	Not reported	Selection bias might occur for this retrospective study and a large-scale nationwide study was needed.
28	Wang D, Hu B, Hu C, et al. Clinical	138 patients	56 (42-68)	75 M 63 F	Retrospectiv, single-centre	Oseltamivir	Antiviral / 124	47 discharged 6 deaths	Not reported	Most patients are still hospitalized at the time of manuscript submission.

	characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020. doi:https://doi.org/10.1001/jama.2020.1585				case series	Moxifloxcain Ceftriaxone Azithromycin Glucocorticoid	Antibacterial /89 Antibacterial /34 Antibacterial /25 Glucocorticoid therapy /62	85 hospitalized.		Therefore, there may have been bias regarding the prognosis of the patients.
29	Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clinical Infectious Diseases. 2020. doi:https://doi.org/10.1093/cid/ciaa272	69 patients	42 (35-62)	32 M 37 F	Retrospective case series	-	Antiviral /66 Antibiotic /66 Antifungal drug /8 Corticosteroids /10 Arbidol /36	44 hospitalised 18 discharged 5 deaths	Not reported	The study did not include the drugs' doses, frequency, and duration).
30	Wu C, Hu X, Song J, et al. Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19). medRxiv. 2020. doi:https://doi.org/10.1101/2020.02.26.20028589	188 patients	52	119 M 69 others	Retrospective cohort study	-	Antibiotics / 185 Antiviral /158 Corticosteroids /59	43 deaths 145 discharged 12 Hospitalised	Not reported	The study did not include the drugs' doses, frequency, and duration)
31	Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269. doi:https://doi.org/10.1038/s41586-020-2008-3	1	41 years	M	Epidemiological investigations	Antiviral therapy Antibiotic Glucocorticoid Oxygen therapy	Oseltamivir Cefoselis Not mentioned Mechanical ventilation	recovered	Not reported	Applicable
32	Xu Y, Li Y, Zeng Q, et al. Clinical characteristics of SARS-CoV-2 pneumonia compared to controls in Chinese	Patients: 69 Normal: 14,117	57 years	Male: 50.7% Female: 49.3%	Retrospectiv, multi-centre case series	Antiviral therapy Antibiotic	Oseltamivir 38 (55.1%) patients Moxifloxacin,	Discharged- 3 Recovered- 1 Died- 1	6 patients significantly increased in IL6 were also treated with methylprednisolone.	Applicable

	Han population. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.08.20031658					Oxygen therapy	ceftriaxone, azithromycin, and tigecycline or linezolid 31 (44.9%) patients. 3 patients used mechanical ventilation; 2 patients used an invasive ventilator.			
33	Xu Y, Xu Z, Liu X, et al. Clinical findings in critical ill patients infected with SARS-Cov-2 in Guangdong Province, China: a multi-center, retrospective, observational study. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.03.20030668	45	56.7 years	Male: 29 (64,4%) Female: 16 (35.6%)	multi-centre, retrospective, observational study	Antiviral agents 45 (100) pateints Antibacterial agents 45 (100) Antifungal agents 19 (42.2) Convalescent plasma 6 (13.3) Glucocorticoids 21 (46.7) Immunoglobulin 28 (62.2) Albumin 35 (77.8)	Osehamivir ribavirin Not mentioned Not mentioned Not mentioned Not mentioned Not mentioned	ICU discharge 23 (51.1%) Hospital discharge 11 (24.4%) Death 1 (2.2%)	37 patients (82.2%) had developed acute respiratory distress syndrome, and 13 (28.9%) septic shock. A total of 20 (44.4%) patients required intubation and 9 (20%) required extracorporeal membrane oxygenation.	At the time of study submission, half of the patients had not been discharged from ICU, it is hard to estimate either ICU stay, ventilation free day, the case fatality rate or the predictors of fatality. The study did not include the drugs' doses, frequency, and duration.
34	Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:m606.	62	41 years	Male: 35 (56%) Female: 27 (44%)	Retrospective study	antiviral treatment 55 (89%)	INFa inhalation 8 (13%); Lopinavir/Ritonavir 4 (6%); Arbidol+interferon alpha inhalation 1(2%); Lopinavir/ritonavir+interferon alpha	No mortality	Not reported	At the time of study submission, most patients had not been discharged, so it is hard to estimate either the case fatality rate or the predictors of fatality.

	doi:https://doi.org/10.1136/bmj.m606					Antibiotics Corticosteroid & gamma globulin	inhalation 21(34%); Arbidol+lopinavir /ritonavir 17(28%); Arbidol+lopinavir /ritonavir+interferon alpha inhalation 4(6%) 28 (45%) pateints 16 (26%) pateints			
35	Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020. doi:https://doi.org/10.1016/S2213-2600(20)30076-X	1	50	Male: 50 years old	Postmortem biopsies	Antiviral therapy Antibiotics Corticosteroid	Interferon alfa-2b atomisation lopinavir plus ritonavir Moxifloxacin Methylprednisolone	Died due to cardiac arrest	Chest x-ray showed progressive infiltrate and diffuse gridding shadow in both lungs. Hypoxaemia and shortness of breath worsened & patient had sudden cardiac arrest.	It is only one case study and it does not represent the whole population. The patient refused ventilator support in the intensive care unit repeatedly because he suffered from claustrophobia; therefore, he received high-flow nasal cannula. Need randomized control trials to be done.
36	Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020. doi:https://doi.org/10.1016/S2213-2600(20)30079-5	52	59·7 years	Male: 35 (67%) Female: 17 (33%)	Single-centre retrospective, observational study.	Vasoconstrictive agents Antiviral agents 23 (44%) Antibacterial agents Glucocorticoids Immunoglobulin	18 (35%) Oseltamivir 18(35%) patients, ganciclovir 14 (27%), lopinavir 7 (13·5%). 49 (94%) 30 (58%)	32 (61·5%) patients had died.	Not reported	Due to the exploratory nature of the study, which was not driven by formal hypotheses, the sample size calculation was waived. The researchers acknowledged that some specific information from the ICU was missing, such as mechanical ventilation settings. The study did not include the drugs' doses, frequency, and duration.

							28 (54%)			
37	Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020. doi:https://doi.org/10.1001/jama.2020.3204	18	47 years;	Male: 9(50%) Female: 9(50%)	Descriptive case series	Antiretroviral drug Antiviral therapy Antibiotics	lopinavir-ritonavir oseltamivir not reported	No deaths	Not reported	Small sample size The study did not include some of the drugs' doses, frequency, and duration
38	Zhang B, Zhou X, Qiu Y, et al. Clinical characteristics of 82 death cases with COVID-19. medRxiv. 2020. doi:https://doi.org/10.1101/2020.02.26.20028191	82	72.5 years	Male: (65.9%)	Death cases	Antiviral therapy Antibiotics Corticosteroids 29 (35.3%) patients	82 (100%) 82 (100%) 29 (35.3%)		Not reported	The study has been done in one setting. There is no information about the hospital's capabilities from personnel or equipment because the mortality rate from this centre is a little higher than the other centres. Traditional Chinese Medicine were given. The study did not include the drugs' doses, frequency, and duration.
39	Zhang G, Hu C, Luo L, et al. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. medRxiv. 2020. doi: https://doi.org/10.1101/2020.03.02.20030452	221	55.0 years	Male: 108(48.9%) Female: 113(51.1%)	Retrospective case study.	Antiviral treatment 196 (88.7%) Antibiotic therapy Corticosteroid therapy 115(52.0%)	Oseltamivir, Arbidol hydrochloride, α-interferon atomization inhalation, Lopinavir/ritonavir) Moxifloxacin hydrochloride; Piperacillin sodium tazobactam sodium; Cefoperazone sulbactam	12 (5.4%) Death	Not reported	The dose and duration of intravenous glucocorticoid treatment showed no difference in outcomes of symptomatic relief and death. The study did not include the drugs' doses, frequency, and duration.

							Glucocorticoid 64 (49.6%) patients			
40	Zhang G, Hu C, Luo L, et al. Clinical Features and Treatment of 221 Patients with COVID-19 in Wuhan, China. China (2/27/2020). 2020 doi:http://dx.doi.org/10.2139/ssrn.3546095.	221	Not mentioned	M=108 F=113	single center, retrospective case series study (Observational)	Antiviral therapy 196 (88.7%) Glucocorticoid 115(52.0)	Not mentioned	A total of 42 (19.0%) patients had been discharged 12 (5.4%) patients died 44 (80%) of them received ICU care 23 of them transferred to the general wards Mortality rate was 21.8%	Not reported	
41	Zhang JC, Zhang X, Wu G, Yi J. The potential role of IL-6 in monitoring coronavirus disease 2019. doi:https://doi.org/10.1101/2020.03.01.20029769	80	53	F= 46(57.5%) M=34(42.5%)	Data collection (Clinical data of COVID-19 patients diagnosed by laboratory test in our institution were collected). observation of clinical manifestation	Antibiotics 73 (91·25) Oseltamivir 20 (25·00) Ribavirin, ganciclovir or peramivir 47 (58·75) Arbidol 49 (61·25) Antifungal medications 10 (12·50) Intravenous immunoglobin 36 (45·00) Corticosteroids 29 (36·25)	Not mentioned	It is suggested that IL-6 may be used as a biomarker for disease monitoring in severe COVID-19 patients.	Not reported	The study did not include the drugs' doses, frequency, and duration. IL-6 and the pathogenesis of COVID-19 remains elusive.
42	Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020. doi:https://doi.org/10.1	191 patients	56·0 years	Male: 119 (62%) Female: 72 (38%)	Retrospective cohort study	Antibiotics 181 (95%) Antiviral treatment 41 (21%) Corticosteroids 57 (30%) Intravenous	Lopinavir/ritonavir	137 were discharged and 54 died in hospital.	191 patients	There was no observation of shortening of viral shedding duration after lopinavir/ritonavir treatment in the current study. The study did not include the drugs' doses, frequency, and duration.

	016/S0140-6736(20)30566-3					immunoglobin 46 (24%)				

Table 3. Data extraction from included papers

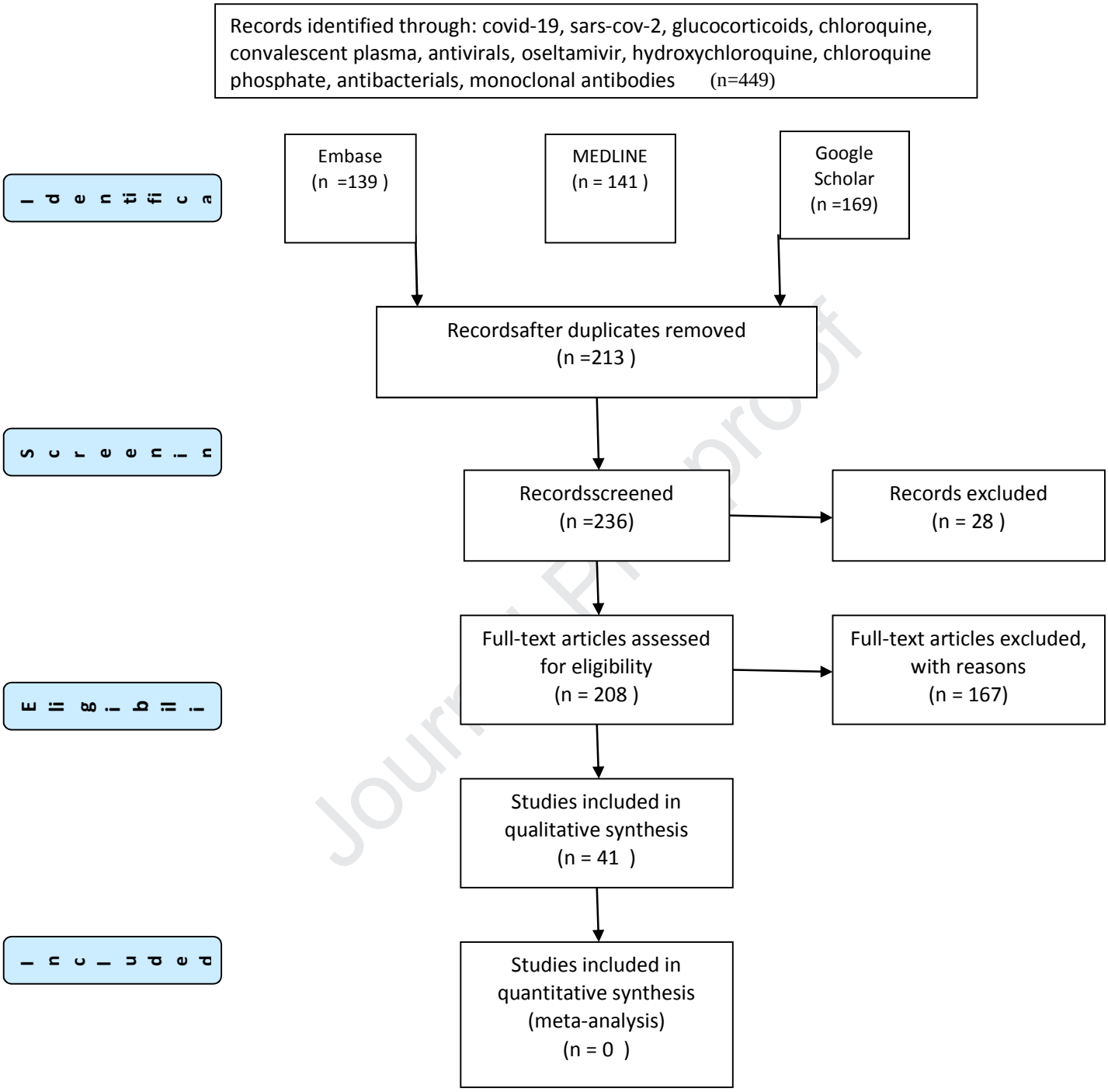

Figure1 PRISMA Flow Diagram reporting search results

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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