The trade-off dilemma in pharmacotherapy of COVID-19: systematic review, meta-analysis, and implications

THE TRADE-OFF DILEMMA IN PHARMACOTHERAPY OF COVID-19: SYSTEMATIC REVIEW, META-ANALYSIS AND IMPLICATIONS

Abstract

Introduction: The novel coronavirus SARS-CoV2/COVID-19 has infected millions of people worldwide and has contributed to over 500,000 deaths. This review synthesizes the literature on SARS-COV2 pharmacotherapy to inform practice and policymaking.

Areas covered: We systematically review the published literature on SARS-CoV2 therapeutics, grouping candidate treatments into repurposed, adjunct, and experimental agents. We conducted meta-analyses where appropriate and provide recommendations based on compilation from real-time/interim therapeutic guidelines. We then advise on how to navigate and advance the evidence in the current context of uncertainty and urgency.

Expert opinion: Current evidence does not support a clear role for pharmacotherapy in COVID-19. While promising signals have been found through limited number of RCTs, these must be interpreted with caution. Without proper protection from bias we risk exposing patients to treatments where the potential for benefit is at best unclear, yet the potential for harm from adverse effects is high leading to a trade-off dilemma in decision making. Advancing the evidence requires a coordinated effort to design and conduct robust trials and to systematically synthesize and critically evaluate findings. Therapies should be reserved for use in clinical trials, emergency or compassionate access until we gain more confidence in the balance of benefit and harm.

Article Highlights

- Numerous pharmacotherapies, novel and repurposed, are being explored to prevent and treat COVID-19 as well as manage associated complications.
- Numerous studies are ongoing to explore the potential of these therapies, yet few robustly protect from bias and confounding.
- The current evidence does not clearly support the use of any pharmacotherapeutic regimen.
- At the time of revision of this manuscript a preprint of dexamethasone trial provides preliminary trend towards reducing mortality in severe COVID-19. Further studies are required for conclusive recommendation.

- At the time of revision of this manuscript hydroxychloroquine papers were retracted from two major medicine journals raising concern over opacity of primary data.
- In context to current and rapidly changing therapeutics this paper provides revised recommendations on hydroxychloroquine (with/without azithromycin), new recommendations on the use of remdesivir and new recommendations on famotidine (based on findings from collated living clinical guidelines).
- Coordinated efforts to design and conduct rigorous randomized controlled clinical trials and synthesize the emerging evidence are necessary to generate evidence that practitioners, patients, and policy makers can have high confidence in.

1. Introduction

1.1 Description of the condition

1.1.1 Epidemiology

The current global pandemic originated as an unexplained respiratory tract infection in the Wuhan province of China in December 2019 [1]. The etiologic agent was identified as a novel coronavirus (SARS CoV2) [1]. COVID-19 infection has spread across the world with reported cases in over 150 countries infecting millions of people worldwide and has contributed to over 500,000 deaths [2, 3]. The median age affected by COVID-19 ranges from 35-60 years [4]. The clinical symptoms include fever, fatigue, dry cough, anorexia, myalgia, dyspnoea, anoxia and ageusia. These symptoms could progress to pneumonia and acute respiratory distress syndrome (ARDS) [5]. At the time of submission of this manuscript the global mortality rate exceeds 5.5% and increases with age (particularly in those over 60 years) and comorbid conditions such as diabetes and chronic cardiovascular, renal, or pulmonary disease [6, 7]. Diagnosis of COVID-19 is made with nasopharyngeal and oropharyngeal swab or wash polymerase chain reaction (PCR) identifying the SARS-CoV2 RNA [8].

1.1.2 Pathogenesis

Coronaviruses are a family of single stranded RNA viruses protected by lipid bilayer and membrane proteins which can infect numerous species. These viruses are zoonotic, crossing species leading to human illness, ranging from the common cold to more severe respiratory tract infections [8]. The virus targets and infects the respiratory system and is transmitted

person-to-person by contact, droplets, and fomites. The incubation period is approximately 2-14 days [1]. During the incubation period the virus causes alveolar epithelial injury and inflammation resulting in respiratory symptoms [9]. The virus binds to angiotensin converting enzyme 2 (ACE 2) receptors on surface of type 2 alveolar cells, suggesting a similar pathogenesis to SARS-CoV [10]. Whilst the virus replicates in the alveolar cells it triggers a systemic inflammatory response, in the form of cytokine storm, through release of cytokines such as tumour necrosis factor-alpha (TNF alpha), interleukins (IL) 1, 6, 8, and chemokines leading to pulmonary and interstitial oedema, which in turn produce dyspnoea and hypoxemia [11]. The inflammatory response likely also involves leukocytes damaging the endothelial cells, releasing further inflammatory mediators such as leukotrienes and prostaglandins. Leukotrienes cause bronchoconstriction, impairing ventilation leading to hypoxemia. Prostaglandin release produces fever. The injured lung parenchyma, accumulation of fluid, ventilation perfusion mismatch and hypoxemia, collectively termed as ARDS, is the leading cause of mortality in COVID-19 [9]. Patients with COVID-19 develop varying degrees of clinical severity [7]. The majority of COVID 19 patients develop mild symptoms such as dry cough and fever. Severe clinical manifestations such as respiratory failure from ARDS, shock and multiorgan dysfunction are triggered through lung, liver and cardiac impairment [7].

1.2 Management approach

COVID-19 treatment is broadly divided into two common approaches, home-based care and hospital care. Home care [12] is appropriate for patients with mild infection who can be adequately isolated in outpatient setting. For these patients the primary goals of care are to prevent transmission to others and to monitor for clinical deterioration. Hospital care [13] is predominantly supportive for severe and critically ill patients. The treatment is symptomatic and oxygen therapy represents the major intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, and hemodynamic support is essential for managing shock.

Given that the majority of current treatment options are supportive, public health measures are vital to control transmission in the community. Measures such as personal hygiene and public isolation are proving beneficial. Proactive isolation measures across various countries has led to a progressive reduction of cases [14].

At present no specific pharmacotherapy is approved by any regulatory bodies that include the US Food and Drug Administration (FDA) [15], the UK Medicines and Healthcare products Regulatory Agency (MHRA) [MHRA] [16] or Australia's by Therapeutics Good Administration (TGA) [17]. Several therapies, however, are being trialled. These include repurposed drugs (antivirals, antimicrobials, 4-aminoquinolines), adjunct therapies (corticosteroids, biological and immunomodulatory agents), and experimental antivirals (remdesivir and favipiravir). There is no vaccine currently available, but several candidates are in various stages of development including several in human trials.

While many potential therapies are being tested to prevent and treat the virus and associated complications, the evidence to support the use many of these therapies is unclear. This review aims to synthesize the disparate literature around pharmacotherapy for SARS-COV2 to inform practice and policymaking within the context of rapidly changing evidence.

2. Methods

This review is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [18] for evidence synthesis.

2.1 Information sources and search strategy

The studies included in this review were identified in the following databases: MEDLINE/PubMed, SCOPUS, Science Direct, the Cochrane Central Register of Controlled Trials (CENTRAL), OVID SP, EMBASE. Portals such as the World Health Organisation (WHO) webpage on COVID-19 evidence, journal specific portals such as The Lancet, The New England Journal of Medicine and Journal of American Medical Association on COVID-19 evidence and the MedrXiv were searched from the year December 2019 to April 30, 2020. At the time of revision of manuscript, we updated the evidence-base on experimental therapies till Mid-June 2020 that also include key changes to recommendations (see current pharmacotherapy recommendation section under results). The keywords/abbreviations included *COVID-19, SARS CoV2, coronavirus, severe acute respiratory syndrome coronavirus 2, SARS CoV, MERS CoV,* in combination with *drug therapy, medication, treatment, pharmacology, pandemic, and infection*. Additional studies were identified through

snowballing search techniques, examining reference lists of the papers identified after the initial screening. Unpublished data or abstracts from conferences were not considered.

2.2 Study criteria and participants

We included peer reviewed randomised controlled trials (RCTs), quasi-RCTs, observational studies (descriptive or analytical) published in English. We included studies that compared an intervention to placebo, to another pharmacotherapy, or to varying dose ranges. We included study participants, regardless of their gender, age and race. Participants were included regardless of comorbidities if a diagnosis of COVID-19 was present and received any pharmacotherapy. The pharmacotherapy for COVID-19, the medication classes were grouped into those re-purposed from currently available drugs for immediate use (4-aminoquinolines, lopinavir/ritonavir, ribavirin, umifenovir, and oseltamivir), adjunct therapies (antimicrobials, corticosteroids, immunomodulators, or complementary/alternative therapies), and experimental therapies (remdesivir and favipiravir).

2.3. Study selection, data extraction and Quality assessment

The titles and abstracts of all reports identified were screened, followed by the full-text papers independently by two review authors (SK and MR). If conflicting opinions arose during screening, a third author (GT) determined if inclusion was appropriate. Studies were assessed and data were extracted with regard to study design, sample size, treatment characteristics, and primary and secondary outcomes. Evidence was assessed in regard to methodological quality using risk of bias assessment tools using the Cochrane Risk of bias Assessment tool [19]. Quality of reporting of observational studies were assessed through the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20]. The risk of bias in reporting of case reports and case series were assessed using the Murad et al. 2018 scale [21]. The decision made by the reviewer (SK) was verified by another reviewer (MG).

2.4 Measures of outcomes and data analysis

Efficacy was defined as the capacity of the intervention to produce a beneficial result in terms of reduction in mortality, frequency of discharge from the hospital, rate of ARDS and the rate of patients on mechanical ventilation. Safety was defined as the capacity of the intervention to cause an adverse effect, which include adverse drug reactions. We performed meta-analysis on studies with homogenous patients, interventions, comparator (if any) and outcome (PICO)

measures. Review Manager Software [22] was used to conduct the meta-analysis. Case reports were excluded from the quantitative synthesis. The outcomes (mortality rate, discharge rate, rate of ARDS, and rate of ventilation) are presented in terms of rate along with the 95% confidence interval (CI). Statistical heterogeneity of data was assessed using the I^2 statistic and the random effect model was applied in case of substantial heterogeneity (I^2 >50% or P≤0.10). We planned to perform a subgroup analysis with respect to study design, treatment, age and gender if possible. A funnel plot was used for visual inspection of publication bias and it was generated by considering logit discharge rate on X-axis and standard error on Y-axis and statistically analysed through Egger's and Begg's test.

3. Results

3.1 Results of the search strategy

The study selection process and justification are provided in Figure 1. We initially screened 1328 records, of which 1163 were excluded based on study criteria. Full texts of the remaining 165 studies were assessed of which 55 studies were qualitatively analysed. Meta-analysis was restricted to 30 studies because of the marked variability in study designs, participants, interventions, and reported outcome measures (figure 1).

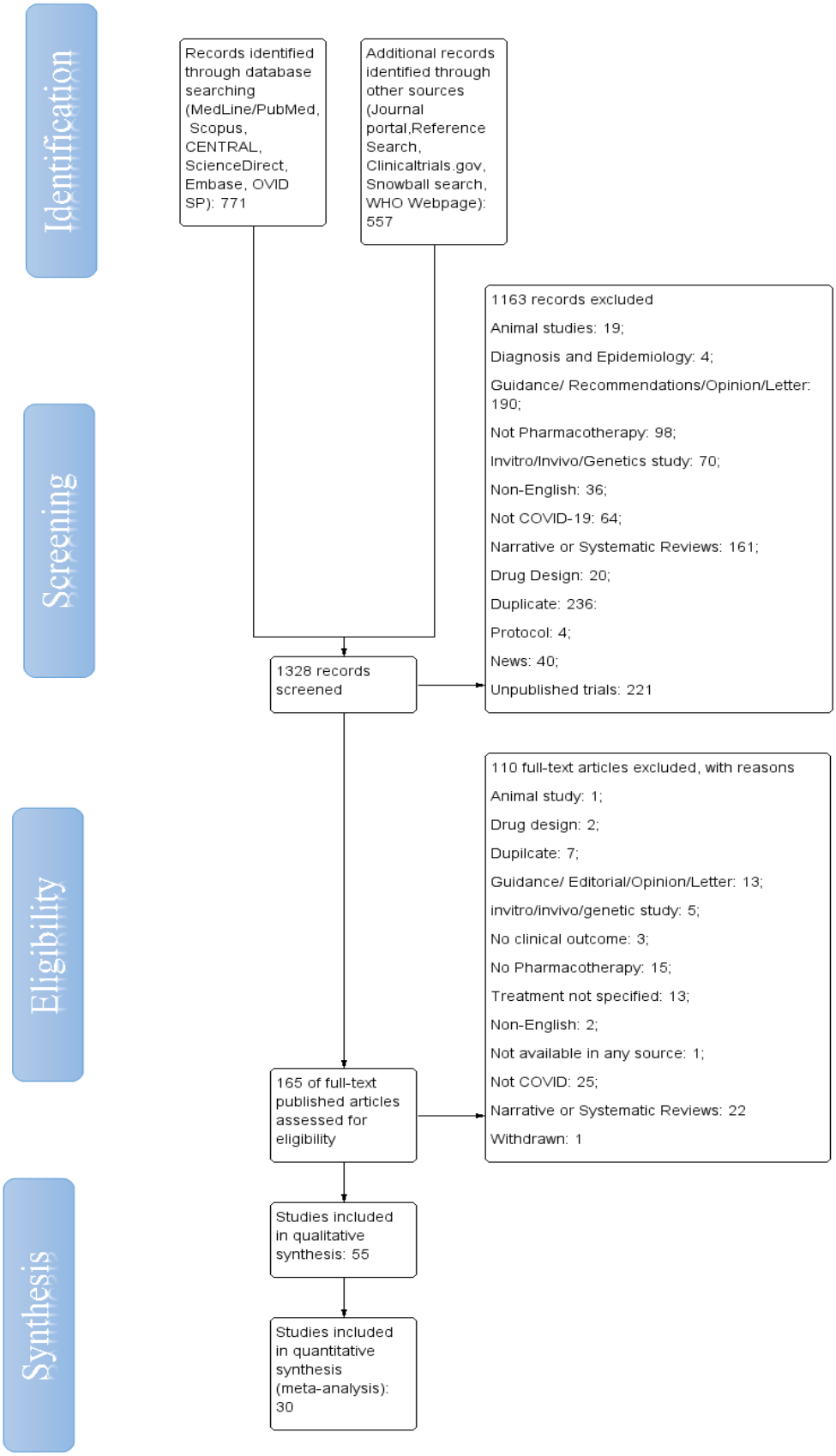


Figure 1. Study flow process

3.2 Characteristics of the included studies, study quality and outcome measure:

Characteristics of included studies are provided in Table 1. The sample sizes ranged from 1 to 1063, with participants aged from 5 to 95 years. Studies were conducted in a variety of settings, including clinic and hospital. The majority of studies were conducted in China and the duration of these studies ranged from early December 2019 to mid-May 2020. Antiviral drugs, anti-malarial agents, antibiotics, biological agents, and corticosteroids were the major treatment strategies adapted along with the supportive care.

Table 1. Characteristics of pharmacotherapy studies in COVID-19 (classified as repurposed therapies, experimental therapies, and adjunct therapies).

Author, year	Country	Age (years)	Participants	Study design/ Study duration	Treatment characteristics		Key outcomes
					Drug class	Intervention	
Repurposed drugs with adjunct therapy							
Li Y et al., 2020 [23]	China	49.4 (14.7) [a] 19-79 [c]	86 (Male: 40; Female: 46)	Exploratory RCT/ Feb 1 to March 28, 2020	Antiviral: (n= 69)	Lopinavir/ritonavir: (n=34); 500 mg BD PO; Umifenovir: (n=35); 200 mg TID PO for 7-14 days	No significant difference (P>0.05) between two groups with respect to negative RT-PCR test, rates of antipyretic, cough alleviation, or improvement of chest CT at days 7 or 14 as per this ELACOI study. Moreover, a total of eight (23.5%) patients progressed to severe stage at day 7 in spite of treatment.
					Control: (n=17)	No antiviral therapy	
					Supportive care (n=86)	Oxygen therapy	
Cao B et al., 2020 [24]	China	58 (49-68)[b]	199 (Male: 120; Female: 77)	Open-label RCT/ January 18 to to February 3, 2020	Antiviral: (n=99)	Lopinavir–ritonavir (400 mg and 100 mg) BD PO for 14 days	No significant difference in the lopinavir–ritonavir treatment group when compared to standard care with respect to the time to clinical improvement, mortality at 28 days, percentages of patients with detectable viral RNA at various time points. However, median time to clinical improvement was shorter by 1 day in treatment group. Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group.
					Interferon: (n=22)	NS	
					Antibiotics: (n=189)	NS	
					Steroids: (n= 67)	Glucocorticoid therapy for 6 (3-11) [b] days	

Huang C et al., 2020 [25]	China	49 (41-58)[b]	41 (Male: 30: Female: 11)	Prospective cohort study/ Dec 16, 2019 to Jan 2, 2020	Antiviral (n=38)	Oseltamivir	68% of the participants were discharged and death rate was 15%.
					Antibiotic (n=41)	NS	
					Systemic corticosteroids (n=9)	NS	
Ye XT et al., 2020 [26]	China	5-68[c]	47 (Male: 22; Female: 25)	Prospective cohort study/ January 22 to 29, 2020	**Test**: Antiviral (n=42)	Lopinavir/ritonavir: (400/100 mg) BD or (800/200 mg) OD with food	Treatment with antiviral regimen showed no difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). Mortality at 28 days was similar in the treatment group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7).
					Control: (n=5)	Interferon aerosol inhalation: 5 MU or equivalent dose for adults, adding 2 ml sterile water for injection, BD; umifenovir: 2 tablets (0.2 g) TID, PO	
					Antibiotics	Moxifloxacin: 0.4 g OD, PO/IV	
					β-adrenergic receptor agonist	Methoxyphenamine: 2 tablets >15 years old; and 1 tablet >8< 15 years old; TID, PO after meals	
Liu F et al., 2020 [27]	China	42 (34-50) [b]	10 (Male: 4; Female: 6)	Prospective cohort study/ January 22 to February 11, 2020	Antiviral: (n=10)	Lopinavir (400mg, Q12H); umifenovir hydrochloride granules (AHG, 0.2g, TID)	70% of the participants got discharged and no deaths were reported in this study. However, respiratory failure and ICU admission was reported in 2 and 3 patients, respectively. Moreover, adverse

					Biologicals: (n=9)	RH-interferon α2b atomization inhalation (5 million U twice daily)	events such as digestive abnormalities, low potassium and hypoalbuminemia was reported by 5, 7 and 1 patients among the included participants
					Steroids: (n=3)	Glucocorticoid; methylprednisolone (40mg, Q12H)	
					Antibiotics: (n=2)	NS	
					Antipyretics: (n=3)	NS	
Deng L et al., 2020 [28]	China	Intervention : 41·8 (14·08); Control: 47·25 (17·25)[a]	33 (Male: 16; Female: 17)	Retrospective cohort study/ Jan 17 to Feb 13, 2020	Antiviral drugs (n=33)	Oral umifenovir and lopinavir combination group (n=16); oral lopinavir monotherapy group (n=17) for 5-21 days	A significant clinical improvement with respect to negative RT-PCR ($p < 0·05$) at 7 days (75% vs 35%) and 14 days (94% vs 52·9%) was observed with combination therapy when compared to lopinavir monotherapy. Similar significant improvement was observed with the chest CT scans (69% vs 29%, $p < 0·05$) with combination therapy compared to the monotherapy. Digestive upset and hyperbilirubinemia were reported in 43·7% and 17.9% patients, respectively.
					Immunoglobulin therapy: (n=24)	NS	
					Steroids: (n=8)	Corticosteroid	
					Antibiotics: (n=21)	NS	
Xu XW et al., 2020 [29]	China	41 (32-52)[b]	62 (Male: 35; Female: 27	Retrospective case-series/10th to 26th January 2020	Antiviral drug (n=55)	Interferon α inhalation (50 µg BD); Lopinavir (400 mg BD)/ritonavir and 100 mg BD; Umifenovir (200 mg TID) for 3-5 days	Anti-viral therapy along with the antibiotics and steroids may help in improving the clinical effect and reducing the complications (2% ICU admission)

					Steroids with immunoglobulins (n= 16)	corticosteroid (40-80 mg/day) and gamma globulin (15- 20 g/day) for 3-5 days	
					Antibiotics (n=28)	Quinolones and second generation beta lactams (oral and intravenous)	
Wang Z et al., 2020 [30]	China	19-63[c]	4 (Male: 3; Female: 1)	Retrospective case-series/ January 21 to 24, 2020	Antiviral treatment with Chinese Traditional medicine	Lopinavir/ ritonavir (400 mg/100 mg) combination BD, PO; Umifenovir (0.2 g, TID, PO); Shufeng Jiedu Capsule (2.08 g, TID, PO) for 6-15 days	All patients demonstrated clinical improvement confirmed through the chest CT scan and presenting symptoms.
Chen N et al., 2020 [31]	China	55·5 ± 13·1[a]	99 (Male: 67; Female: 32)	Retrospective cohort study/ Jan 1 to 20, 2020	Antiviral (n=75)	Oseltamivir (75 mg, BD, PO), ganciclovir (0·25 g, BD, IV), lopinavir and ritonavir tablets (500 mg, BD, PO) for 3-14 days	Death rate was 11% and the complications such as acute respiratory distress syndrome or ventilation requirement occurred in 20% of the patients treated with these drugs.
					Antibiotics (n=70)	Cephalosporins, quinolones, carbapenems, tigecycline, linezolid, 3-17 days [c]	
					Steroids (n=19)	methylprednisolone sodium succinate,	

						methyl prednisolone, and dexamethasone for 3-15 days [c]	
					Antifungal (n=15)	NS	
					Immunoglobulin (n=27)	IV immunoglobulin	
Wang D et al., 2020 [32]	China	56 (IQR: 42-68)[b]	138 (Male: 75; Female: 63)	Retrospective case-series/ January 1 to 28, 2020	Antiviral (n=124)	Oseltamivir	Death rate was 4.3% among the treated patients and 34% were successfully discharged.
					Antibiotics (n=138)	Moxifloxacin (n=89); Ceftriaxone (n=34); azithromycin (n=25)	
					Steroids (n=62)	Glucocorticoid	
Yang X et al., 2020 [33]	China	59·7 (13·3)[a]	52 (Male: 35; Female: 17)	Retrospective case-series/ late December, 2019 to Jan 26, 2020	Antiviral agents (n=23)	Oseltamivir: (n=18); ganciclovir: (n=14), and lopinavir (n=7)	The mortality, complications (ARDS) and oxygen requirement was reported among more than 60% of population. Carbapenem induced pulmonary and blood stream infection was reported in one patient.
					Antibacterial agents: (n=49)	Carbapenem	
					Glucocorticoids: (n=30)	NS	
					Vasoconstrictive agents (n=18)	NS	
					Immunoglobulin: (n=28)	NS	
Hu Z et al., 2020 [34]	China	32.5 (19-57)[b] 5-95 [c]	24 (Male: 8; Female: 16)	Retrospective case-series/ Jan 28 to Feb 9, 2020	Antiviral drug: (n=21)	NS	No deaths were reported and 37.5% of the patients were discharged. The median time for the viral clearance was 9.5 (3.5-13.0). Immunoglobulin infusion related
					Biologicals: (n=24)	Interferon atomization	

					Antibiotics: (n=1)	NS	fever with chills (n=1), diarrhoea (n=2) and lopinavir/ritonavir induced rashes (n=2) were observed
					Antifungals: (n=1)	NS	
					Immunoglobulin: (n=3)	IV	
Zhou F et al., 2020 [35]	China	56 (46-67)[b]	191(Male: 119; Female: 72)	Retrospective cohort study/ Dec 29, 2019 to Jan 31, 2020	Antiviral drugs (n=41)	lopinavir/ritonavir	A higher rate of discharge (71.7%) with reduction in requirement of oxygen support (<21%). However, major complications were high among the treated group (up to 60%)
					Antibiotics: (n=181)	NS	
					Corticosteroids: (n=57)	NS	
					Immunoglobin: (n=46)	Intravenous	
Wu C et al., 2020 [36]	China	51 (43-60)[b]	201 (Male: 128; Female: 73)	Retrospective cohort study/ December 25, 2019, to January 26, 2020	Antiviral drugs: (n= 170)	Oseltamivir: (n=134); ganciclovir: (n=81); lopinavir/ritonavir: (n=30)	Discharge rate (71.6%) with fewer complications such as ARDS (21.9%), ICU admission (26.4) and mechanical ventilation (less than 30) with a median hospitalization of 13 days (IQR, 0-16)
					Steroids: (n=62)	Methylprednisolone	
					Antibiotic: (n= 196)	NS	
					Immunomodulator: (n=70)	Immunoglobulin, thymosin, and recombinant human granulocyte colony stimulating factor	
					Biologicals: n=(22)	Interferon alfa	
					Antioxidant: (n=106)	Glutathione and N-acetyl-L-cysteine	

Tang X et al., 2020 [37]	China	67 (57-72)[b]	73 (Male: 45; Female: 28)	Retrospective case-control study/ December 24, 2019 and February 7, 2020	Anti-viral drugs	Interferon α2b: (n=42); Ganciclovir: (n=24); Lopinavir/ritonavir: (n=61); Oseltamivir: (n=34) for 8 (IQR 5, 11)[b]	No significant difference in death (28.8%), discharged (35.6) patients and hospitalized (35.6) patients between arms. Ventilation requirement among the patients was within 20% across the arms.
					Herbal (n=20)	Chinese traditional medicine	
					Steroids	Glucocorticoid: (n=58) with a median initial dosage of 80 mg/day (IQR 40, 80)	
					Immunoglobulin (n=43)	-	
Chen J et al., 2020 [38]	China	51 (36-64)[b]	249 (Male: 126; Female: 123)	Retrospective cohort study/ Jan 20 to Feb 6, 2020	Antiviral drugs (n=NR)	lopinavir/ritonavir; umifenovir	Discharge rate (86.3%). Mortality rate of 0.8%
					Corticosteroid: (n=32)	NS	
Zhang L et al., 2020 [39]	China	65 (56-70)[b]	28 (Male: 17; Female: 11)	Retrospective cohort study/ Jan 13, to Feb 26, 2020	Antiviral drugs: (n=20)	lopinavir/ritonavir (400/100mg, BID, PO): n=10; Umifenovir (200mg, TID, PO): n=14; Ganciclovir (500mg, BID, IV): n=9; Ribavirin (500mg, BID, IV): n=1; Combination (> 1 drug): n=9	Discharge rate was 35.7% with a maximum complication rate of 28.6% (ARDS and ventilation need). Median duration of hospitalization was 13.5 (10.8-17.8).

					Antibiotics: (n=23)	NS	
					Steroids: (n= 15)	Systemic corticosteroids	
					Immunoglobin: (n=10)	Intravenous Ig for 3.0 (1.0-3.0)[b] days	
Yang W et al., 2020 [40]	China	45.11 ± 13.35[a]	149 (Male: 81; Female: 68)	Retrospective cohort study/ January 17th to February 10th, 2020	Antiviral drugs: (N=140)	NS	Discharge rate was 48.99% and mortality rate was zero. However, 89.93% patients received oxygen therapy
					Antibiotics: (N=34)	NS	
					Biologicals (n=144)	Interferon	
					Steroids (n=5)	Glucocorticoids	
					Immunoglobulin: (n=19)	IV	
Liu K et al., 2020 [41]	China	Elderly: 68 (65.25-69.75); Young: 47 (35.75-51.25)[b]	56 (Male: 31; Female: 25)	Retrospective cohort study / January 1 to February 15, 2020	Anti-viral: (n=53)	Lopinavir and Ritonavir tablets: n=53; Interferon inhalation: n=21	Discharge rate was 94.7% with 5.3% mortality.
					Herbal: (n=46)	Traditional Chinese medicine	
					Antibiotic: (n=40)	NS	
					Immunoglobulin: (n=9)	NS	

					Biologicals: (n=46)	NS	
Guo T et al., 2020 [42]	China	58.50 (14.66)[a]	187 (Male 91; Female: 96)	Retrospective case-series/ January 23 to February 23, 2020	Antiviral: 166 (88.8)	NS	Mortality rate was 23% and myocardial infarction was the major reason for the death.
					Antibiotic: 183 (97.9)	NS	
					Steroids: 106 (56.7)	Glucocorticoid	
					Immune globulin: 21 (11.2)	NS	
Shen C et al., 2020 [43]	China	36-65	5 (Male: 3; Female: 2)	Retrospective case-series/ January 20, to March 25, 2020	Antiviral drugs: (n=5)	Lopinavir/ritonavir: 4; favipiravir: 2; umifenovir: 1; darunavir: 1; Interferon alfa-1b (n=4)	All patients got discharged and the median hospitalization time was 11 to 13 days
					Steroids (n=5)	Methylprednisolone	
Shi et al., 2020 [44]	China	42	1 (Male)	Case Report/ January 1 to 25, 2020	Antiviral drugs with antibiotics	Ganciclovir and oseltamivir; Meropenem and linezolid for 25 days	Improvement in chest radiograph confirmed through CT scan
Wei et al., 2020 [45]	China	40	1 (Female)	Case Report/12 days [d]	Antiviral with antibiotics	Lopinavir: 200 mg, 2 capsules BD PO; Tabaxin (piperacillin plus tazobactam) for 12 days	Clinical improvement with respect to negative RT-PCR, chest CT scans and symptom resolution
Chen D et al.,2020 [46]	China	46	1 (Female)	Case Report/17 January to 7	Antiviral	Oseltamivir, umifenovir, Lopinavir/ ritonavir	Symptoms were completely based on chest CT scan. Patient got discharged on

				February, 2020	Antibiotic	moxifloxacin	10th day. RT-PCR test remained negative in her follow-up visit after 14 days
Han W et al.,2020 [47]	China	47	1 (Male)	Case Report/21 to 30 January 2020	Antiviral	lopinavir and ritonavir tablets (800/200 mg daily),	Patient was discharged on day 10 according to the persistent negative results of SARS-CoV-2 on days 6 and 7 as well as lung findings
					Biologicals	Interferon-alpha2b (10 million IU daily)	
					Steroids	Methylprednisolone (40 mg daily); reduced to 20 mg daily on 3rd day and withdraw on day 5	
					Mucolytic agent	ambroxol hydrochloride (60 mg daily)	
					Antibiotics	moxifloxacin hydrochloride (0.4 g daily)	
Xu Z et al., 2020 [48]	China	50	1 (Male)	Case Report/ Jan 21 to 26, 2020	Anti-viral drugs	Lopinavir plus ritonavir (500 mg twice daily, orally); Interferon alfa-2b (5 million units twice daily, atomisation inhalation)	Patient died
					Antibiotics	Moxifloxacin (0·4 g once daily, IV)	

					Steroids	Methylprednisolone (80 mg twice, daily, intravenously)	
Inciardi RM et al., 2020 [49]	Italy	53	1 (Female)	Case Report/6 days [d]	Anti-viral drugs	lopinavir/ ritonavir (2 tablets of 200/50 mg twice daily)	Patient demonstrated progressive clinical and hemodynamic improvements
					Cardiac drugs	Dobutamine, kanrenone (50 mg), furosemide (25-50 mg), and bisoprolol (2.5 mg), aspirin (500 mg twice daily)	
					Anti-malarial	Hydroxychloroquine (200 mg twice daily)	
					Steroids	Intravenous methylprednisolone (1 mg/kg daily) for 3 days	
Chen Z et al., 2020 [50]	China	44.7 (15.3) [a]	62 (Male: 29; Female: 33)	Parallel group RCT/4 to 28 February, 2020	Int: Antimalarial: (n=31)	HCQ 400 mg/d (200 mg/bid) along with other therapy for 5 days	HCQ can increase pneumonia cure (80.6%) compared with the control group (54.8%). Besides, 61.3% of patients in the HCQ treatment group had a significant pneumonia absorption.
					Control: (n=31)	Antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids for 5 days	
Gautret et al., 2020 [51]	France	45.1 ± 22[a]	36 (Male: 15; Female: 21)	Single arm Open label	Antimalarial	HCQ 200 mg, TID PO for 10 days	Virological cure on day 6 post-inclusion was significantly higher with HCQ

				non-RCT/ Early March to March 16th	Antimalarial with antibiotics	HCQ 200 mg, TID PO + AZM 500 mg on day1, followed by 250mg per day for 5 days	compared to control (70% vs 12.5%; p=0.001); Moreover, increased virological cure with HCQ+AZM (100%) compared to HCQ (57.1%) and control (12.5%); p<0.001
Borba MG et al., 2020 [52]	Brazil	51.1 (13.9) [a]	81 (Male: 60; Female: 21)	Parallel, double-masked, Phase II b, RCT/ March 23 to April 5, 2020	Anti-malarial: (n=81; High dose: 41; low dose: 40)	***High-Dose:*** Chloroquine (600 mg; 4 × 150 mg tablets twice daily; total dose 12 g) for 10 days ***Low-dose:*** Chloroquine (450 mg; 3 × 150 mg tablets and 1 placebo tablet twice daily; total dose 2.7 g) for 9 days	The high-dosage group presented more instances of QTc interval greater than 500 milliseconds (7 of 37 [18.9%]) compared with the low-dosage group (4 of 36 [11.1%]).
					Anti-microbial: (n=81)	IV ceftriaxone (1 g BD) 7 days PLUS azithromycin (500 mg OD) 5 days	
					Anti-viral: (n=70)	Oseltamivir (75 mg BD) for 5 days	
Xu X et al., 2020 [53]	China	56.8 ± 16.5[a] 25-88[c]	21 (Males: 18; Females: 3)	Retrospective cohort study/5 to 14 February, 2020	Biological agents	Tocilizumab 400 mg OD IV	Biological agents were effective in terms of resolving symptoms; improvement in oxygen saturation; chest radiograph; bringing back the lab parameters to normal and improved discharge rate (90.5%) with no death
					Antiviral	Lopinavir	
					Steroids	Methylprednisolone	

Ferrey A et al., 2020 [54]	United States	56	1 (Male)	Case Report/1 Jan to 14 March, 2020	Biological agents	Tocilizumab	Patient remained in critical care. No clinical benefit with respect to CT improvement and lab parameters
					Antibiotics	Azithromycin, ceftriaxone, vancomycin, piperacillin-tazobactom	
					Antimalarial	Hydroxychloroquine	
Michot J et al., 2020 [55]	France	42	1 (Male)	Case Report/12 to 24 March 2020	Biological agents	Tocilizumab 8 mg/kg IV Q8H for 5 days	Treatment was effective in decreasing CRP, oxygen requirement and recovery from symptoms. However, no change in lymphocyte and increased CD4 + CD25 + lymphocytes
					Antibiotics	Ceftriaxone	
					Antiviral	Lopinavir/ritonavir (400mg/100mg) PO for 5 days	
Zhang X et al., 2020 [56]	China	60	1 (Male)	Case Report/1 to 16 February 2020	Biological agents	Tocilizumab, 8mg/kg body weight IV	Tocilizumab was effective in COVID-19 in a patient with multiple myeloma. IL 6 levels were low following 10 days of treatment with no symptoms
					Antibiotics	Moxifloxacin 400 mg IV OD for 3 days	
					Antiviral	Umifenovir (Umifenovir): 200mg PO TID	
					Chemotherapy	Bortezomib, thalidomide, and dexamethasone	
Wang Y et al., 2020 [57]	China	54 (48-64)[b]	46 (Male: 26; Female:20)	Prospective cohort study/ January 20 to February 25, 2020	Corticosteroids: (n=26)	Methyl prednisolone: 1-2mg/kg/d IV for 5-7 days	There was no difference with respect to inflammatory markers such as WBC, PMN, LYM, CPR, PCT 0.55, IL- 2, IL-4, IL-6 and IL-10 on day 6 after the treatment. However, there was a significant improvement with respect to
					Antiviral (n=46)	a-interferon, lopinavir/ritonavir for 5-7 days	

					Immunoenhancement therapy: (n=46)	Thymosin for 5-7 days	the chest radiograph and oxygen saturation
					Antibiotic and cough preparation: (n=46)	NS	
Zha L et al., 2020 [58]	China	39 (32-54)[b]	31 (Male: 20; Female: 11)	Retrospective cohort study/ 24 January to 24 February, 2020	Corticosteroid: n= 11	Methylprednisolone (40 mg OB or BD) for 5 (4.5-5.0)[b]	No clinical benefit with corticosteroid therapy in terms of virus clearance time (hazard ratio [HR]: 1.26; 95% CI: 0.58-2.74); hospital length of stay (HR: 0.77; 95% CI: 0.33-1.78); duration of symptoms (HR: 0.86; 95% CI: 0.40-1.83)
					Antibiotics: n=15	Moxifloxacin for 6.5 (3.5-7.0)[b]: n=14	
					Antiviral: 26	Lopinavir/ritonavir for 10 (8-11.5) [b] and interferon alfa for 15 (10–17)[b]: 26; Umifenovir for 10 (8-11.5) [b]: 5	
Repurposed drugs without adjunct therapy							
Young BE et al., 2020 [59]	Singapore	47 (31-73)[b]	18 (Male: 9; Female: 9)	Case-series/ January 23 to February 3, 2020	Antiviral (n=5)	Lopinavir-ritonavir for 14 days	Antiviral therapy was provided in 5 patients and 1 patient completing the course with remaining discontinuing because of side effects such as nausea, vomiting, and/or diarrhoea (n=4); abnormal liver function test (n=3)
Lan L et al., 2020 [60]	China	30 - 36	4 (Male: 2; Female: 2)	Retrospective Case-series/ January 1, to	Antiviral drug: (n=4)	75 mg of oseltamivir taken orally every 12 hours	75% of the patients were discharged and 25% remained in the hospital. However, the RT-PCR tests appeared to be positive when repeated 5 to 13 days later

				February 15, 2020			
Lim et al., 2020 [61]	Korea	54	1 (Male)	Case Report/ January 25, 2020	Antiviral drugs	Lopinavir 200 mg/ritonavir 50 mg BID PO	Antiviral therapy improved the clinical symptoms and reduced the viral loads.
Kim JY et al., 2020 [62]	Korea	35	1 (Female)	Case Report/19 to 31 January, 2020	Anti-viral drugs	lopinavir 400 mg/ Ritonavir 100 mg	Clinical improvement with respect to symptom resolution and reduction in oxygen requirement was observed
Qiu H et al., 2020 [63]	China	8·3 (3·5)[a]	36 (Male: 23; Female: 13)	Retrospective cohort study/ Jan 17 to March 1, 2020	Antiviral drug: (n=36)	Interferon alfa by aerosolisation twice a day: 36 (100%); Lopinavir–ritonavir syrup twice a day: 14 (39%)	All patients were discharged following antiviral therapy with a 17% of oxygen requirement and median duration hospitalization days of 14 (10-20) days
Experimental with adjunct therapy							
Wang Yeming et al., 2020 [64]	China	65 (56-71) [b]	236 (Male: 140; Female: 96)	Investigator-initiated double-blind, placebo-controlled, multicentre RCT/ Feb 6, to April 10, 2020	Antiviral	Remdesivir: (n=158) (200 mg on day 1 followed by 100 mg in single daily infusions); Lopinavir–ritonavir: (n=67); Interferons: (n=76) for 10 days	No significant effect was observed with remdesivir in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]) compared to the placebo. Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early and the trial was terminated.
					Placebo (n=79)	200 mg on day 1 followed by 100 mg in single daily infusions for 10 days	
					Steroids (n=155)	Corticosteroids for 9 (5-15) [b]	

					Antimicrobial (n=215)	-	
Chen C et al., 2020 [65]	China	<65: 166; ≥ 65: 70	236 (Male: 110; Female: 126)	Prospective, multicentre, open-label, superiority RCT/ February 20 to March 12, 2020	Antiviral: n=236	Favipiravir: n=116; 1600mg BD on the first day; 600mg BD from the second day for 7-10 days Umifenovir: n=120; 200mg TID, from the first day for 7-10 days	Favipiravir was effective with respect to the latency to fever reduction and cough relief (P<0.0001) compared to umifenovir. However, no significant difference was observed in terms of clinical recovery rate (P=0.1396) and auxiliary oxygen therapy or non-invasive mechanical ventilation rate (both P>0.05) between the groups. The AEs associated with favipiravir includes elevation of serum uric acid (13.79%), elevated LFT (8.62%), psychiatric dysthesia (4.31%) and GI problems (13.79%) among the 116 patients treated.
					Antibiotics: n=40	Moxifloxacin Hydrochloride: n=40; Cephalosporins: 24	
					Antiviral drugs other than the experimental drugs: 38	NS	
					Steroids: n=15	Glucocorticoid	
					Blood products: n= 9	Human Serum Albumin	
					Chinese herbal Medicine: n=53	Lianhua Qingwen Capsule and Xuebijing Injection	
Cai Q et al., 2020 [66]	China	47 (35.75–61) [b]	80 (Male: 35; Female: 45)	Open-label non-RCT/ January 30 to 14 February 2020	Antiviral: (n=80)	Favipiravir (n=35): (1600 mg BD on day 1; 600 mg BD from day2); Lopinavir/ritonavir	The favipiravir arm showed significant improvement in chest imaging compared with lopinavir/ritonavir arm, with an improvement rate of 91.43% versus 62.22% (P = 0.004). Moreover, viral clearance was also faster with

						(n=45): (400 mg/100 mg BD); Interferon-α: (n=80) (aerosol inhalation, 5 million U BD) for 14 days	favipiravir arm. However, adverse events were more among the FPV group.
					Standard Care	oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drugs	
Kujawski SA et al., 2020 [67]	United States	53 (21-68) [b]	12 (Male:8; Female: 4)	Case-series/ January 20 to February 5, 2020	Antivirals: (n=3)	Remdesivir for 4-10 days	Treatment was effective in resolving symptoms; improvement in chest radiograph; and negative report of RT-PCR
					Antibiotics: (n=5)	Vancomycin; Cefepime; Levofloxacin; Ceftriaxone; Azithromycin; Metronidazole for 4-12 days	
					Steroids: (n=2)	Methylprednisolone; Prednisone for 8-10 days	
Lescure FX et al., 2020 [68]	France	30-80 [c]	5 (Male: 3; Female: 2)	Case-Series/ Jan 24 to Jan 29, 2020	Antiviral drugs: (n=3)	Remdesivir: loading dose of 200 mg, then maintenance daily dose of 100 mg, IV for 10 days	Mortality, complications and ventilation was recorded in one (20%) patient. Rash and elevated aminotransferase was observed in one patient.

					Antibiotics (n=1)	Meropenem, tigecycline, and colimycin followed by meropenem and levofloxacin	
					Antifungals (n=1)	Case 3: voriconazole but switched to isavuconazole	
Holshue et al., 2020 [69]	USA	35	1 (Male)	Case Report/ January 19 to 30, 2020	Antiviral	IV remdesivir for 3 days	Patient was improved with respect to oxygen saturation, chest CT, clinical condition and all other symptoms
					Antibiotics	Vancomycin (1750-mg loading dose followed by 1g IV, TID); Cefepime (IV, TID) for 7 days	
					NSAIDS	Acetaminophen (650 mg, Q4H); ibuprofen (600 mg Q6H) for 10 days	
					Expectorant	Guaifenesin (600 mg) and approximately 6 litres of normal saline for 10 days	
Durante-Mangoni E et al., 2020 [70]	Italy	NR	4	Case Series/ 7 March to15 April, 2020	Antiviral: n=4	Remdesivir: n=4; 200 mg loading dose, followed by 100 mg daily intravenously for up to 10 days	One patient experienced a torsade de pointes requiring cardiac resuscitation and one died due to multiple organ failure. Three patients showed biochemical signs of liver injury. Lymphocyte count increased in all patients soon after remdesivir initiation. Nasal swab
						LPV/r: N=4; 400/100 mg twice daily PO	

						Darunavir/cobicistat: n=2; 800/150 mg once daily PO	SARS-CoV-2 RNA became negative in three of four patients after 3 days of therapy.
					Antimalarial: n=4	HCQ: n=4; 200 mg twice daily PO	
					Biological agents: n=4	Tocilizumab: n=4; 800 mg IV infusion in the days immediately preceding RDV start	
Experimental therapy without adjunct therapy							
Beigel JH et al., 2020 [71]	60 trial sites and 13 subsites in the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1)	All: 58.9±15.0[a] Remdesivir: 58.6±14.6[a] Placebo: 59.2±15.4[a]	1063 (Male: 684 ; Female: 379)	Double-blind, placebo-controlled, multicentre RCT/ February 21, 2020 to and ended on April 19, 2020	Antiviral (n= 541)	Remdesivir: n=541; 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death	Remdesivir had a significant better recovery rate (rate ratio, 1.32; 95% CI, 1.12 to 1.55; P<0.001) with a better median recovery time (11 days [9 to 12] vs 15 days [13 to 19]) than who received placebo. The Kaplan Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).
					Placebo (N =522)	200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death	
Goldman J et al., 2020 [72]	55 hospitals in the United	5-Day Group: 61 (50–69)[b]; 10-	397 (Male: 253; Female: 144)	Randomized, open-label, phase 3, multi-	Antiviral: (N=397); 5-Day Group (n = 200)	200 mg of remdesivir on day 1, followed	No significant difference (P=0.14) were observed between the 5 days and 10-day course of remdesivir in patients with severe

	States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan	Day Group: 62 (50–71)[b]		centre trial/ March 6 to 26, 2020 (5 day versus 10 day courses)	10-Day Group (n =197)	by 100 mg of remdesivir once daily for the subsequent 4 or 9 days	Covid-19 not requiring mechanical ventilation.
Grein J et al., 2020 [73]	United States	64 (48–71) [b]	53 (Male: 40; Female: 13)	Prospective cohort study/ January 25, to March 7, 2020	Antiviral: (n= 53)	10-day course of remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days	Remdesivir treatment showed improvement in oxygen-support status (68%) with mortality (13%). However, virological cure was not recorded
Adjuvant therapy only							
Cheng SC et al., 2020 [74]	Taiwan	55	1 (Female)	Case Report/ January 20 to February 07, 2020	Antitussive agent	NS	Antibiotic therapy improved oxygen saturation and clinical condition and got discharged. Repeated RT-PCT reported negative.
					Antibiotics	Ceftriaxone (2 gm loading dose and 2 gm IV OD) and later replaced with amoxicillin/clavulanate 875/125 mg BD for one week	
Huang WH et al., 2020 [75]	Taiwan	74 and 73	2 (Females)	Case Report/ NS	Antibiotics	Case 1: Levofloxacin; Case 2: Cefepime IV and Clarithromycin PO as an empirical	General condition were improved and patients were symptom free following the antibiotics therapy with an unimproved chest radiograph findings.

						therapy later shifted to moxifloxacin	
Luo P et al., 2020 [76]	China	73 (62-80)[b]	15 (Male: 12; Female: 3)	Retrospective cohort study/ Jan 27 to Mar 5, 2020	Biological agents: n=15	Tocilizumab: Range: 80 mg to 600 mg	Tocilizumab was effective in reducing the CRP level among the ill patients and repeated dose were effective in controlling the IL-6 levels.
					Steroids: n=8	Methylprednisolone: 40mg or 80mg	
Mihai et al., 2020 [77]	Switzerland	57	1 (Female)	Case Report/ Feb 27 to March 30, 2020	Biological agents	Tocilizumab, 8mg/kg body weight every 4 weeks IV for 4 weeks	The patient reported to be free of symptoms and negative nasopharyngeal swab for SARS-Cov2

RT-PCR: Reverse transcription polymerase chain reaction; mg: Milligram; Kg: Kilogram; OD: Once daily; BD: Twice daily; TID: Thrice a day; PO: Per oral; IV: Intravenous

[a] indicates mean with standard deviation

[b] indicates median and Interquartile range

[c] indicate the range of values

[d] indicate follow-up period ; NS: Not specified

3.3 Risk of Bias and quality of reporting

The Cochrane risk of bias assessment was used to assess the 10 RCTs. Risk of selection bias was low to moderate among the studies. However, risk of performance bias was high among 60% studies (n=6) being open labelled. Among the studies included, the risk of detection, attrition and reporting bias appeared to be low. The quality of reporting of analytical observational studies were assessed based on STROBE checklist. Studies were scored 1 against each checklist item and 0 for none with a total scoring out of 22. A total of 14 studies (56%) scored 21 out of 22 except for sample size calculation. Two studies (8%) acquired complete score [33, 70]. The overall score ranged from 12 to 22 out of 22. The scale developed by Murad et al., which focused on selection, ascertainment, causality and reporting with a score of 8 was used to assess the quality of 20 descriptive observational studies. A score of 5 was considered as maximum. Majority (n=17; 89%) scored 5. Durante-Mangoni E et al., 2020 [70] did not provide any information on demographics such as gender and age, which made difficult to understand the real effect of drug in aged people among they included. Huang WH et al., 2020 [75] and Shi et al., 2020 [44] did not follow the patients adequately and all three studies scored as 4. A detailed assessment of risk of bias assessment is described in Appendix A-C.

Appendix A. Risk of bias in RCTs using Cochrane Risk of Bias assessment

S.N	Domain	Cao B et al., 2020 [24]	Chen Z et al., 2020 [50]	Gautret et al., 2020 [51]	Chen C et al., 2020 [65]	Borba MG et al., 2020 [52]	Cai Q et al., 2020 [66]	Li Y et al., 2020 [23]	Wang Yeming et al., 2020 [64]	Beigel JH et al., 2020 [71]	Goldman J et al., 2020 [72]
1	Random sequence generation	Unclear	Low	High	High	Low	High	Low	Low	Low	High
2	Allocation concealment	Unclear	Unclear	High	Unclear	Low	Unclear	Low	Low	Unclear	Unclear
3	Blinding of participants and personnel	High	Low	High	High	Low	High	High	Low	Low	High
4	Blinding of outcome assessment	High	Unclear	High	High	Unclear	High	Unclear	Unclear	Low	Unclear
5	Incomplete outcome data	Low	Low	High	Low	Low	High	Low	Low	Low	Low
6	Selective reporting	Low	Low	High	Low	Low	High	Low	Low	Low	Low

Appendix B. Assessment of reporting standards observational studies using STROBE checklist

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
Xu XW et al., 2020 [29]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Wang Z et al., 2020 [30]	1	1	0	1	1	1	0	0	0	0	0	0	1	1	1	1	0	1	0	1	1	0	12
Chen N et al., 2020 [31]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Huang C et al., 2020 [25]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Wang D et al., 2020 [32]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21

Young BE et al., 2020 [59]	1	1	0	1	1	1	0	0	0	0	0	0	1	1	1	1	0	1	0	1	1	1	13
Yang X et al., 2020 [33]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22
Zhou F et al., 2020 [35]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Hu Z et al., 2020 [34]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	20
Wu C et al., 2020 [36]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Qiu H et al., 2020 [63]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Tang X et al., 2020 [37]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Chen J et al., 2020 [38]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Zhang L et al., 2020 [39]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Yang W et al., 2020 [40]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Liu F et al., 2020 [27]	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	19
Deng L et al., 2020 [28]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Liu K et al., 2020 [41]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Guo T et al., 2020 [42]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	21
Xu X et al., 2020 [53]	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	1	1	1	1	18
Ye XT et al., 2020 [26]	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	20

Wang Y et al., 2020 [57]	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	19
Luo P et al., 2020 [76]	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	19
Zha L et al., 2020 [58]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	20
Grein J et al., 2020 [73]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	22

1: Yes; the reporting standard were met; 0: Reporting standards were not met.

Appendix C. Risk of bias in descriptive observational studies using Murad et al., 2018

Reference	**Selection**	**Ascertainment**		**Causality**				**Reporting**	**Total**
	Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent That other patients with similar presentation may not have been reported?	Was the exposure adequately ascertained?	Was the outcome adequately ascertained?	Were other alternative causes that may explain the observation ruled out?	Was there a challenge/rechallenge phenomenon?	Was there a dose-response effect?	Was follow-up long enough for outcomes to occur?	Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	
Wei et al., 2020 [45]	1	1	1	NA	NA	NA	1	1	5
Shi et al., 2020 [44]	1	1	0	NA	NA	NA	0	1	3
Holshue et al., 2020 [69]	1	1	1	NA	NA	NA	1	1	5

Chen D et al., 2020 [46]	1	1	1	NA	NA	NA	1	1	5
Cheng SC et al., 2020 [74]	1	1	1	NA	NA	NA	1	1	5
Lim et al., 2020 [61]	1	1	1	NA	NA	NA	1	1	5
Huang WH et al., 2020 [75]	1	1	1	NA	NA	NA	0	1	4
Lescure FX et al., 2020 [68]	1	1	1	NA	NA	NA	1	1	5
Han W et al., 2020 [47]	1	1	1	NA	NA	NA	1	1	5
Kim JY et al., 2020 [62]	1	1	1	NA	NA	NA	1	1	5
Xu Z et al., 2020 [48]	1	1	1	NA	NA	NA	1	1	5
Lan L et al., 2020 [60]	1	1	1	NA	NA	NA	1	1	5
Shen C et al., 2020 [43]	1	1	1	NA	NA	NA	1	1	5
Inciardi RM et al., 2020 [49]	1	1	1	NA	NA	NA	1	1	5

Ferrey A et al., 2020 [54]	1	1	1	NA	NA	NA	1	1	5
Michot J et al., 2020 [55]	1	1	1	NA	NA	NA	1	1	5
Mihai et al., 2020 [77]	1	1	1	NA	NA	NA	1	1	5
Zhang X et al., 2020 [56]	1	1	1	NA	NA	NA	1	1	5
Kujawski SA et al., 2020 [67]	1	1	1	NA	NA	NA	1	1	5
Durante-Mangoni E et al., 2020 [70]	1	1	1	NA	NA	NA	1	0	4

NA: Not applicable

Funnel plot depiction

Visual inspection of the funnel plot demonstrated an obvious asymmetry, which could be due to publication bias, significant heterogeneity among study participants, selective outcome reporting, or chance. The visual suspicion of publication bias was not confirmed statistically according to Egger's (0.908) and Begg's test (0.940) (Figure 2). A comprehensive literature search, systematic review process might have resulted in an insignificant statistical evidence of publication.

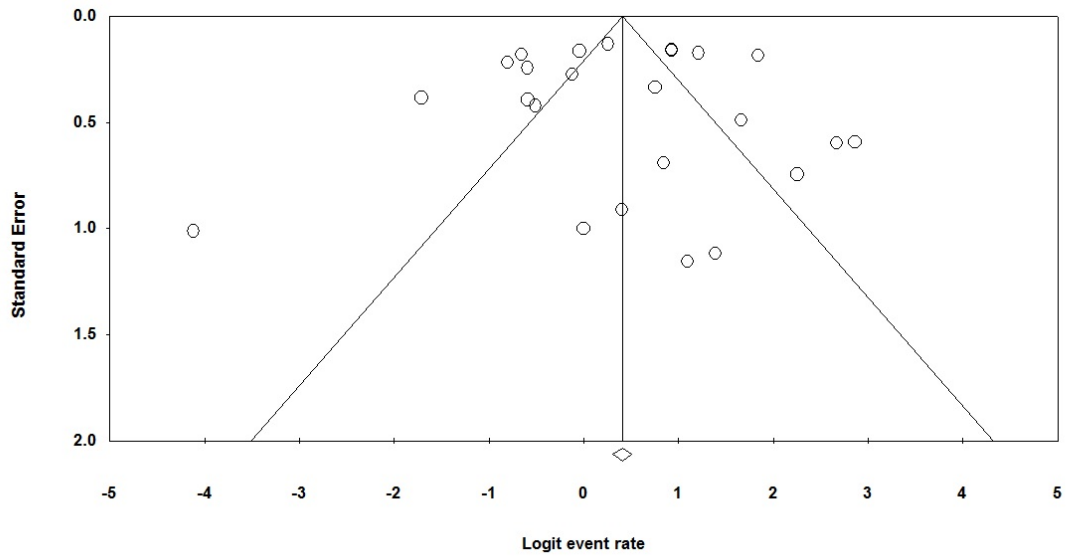


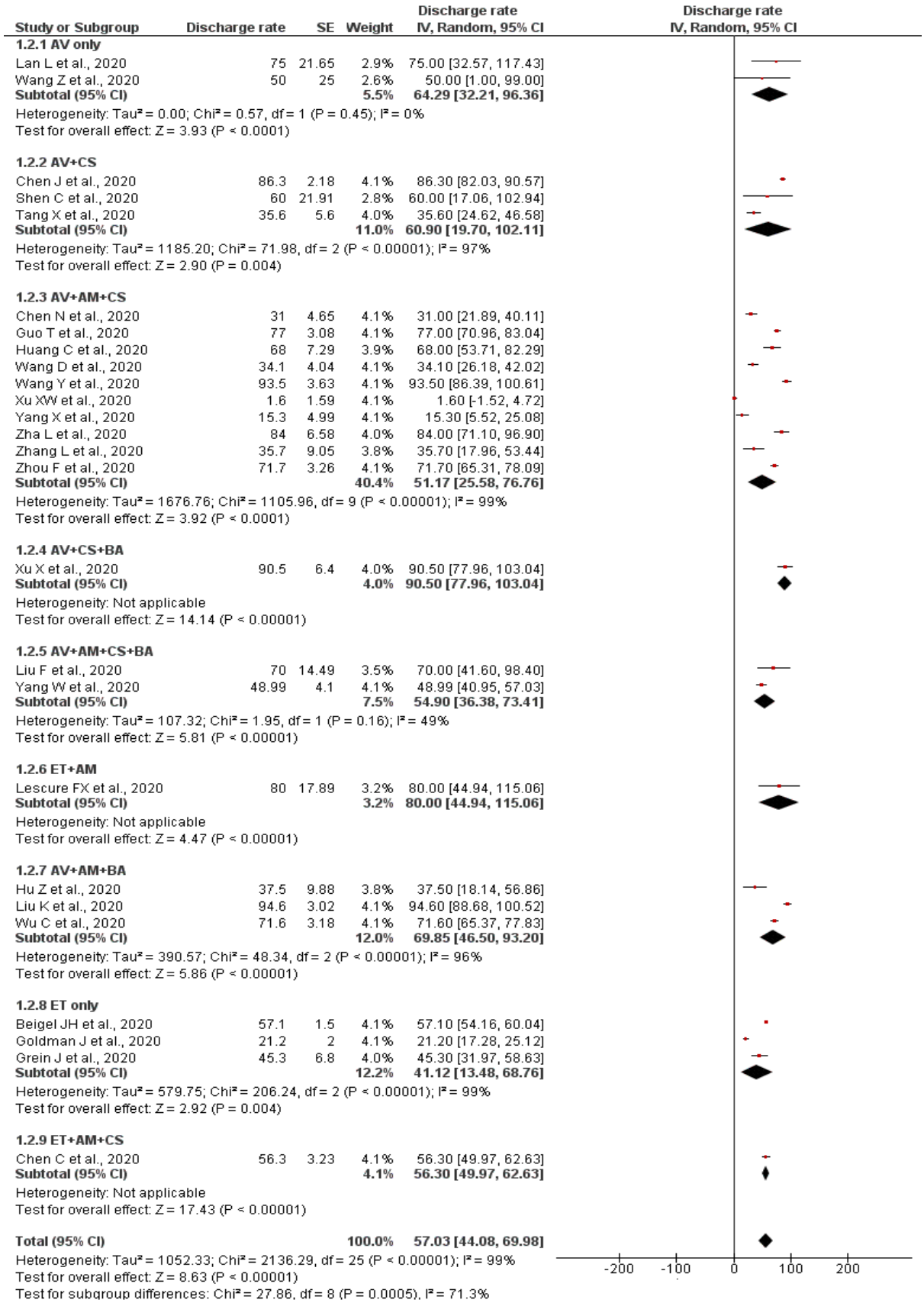
Figure 2. Funnel plot depiction of pharmacotherapy evidence of COVID-19

3.4 Pooled analysis of outcomes in context to drug classes

A description of outcomes in context to various drug classes were presented through pooled analysis. While we present the pooled rates of outcomes, the observational nature of primary studies, lack of control group, high risk of bias, and poor study methodology mean the findings are likely confounded by number of key factors. These include severity of the condition, characteristics of study participants, varied comorbidity, varied medication history (including exposure to corticosteroid and biological agents), difference in clinical setting, time from symptom to hospital admission, variation in treatment approach and in provision of supportive care. As such, these results should be interpreted cautiously.

3.4.1 Rate of hospital discharge

A pooled analysis of 26 studies (19 repurposed drugs with adjuvant therapy; 2 repurposed drug without adjuvant therapy; 3 experimental drug without adjuvant therapy and 2 experimental drug with adjuvant therapy) demonstrated a discharge rate of 57.03 % (95% CI: 44.08 to 69.98) which ranged from 1.6% to 94.6% in patients treated with various different pharmacotherapies for COVID-19 (Figure 3). Heterogeneity was very high (I^2=99%).



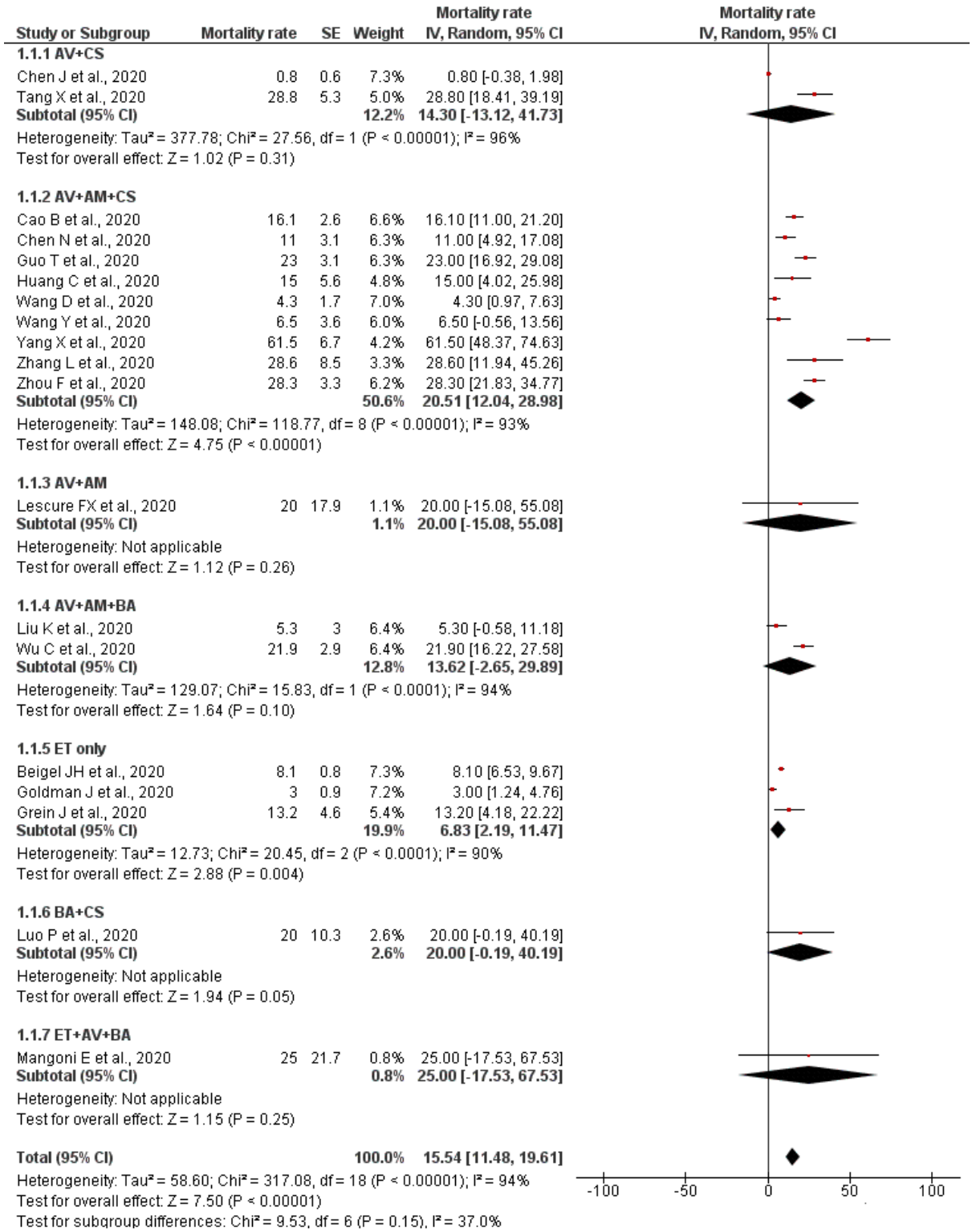
AV: Antiviral drug; CS: Corticosteroids; AM: Antimicrobials;

BA: Biological agents; ET: Experimental therapy

Figure 3. Rate of hospital discharge in patients on pharmacotherapy for COVID-19

3.4.2 Mortality

Meta-analysis of 19 (14 repurposed drugs with adjuvant therapy; 3 experimental drug without adjuvant therapy; 1 experimental therapy with adjuvant therapy; 1 with only adjuvant therapy) studies estimated a mortality rate of 15.54% (95%CI: 11.48-19.61) among hospitalised patients (range: 0.8% to 288%) with significant heterogeneity (I^2=95%) (Figure 4).

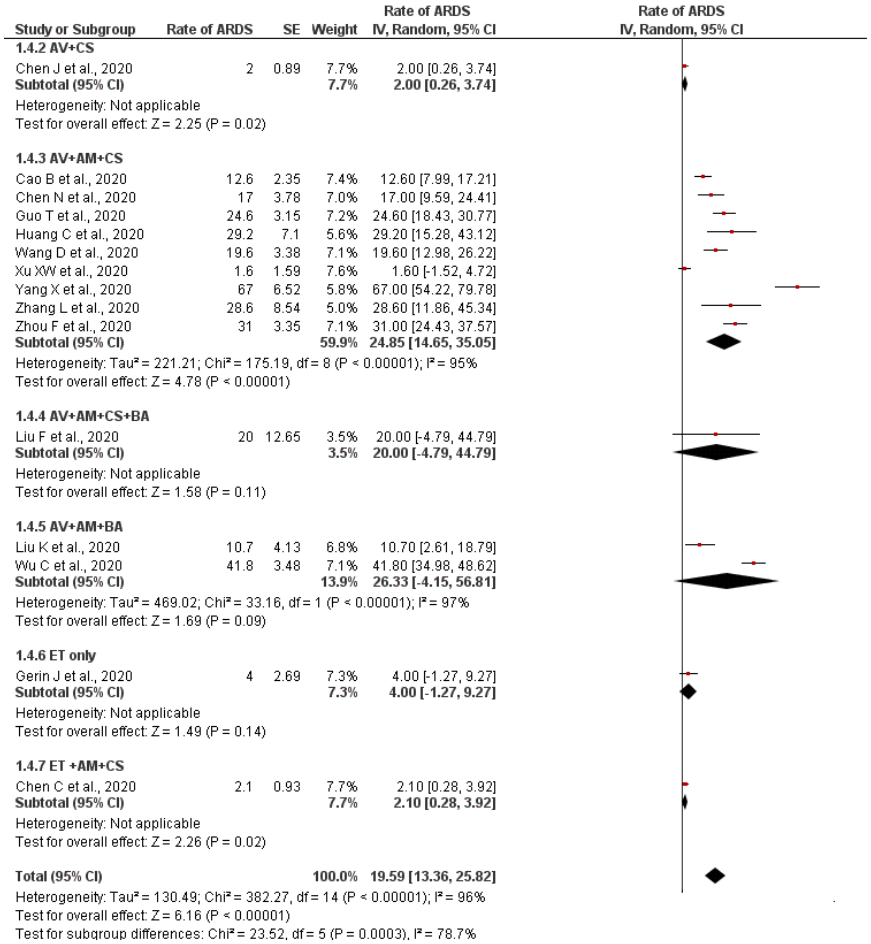


AV: Antiviral drug; CS: Corticosteroids; AM: Antimicrobials; BA: Biological agents; ET: Experimental therapy

Figure 4. Mortality rate in patients on pharmacotherapy for COVID-19.

3.4.3 Rate of ARDS

Pooled analysis of 15 (13 repurposed drugs with adjuvant therapy; 1 experimental drug without adjuvant therapy; and 1 experimental drug without adjuvant therapy) studies estimated an ARDS rate of 19.59% (95% CI: 13.36-25.82 among the treated patients with a range from 1.6% to 41.8%. There was a significant heterogeneity (I^2=96%). However, we were unable to perform subgroup analysis on treatment, age, and gender because of inadequate data. (Figure 5). Rate of occurrence of ARDS was highest among patients on combination therapies (e.g. antiviral, antimicrobials and biological agent).

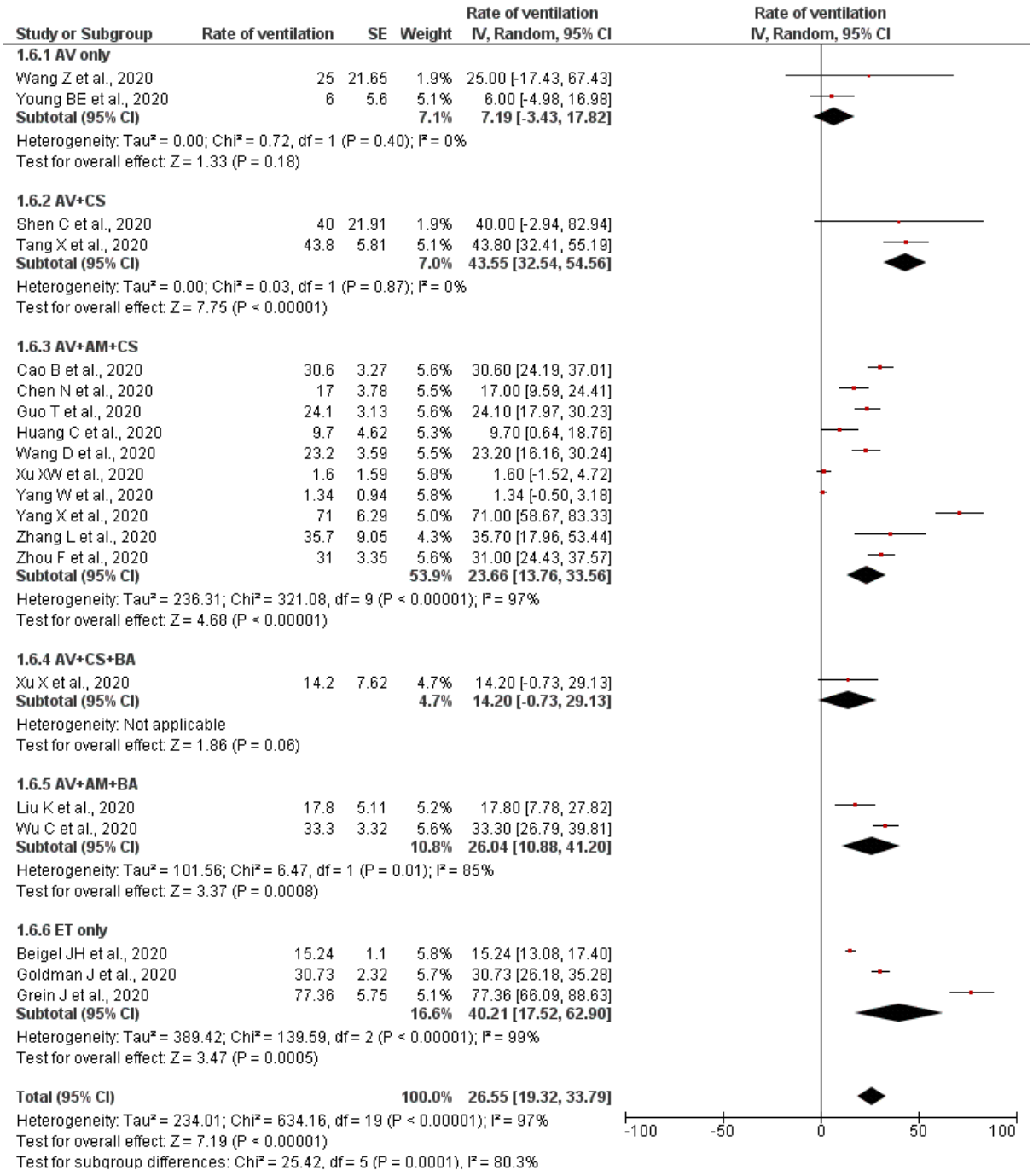


AV: Antiviral drug; CS: Corticosteroids; AM: Antimicrobials; BA: Biological agents; ET: Experimental therapy

Figure 5. Rate of acute respiratory distress syndrome (ARDS) in patients on pharmacotherapy for COVID-19.

3.4.4 Rate of patients on mechanical ventilation

Summary analysis of 20 (15 repurposed drugs with adjuvant therapy; 2 repurposed drugs without adjuvant therapy; 3 experimental drug without adjuvant therapy) studies recorded a ventilation requirement among the 26.55% (95%CI: 19.32-33.79) among the treated patients which ranged from 1.6% to 77.36%. There was significant heterogeneity (I^2=97%) among the studies, which was zero among those who used antivirals alone and antivirals along with corticosteroids as treatment strategy. However, we were unable to perform subgroup analysis on treatment, age, and gender because of inadequate data. (Figure 6). Patients on experimental therapy and patients on combination therapy (e.g. antiviral with corticosteroid) had the highest rate of mechanical ventilation.



AV: Antiviral drug; CS: Corticosteroids; AM: Antimicrobials; BA: Biological agents; ET: Experimental therapy

Figure 6. Rate of patients on mechanical ventilation

3.5 Findings from drug classes

We obtained a total of 52 studies pertaining to various drug classes divided into repurposed drugs, adjunct therapies and experimental agents. A total of 41 studies were reported on repurposed drugs (4-aminoquinolines, lopinavir/ritonavir, ribavirin, umifenovir, oseltamivir, interferons) with (n=36) and without (n=5) adjunct therapies (antimicrobials, corticosteroids, immunomodulators, or complementary/alternative therapies) and a total of 7 studies on experimental agents (remdesivir and favipiravir) with (n=6) or without (n=1) adjunct therapies. Four studies administered adjunct therapies only.

3.5.1 Repurposed Drugs

4-Aminoquinolines

Chloroquine (CQ) and hydroxychloroquine (HCQ) are traditionally prescribed as antimalarials and anti-inflammatories. The most common HCQ dosing regimen, also based on pharmacokinetic modelling study [78] was a loading dose of 400 mg twice day for the first day followed by 200 mg twice daily for the next four days. CQ dosing consisted of 500 mg once or twice daily. The antiviral properties of both medications have been researched in recent years. Based on the theoretical possibility for a broad range of actions against COVID-19 there is widespread enthusiasm for their potential role among certain policymakers.

Hydroxychloroquine was trialled in total of 47 COVID-19 patients from two open label trials. Chen Z et al. conducted an intention to treat analysis and found no difference with control group in terms of efficacy and duration of treatment [50]. The second open label non-randomised trial was conducted among 36 patients from France [51]. The study found that patients in the treatment group were more likely to test negative for SARS-CoV- 2 on Day 6 than controls (70% versus 12.5% virologically cured, $P<0.001$). All six patients treated with HCQ and azithromycin tested negative on Day 6. However, one patient who tested negative on day 6 was subsequently tested positive on day 8. The study, however, was flawed by poor design, inadequate sample size, attrition bias (6 dropouts from treatment arm), lack of intention to treat analysis and clinically relevant endpoint. Two case reports [49, 54] also reported the use of 4-aminoquinolones for COVID-19 treatment with inconclusive outcomes. Additionally, there are several RCTs of CQ/HCQ underway including examining their potential role as prophylaxis in health care workers and for postexposure prophylaxis after high-risk exposures. Overall, the studies to date are limited both in number and design, suffering from flawed methodology and lacking meaningful comparison groups. Outcomes of these studies are further

limited by concerns over additive cardiotoxicity of combination therapy (HCQ with azithromycin). In addition, current studies suffer from an overreliance on endpoints such as viral clearance/load, ICU admission, and reduction in development of pneumonia without assessing patient-relevant outcomes such as quality of life, adverse events, and survival.

Antivirals

We identified a total of 35 observational studies and 2 open label trial examining repurposed antivirals. The current antiviral agents against COVID-19 are being trialled based on their previous experience in treating patients with SARS, MERS, Ebola and HIV infection. One of the most promising was the combination of lopinavir and ritonavir. A systematic review [79] of lopinavir/ritonavir for management of SARS and MERS coronavirus found reduced mortality and intubation rates. It was noted that timing of administration was crucial (initial 7-10 days) as delayed therapy had no effect on clinical outcomes. This finding appears to also apply to COVID-19.

A lopinavir/ritonavir-based regimen was examined in one RCT and 10 observational studies. In an open label RCT [24] from Wuhan, China at the peak of the epidemic, lopinavir/ritonavir 400 mg/100 mg twice a day for 14 days was compared with standard care in 99 patients (most identified as severe by treating clinicians). Intention to treat analysis after 28 days showed no difference in the primary outcome of time to clinical improvement between the two arms (16 days in both groups; hazard ratio 1.31; 95% CI: 0.95 to 1.85; p=0.09). The authors did note a shortened time to hospital discharge by 1 day. We assessed 10 observational studies that provided empirical data of lopinavir/ritonavir on clinical outcomes. A retrospective study [80] of 120 COVID-19 patients highlighted increased odds of prolonged viral shedding if patients were not treated with this combination regimen (adjusted odds ratio 2.42; 95% CI 1.10 – 5.36; p=0.03). Patients who started the regimen within 10 days of symptom onset had a shorter duration of viral shedding than patients that started treatment later (median 19 days versus 27.5 days respectively, $p < 0.001$). No significant difference in the median duration of viral shedding was found between patients who initiated treatment more than 10 days after symptom onset (vs. those who did not initiate; median 27.5 days versus 28.5 days, p=0.86). The observational studies should be interpreted with caution due to the high risk of bias. This combination has potential for significant drug-drug interactions and adverse drug reactions and as such need to be administered with caution in patients with COVID-19. For example, lopinavir/ritonavir combination could predispose patient to drug induced liver toxicity thereby potentially limiting

access to other medications metabolised through the liver. Close to 15% of lopinavir/ritonavir patients were unable to complete the full 14-day course of therapy due to gastrointestinal side effects (e.g. anorexia, nausea and abdominal discomfort). Patients in some of these observational studies were also on other adjunct therapies including umifenovir, corticosteroids, biologic immunomodulators, oseltamivir, and antimicrobials that may have impacted the clinical outcomes.

Other existing antivirals are also being examined alone and in combination including ribavirin, oseltamivir, umifenovir, and darunavir/cobicistat.

3.5.2 Adjunct therapies

Antimicrobials

The role of broad-spectrum antimicrobials in COVID-19 was assessed in many studies with or without repurposed or experimental drugs. Ceftriaxone, cefepime, azithromycin, levofloxacin, moxifloxacin, amoxicillin with clavulanic acid, carbapenems, tigecycline, linezolid, colimycin and piperacillin tazobactam were administered in patients with COVID-19 infection and suspected bacterial pneumonia/superinfection. There were no RCTs to assess their effectiveness and the existing observational studies should be interpreted with cation due to the high risk of bias. Two case reports [71, 72] predominantly treating with antimicrobial therapy (ceftriaxone, amoxicillin with clavulanic acid, levofloxacin, cefepime, clarithromycin and moxifloxacin) found limited benefits on clinical outcomes. Moderate to severe cases of COVID-19 are at high risk of developing secondary infection and superinfection. Mechanical ventilation also contributes to this risk. Broad spectrum coverage is preferred, and combination of antibiotics are currently being trialled. It is crucial that local antimicrobial sensitivity pattern is considered for choice of antimicrobial to prevent further drug induced risk in patients with COVID-19.

Corticosteroids

Corticosteroids may prevent or mitigate the harmful effects in patients with severe COVID-19 who are likely to develop a systematic inflammatory response that could lead to lung injury and multisystem organ dysfunction. A total of 23 studies, all observational, examined the value of corticosteroids in COVID-19 infection. A retrospective study from Wuhan, China [36] of 201 patients found that, for those who developed ARDS, treatment with methylprednisolone

was associated with a decreased risk of death (23/50 [46%] with steroids vs 21/34 [62%] without; HR, 0.38 [95% CI, 0.20-0.72]). However, the authors noted the likely presence of bias and residual confounding between those who did or did not receive steroids. Zha et al., [58] observed no significant beneficial effect of steroids on time to virus clearance (HR, 1.26; 95% CI, 0.58-2.74), duration of hospitalization (HR, 0.77; 95% CI, 0.33-1.78), or duration of symptoms (HR, 0.86; 95% CI, 0.40-1.83). Thus, the role of systemic corticosteroids in the management of ARDS secondary to COVID-19 remains controversial. Corticosteroids have caused adverse outcomes in patients with MERS with increased mortality and higher likelihood of invasive mechanical ventilation [81]

A meta-analysis [82] of corticosteroids in COVID-19 highlights patients with severe conditions are more likely to require corticosteroids with their usage is associated with increased mortality in patients with coronavirus pneumonia. The review, however, was collation of findings from SARS CoV and SARS CoV2 and as such was not specific to COVID-19 outcomes. Potential harm with inconclusive efficacy limits their use in COVID-19 and treatment decision need to be considered on case-by-case basis or unless a concomitant compelling indication, such as chronic obstructive pulmonary disease exacerbation or asthma exist. For example, in conditions such as refractory shock in patients with COVID-19 a low dose corticosteroid over no corticosteroid could be used as a conditional recommendation within the context of a clinical trial. At the time of revision of this manuscript a preprint [83] analysis from a multicentre, randomized, open-label trial of dexamethasone for hospitalized patients in the United Kingdom (RECOVERY trial) showed reduced rate of mortality in critically ill COVID-19 patients by one-third for those on ventilators (rate ratio 0.65 [95% CI 0.48-0.88]; p=0.0003) and by one-fifth for those on oxygen along (0.80 [0.67 - 0.96]; p=0.0021]. There was no benefit among those patients who did not require respiratory support (1.22 [0.86-1.75]; p=0.14).

Biological agents

Monoclonal antibodies against pro-inflammatory cytokines or innate immune response are potential adjunctive therapies for COVID-19. IL 6 plays a prominent role in acute inflammation and its elevated level during cytokine storm suggest potential role of tocilizumab, a recombinant humanised monoclonal antibody against IL 6 receptor. Early reports from case series suggests potential of tocilizumab in critically ill COVID-19 patients who have significantly higher level of IL 6 in the form of improved respiratory function and hospital discharge. A 60-year-old man from China [56] with multiple myeloma improved (on day 12)

in clinical symptoms (reduction in IL6 and improved findings on chest CT imaging) after administration (day 9) of 8 mg/kg IV tocilizumab. This patient was also on umifenovir and methylprednisolone. In another case report [54], a 56-year-old patient from USA with end stage renal disease (ESRD) received tocilizumab along with broad spectrum antimicrobials and HCQ, but developed rapidly deteriorating pulmonary function transitioning to ARDS. In two other case reports [55, 74] patients with COVID-19 and multiple comorbidities (e.g. systemic sclerosis and renal cell carcinoma) received tocilizumab and had a favourable outcome. In a retrospective observational study [73] of 15 patients with hypertension and diabetes at risk of developing cytokine storm, receipt of tocilizumab was also associated with beneficial outcome. Several RCTs are underway to elucidate the potential role of tocilizumab in COVID-19 infection.

Sarilumab, another IL 6 receptor antagonist is being trialled in a double-blind study (Sanofi Trial 2020) [84]. Trials are also underway with biologics such as bevacizumab (anti-vascular endothelial growth factor) [85], fingolimod (sphingosine-1-phosphate receptor modulator) [86] and eculizumab (antibody targeting complement protein C5) [87]. Immunoglobulin therapy [88] against COVID-19 is also under evaluation with a potential for COVID-19 convalescent plasma through emergency experimental new drug application.

3.5.3 Experimental therapies

Remdesivir

A broad-spectrum antiviral, remdesivir, was trialled against a range of RNA viruses including Ebola virus, MERS CoV and SARS CoV. Current experimental dosing regimen includes a single 200 mg loading dose followed my 100 mg daily infusion. It is not recommended in patients with estimated glomerular filtration rate of less than 30 mL/min. The first randomised, double-blind, placebo-controlled trial [64] assessing the effect of intravenous remdesivir in adults with severe COVID-19 was terminated before attaining the pre specified sample size because of difficulty recruiting patients after the outbreak in Wuhan, China. Intention to treat analyses suggested the time to clinical improvement and duration of mechanical ventilation was not significantly different between groups, although numerically shorter in the remdesivir group than the placebo, particularly those treated within 10 days of symptom onset. The antiviral was tested in three observational studies and was associated with improvement in chest CT scan, oxygen saturation and discharge rate. These patients were also on antimicrobials

and adjuvant therapies (analgesics and anti-inflammatory). In a case series of patients with severe COVID-19, patients had a decrease in the need for oxygen support after receiving remdesivir, but there was no comparison group. In two case reports [67, 69] patients with COVID-19 who received remdesivir had favourable clinical outcomes. At the time of revision of this manuscript a multicentre RCT [71] demonstrated better recovery rate (rate ratio, 1.32; 95% CI, 1.12 to 1.55; P<0.001) with a median recovery time (11 days [9 to 12] vs 15 days [13 to 19]) than who received placebo. The Kaplan Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%). Another RCT [72] demonstrated no significant difference while a cohort study [73] showed improvement in oxygen support status. At present, remdesivir must be obtained via compassionate access, expanded access or through enrolment in a clinical trial as investigational therapy.

Favipiravir

Favipiravir, a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5'triphosphate inhibits the RNA polymerase, thereby stopping the viral replication is another experimental therapy with limited clinical evidence. A prospective, randomised, multicentric study [65] compared favipiravir with umifenovir for moderate to severe COVID-19 with no significant difference in clinical recovery in 236 (116 on favipiravir vs. 120 on umifenovir) moderate to severe COVID-19 patients. There was no significant difference in clinical recovery at day 7, however, favipiravir seems efficacious in regard to latency to fever reduction and cough relief compared to umifenovir [65]. No significant differences were observed with respect to adverse events such as abnormal LFT (P=0.7156), psychiatric symptom reactions (P=0.1149), gastrointestinal reactions (P=0.6239). Increased uric acid (P=0.0014) was observed in favipiravir group.

The adverse events as well as the management of treatment-emergent adverse effects were poorly reported in all the included studies across the drug classes. Short term follow-up and descriptive nature of many studies made it difficult to provide data on safety concerns of the treatments. However, GI disturbance [24,28,59], hypokalaemia [27] and hypoalbuminemia [27], abnormal liver function tests [59], rash, anaemia [24], GI haemorrhage [28], intravascular coagulation [24], and hyperbilirubinemia [28] were reported mostly with antiviral drugs.

Remdesivir was associated with rash and aminotransferase elevation [68]. Immunoglobulin infusion related fever with chills and diarrhoea were observed [34]. The AEs associated with favipiravir included elevation of serum uric acid, elevated liver function tests, psychiatric dysthesia and adverse gastrointestinal events [65].

3.6 Current pharmacotherapy recommendation

With numerous pharmacotherapies currently undergoing evaluation and the rapid evolution of the evidence, real-time, interim evidence-based guidelines are being made available. We compiled recommendations from such guidelines published [89-95] in the US, Canada, UK and India (Table 4). The compilation is presented as COVID-19 disease severity against status of pharmacotherapy recommendation.

Table 2. Pharmacotherapy of COVID 19 in adults - compilation of recommendations from clinical guidelines

COVID-19 staging*	**Repurposed drugs**	**Adjunct therapies (antimicrobials)**	**Immunomodulators**	**Experimental therapies**	**Other therapies**
Mild **Moderate**	Insufficient data to recommend either for or against repurposed drugs in patients with COVID-19 for mild/moderate illness. **Chloroquine** or **hydroxychloroquine** (with or without azithromycin) is **not** recommended outside of approved clinical trials or where other indications would justify its use because of the potential for toxicities. If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects, especially prolonged QTc interval.	**Mild** - Antimicrobial therapy is **not** routinely recommended outside of approved clinical trials or where other indications would justify its use **Moderate** - If bacterial pneumonia or sepsis is strongly suspected, administer empiric antibiotic treatment for community-acquired pneumonia, re-evaluate daily, and if there is no evidence of bacterial infection, de-escalate or stop antibiotics.	**Corticosteroids** should **not** be offered outside of approved clinical trials unless there are other indications for its use. Guidelines recommends **against** the routine use of systemic corticosteroids in patients with COVID-19 who do not require supplemental oxygen. **Tocilizumab** is **not** recommended outside of approved clinical trials	Insufficient clinical data to recommend either for or against using the experimental antiviral drug **remdesivir**	**Zinc** - Not recommended outside the context of clinical trial **Vitamin C** - Not recommended outside the context of clinical trial

	Lopinavir/ritonavir is **not** recommended outside of approved clinical trials because of unfavourable pharmacodynamics and adverse clinical trial outcomes.				
Severe/Critical	**Chloroquine** or **hydroxychloroquine** is **not** recommended outside of approved clinical trials or where other indications would justify its use because of the potential for toxicities. If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects, especially prolonged QTc interval **Lopinavir/ritonavir** is **not** recommended	**Ceftriaxone 1 g IV q24h x 5 days** is recommended if there is concern for bacterial co-infection (Alternative for severe beta-lactam hypersensitivity: levofloxacin 750 mg IV or moxifloxacin 400 mg IV q24h x 5 days) Add **azithromycin** 500 mg IV q24h x 5 days to ceftriaxone empiric therapy if Legionella infection is suspected (azithromycin is not needed if empiric therapy is levofloxacin or moxifloxacin) De-escalate on the basis of microbiology results and clinical judgment.	**Corticosteroids**: Among hospitalized patients **dexamethasone** (6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated. Equivalent total daily doses of alternative glucocorticoids to **dexamethasone** 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.	In hospitalised patients with severe COVID-19 **remdesivir** over no antiviral treatment is suggested (conditional recommendation only). For consideration in contingency or crisis capacity settings, for example, limited remdesivir supply: Remdesivir appears to demonstrate benefit in those with severe COVID-19 on supplemental oxygen rather that mechanical ventilation or extracorporeal mechanical ventilation. Five days therapy of **remdesivir** (rather than 10 days) for severe COVID-19 patients on supplemental oxygen but not on mechanical ventilation or	**Famotidine** - Among hospitalized patients with severe COVID-19, famotidine is not recommended for the sole purpose of treating COVID-19 outside the context of a clinical trial (conditional recommendation only).

	outside of approved clinical trials because of unfavourable pharmacodynamics and adverse clinical trial outcomes.		For adults with COVID-19 and refractory shock, low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids could be trialled (conditional recommendation). **Tocilizumab -** Among patients who have been admitted to the hospital with COVID-19, tocilizumab could be administered only in the context of a clinical trial. On an an individual basis in patients with cytokine storm (with expert consultation).	extracorporeal mechanical oxygenation.	
Asymptomatic or Presymptomatic	No specific treatment/prophylaxis approach for persons with suspected or confirmed asymptomatic or presymptomatic SARS CoV 2 infection. Health care workers who test positive and are asymptomatic may obtain additional guidance from their health service providers/health advisory. Indian Council of Medical Research (ICMR) Guidelines recommends HCQ as prophylaxis in symptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID 19 and asymptomatic household contacts of laboratory confirmed cases.				

**Mild - Patients may have mild illness defined by any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath or dyspnea or abnormal imaging. Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or remote visits.*

***Moderat**e - Evidence of lower respiratory disease by clinical assessment or imaging with SpO_2 >93% on room air at sea level.*

***Severe/critically ill** - SpO_2 ≤94% on room air at sea level, respiratory rate >30, PaO_2/FiO_2 <300, or lung infiltrates >50%. These patients may experience rapid clinical deterioration. Severe cases may be associated with acute respiratory distress syndrome (ARDS), septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevations in multiple inflammatory cytokines that provoke a cytokine storm, and/or exacerbation of underlying co-morbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease.*

4. Expert opinion

4.1 Key findings and weaknesses in the research

Despite an admirable effort by practitioners and researchers across the globe to generate evidence to inform practice and policy, the current evidence base for the pharmacotherapeutic management of SARS-CoV2 is difficult to interpret. While promising signals have been found, these signals must be interpreted with caution due to a high risk of bias. Without proper protection from bias and confounding we risk exposing patients to treatments where the potential for benefit is at best unclear, yet the potential for harm from adverse effects is high.

Current data do not support the use of any pharmacotherapy for COVID-19 outside the context of randomized controlled trials. Studies of experimental antiviral and immunomodulatory agents for COVID-19 have been marred by design flaws such as failure to include adequate control groups, biased patient enrolment, small sample size, focus on dubiously relevant laboratory and clinical outcomes, and inadequate monitoring for and reporting of treatment-related adverse events. Those studies that have more rigorous designs have failed to consistently show meaningful benefits. At this time, supportive treatment remains the standard of care.

Beyond the biases inherent in the studies themselves, the evidence is difficult to synthesize due to high amounts of heterogeneity resulting from differences in populations, interventions, comparisons, and outcomes. Further, small sample sizes limited the precision of available estimates. While combining small sample sizes in meta-analysis can help identify heterogeneity and address issues related to power, trialists should strive to design adequately powered trials wherever possible. Our review was restricted to studies published in English language and as such could have an impact on summary treatment effect estimates. Studies in non-English language were mostly observational in nature.

Finally, while some of these therapies have well established safety data, others are more novel. Existing studies inconsistently and haphazardly collect and report on adverse event data. Yet, this information is crucial for decision makers to determine the balance of benefit and harm. As COVID-19 is a an emerging, rapidly evolving situation we discuss an overview of key updates at the time of revision of this manuscript: (i) The FDA revoked its emergency use

authorization for CQ/HCQ stating adverse events including the serious cardiac outcomes and failure to demonstrate efficacy in COVID-19 [96]; (ii) The FDA issued warning that co-administration of remdesivir and CQ/HCQ is not recommended as it may results in reduced antiviral activity of remdesivir [97]. However there are instances of this reduced activity occurring in the clinical setting; (iii) The WHO has dropped the HCQ treatment arm of the SOLIDARITY trial [98] as a result of failure to prove efficacy based on preliminary findings from RECOVERY [99] and other studies; (iv) With press release [100] of findings from RECOVERY trial on dexamethasone showing reduced mortality the low coast and hope to save lives could have a positive impact on therapeutic options in severe COVID-19 cases in particular in low and middle income countries; (v) The Lancet recently retracted a published multicentre observational study [101] that raised concern on adverse cardiovascular effect and decreased hospital survival rates with HCQ. Retraction was based on request from three of the primary study authors who can no longer vouch for veracity of the primary data sources. This raises several questions on peer-review process of primary studies/data in event of uncertainty and the trade-off dilemma in need for rapidly sharing therapeutic information with global consequences vs. the scientific importance of evaluating the submitted work carefully and the transparency process of primary data analysis in such research; (vi) The same day of Lancet's retraction, New England Journal of Medicine retracted the HCQ study [102] alarming medical community who fear that the pressure for research on COVID-19 has overwhelmed the peer review process and has opened the possibility of dubious data thereby threatening the credibility of medical publishing in times when it is of upmost importance.

4.2 Potential direction of future research and practice goal in this field

To advance practice and policy the global community needs to work together to generate evidence in which stakeholders (e.g. patients, providers, policymakers) can have high confidence for both the effectiveness and the safety of treatments. Future studies should have adequate protection from bias and confounding, utilizing randomization and other tools (e.g. blinding) to protect from bias wherever possible. Studies should also measure all relevant outcomes, including adverse events so that stakeholders can make informed decisions about treatment. For example, the uncertainty in the balance of benefits and harms, or a greater risk of harm, is more likely to be acceptable among the critically ill as compared to those taking medications for prophylaxis. To generate this evidence there needs to be transparent reporting of all studies (including of the harms of treatment), international collaboration on the conduct

of adequately powered studies to improve our ability to adequately detect differences, and the utilization of technology to enable real-time evidence synthesis through methods such as living cumulative meta-analysis.

The most urgent need in COVID-19 pharmacotherapeutic research is for studies that move away from small observational-anecdotal reports and toward greater scientific rigor (i.e. adequately designed, powered, conducted, analysed and reported RCTs). The widespread dissemination of studies at a high risk of bias coupled with the severity COVID-19 and the lack of existing treatments has led stakeholders to endorse therapies without fully understanding the balance of benefit and harm. In the case of HCQ this may result in increased rates of serious adverse cardiovascular events with minimal impact on the disease course of COVID-19. Randomized, controlled clinical trials that predominantly enrol moderately to severely ill patients, assess meaningful patient-centred endpoints, and carefully document adverse events are desperately needed to determine whether the off-label treatments we have already adopted as "standard of care" are either safe or effective.

Ongoing molecular modelling work [9,10, 103] to better elucidate the structure and lifecycle of COVID-19 may identify either novel pharmacotherapeutic targets or targets which may be amenable to existing treatments. For example, studies [103] suggest that the virus utilises angiotensin converting enzyme 2 (ACE 2) receptor for cellular entry. Patients with comorbidities such as hypertension and/or are on ACE inhibitors may overly express ACE 2 thus facilitating viral entry through lower airways. Non-steroidal anti-inflammatory drugs such as ibuprofen are also believed to increase the expression of ACE 2 [103, 104]. To that end, it remains to be seen whether ACE inhibitor medications contributed to the incidence or severity of COVID-19, and whether therapies such as soluble recombinant human ACE2 protein and angiotensin II receptor antagonists might exert a protective effect. At the time of revision of this manuscript a retrospective cohort study [105] on another potential repurposed therapy, an H2 receptor antagonist famotidine highlighted decrease in the composite outcome of death or intubation (HR: 0.42; 95% CI: 0.21, 0.85). The evidence, however, however, is very uncertain. Famotidine is being trialled for its potential role in binding to viral enzyme called the papain like protease, which helps the pathogen replicate.

Management of COVID -19 is not a "one-size-fits-all" protocol. The current pattern of disease progression [8, 9] follows two distinct but overlapping subsets, the first triggered by virus itself

and the second, the host response. It is possible that antiviral agents are useful early in the course of illness, and immunomodulatory agents later in the course, but not vice versa. For example, administration of adjuvant therapy such as corticosteroids at early stage could provoke viral replication, but with thrombosis being commonly observed in the later stages of COVID-19, anti-inflammatory and anticoagulation therapies seem rational and warrant research [106]. We recommend pharmacokinetics-pharmacodynamics (PK-PD) studies at various staging of COVID-19 to inform dosing, duration and safety. Disease staging (mild-moderate-severe) based on objective measures of clinical severity could help provide a better understanding of the role of specific drugs and when they are likely to be beneficial in COVID-19. Practitioners could then adopt a universal consolidated framework to assess the staged progression of COVID-19 in order to select or investigate targeted therapy in a timely manner. This could also address the ongoing dilemma on the place of therapies in patients with apparently self-limiting infection compared to those with severe infections with poor prognosis.

An effective long-term strategy for prevention of future outbreaks of COVID-19 would be successful development and testing of a vaccine. A comprehensive review of vaccine research for SARS-CoV-2 is beyond the scope of this review.

Long-term planning for pandemic response should also include a robust pipeline of pharmacotherapies. For example, although challenging, there is a greater need for investment in developing a pipeline of broad-spectrum antiviral therapies to stockpile so that promising agents are available in quantity for future pandemics. Given the considerable limitations of the current available evidence, there is an urgent need for more, adequately powered, high quality randomised controlled trials to enable a better understanding of the effectiveness of pharmacotherapies. These studies need to rigorously report safety data now and commit to timely publication of medium and long-term follow-up data once this becomes available. The majority of studies in our review were conducted in secondary care. Studies in primary care settings are required to assess drug utilisation in community settings, for patients who are asymptomatic or who may need prophylaxis, for example. The role of prophylactic therapies against COVID-19 is an area of further research as current guidelines recommend prophylaxis with therapies such as HCQ with limited evidence. As the evidence evolves on prophylaxis and treatment of COVID-19 policy makers and guideline developers need to respond in a timely manner, but also ensure that they are making decisions which account for patient-

important outcomes and not rely on surrogates or other outcomes which may not reflect the patient experience.

Beyond the direct disease process, COVID-19 has impacts on the mental health of providers and patients and threatens the financial stability of both healthcare systems and patients. Research understanding the impact of these psychosocial and socioeconomic factors on risk for COVID-19 as well as the impact on comorbidities as well as health disparities, although beyond the scope of this review, is necessary to prevent additional morbidity and mortality.

4.3 Research/knowledge to achieve the goal with key challenges and future directions

The coordinated design and conduct of rigorous randomized trials utilizing a consistent set of outcome measures which includes outcomes which matter to a variety of stakeholders (including patients, providers, and policymakers) is necessary to improve the confidence in the evidence base and reduce waste. Standardized design and outcome frameworks need to be developed and adhered to, to ensure clear definitions of patient populations, clinical syndromes, disease severity and outcomes. Clearly distinguishing between various stages and severities of disease are needed to better target therapies and understand heterogeneity of treatment effect.

With more than 400 clinical trials underway, ongoing investigations into COVID-19 will hopefully yield high quality, evidence-based, prophylaxis and treatment recommendations in the near future. Treatment approach based on clinical severity may help guide recommendations. This includes “wait and watch” for younger patients with mild symptoms without comorbidities versus initiating repurposed drugs such as HCQ and antivirals in older patients with moderate-severe symptoms and comorbidities. Combination therapies need to be prescribed with caution, as several of the drugs under consideration have the potential for additive toxicity. For example, HCQ and lopinavir/ritonavir both prolong the QT interval and could predispose to fatal cardiac arrhythmias, particularly among elderly patients with underlying cardiovascular disease.

Ongoing research into the molecular biology and pathogenesis of COVID-19 will help inform therapeutic strategies. The cytokine storm responsible for severe COVID-19 may respond to immunomodulators such as tocilizumab and anakinra. The role of “immune boosting”

supplements like vitamin C, vitamin D and zinc is a topic of numerous hypotheses for COVID-19 and many other infections, but is supported by little empirical data again highlighting the need for well-designed clinical trials.

With multiple ongoing trials, some with adaptive designs, the importance of data monitoring team is highly evident. Judgements on interim analysis need to be collective decisions with key inputs from the data monitoring group. Having highly experienced data monitoring teams will be invaluable as results from interim analysis may overestimate the benefit from treatment [107].

There is an understandable urgency for evidence-based data synthesis and dissemination during the current crisis and the work being conducted by providers and researchers across the globe is commendable. The pressure to provide promising data and the race to achieve recognition, however, should not compromise on quality of evidence through publication bias and poor study methods. With rapidly changing clinical dynamics and disease progression among COVID-19 patients it is critically important to assess relevant endpoints. This could be achieved through balanced and well-informed actions by practitioners and researchers alike. Uncertainty around optimal pharmacotherapy warrants decision making on a case-to-case basis informed through interim/real-time local guidelines. Multiple RCTs are underway which may add clarity to the evidence base. The need to critically evaluate studies of pharmacotherapy and to identify their proper placement in practice crucial in this uncertain environment. Rigorous, pragmatic, collaborative research measuring, patient-centred outcome is vital ensure safe and efficacious use of pharmacotherapy in the management of COVID-19.

Funding

This manuscript has not been funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclosure.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020; 382:1199-1207.

   ***Key paper on early transmission dynamics based on findings from Wuhan, China.**
2. Center for Systems Science and Engineering. John Hopkins University and Medicine 2020 [cited 2020 June 20]. Available from https://coronavirus.jhu.edu/map.html
3. Coronovirus disease (COVID-19) situation reports: World Health Organisation 2020 [cited 2020 June 20]. Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
4. Sun K, Chen J, Viboud C. Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study. Lancet Digit Health. 2020;2:e201-08.
5. Guan W, Ni Zheng-yi, Hu Yu, et al. Clinical characteristics of Coronovirus Disease 2019 in China. N Engl J Med. 2020;382:708-1720.
6. Centre for Disease Control (CDC) - Morbidity and mortality weekly report. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019-United States, February 12–March 28, 2020 [cited 2020 May 2]. Available from https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm
7. Wu Z, McGoogan J. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323:1239-1242.
8. McIntosh K, Hirsch M, Bloom A. Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention. UpToDate. Waltham, MA: UpToDate Inc [cited 2020 May 15]. Available from https://www.uptodate.com
9. Cao W, Li Taisheng. COVID-19: towards understanding of pathogenesis. Cell Res. 2020; 30:367-369.

10. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565-574.
11. Jose R, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020. https://doi.org/10.1016/S2213-2600(20)30216-2
12. Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts. World Health Organisation (WHO) - Interim Guidance 17 March 2020 [cited 2020 June 4]. Available from https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
13. Kim A, Gandhi R. Coronavirus disease 2019 (COVID-19): Management in hospitalized adults. UpToDate. Waltham, MA: UpToDate Inc. [cited 2020 Mayl 20]. Available from https://www.uptodate.com
***Comprehensive update on management of COVID-19.**
14. Considerations in adjusting public health and social measures in the context of COVID- World Health Organisation (WHO) - Interim Guidance 16th April 2020. [cited 2020 May 5]. Available from https://apps.who.int/iris/bitstream/handle/10665/331773/WHO-2019-nCoV-Adjusting_PH_measures-2020.1-eng.pdf
15. Food and Drug Administration: COVID-19 related guidance documents [cited 2020 April 10]. Available from https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders
16. Medicines and Healthcare Products Regulatory Agency (MHRA) [cited 2020 April 10]. Available from https://www.gov.uk/coronavirus
17. Therapeutics Good Administration (TGA): Coronavirus (COVID-19) - Information on medicine and medical devices [cited 2020 May 20]. Available from https://www.tga.gov.au/collection/covid-19
18. Moher D, Liberati A, Tetzlaff J, Altman D. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535.
19. Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for

Systematic Reviews of Interventions Version 6.0 [updated July 2019]. The Cochrane Collaboration, 2011 [cited 2020 April 20]. Available from www.cochrane-handbook.org

20. von Elm E, Altman DG, Egger M, et al. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;6:344-349.
21. Murad M, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23:60–63.
22. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
23. Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). MedRxiv. 2020 Jan 1 [cited 2020 April 12]. Available from https://doi.org/10.1101/2020.03.19.20038984
24. 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;382:1787-1799.
25. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
26. Ye XT, Luo YL, Xia SC, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020; 24:3390-3396.
27. 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. Int J Infect Dis. 2020. https://doi.org/10.1016/j.ijid.2020.03.013
28. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study. J Infect. 2020. https://doi.org/10.1016/j.jinf.2020.03.002
29. 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. https://doi.org/10.1136/bmj.m606
30. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends. 2020;14:64-68. https://doi.org/10.5582/bst.2020.01030

31. 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;15:395:507-13. https://doi.org/10.1016/S0140-6736(20)30211-7
32. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-1069. https://doi.org/10.1001/jama.2020.1585
33. 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. Lancet Respir Med. 2020;5:475-481. https://doi.org/10.1016/S2213-2600(20)30079-5
34. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020;63:706-711. https://doi.org/10.1007/s11427-020-1661-4
35. 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. Lancet. 2020;395:1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
36. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13. https://doi.org/10.1001/jamainternmed.2020.0994
37. Tang X, Du R, Wang R, et al. Comparison of Hospitalized Patients with Acute Respiratory Distress Syndrome Caused by COVID-19 and H1N1. Chest. 2020 Mar 26. https://doi.org/10.1016/j.chest.2020.03.032.
38. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020 Mar 11. https://doi.org/10.1016/j.jinf.2020.03.004
39. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020 Mar 26. https://doi.org/10.1016/j.annonc.2020.03.296
40. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020 Feb 26. https://doi.org/10.1016/j.jinf.2020.02.016
41. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020 Mar 27. https://doi.org/10.1016/j.jinf.2020.03.005

42. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27. https://doi.org/10.1001/jamacardio.2020.1017
43. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020 Mar 27. https://doi.org/10.1001/jama.2020.4783
44. Shi H, Han X, Zheng C. Evolution of CT manifestations in a patient recovered from 2019 novel coronavirus (2019-nCoV) pneumonia in Wuhan, China. Radiology. 2020 Feb 7:200269. https://doi.org/10.1148/radiol.2020200269
45. Wei J, Xu H, Xiong J, Shen Q, et al. 2019 Novel Coronavirus (COVID-19) Pneumonia: Serial Computed Tomography Findings. Korean Journal of Radiology. 2020;21:501-4. https://doi.org/10.3348/kjr.2020.0112
46. Chen D, Xu W, Lei Z, et al. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. Int J Infect Dis. 2020 Mar 5. https://doi.org/10.1016/j.ijid.2020.03.003
47. Han W, Quan B, Guo W, et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019. J Med Virol. 2020 May 1. https://doi.org/10.1002/jmv.25711
48. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Feb 17. https://doi.org/10.1016/S2213-2600(20)30076-X
49. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27. https://doi.org/10.1001/jamacardio.2020.1096
50. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv. 2020 Jan 1. https://doi.org/10.1101/2020.03.22.20040758
51. Gautret P, Lagier JC, 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 Mar 20:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949
52. Borba MG, Val FF, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020;3:e208857.

53. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020 Apr 29 https://doi.org/10.1073/pnas.2005615117
54. Ferrey AJ, Choi G, Hanna RM, et al. A case of novel coronavirus disease 19 in a chronic hemodialysis patient presenting with gastroenteritis and developing severe pulmonary disease. Am J Nephrol. 2020 Mar 28. https://doi.org/10.1159/000507417
55. Michol J, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann Oncol. 2020;31:961-964 https://doi.org/10.1016/j.annonc.2020.03.300
56. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020;4:1307-1310.
57. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv. 2020 Jan 1 [cited on 2020 March 20]. Available on https://doi.org/10.1101/2020.03.06.20032342
58. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust. 2020 Apr 8. https://doi.org/10.5694/mja2.50577
59. Young BE, Ong SW, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020 Mar 3. https://doi.org/10.1001/jama.2020.3204
60. Lan L, Xu D, Ye G, et al. Positive RT-PCR test results in patients recovered from COVID-19. JAMA. 2020 Feb 27. https://doi.org/10.1001/jama.2020.2783
61. Lim J, Jeon S, Shin HY, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020 35(6). https://doi.org/10.3346/jkms.2020.35.e79
62. Kim JY, Choe PG, Oh Y et al. The first case of 2019 novel coronavirus pneumonia imported into Korea from Wuhan, China: implication for infection prevention and control measures. J Korean Med Sci. 2020;35:e61. doi: 10.3346/jkms.2020.35.e61
63. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020 Mar 25. https://doi.org/10.1016/S1473-3099(20)30198-5

64. Wang Y, Zhang D, Du G et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020 Apr 29. https://doi.org/10.1016/S0140-6736(20)31022-9
65. Chen C, Huang J, Cheng Z, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020 Jan 1. https://doi.org/10.1101/2020.03.17.20037432
66. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020 Mar 18. https://doi.org/10.1016/j.eng.2020.03.007
67. Kujawski SA, Wong KK, Collins JP, et al. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. medRxiv. 2020 Jan 1. https://doi.org/10.1101/2020.03.09.20032896
68. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis. 2020 Mar 27. https://doi.org/10.1016/S1473-3099(20)30200-0
69. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382;929-936. https://doi.org/10.1056/NEJMoa2001191
70. Durante-Mangoni E, Andini R, Bertolino L, Mele F, Florio LL, Murino P, Corcione A, Zampino R. Early experience with remdesivir in SARS-CoV-2 pneumonia. Infection. 2020 May 16:1. https://dx.doi.org/10.1007%2Fs15010-020-01448-x
71. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D. Remdesivir for the treatment of Covid-19—preliminary report. N Engl J Med. 2020 May 22. https://doi.org/10.1056/NEJMoa2007764
72. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020 May 27.
73. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. New England Journal of Medicine. 2020 Apr 10. https://doi.org/10.1056/NEJMoa2007016
74. Cheng SC, Chang YC, Chiang YL, et al. First case of Coronavirus Disease 2019 (COVID-19) pneumonia in Taiwan. J Formos Med Assoc. 2020 Feb 26. https://doi.org/10.1016/j.jfma.2020.02.007

75. Huang WH, Teng LC, Yeh TK, et al. 2019 novel coronavirus disease (COVID-19) in Taiwan: Reports of two cases from Wuhan, China. J Microbiol Immunol Infect. 2020 Feb 19. https://doi.org/10.1016/j.jmii.2020.02.009
76. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020 Apr 6. https://doi.org/10.1002/jmv.25801
77. Mihai C, Dobrota R, Schröder M, et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. Ann Rheum Dis. 2020;79:668-9. https://doi.org/10.1136/annrheumdis-2020-217442
78. Yao X, Ye F, Zhang M, et al. 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). Clin Infect Dis. 2020 Mar 9. https://doi.org/10.1093/cid/ciaa237
79. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020 Feb 27. https://doi.org/10.1002/jmv.25729
80. Yan D, Liu XY, Zhu YN, et al. Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in patients with SARS-CoV-2 infection. Medrxiv. 2020 Jan 1. https://doi.org/10.1101/2020.03.22.20040832
81. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. 2018;197:757-67.
82. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020 Apr 10. https://doi.org/10.1016/j.jinf.2020.03.062
83. Horby P, Lim Shen W, Emberson J, et al. Effect of dexamethasone in hospitalised patients with COVID-19: preliminary report. MedRxiv Pre Print doi: https://doi.org/10.1101/2020.06.22.20137273
84. First patient outside U.S. treated in global Kevzara® (sarilumab) clinical trial program for patients with severe COVID-19 [cited 2020 April 15]. Available from https://www.sanofi.com/-/media/Project/One-Sanofi-web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2020/2020-03-30-07-00-00-2008040-en.pdf
85. ClinicalTrials.gov [Internet]. Cao Y (Dr). Qilu Hospital of Shandong University, Karolinska Institutet. ID: NCT04305106. Bevacizumab in Severe or Critically Severe

Patients With COVID-19 Pneumonia-RCT (BEST-RCT). March 12, 2020. Cited on 6th April 2020. Available at https://clinicaltrials.gov/ct2/show/NCT04305106

86. Ying Fu. First Affiliated Hospital of Fujian Medical University. ID: NCT04280588. Fingolimod in COVID-19. February 21, 2020 [cited 2020 April 6]. Available from https://clinicaltrials.gov/ct2/show/ NCT04280588
87. Pitts TC. Hudson Medical. ID: NCT04288713. Eculizumab (Soliris) in Covid-19 Infected Patients (SOLID-C19). February 28, 2020 [cited 2020 April 6]. Available from https://clinicaltrials.gov/ct2/show/ NCT04288713
88. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20:398-400. https://doi.org/10.1016/S1473-3099(20)30141-9
89. Bhimraj A, Morgan R, Shumaker A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19**.** Clinical Infectious Diseases 2020. ciaa478, https://doi.org/10.1093/cid/ciaa478

    ****An important interim guidelines on the treatment and management of patients with COVID-19.**
90. National Institute of Health (NIH): COVID-19 Treatment Guidelines 2020 [cited 2020 June 25]. Available from https://www.covid19treatmentguidelines.nih.gov/
91. Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI) Canada. Clinical management of patients with moderate to severe COVID-19 - Interim guidance. April 2, 2020 [cited 2020 April 25]. Available from https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html
92. National COVID-19 Clinical Evidence Taskforce: Living Guidelines, Australia 2020 [cited 2020 May 20]. Available from http://www.covid19evidence.net.au
93. National Institute for Health and Care Excellence (NICE): COVID-19 Rapid Guidelines, United Kingdom, 2020 [cited 2020 June 24]. Available from https://www.nice.org.uk/guidance/ng163

    ****Comprehensive rapid clinical guidelines on management of COVID-19.**
94. Indian Council of Medical Research (ICMR): Advisory on the use of hydroxychloroquine as prophylaxis for SARS-C0V-2 infection, 2020 [cited 2020 June 25]. Available from https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf

95. Ontario Clinical Practice Guidelines for Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19 [cited 2020 June 20]. Available from https://www.antimicrobialstewardship.com/covid-19
96. FDA news release. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine [cited 2020 June 15]. Available from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and
97. FDA news release. Remdesivir by Gilead Sciences: FDA warns of newly discovered potential drug interaction that may reduce effectiveness of treatment. [cited 2020 June 15]. Available from https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce
98. World Health Organization - SOLIDARITY clinical trial for COVID-19 treatments. Update on hydroxychloroquine. [cited 2020 17 June]. Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
99. University of Oxford, press release: No clinical benefits from use of hydroxychloroquine in hospitalised patients with COVID-19. [cited 2020 June 5]. Available from http://www.ox.ac.uk/news/2020-06-05-no-clinical-benefit-use-hydroxychloroquine-hospitalised-patients-covid-19
100. University of Oxford, press release: Dexamethasone reduces death in hospitalised patients with severe respiratory complications of COVID-19. [cited 2020 June 16]. Available from http://www.ox.ac.uk/news/2020-06-16-dexamethasone-reduces-death-hospitalised-patients-severe-respiratory-complications
101. Mehra M, Ruschitzka F, Patel A. Retraction - Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet 2020;395:1820. DOI:https://doi.org/10.1016/S0140-6736(20)31324-6.
102. Mehtra M, Desai S, Kuy S, Henry T, Patel A. Retraction: Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med 2020;382:2582. DOI: 10.1056/NEJMoa2007621.
103. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs

vulnerable to 2019-nCoV infection. Front Med. 2020. https://doi.org/10.1007/s11684-020-0754-0

104. Gracia-Ramos E. Is the ACE2 overexpression a risk factor for COVID-19 infection? Arch Med Res. 2020 doi: 10.1016/j.arcmed.2020.03.011

105. Freedberg D, Conigliaro J, Wang T, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Gastroenterology 2020; S0016-5085:34706-5 doi https://doi.org/10.1053/j.gastro.2020.05.053

106. Klok F, Kruip MJHA, van der Meer N, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Throm Res 2020 April 30. doi: 10.1016/j.thromres.2020.04.041

107. Montori V, Devereaux P, Adhikari N, et al. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-2209.