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Review

Therapeutic management of patients with COVID-19: a systematic review

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SUMMARY

Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which was declared a global pandemic by the World Health Organization on 11th March 2020. The treatment guidelines for COVID-19 vary between countries, yet there is no approved treatment to date.
Aim: To report any evidence of therapeutics used for the management of patients with COVID-19 in clinical practice since emergence of the virus.
Methods: A systematic review protocol was developed based on the PRISMA statement. Articles for review were selected from Embase, Medline and Google Scholar. Readily accessible peer-reviewed, full articles in English published from 1st December 2019 to 26th March 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 types of study eligible for inclusion.
Results: Four hundred and forty-nine articles were identified in the literature search; of these, 41 studies were included in this review. These were clinical trials (*N*=3), case reports (*N*=7), case series (*N*=10), and retrospective (*N*=11) and prospective (*N*=10) observational studies. Thirty-six studies were conducted in China (88%). Corticosteroid treatment was reported most frequently (*N*=25), followed by lopinavir (*N*=21) and oseltamivir (*N*=16).

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Conclusions: This is the first systematic review to date related to medication used to treat patients with COVID-19. Only 41 studies were eligible for inclusion, most of which were conducted in China. Corticosteroid treatment was reported most frequently in the literature.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which was declared a global pandemic by the World Health Organization (WHO) on 11th March 2020. SARS-CoV-2 was discovered in December 2019 in Wuhan City, 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, a novel enveloped RNA betacoronavirus, has phylogenetic similarity to severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus [2].

One of the characteristics of COVID-19 is that it is highly contagious; China and 164 other countries have been affected in less than 3 months. Despite China reaching 81,151 confirmed cases with 3242 deaths, the country has reported only one new domestic case since 18th March 2020. As of that date, the total worldwide confirmed cases was 193,475 with 7864 deaths (WHO). Although protective measures have been implemented in China (e.g. isolation from confirmed and suspected cases) to reduce 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 the onset of the outbreak, many agents that could have efficacy against COVID-19 have been proposed. Various antiviral agents were included in the latest guidelines from the National Health Commission, including interferon, lopinavir/ritonavir, chloroquine phosphate, ribavirin and arbidol [3]. Angiotensin receptor blockers, such as losartan, have also been suggested for the treatment of COVID-19 [4].

The treatment guidelines for COVID-19 vary between countries. The WHO guidelines are very general, recommending management of symptoms, and advise caution with paediatric patients, pregnant women and patients with underlying co-morbidities. There is no approved treatment for COVID-19; the recommendation is to provide supportive management according to each patient's need (e.g. antipyretics for fever, oxygen therapy for respiratory distress). Moreover, WHO recommendations indicate that severe cases should be given empiric antimicrobial therapy, with mechanical ventilation implemented depending on the patient's clinical condition. Some of the Asian guidelines (e.g. the Japanese guidelines) were not easy to interpret as they have not yet been translated into English. However, the treatment protocols across countries are similar, and include hydroxychloroquine, chloroquine phosphate, remedesivir and lopinavir/ritonavir [5–7]. Treatment guidelines between countries differ slightly, as shown in Table I [8–11].

In light of limited evidence in the literature regarding medication used to treat COVID-19, this review aims to retrospectively evaluate the therapeutic management received by patients with COVID-19 since emergence of the virus.

Table I
Comparison between the treatment guidelines for coronavirus disease 2019 in Saudi Arabia, the USA, Europe and Egypt [8–11]

	Saudi Arabia (Ministry of Health)	USA (Massachusetts General Hospital)	Europe (Ireland)	Egypt
Mild-to-moderate	Hydroxychloroquine Chloroquine Chloroquine phosphate	Clinical trial of remdesivir	Chloroquine (oral) Hydroxychloroquine (oral) Lopinavir/ritonavir (oral)	Oseltamivir Hydroxychloroquine Chloroquine phosphate
Severe	Hydroxychloroquine Chloroquine Chloroquine phosphate Combination therapy (lopinavir/ritonavir)	Hydroxychloroquine Chloroquine Lopinavir/ritonavir Darunavir/cobicistat	Remdesivir (intravenous)	Oseltamivir Hydroxychloroquine Chloroquine phosphate Lopinavir/ritonavir Serum ferritin, D-dimer Antibiotics
Critical	Combination therapy (lopinavir/ritonavir) Hydroxychloroquine Remdesivir	With USA United States of America, interferon-β B1 (Betaseron)		Oseltamivir Hydroxychloroquine (or chloroquine phosphate) Azithromycin Hydrocortisone Therapeutic anticoagulants if D-Dimer Invasive

Methods

A systematic review protocol was developed based on PRISMA-P and the PRISMA statement. Articles for review were selected from Embase, Medline and Google Scholar. Readily accessible peer-reviewed, full articles in English, published from 1st December 2019 to 26th March 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 types of study eligible for inclusion; however, these were likely to be quantitative studies and randomized clinical trials. The focus of this review was therapeutics for the management of patients with COVID-19.

The primary outcomes were: (1) evidence of therapeutics used for the management of patients with COVID-19 in clinical practice, irrespective of patient characteristics, setting and outcome measures, in order to discuss the most commonly reported medicines; and (2) clinical outcomes of therapeutic treatment (i.e. recovery, mortality) in patients with COVID-19. The secondary outcome of this review was adverse events associated with treatment.

Duplicate articles were removed. Titles and abstracts were screened independently by two reviewers, followed by review of full articles where any doubt remained. Inclusions and exclusions were recorded following PRISMA guidelines, and detailed reasons for exclusion were recorded. Critical appraisal checklists appropriate to each study design were applied and checked by a second team member. Any bias or quality issues

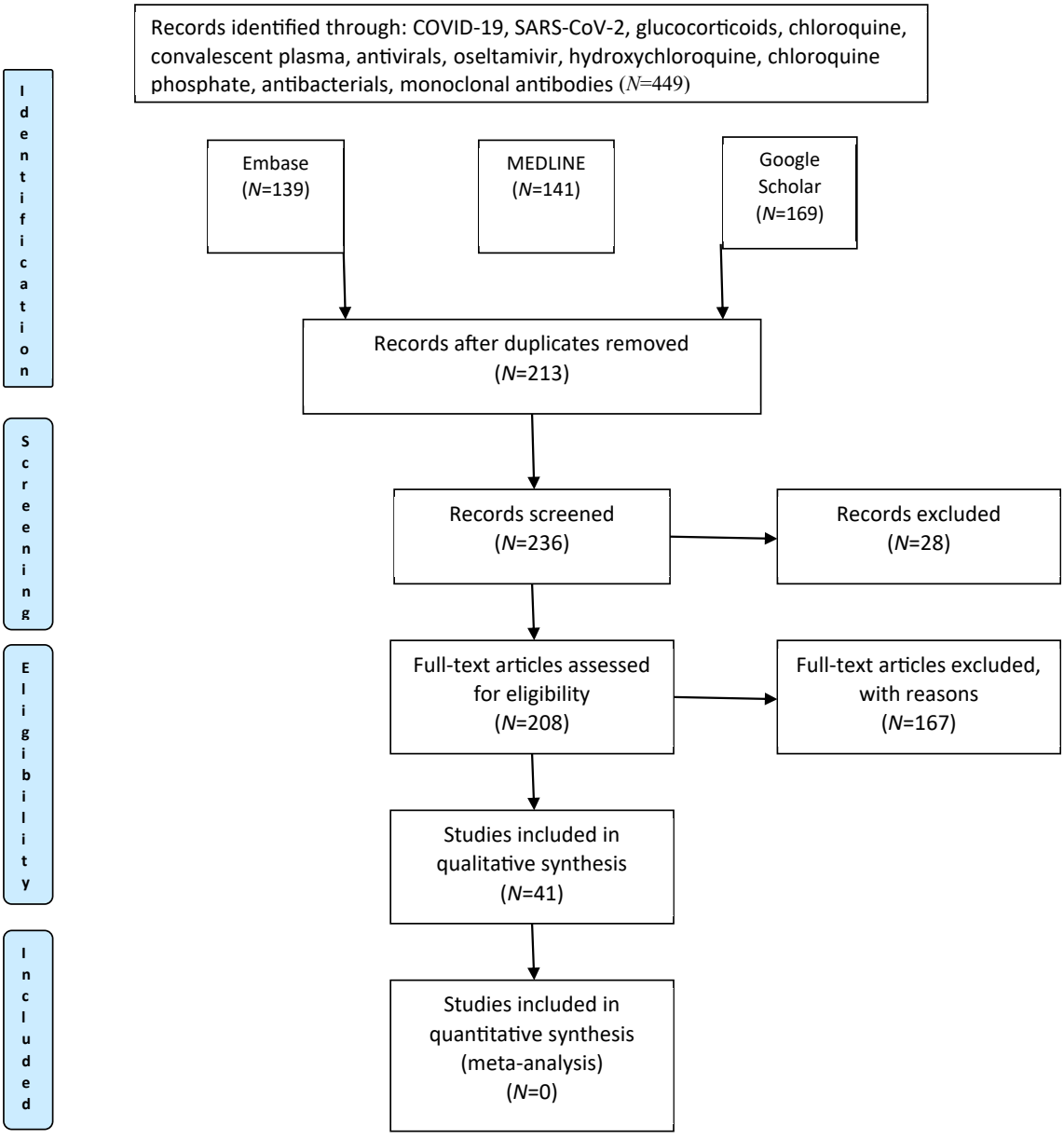

Figure 1. PRISMA flow diagram reporting search results. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Table II
Excluded papers and reasons for exclusion

No.	Authors	Title	COVID-19 Yes/no	Reason for exclusion
1	Chughtai 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, 2020	Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics	Yes	Commentary
3	Wang et al., 2020	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro	Yes	Commentary
4	Colson et al., 2020	Chloroquine and hydroxychloroquine as available weapons to fight COVID-19	Yes	Commentary
5	Liu et al., 2020	Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy	Yes	No details on therapeutics/commentary
6	Baron et al., 2020	Teicoplanin: an alternative drug for the treatment of coronavirus COVID-19?	Yes	Commentary
7	Mitja and Clotet, 2020	Use of antiviral drugs to reduce COVID-19 transmission	Yes	Commentary
8	Colson et al., 2020	**Chloroquine for the 2019 novel coronavirus SARS-CoV-2**	Yes	Commentary
9	Morse 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 et al., 2020	Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19	Yes	Commentary
11	Elfiky, 2020	Anti-HCV, nucleotide inhibitors, repurposing against COVID-19	Yes	Commentary
12	Ung, 2020	Community pharmacist in public health emergencies: quick to action against the coronavirus 2019-nCoV outbreak	Yes	Commentary
13	Gupta, 2020	Clinical considerations for patients with diabetes in times of COVID-19 epidemic	Yes	Commentary
14	Dong et al., 2020	Discovering drugs to treat coronavirus disease 2019 (COVID-19)	Yes	Commentary
15	Zhang et al., 2020	Liver injury in COVID-19: management and challenges	Yes	Commentary
16	Cunningham et al., 2020	Treatment of COVID-19: old tricks for new challenges	Yes	Commentary
17	Ko et al., 2020	Arguments in favour of remdesivir for treating SARS-CoV-2 infections	Yes	Commentary
18	Arabi et al., 2020	COVID-19: a novel coronavirus and a novel challenge for critical care	Yes	Commentary
19	Wang and Shi, 2020	Managing neonates with respiratory failure due to SARS-CoV-2	Yes	Commentary
20	Stebbing et al., 2020	COVID-19: combining antiviral and anti-inflammatory treatments	Yes	Commentary
21	Touret and Lamballerie, 2020	Of chloroquine and COVID-19	Yes	Commentary
22	Porcheddu 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 et al., 2020	Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics	Yes	Commentary
24	Baden and Rubin, 2020	COVID-19 — the search for effective therapy	Yes	Commentary
25	Baud et al., 2020	COVID-19 in pregnant women	Yes	No therapeutic data/commentary

26	Ortega 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 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 et al., 2020	2019 novel coronavirus: an emerging global threat	Yes	Commentary
29	Barry et al., 2020	COVID-19 in the shadows of MERS-CoV in the Kingdom of Saudi Arabia	Yes	Commentary
30	Wang et al., 2020	A precision medicine approach to managing 2019 novel coronavirus pneumonia	Yes	No therapeutic data/commentary
31	Singhal, 2020	A Review of coronavirus disease-2019 (COVID-19)	Yes	Review article
32	Li et al., 2020	A simple laboratory parameter facilitates early identification of COVID-19 patients	Yes	Retrospective case-negative control study
33	Guo et al., 2020	A survey for COVID-19 among HIV/AIDS patients in two districts of Wuhan, China	Yes	No therapeutic data
34	Gao et al., 2020	Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies	Yes	Commentary
35	Deng 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 et al., 2020	Care for critically ill patients with COVID-19	Yes	Commentary
37	Deng and Peng, 2020	Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China	Yes	Review
38	Wang et al., 2020	Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China	Yes	No therapeutic data
39	Xiong et al., 2020	Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes	Yes	No therapeutic data
40	Chen et al., 2020	Clinical and immunologic features in severe and moderate forms of coronavirus disease 2019	Yes	No therapeutic data
41	Chen 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 et al., 2020	Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children	Yes	Perspectives/no therapeutic data
43	Ye et al., 2020	Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation	Yes	No therapeutic data
44	Anderson et al., 2020	Clinical management of suspected or confirmed COVID-19 disease	Yes	Review
45	Zhang et al., 2020	Clinical trials for the treatment of coronavirus disease 2019 (COVID-19): a rapid response to urgent need	Yes	Commentary
46	Chen et al., 2020	Convalescent plasma as a potential therapy for COVID-19	Yes	Commentary
47	Yang et al., 2020	Corona virus disease 2019: a growing threat to children?	Yes	Commentary/no therapeutic data
48	Kooraki et al., 2020	Coronavirus (COVID-19) outbreak: what the department of radiology should know	Yes	Commentary/no therapeutic data
49	Rasmussen et al., 2020	Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know	Yes	Commentary/no therapeutic data

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Table II (*continued*)

No.	Authors	Title	COVID-19 Yes/no	Reason for exclusion
50	Liu et al., 2020	Coronavirus disease 2019 (COVID-19) during pregnancy: a case series	Yes	No therapeutic data
51	Mclntosh et al., 2020	Coronavirus disease 2019 (COVID-19)	Yes	Review
52	He and Li, 2020	Coronavirus disease 2019 (COVID-19): what we know?	Yes	Review
53	Xiong et al., 2020	Coronaviruses and the cardiovascular system: acute and long-term implications	Yes	Commentary
54	Gong et al., 2020	Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia	Yes	No therapeutic data
55	Dong et al., 2020	Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China	Yes	No therapeutic data
56	Shereen et al., 2020	COVID-19 infection: origin, transmission, and characteristics of human coronaviruses	Yes	Review
57	Rio and Malani, 2020	COVID-19 — new insights on a rapidly changing epidemic	Yes	Review
58	Yi et al., 2020	COVID-19: what has been learned and to be learned about the novel coronavirus disease	Yes	Review
59	Rezaeetalab et al., 2020	COVID-19: a new virus as a potential rapidly spreading in the worldwide	Yes	Review
60	Shaker et al., 2020	COVID-19: pandemic contingency planning for the allergy and immunology clinic	Yes	No therapeutic data
61	Aslam and Mehra, 2020	COVID-19: yet another coronavirus challenge in transplantation	Yes	Commentary
62	Padmanabhan, 2020	Potential dual therapeutic approach against SARS-CoV-2/ COVID-19 with nitazoxanide and hydroxychloroquine	Yes	Commentary
63	Hick et al., 2020	Duty to plan: health care, crisis standards of care, and novel coronavirus SARS-CoV-2	Yes	Discussion
64	Yang et al., 2020	Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China	Yes	No therapeutic data
65	Khan, 2020	Epidemiology of corona virus in the world and its effects on the China economy	Yes	Review
66	Hoehl et al., 2020	Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China	Yes	Commentary
67	Yang 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 et al., 2020	Features, evaluation and treatment of coronavirus (COVID-19)	Yes	Review
69	Erol, 2020	High-dose intravenous vitamin C treatment for COVID-19 (a mechanistic approach)	Yes	Review
70	Liu et al., 2020	Highly ACE2 expression in pancreas may cause pancreas damage after SARS-CoV-2 infection	Yes	Commentary
71	Zhang 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 et al., 2020	Implications of COVID-19 for patients with pre-existing digestive diseases	Yes	Commentary
73	Ferguson et al., 2020	Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand	Yes	No therapeutic data
74	Qiu et al., 2020	Intensive care during the coronavirus epidemic	Yes	Commentary
75	Poon et al., 2020	ISUOG interim guidance on 2019 novel coronavirus infection during pregnancy and puerperium: information for healthcare professionals	Yes	Review
76	Khan et al., 2020	The emergence of a novel coronavirus (SARS-CoV-2), their biology and therapeutic options	Yes	Discussion
77	Sun et al., 2020	Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province	Yes	Commentary
78	Guzzi et al., 2020	Master regulator analysis of the SARS-CoV-2/human interactome	Yes	No therapeutic data
79	Memish et al., 2020	Middle East respiratory syndrome	No	Review
80	Nicastri, 2020	Recommendations for COVID-19 clinical management	Yes	Commentary
81	Li et al., 2020	Network bioinformatics analysis provides insight into drug repurposing for COVID-2019	Yes	No therapeutic data
82	Xiong 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 et al., 2020	Novel coronavirus (COVID-19): a new emerging pandemic threat	Yes	Survey/no therapeutic data
84	Ai et al., 2020	Optimizing diagnostic strategy for novel coronavirus pneumonia, a multi-center study in Eastern China	Yes	No therapeutic data
85	Qiu et al., 2020	Outcome reporting from protocols of clinical trials of coronavirus disease 2019 (COVID-19): a review	Yes	No therapeutic data
86	Bajema et al., 2020	Persons evaluated for 2019 novel coronavirus — United States, January 2020	Yes	Commentary
87	Shanmugaraj et al., 2020	Perspectives on monoclonal antibody therapy as potential therapeutic intervention for coronavirus disease-19 (COVID-19)	Yes	Review
88	Zhou and Zhao, 2020	Perspectives on therapeutic neutralizing antibodies against the novel coronavirus SARS-CoV-2	Yes	Review
89	Hoffmann 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 and Liu, 2020	Potential interventions for novel coronavirus in China: a systematic review	Yes	Review
91	Vasylyeva, 2020	Pregnancy and COVID-19: a brief review	Yes	Review
92	Alamri et al., 2020	Pharmacoinformatics and molecular dynamic simulation studies reveal potential inhibitors of SARS-CoV-2 main protease 3CLpro	Yes	No therapeutic data
93	Fisher and Heymann, 2020	Q&A: The novel coronavirus outbreak causing COVID-19	Yes	Commentary
94	Goh 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 et al., 2020	Restoration of leukomonocyte counts is associated with viral clearance in COVID-19 hospitalized patients	Yes	No therapeutic data

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Table II (*continued*)

No.	Authors	Title	COVID-19 Yes/no	Reason for exclusion
96	Bouadma et al., 2020	Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists	Yes	Review
97	Zhu et al., 2020	Systematic review of the registered clinical trials of coronavirus disease2019 (COVID-19)	Yes	Review
98	Yang et al., 2020	The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China	Yes	Review
99	Li et al., 2020	The neuroinvasive potential of SARS CoV2 may play a role in the respiratory failure of COVID 19 patients	Yes	Review
100	Naicker et al., 2020	The novel coronavirus 2019 epidemic and kidneys	Yes	Review
101	Fang et al., 2020	Transmission dynamics of the COVID 19 outbreak and effectiveness of government interventions: a data driven analysis	Yes	No therapeutic data
102	Sun et al., 2020	Understanding of COVID 19 based on current evidence	Yes	Review
103	Wang 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 et al., 2020	What nephrologist should know about COVID-19 outbreak?	Yes	Commentary
105	Cortegiani et al., 2020	A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19	Yes	Review
106	Ryu et al., 2020	An interim review of the epidemiological characteristics of 2019 novel coronavirus	Yes	Review
107	Yang and Shen, 2020	Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19	Yes	Review
108	Fan et al., 2020	Bat coronaviruses in China	Yes	Review
109	Russell et al., 2020	Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury	Yes	Commentary
110	Liang 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 et al., 2020	Co-infection with SARS-CoV-2 and influenza A virus in patient with pneumonia, China	Yes	Commentary
112	Martinez et al., 2020	Compounds with therapeutic potential against novel respiratory 2019 coronavirus	Yes	Commentary
113	Tang et al., 2020	Coronavirus disease 2019 (COVID-19) pneumonia in a hemodialysis patient	Yes	No therapeutic data
114	Chang et al., 2020	Coronavirus disease 2019: coronaviruses and blood safety	Yes	Review
115	Walker, 2020	COVID-19, Australia: Epidemiology Report 2	Yes	Commentary
116	Lu, 2020	Drug treatment options for the 2019-new coronavirus (2019-nCoV)	Yes	Commentary
117	Hellewell et al., 2020	Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts	Yes	No therapeutic data
118	Prompetchara et al., 2020	Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic	Yes	Review

119	Ashour et al., 2020	Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks	Yes	Review
120	Zhou et al., 2020	Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2	Yes	No therapeutic data
121	Devaux et al., 2020	New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?	Yes	Review
122	Cauchi and Locht, 2020	Non-specific effects of live attenuated pertussis vaccine against heterologous infectious and inflammatory diseases	Yes	Review
123	Chang 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 et al., 2020	Potential rapid diagnostics, vaccine and therapeutics for 2019 novel coronavirus (2019-nCoV): a systematic review	Yes	Review
125	Chen et al., 2020	Recurrence of positive SARS-CoV-2 RNA in COVID-19: a case report	Yes	Commentary
126	Liu et al., 2020	Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases	Yes	Review
127	Gralinski and Menachery, 2020	Return of the coronavirus: 2019-nCoV	Yes	Commentary
128	Cao et al., 2020	SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics	Yes	Commentary
129	Walls et al., 2020	Structure, function and antigenicity of the SARS-CoV-2 spike glycoprotein	Yes	Commentary
130	Xu et al., 2020	Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-	Yes	Review
131	Garrett, 2020	The art of medicine COVID-19: the medium is the message	Yes	Commentary
132	Habibzadeh and Stoneman, 2020	The novel coronavirus: a bird's eye view	Yes	Review
133	Wu et al., 2020	The SARS-CoV-2 outbreak: what we know	Yes	Review
134	Nezhad et al., 2020	Therapeutic approaches for COVID-19 based on the dynamics of interferon-mediated immune responses	Yes	No therapeutic data
135	Lu, 2020	Timely development of vaccines against SARS-CoV-2	Yes	Commentary
136	Kim et al., 2020	Viral load kinetics of SARS-CoV-2 infection in first two patients in Korea	Yes	Commentary
137	Sekhar, 2020	Virtual screening based prediction of potential drugs for COVID-19	Yes	No therapeutic data
138	Park et al., 2020	Virus isolation from the first patient with SARS-CoV-2 in Korea	Yes	Commentary
139	Lake, 2020	What we know so far: COVID-19 current clinical knowledge and research	Yes	Review
140	Ralph et al., 2020	2019-nCoV (Wuhan virus), a novel coronavirus: human-to-human transmission, travel-related cases, and vaccine readiness	Yes	Review
141	Jin, 2020	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)	Yes	Review
142	Liu et al., 2020	Association of cardiovascular manifestations with in-hospital outcomes in patients with COVID-19: a hospital staff data	Yes	No therapeutic data

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Table II (*continued*)

No.	Authors	Title	COVID-19 Yes/no	Reason for exclusion
143	Lai 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 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, 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 and Karako, 2020	COVID-19: real-time dissemination of scientific information to fight a public health emergency of international concern	Yes	Commentary
147	Vankadari and Wilce, 2020	Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26	Yes	Review
148	Hsih 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 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 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 and Geraghty, 2020	Geographical tracking and mapping of coronavirus disease COVID-19/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic and associated events around the world: how 21st century GIS technologies are supporting the global fight against outbreaks and epidemics	Yes	No therapeutic data
152	Zeng 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 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 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 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 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 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 et al., 2020	Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction	Yes	No therapeutic data
159	World Health Organization, 2020	Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected	Yes	Guidelines
160	Li 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 et al., 2020	Clinical and pathological characteristics of 2019 novel coronavirus disease (COVID-19): a systematic reviews	Yes	Review
162	Cui 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, 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 et al., 2020	Journey of a Thai taxi driver and novel coronavirus	Yes	No therapeutic data
166	Liu et al., 2020	A locally transmitted case of SARS-CoV-2 infection in Taiwan	Yes	No therapeutic data
167	Velavan and Meyer, 2020	The COVID-19 epidemic	Yes	Commentary

identified were considered prior to a quantitative meta-analysis and meta-narrative. Critical Appraisal Skills Programme checklist tools were used for quality assessment. 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

Four hundred and forty-nine articles were identified in the literature search. Inclusions and exclusions are reported following PRISMA guidelines in Figure 1, with reasons for exclusion recorded (Table II). In total, 213 duplicate studies were excluded. In addition, 18 studies were excluded due to language (Chinese *N*=9, Dutch *N*=2, Vietnamese *N*=1, Spanish *N*=1, Italian *N*=1, Russian *N*=1, Portuguese *N*=1, Iranian *N*=1, German *N*=1), and 10 studies 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 III.

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

Patient characteristics

In total, 8806 patients were reported in the 41 studies included in this review. The mean age of patients was 50.8 years based on 39 studies; age was not specified in two studies.

Reported therapeutics

Corticosteroids, an anti-inflammatory medication, were reported most commonly in this systematic review (*N*=25), using different names and product characteristics (corticosteroid *N*=21, methylprednisolone *N*=3, dexamethasone *N*=1). Use of lopinavir, an antiviral HIV medication (*N*=21) — in combination with ritonavir (*N*=18) or alone (*N*=3) — oseltamivir (*N*=16) and arbidol hydrochloride (*N*=8) was also reported.

In terms of antibacterial agents, moxifloxacin (*N*=4) and tigecycline were reported most frequently.

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

Treatment outcome

The outcome measures recorded were patient discharge and recovery, ongoing hospitalization and mortality (Table III).

Discussion

To the authors' knowledge, this is the first systematic review related to medication used to treat patients with COVID-19. Only 41 eligible research articles were identified and included in this review [2,5,12–49]. Of these, three studies were clinical trials; the rest were case reports, case series, or prospective or retrospective observational studies. Systemic

Table III
Data extracted from included papers

	Author/title/DOI	Sample size	Mean age (years)	Gender	Type of study	Therapeutic treatment	Type: *N* (%)	Outcomes (recovery/ mortality)	Adverse events	Quality assessment (applicable/ inapplicable)
1	Cao *et al*. A trial of lopinavir—ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2001282	199	58	120 M 79 F	Randomized clinical trial	Lopinavir and ritonavir	Lopinavir and ritonavir: 50% Standard care: 50%	In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir—ritonavir treatment beyond standard careNineteen deaths among patients who received the intervention	14% of patients who received lopinavir—ritonavir developed gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort or diarrhoea, as well as two serious adverse events (both acute gastritis)Two recipients had self-limited skin eruptions	The study addressed a focused issue Randomization with intention-to-treat analysis The population who entered the study were accounted for properly in the conclusion Not blinded The two groups who entered the study were similar and treated equally The primary outcome was specified clearly
2	Cao *et al*. Clinical features and short-term outcomes of 18 patients with coronavirus disease 2019 in intensive care unit. Intensive Care Med 2020.https://doi.org/10.1007/s00134-020-05987-7	41	49	30 M 11 F	Prospective	Antibiotics and oseltamivir (orally 75 mg twice daily) Corticosteroid was given as a combined regimen if severe community-acquired pneumonia was diagnosed by physicians at the designated hospital	All patients received empirical antibiotic treatmentAntiviral (oseltamivir): 38 (93%)Systemic corticosteroid: 9 (22%)	Antiviral: 12 ICU admissions (92%) Antibiotic: 13 ICU admissions (100%) Corticosteroid: six ICU admissions (46%)	Not reported	Adverse events not reported Treatment given not specified Types of antibiotics given not mentioned
3	Chen *et al*. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv 2020. https://doi.org/10.1101/2020.03.17.200	236	56 (25—86)	Favipiravir group:59 M 57 FArbidol group:51 M 69 F	Randomized controlled trial	Favipiravir Arbidol	Antiviral: 116 Antiviral: 120	71 patients recovered	Abnormal liver function tests, raised serum uric acid, psychiatric symptom reactions and digestive tract reactions	No effective antiviral drug was reported, and the drugs mentioned were based on the sixth edition of the guidelines of Chinese diagnosis and treatment plan of COVID-19 patients
4	Chen *et al*. Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19 pneumonia	1	45	F	Case report	Thalidomide and low-dose glucocorticoid. The patient was first treated with oral ofloxacin and oseltamivir, but her		Thalidomide inhibits the cytokine surge and regulates immune functions. In addition, it can be used to calm patients	Not reported	Randomized controlled trials are needed

	2020. Preprints 2020; 2020020395. https://www.preprints.org/manuscript/202002.0395/v1					condition deteriorated. The patient was subsequently treated with lopinavir/ritonavir		down in order to reduce oxygen consumption and relieve digestive symptoms		
5	Chen *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. https://doi.org/10.1016/j.eng.2020.02.006	61	62	Not mentioned	Open labelled clinical trial	Oseltamivir or peramivir (according to standard therapy) and antibiotics were given based on positive blood test results	Not mentioned	17.6% of patients in the experimental group and 54.5% of patients in the control group died	Not reported	With only 17 patients using mesenchymal stem cells, it cannot be guaranteed that every step was perfect during the phase with a single clinical trialSome patients refused to attend and some did not complete follow-up. Thus, there is still concern about the long-term safety of mesenchymal stem cell transplantation for the treatment of H7N9-induced ARDS, despite the lack of side-effects observed in this clinical trial This study was undertaken on patients with H7N9 not COVID-19
6	Chen *et al*. Retrospective analysis of clinical features in 101 death cases with COVID-19. medRxiv 2020. https://doi.org/10.1101/2020.03.09.20033068	101	65.46	64 M 37 F	Single centre and observational study (retrospective)	Antiviral drugs, including oseltamivir, ribavirin, lopinavir, ritonavir, ganciclovir and interferon Glucocorticoids, IV immunoglobulins and thymosin preparations Antibiotic treatment, including cephalosporins, quinolones, carbapenems, linezolid and tigecycline	Antiviral: 61 (60.4%) Glucocorticoid: 59 (58.42%)IV immunoglobulin: 63.37% Thymosin: 44.55% Antibiotic: 101 (100%)Restricted antibiotic: 63 (62.38%)Antifungal: 23 (22.78%)	101 patients died	Not reported	Only the critical death patients are included No comparison was made between the improvement groups

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Table III (*continued*)

	Author/title/DOI	Sample size	Mean age (years)	Gender	Type of study	Therapeutic treatment	Type: *N* (%)	Outcomes (recovery/ mortality)	Adverse events	Quality assessment (applicable/ inapplicable)
7	Chen *et al*. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect 2020. https://doi.org/10.1016/j.jinf.2020.03.004	249	51	126 M 123 F	Retrospective, single-centre study	Antiviral drugs (e.g. lopinavir/ritonavir, arbidol) were used in a small proportion of patients Corticosteroids were not used unless considered necessary by an expert panel (e.g. ARDS)	Not mentioned	Two patients died (0.8%) 22 patients were admitted to ICU (8.8%) Eight patients developed ARDS (3.2%) 215 patients were 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 needed SARS-CoV-2 was not tested daily for all patients. Hence, the actual time to viral clearance should be shorter than the estimated value
8	Chen *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395:507−13.	99	55.5	67 M 32 F	Retrospective, single-centre descriptive study	Antibiotic: cephalosporins, quinolones, carbapenems, tigecycline against meticillin-resistant *Staphylococcus aureus*, linezolid Antifungal Antiviral: oseltamivir, ganciclovir and lopinavir/ritonavir Glucocorticoid: methylprednisolone sodium succinate, methylprednisolone and dexamethasone- Immunoglobulin	Antibiotic: 70 (71%) Antifungal: 15 (15%) Antiviral: 75 (76%), including oseltamivir (75 mg every 12 h, orally), ganciclovir (0.25 g every 12 h, intravenously), and lopinavir/ritonavir (500 mg twice daily, orally). The duration of antiviral treatment was 3−14 days Glucocorticoid: 19 (19%) IV immunoglobulin: 27 (27%)	11 (11%) patients 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
9	Chen *et al*. Epidemiological and clinical features of 291 cases with coronavirus disease 2019 in areas adjacent to Hubei, China: a double-	291	46	145 M 146 F	Double-centre observational study	Antiviral including lopinavir and ritonavir Recombinant human interferon-α2b Recombinant cytokine gene-derived protein	Antiviral: 285 (97.9%) Lopinavir/ritonavir: 75.9% Recombinant human interferon-α2b: 45.4% Recombinant cytokine gene-derived protein:	Two (0.7%) patients died	Not reported	Due to limitations of the retrospective study, laboratory examinations were performed according to the clinical care needs of the patients; as such,

	center observational study. medRxiv 2020. https://doi.org/10.1101/2020.03.03.20030353					Arbidol hydrochloride Chinese medicine	18.9% Arbidol hydrochloride: 17.2% Chinese medicine: 281 (96.6%)			some laboratory examinations were not completed Given the short observation period, nearly half of the patients were still receiving treatment in hospital at the end of the follow-up period, and it was not possible to determine mortality and prognosis of the whole case series
10	Cui *et al*. A 55-day-old female infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage. J Infect Dis 2020. https://doi.org/10.1093/infdis/jiaa113	1	55 days	F	Case report	Inhaled interferon-α1b (15 μg, bid); amoxicillin potassium clavulanate (30 mg/kg, Q8H, ivgtt)	NA	NA	NA	Case report for infant patient Adverse events and outcomes not reported
11	Du *et al*. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. SSRN 2020. https://ssrn.com/abstract=3546088	191	56	119 M 72 F	Retrospective, multi-centre cohort study	Antibiotic Antiviral (lopinavir and ritonavir) Corticosteroid IV immunoglobulin	Antibiotic: 181 (95%) Antiviral (lopinavir and ritonavir): 41 (21%) Corticosteroid: 57 (30%) IV immunoglobulin: 46 (24%)	181 (95%) patients received antibiotics: 53 (98%) died, 128 (93%) survived (P=0.15) 41 (21%) patients received antivirals: 12 (22%) died, 29 (21%) survived (P=0.87) 57 (30%) patients received corticosteroid: 26 (48%) died, 31 (23%) survived (P=0.0005) 46 (24%) patients received IV immunoglobulin: 36 (67%) died, 10 (7%) survived (P<0.0001) 54 patients died in hospital	Not reported	Lack of effective antivirals, inadequate adherence to standard supportive therapy, and high-dose corticosteroid use may also have contributed to the poor clinical outcomes in some patients
12	Gautret *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-	Treated: 20 Control: 16 Total: 36	45.1	15 M 21 other	Open label non-randomized clinical trial	Hydroxychloroquine and azithromycin	Hydroxychloroquine sulfate 200 mg, three times per day for 10 days	On day 6 post inclusion, 100% of patients treated with a combination of	One patient stopped treatment on day	Clinical follow-up and occurrence of side-effects were not discussed

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Table III (*continued*)

	Author/title/DOI	Sample size	Mean age (years)	Gender	Type of study	Therapeutic treatment	Type: *N* (%)	Outcomes (recovery/ mortality)	Adverse events	Quality assessment (applicable/ inapplicable)
	19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949							hydroxychloroquine and azithromycin were virologicaly cured, compared with 57.1% of patients treated with hydroxychloroquine alone and 12.5% of patients in the control group	3 post inclusion due to nausea	
13	Guan *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032	1099	47.9	41.1% F	Retrospective observational study	IV antibiotic Oseltamivir Antifungal Systemic glucocorticoid	Antibiotic: 637 (58%) Oseltamivir: 393 (35.8%) Antifungal: 31 (2.8%) Glucocorticoid: 204 (18.6%)	5.0% of patients were admitted to the ICU, 2.3% underwent invasive mechanical ventilation and 1.4% died among the 173 patients with severe disease	Not reported	Drug dose, frequency and duration were not included
14	Holshue *et al*. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2001191	1	35	M	Case report	Antipyretic consisting of guaifenesin	650 mg 600 mg	Discharged with no symptoms	Not reported	This was only a single case study and does not represent the whole population As this was a case report, it is not certain that the positive impact on the patient's health was due to the medication taken Randomized controlled trials are needed
15	Huang *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497−506.	41	49	30 M (73%) 11 F (27%)	Prospective collection and analysed data for patients with pneumonia	Antiviral: 38 (93%) Antibiotic: 41 (100%) Corticosteroid: 9 (22%)	Not mentioned	One patient was admitted to ICU Six patients died	Not reported	As 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 *et al*. Early and critical care in severe patients with COVID-19 in Jiangsu Province, China: a descriptive study. 2020. https://doi.	60	57	58.3% M 42.8% other	Multi-centre retrospective cohort study was conducted to extract and analyse epidemiological, clinical and	Antiviral: 60 (100%) Abidor: 50 (83.3) Lopinavir/ritonavir: 41 (68.3) Interferon: 12 (20.0) Ribavirin: 7 (11.7) Oseltamivir: 2 (3.3)	34 patients (56.7%) received IV glucocorticoids at doses ranging from 40 to 80 mg/day 28 patients (46.7%) received immunoglobulin (IgG	50 patients improved significantly Two patients were discharged Eight patients remained in a serious condition	Four patients who developed secondary infections received glucocorticoids	Most drug doses, frequencies and durations were not included The effect of glucocorticoids was not significant

	org/10.21203/rs.3.rs-17397/v1				laboratory data and treatment of 60 severe cases	Fluoroquinolone: (61.7%)	enriched) injections for 5—9 days of immunoregulation			
17	Huang *et al*. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. medRxiv 2020. https://doi.org/10.1101/2020.02.27.20029009	36	69.22	25 M (69.44%) 11 F (30.56%)	Retrospective, single-centre study	Antibiotic: 36 (100%) Antiviral: 35 (97.22%) Glucocorticoid: 25 (69.44%)	Not mentioned	All patients died	All patients died	Drug dose, frequency and duration were not included
18	Jian-ya G. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. medRxiv 2020. https://doi.org/10.1101/2020.02.20.20025536	51	45	32 M (62.7%) 19 F (37.3%)	Retrospective, single-centre case series	Oseltamivir (oral): 7 (13.7%) Interferon (oral): 51 (100%) Kaletra (oral): 51 (100%) Thymopentin (IM): 48 (94.1%) Traditional Chinese medicine decoction (oral): 28 (54.9%) Reduling (IV): 30 (58.8%) Xuebijing (IV): 2 (3.9%)	Not mentioned	One patient died with shock complications	Six patients had an obvious decline in appetite .	Drug dose, frequency and duration were not included
19	Liang *et al*. Clinical characteristics of 457 cases with coronavirus disease 2019. Available at SSRN. 2020. https://doi.org/10.2139/ssrn.3543581	457	Varies	267 M (58%) 9 pregnant women (2%)	Systematic review	Antiviral: 352 (77%) Antibacterial: 258 (56%) Glucocorticoid: 130 (28%)	Not mentioned	195 patients improved and were discharged	35 patients died	Drug dose, frequency and duration were not included
20	Liao *et al*. Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. medRxiv 2020. https://doi.org/10.1101/2020.03.10.20032136	46	Not mentioned because they were two groups	17 M (53.1) 15 F (46.9)	Retrospective case series data	Antiviral: 46 (100.0%) Antifungal: 5 (10.9%) Glucocorticoid	Not mentioned	78.3% of patients were discharged	Three patients developed acute kidney injury during treatment	At the end of this study, nearly 20% of the patients were still hospitalized
21	Lim *et al*. Case of the index patient who caused tertiary transmission of coronavirus disease	1	54	M	Case report	Lopinavir/ritonavir	200 mg 50 mg (two tablets bid)	Reduced viral load and improved clinical symptoms	The patient also complained of psychiatric symptoms such as depression,	This was a single case and does not represent the whole population Randomized

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Table III (*continued*)

	Author/title/DOI	Sample size	Mean age (years)	Gender	Type of study	Therapeutic treatment	Type: *N* (%)	Outcomes (recovery/ mortality)	Adverse events	Quality assessment (applicable/ inapplicable)
	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. https://doi.org/10.3346/jkms.2020.35.e79								insomnia and suicidal thoughts after isolation	controlled trials are needed
22	Liu *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. Int J Infect Dis 2020. https://doi.org/10.1016/j.ijid.2020.03.013	10	42	6 F 4 other	Retrospective observational single-centre study	Lopinavir, Interferon-α2b atomization inhalation	400 mg every twelve hours	Oeosinophil counts presented potential as predictor of the development of COVID-19 Seven patients were discharged Three patients stopped lopinavir: two deteriorated and one was hospitalized for longer than other patients who continued taking lopinavir	Digestive adverse effect and hypokalaemia	Small sample size
23	Liu *et al*. Epidemiological, clinical characteristics and outcome of medical staff infected with COVID-19 in Wuhan, China: a retrospective case series analysis. medRxiv 2020. https://doi.org/10.1101/2020.03.09.20033118	64	35 (29—43)	23 M 41 F	Single centre-retrospective-observational study	Immunoglobulin Thymosin Corticosteroid	Antibody: 23 Hormone: 33 Steroid hormone: 7	34 patients were discharged 30 patients were still hospitalized	Not reported	Preliminary insight into epidemiological features and clinical outcomes Single centre
24	Liu *et al*. Detection of COVID-19 in children in early January 2020 in Wuhan, China. N Engl J Med 2020. https://	Six	3 (1—7)	2 M 4 F	Retrospective case series analysis	Ribavirin Oseltamivir Glucocorticoid IV immunoglobulin	Antiviral: 2 Antiviral: 6 Steroid hormone: 4 Antibody: 1	Six patients recovered	Not reported	Small sample size

	doi.org/10.1056/NEJMc2003717									
25	Liu *et al*. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv 2020. https://doi.org/10.1101/2020.02.17.20024166	109	55	59 M 50 F	Retrospective case series analysis	Glucocorticoid IV immunoglobulin	Steroid hormone: 43 Antibody: 32 Antibiotic: 105 Antiviral: 105	31 patients died	Not reported	This study did not mention the names of the therapeutic treatment used among patients with ARDS
26	Lo *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; 16:1698—707. https://doi.org/10.7150/ijbs.45357	10	54 (27—64)	3 M 1 teenager 6 other	Retrospective case series analysis	Lopinavir Ritonavir	Antiviral: 10	Five patients were discharged Five patients were still hospitalized	Not reported	Small sample size, so difficult to draw a definite conclusion Single centre Half of the enrolled patients were still hospitalized at the time of submission of this paper. Therefore, there may have been bias regarding the prognosis of the patients
27	Mo *et al*. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa270	155	54 (42—66)	86 M 69 other	Single-centre, retrospective case series analysis	Arbidol Lopinavir and ritonavir Interferon inhalation Immune enhancer	Antiviral: 31 Antiviral: 27 Antiviral: 30 Immune enhancer: 14	22 patients died	Not reported	Selection bias may have occurred, and a large-scale nationwide study is needed
28	Wang *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020. https://doi.org/10.1001/jama.2020.1585	138	56 (42—68)	75 M 63 F	Retrospective, single-centre case series	Oseltamivir Moxifloxcain Ceftriaxone Azithromycin Glucocorticoid	Antiviral: 124 Antibacterial: 89 Antibacterial: 34 Antibacterial: 25 Glucocorticoid: 62	47 patients were discharged Six patients died 85 patients were still hospitalized	Not reported	Most patients were still hospitalized at the time of manuscript submission. Therefore, there may have been bias regarding the prognosis of the patients.
29	Wang *et al*. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020.	69	42 (35—62)	32 M 37 F	Retrospective case series	-	Antiviral: 66 Antibiotic: 66 Antifungal: 8 Corticosteroid: 10 Arbidol: 36	44 patients were still hospitalized 18 patients were discharged Five patients died	Not reported	Drug dose, frequency and duration were not included

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Table III (*continued*)

	Author/title/DOI	Sample size	Mean age (years)	Gender	Type of study	Therapeutic treatment	Type: *N* (%)	Outcomes (recovery/ mortality)	Adverse events	Quality assessment (applicable/ inapplicable)
	https://doi.org/10.1093/cid/ciaa272									
30	Wu *et al*. Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19). medRxiv 2020. https://doi.org/10.1101/2020.02.26.20028589	188	52	119 M 69 other	Retrospective cohort study	-	Antibiotic: 185 Antiviral: 158 Corticosteroid: 59	43 patients died 145 patients were discharged 12 patients were still hospitalized	Not reported	Drug dose, frequency and duration were not included
31	Wu F *et al*. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579:265−9.	1	41	M	Epidemiological investigations	Antiviral Antibiotic Glucocorticoid Oxygen	Oseltamivir Cefoselis Not mentioned Mechanical ventilation	Recovered	Not reported	Applicable
32	Xu *et al*. Clinical characteristics of SARS-CoV-2 pneumonia compared to controls in Chinese Han population. medRxiv 2020. https://doi.org/10.1101/2020.03.08.20031658	Patients: 69 Controls: 14,117	57	50.7% M 49.3% F	Retrospective, multi-centre case series	Antiviral Antibiotic Oxygen	Oseltamivir: 38 (55.1%) Moxifloxacin, ceftriaxone, azithromycin, tigecycline or linezolid: 31 (44.9%) Mechanical ventilation: 2 Invasive ventilator: 2	Three patients were discharged One patient recovered One patient died	Six patients with a significant increase in IL6 were also treated with methyl-prednisolone	Applicable
33	Xu *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. https://doi.org/10.1101/2020.03.03.20030668	45	56.7	29 M (64.4%) 16 F (35.6%)	Multi-centre, retrospective, observational study	Antiviral: 45 (100) patients Antibacterial: 45 (100) Antifungal: 19 (42.2) Convalescent plasma: 6 (13.3) Glucocorticoid: 21 (46.7) Immunoglobulin: 28 (62.2) Albumin: 35 (77.8)	Osehamivir ribavirin Not mentioned Not mentioned Not mentioned Not mentioned Not mentioned	23 (51.1%) patients were discharged from the ICU 11 (24.2%) patients were discharged One (2.2%) patient died	37 (82.2%) patients developed ARDS and 13 (28.9%) patients developed septic shock 20 (44.4%) patients required intubation and nine (20%) patients required extracorporeal membrane oxygenation	At the time of study submission, half of the patients had not been discharged from the ICU; as such, it was difficult to estimate ICU stay, ventilation-free days, case fatality rate and the predictors of fatality Drug dose, frequency and duration were not included
34	Xu *et al*. Clinical findings in a group of	62	41	35 M (56%) 27 F (44%)	Retrospective study	Antiviral: 55 (89%) Antibiotic	Interferon-α inhalation: 8 (13%)	No deaths	Not reported	At the time of study submission, most

	patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020; 368:m606.					Corticosteroid and gamma globulin	Lopinavir/ritonavir: 4 (6%) Arbidol + interferon-α inhalation: 1 (2%) Lopinavir/ritonavir + interferon-α inhalation: 21 (34%) Arbidol + lopinavir/ritonavir: 17 (28%) Arbidol + lopinavir/ritonavir + interferon-α inhalation: 4 (6%) 28 (45%) 16 (26%)			patients had not been discharged, so it was difficult to estimate the case fatality rate or the predictors of fatality
35	Xu *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020. https://doi.org/10.1016/S2213-2600(20)30076-X	1	50	M	Postmortem biopsies	Antiviral Antibiotic Corticosteroid	Interferon-α2b atomization Lopinavir + 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 and patient had sudden cardiac arrest	This was a single case study and does not represent the whole population The patient refused ventilator support in the ICU repeatedly because he suffered from claustrophobia; therefore, he received high-flow nasal cannula There is a need for randomized controlled trials
36	Yang *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020. https://doi.org/10.1016/S2213-2600(20)30079-5	52	59.7	35 M (67%) 17 F (33%)	Single-centre retrospective, observational study	Vasoconstrictor Antiviral: 23 (44%) Antibacterial Glucocorticoid Immunoglobulin	18 (35%) Oseltamivir: 18 (35%) Ganciclovir: 14 (27%) Lopinavir: 7 (13.5%). 49 (94%) 30 (58%) 28 (54%)	32 (61.5%) patients 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 Drug dose, frequency and duration were not included
37	Young *et al*. Epidemiologic	18	47	9 M (50%) 9 F (50%)	Descriptive case series			No deaths	Not reported	Small sample size Drug dose, frequency

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Table III (*continued*)

	Author/title/DOI	Sample size	Mean age (years)	Gender	Type of study	Therapeutic treatment	Type: *N* (%)	Outcomes (recovery/ mortality)	Adverse events	Quality assessment (applicable/ inapplicable)
	features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020. https://doi.org/10.1001/jama.2020.3204					Antiretroviral Antiviral Antibiotic	Lopinavir/ritonavir Oseltamivir Not reported			and duration were not included
38	Zhang *et al*. Clinical characteristics of 82 death cases with COVID-19. medRxiv 2020. https://doi.org/10.1101/2020.02.26.20028191	82	72.5	65.9% M	Death cases	Antiviral Antibiotic Corticosteroid	82 (100%) 82 (100%) 29 (35.3%)		Not reported	The study was performed in one setting. No information was given about the hospital's capabilities in terms of personnel or equipment because the mortality rate from this centre was a little higher than other centres Traditional Chinese medicine was given Drug dose, frequency and duration were not included
39	Zhang *et al*. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. medRxiv 2020. https://doi.org/10.1101/2020.03.02.20030452	221	55	108 M (48.9%) 113 F (51.1%)	Retrospective case study	Antiviral: 196 (88.7%) Antibiotic Corticosteroid: 115 (52.0%)	Oseltamivir Arbidol hydrochloride Interferon-α atomization inhalation Lopinavir/ritonavir Moxifloxacin hydrochloride Piperacillin sodium tazobactam sodium Cefoperazone sulbactam Glucocorticoid: 64 (49.6%)	12 (5.4%) patients died	Not reported	The dose and duration of IV glucocorticoid treatment showed no difference in symptomatic relief and death Drug dose, frequency and duration were not included
40	Zhang *et al*. The potential role of IL-6 in monitoring coronavirus disease 2019. https://doi.	80	53	46 F (57.5%) 34 M (42.5%)	Data collection (clinical data from patients with COVID-19 diagnosed by	Antibiotic: 73 (91.25%) Oseltamivir: 20 (25%) Ribavirin, ganciclovir or peramivir: 47	Not mentioned	IL-6 may be used as a biomarker for disease monitoring in severe cases of COVID-19	Not reported	Drug dose, frequency and duration were not included IL-6 and the pathogenesis of

					laboratory test in study institution) Observation of clinical manifestation	(58.75%) Arbidol: 49 (61.25%) Antifungal: 10 (12.5%) IV immunoglobin: 36 (45%) Corticosteroid: 29 (36·25%)			COVID-19 remains elusive
org/10.1101/2020.03.01.20029769	41	Zhou *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30566-3	191	56	119 M (62%) 72 F (38%)	Retrospective cohort study	Antibiotic: 181 (95%) Antiviral: 41 (21%) Corticosteroid: 57 (30%) IV immunoglobin: 46 (24%)	Lopinavir/ritonavir	137 patients were discharged 54 patients died	191 patients	There was no observation of a shortening of the duration of viral shedding after lopinavir/ritonavir treatment Drug dose, frequency and duration were not included

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; IL-6, interleukin-6; NA, not applicable; IV, intravenous; IM, intramuscular.

corticosteroids with different names and formulations were reported most frequently, followed by the antivirals lopinavir, oseltamivir and arbidol hydrochloride. Convalescent plasma therapy was reported in one multi-centre retrospective observational study and was administered to six patients.

Although quality assessment was applied to the research articles included in this review, there was insufficient evidence to conduct a meta-analysis, and it was not possible to conduct subgroup analysis (adults and children; different formulations, dosages and durations).

Most studies included in this review were of low quality, with incomplete or inconsistent information on study design and outcome. As such, it was difficult to analyse the medication in terms of efficacy and safety.

Despite these limitations, this is the first systematic review on medication used to treat patients with COVID-19, and provides up-to-date insight on the current therapeutic guidelines for management of these patients. Most of the medications reported in this review are available in the USA, Saudi Arabia, Europe and Egypt (Table I).

Corticosteroids were the most commonly reported medication in this review; however, they are not recommended in any guidelines. In the absence of conclusive scientific evidence, WHO and the US Centers for Disease Control and Prevention (CDC) have recommended that corticosteroids should not be used routinely 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 exacerbation, or septic shock [5,50,51]. Careful use of low-to-moderate doses of corticosteroids as a short course is advised. Hyperglycaemia, hypernatraemia and hypokalaemia are the most common adverse effects associated with the use of corticosteroids and should be monitored routinely [5,51].

Lopinavir/ritonavir (Kaletra) was the second most commonly reported medication in this review. A randomized clinical trial reported that this HIV treatment had negative outcomes for patients with COVID-19 (Table II) [30,52—54]. No benefit of lopinavir/ritonavir treatment compared with standard care was observed in this study, and 19 patients who received the intervention died. However, some study limitations were observed, including lack of blinding. RCT NCT04252885 and the SOLIDARITY trial are ongoing to determine the efficacy of lopinavir/ritonavir in patients with COVID-19 [52].

Oseltamivir (Tamiflu), used to treat influenza A and influenza B, was the third most commonly reported medication in this review. Oseltamivir has been recommended by WHO for people at high risk of infection for prevention of pandemic influenza. A retrospective observational study reported the use of oseltamivir in 1099 patients with COVID-19; however, the study was not able to provide any solid data on the effectiveness of oseltamivir in the prevention or treatment of COVID-19. Study limitations included incomplete documentation of patient data and recall bias [55,56].

Arbidol hydrochloride was the fourth most commonly reported medication in this review. It is a broad-spectrum inhibitor of influenza A and B virus, parainfluenza virus and other viruses, including hepatitis C virus. Arbidol hydrochloride is used in Russia and China, but has not yet been approved for use in other countries [52]. However, no conclusive evidence of its efficacy in patients with COVID-19 was reported. In this

review, it was reported together with favipiravir, which was approved for the treatment of novel influenza on 15th February 2020 in China [52].

Chloroquine phosphate and hydroxychloroquine were reported in this review and showed favourable outcomes in the recovery of patients with COVID-19 [6,7,57—60]. These two medications are likely to share the same mechanism of action. Chloroquine, an antimalarial, has shown positive outcomes in patients with COVID-19. Furthermore, hydroxychloroquine has shown significant effectiveness against intracellular pathogens such as *Coxiella burnetii*, the agent of Q fever [22]. This French open label, non- randomized clinical trial was promising and the first clinical trial of these medications in patients with COVID-19. The effect of hydroxychloroquine was significant because it showed a reduction in the viral load compared with the control group [22]. Moreover, the effect of hydroxychloroquine was significantly more potent when given in conjunction with azithromycin. However, clinical follow-up and the occurrence of adverse effects were not discussed in the study, and further work is needed to reduce the morbidity and mortality of COVID-19 [57—59]. Although chloroquine and hydroxychloroquine 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 cases of suspected/confirmed COVID-19 should be restricted to hospitalized patients. On 30th March 2020, the US Food and Drug Administration (FDA) issued an emergency use authorization for chloroquine and hydroxychloroquine to treat patients hospitalized with COVID-19 [60].

Convalescent plasma therapy was reported in a multi-centre cohort research trial of 45 critically ill patients with COVID-19 admitted to an intensive care unit in Wuhan. The findings showed that convalescent plasma therapy was administered to six patients and no transfusion reactions occurred; however, the study did not provide adequate information about the efficacy of convalescent plasma therapy due to the limited sample size and lack of a randomized control group [61,62].

Convalescent plasma therapy could be a promising treatment method for patients with COVID-19. A recent case series 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 four of the five patients), their viral loads became undetectable within 12 days, and three of the five patients were discharged from hospital and were in a stable condition at 37 days post transfusion [63]. On 24th March 2020, the US FDA approved convalescent plasma therapy for investigational use under the traditional Investigational New Drug Applications regulatory pathway, and for eligible 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 potential risks and ethical issues associated with convalescent plasma therapy, including increased risk of a thrombotic event (from 0.04% to 14.9%), lack of high-quality research in this particular area, and the selection of donors with high neutralizing antibody titres [65].

In conclusion, this is the first systematic review of medication used to treat patients with COVID-19. Only 41 research articles were eligible for inclusion in this review, mainly conducted in China, of which only three were clinical trials.

The use of corticosteroids to treat patients with COVID-19 was reported most frequently in this review, despite safety alerts issued by WHO and CDC, followed by lopinavir, oseltamivir and arbidol hydrochloride.

Although further research is warranted as the amount of the evidence increases, this review 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.

Conflict of interest statement

None declared.

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