EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2022.1997587

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META-ANALYSIS

Comparative effectiveness of pharmacological interventions on mortality and the average length of hospital stay of patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Up to now, numerous randomized controlled trials (RCTs) have examined various drugs as possible treatments for Coronavirus Disease 2019 (COVID-19), but the results were diverse and occasionally even inconsistent with each other. To this point,we performed a systematic review and meta-analysis to assess the comparative effectiveness of pharmacological agents in published RCTs.

Areas covered: A literature search was performed using PubMed, SCOPUS, EMBASE, and Web of Science databases. RCTs evaluating mortality and the average length of hospital stay to standard of care (SOC)/placebo/control were included. RCTs mainly were classified into five categories of drugs, including anti-inflammatory, antiviral, antiparasitic, antibody and antibiotics. Meta-analysis was done on 5 drugs classes and sub-group meta-analysis was done on single drugs and moderate or severe stage of disease.

Expert opinion: Mortality and the average length of hospital stay of COVID-19 patients were significantly reduced with anti-inflammatory drugs (odds ratio [OR]: 0.77, 95% confidence interval [CI]: 0.69 to 0.85, P<0.00001, and mean difference [MD]: −1.41, CI:-1.75 to −1.07, P<0.00001, respectively) compared to SOC/control/placebo. Furthermore, antiparasitic was associated with reduced length of hospital stay (MD: −0.65, CI: −1.26 to −0.03, P<0.05) in comparison to SOC/placebo/control. However, no effectiveness was found in other pharmacological interventions.

ARTICLE HISTORY
Received 30 June 2021
Accepted 22 October 2021

KEYWORDS
Pharmacological intervention; COVID-19; treatment; systematic review; meta-analysis; randomized controlled trial

1. Introduction

In December 2019, Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV -2) was reported for the first time in Wuhan, China, and then spread rapidly out to the rest of the world [1]. The COVID-19 outbreak has been announced a *pandemic* by the World Health Organization (WHO). The major clinical symptoms of COVID-19 are associated with multiple organs, such as respiratory, cardiovascular, central nervous system, and digestive systems [1]. As of 8 August 2021, global coronavirus deaths stand at about 4.3 million deaths out of 202 million confirmed cases [2]. The overall Case Fatality Rate (CFR) is estimated to be 2%. Up to now, several investigations focusing on factors affecting the mortality of COVID-19 have been published [3,4]. Among them, the possible risk factors of death in patients with COVID-19, such as age, gender and comorbidities such as diabetes mellitus, hypertension, kidney disorders, and heart disease were systematically reviewed [5]. On the other hand, long-term hospitalization is a major challenge for patients with severe forms of COVID-19. To decrease mortality and long-term hospitalization, numerous trials have been investigated around the world [6–8]. However, conclusion on individual studies would be difficult and may be inaccurate. Therefore, it is necessary to combine and synthesize the results of interventional studies. In the same way, there are several systematic reviews on clinical trials in the field of COVID-19 treatment [9–12]. However, many published systematic reviews did not provide adequate summaries of phase III clinical trials of different drugs (Table S3). To this point, a comparative systematic review and meta-analysis on most effective drugs, which have been investigated in severe form of COVID-19, can get us a comprehensive conclusion. Therefore, we aimed to conduct a systematic review on major outcomes of patients (i.e. mortality and length of hospitalization) from phase III clinical trials data and to compare different drugs that have been investigated in the course of COVID-19.

2. Method

2.1. Overview

The present systematic review and meta-analysis study was conducted to evaluate studies on pharmacological interventions (i.e. antiparasitic, antiviral, antibacterial, anti-inflammatory, and antibody drugs) on mortality and length

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of stay in hospital of COVID-19 patients with mild to severe illness. We reviewed all studies based on Joanna Brigs Institute (JBI) Principles and advices to write a systematic review and meta-analysis [13]. This paper is reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Population, interventions, control, outcomes, study design, and time frame (PICOST) in this review article are as follows:

- **Population**: Any cases with positive PCR-test for COVID-19 or computed tomographic (CT) scans manifestation of COVID-19 patients
- **Intervention**: In the intervention group, only one main drug is different from standard of care (SOC)/control/placebo group. In comparison, a mechanism of drug action was used. Thus, drugs were classified into five categories: antiviral, antiparasitic, antibody, antibacterial, and anti-inflammatory.
- **Control**: SOC/control/placebo;
- **Outcomes**: Mortality and the average length of hospital stay of COVID-19 patients
- **Study design**: Randomized controlled trials (RCTs) Phase III of FDA approved drugs published in peer-reviewed journals
- **Time frame**: Studies published from December 2019 till 2 August 2021.

2.2. Search strategy

Two independent inspectors (A.A. and M.R.) searched databases including PubMed, SCOPUS, EMBASE, and Web of Science up to 2 August 2021. Our systematic search was performed to find RCTs (phase III) on pharmacological interventions for COVID-19 patients. Keywords of search strategy are described in Table S1. Reference lists of all selected articles and previous systematic reviews on clinical trials were searched to look for possible missing articles.

2.3. Eligibility criteria

After searching mentioned databases, we included all studies which have met the following criteria:

- Clinical trial
- Phase III or Phase II/III or Phase IV
- RCTs
- Intervention group compared with control group which only one drug is different.
- Conducted on pharmacological drugs

The excluded studies were animal studies, case control studies, case reports, case series studies, cohort studies, cross sectional studies, *in vitro* and *in vivo* studies, review articles and protocol for future studies. We also omitted all studies published before December 2019 (the beginning of COVID-19). Any Clinical trials with no control groups, not randomized, existing in phase I or phase I/II or phase II or having a not applicable phase were excluded from our study.

2.4. Study selection

Six investigators (A.A., M.R., M.A.D., A.M.H., S.Y., and M.A.) independently screened the remaining studies for the inclusion criteria. For RCTs, patients were defined as receiving intervention or control if they were randomly allocated to receive either treatment. RCTs with English language full text were included. Full details of excluded studies are mentioned in PRISMA flow diagram (Figure 1).

2.5. Critical appraisal

Any selected study was reviewed again for quality assessment by the JBI checklist for RCTs [13]. This checklist was an appraisal tool to use systematic reviews. Four authors in pairs (M.A.D., A.M.H., M.R. and S.Y.) independently screened included and relevant trials for quality assessment of studies (Table S2). Any controversy between investigators was resolved through discussion or if required, through discussion by other authors (S.S.N. and A.S.).

2.6. Data extraction

Six investigators (A.A., M.R., M.A.D., A.M.H., M.A., and S.Y.) extracted the data from the included studies and possible disagreements were resolved by discussion or if required discussion with another two investigators (S.S.A. and A.S.). Demographic data, the number of death in the first month after randomization, length of hospitalization, and main findings of all studies extracted. We reviewed full text, supplementary data of articles, and results in registered portals to find and extract data needed for our analysis. We try to contact study authors if the data demanding was missing.

2.7. Drug classification

At first, we classified drugs according to their mechanism of action in the context of COVID-19 (act on the virus or the immune system). Then, the common use of the drug separated them into smaller groups. Table 1 presents the information about drugs and their classification. Following mechanism of action classification, studies are classified into subgroups according to the stage of disease (moderate or severe) and single drugs.

2.8. Publication bias

The risk of bias with data was extracted from each drug category in the study and checked with the funnel plots. Two investigators (S.S.N. and A.S.) independently assessed the risk of bias. Any controversy between investigators was resolved through discussion.

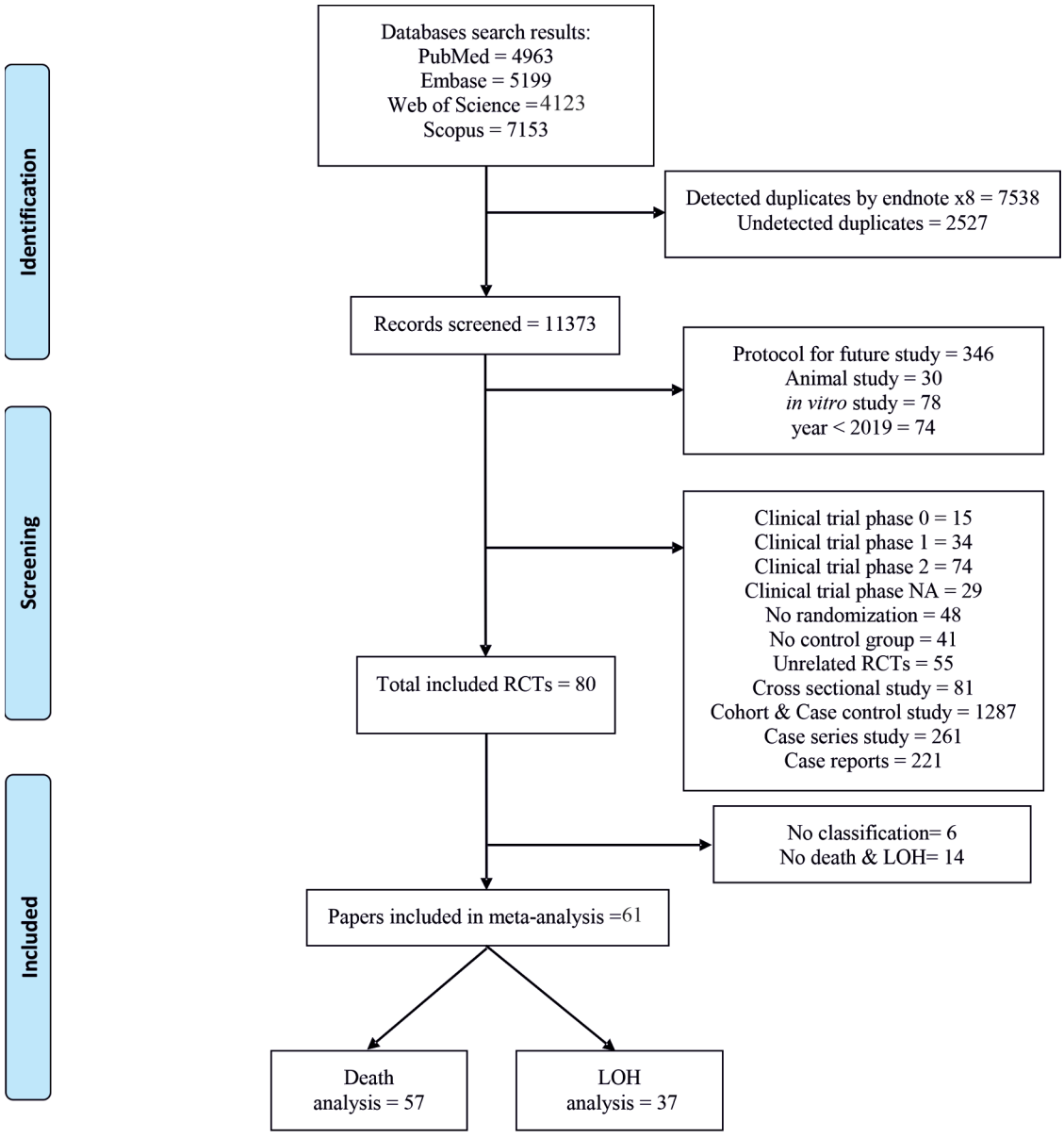

Figure 1. PRIZMA flow diagram of study selection. (Abbreviation: LOH: Length of Hospitalization).

2.9. Statistical analysis

The effect estimation was in odds ratios (OR) for mortality as a dichotomous variable and mean difference (MD) for the average length of hospitalization as a continuous variable, both with 95% confidential intervals (CI). Mantel–Haenszel random-effect models provided methods to calculate OR for mortality outcome. Statistical heterogeneity was assessed using constrained maximum likelihood method [47] and presented with Higgins I^2 statistics and the Cochran Q test [48]. Sensitivity analyses were performed by altering the statistical model and removing large trials (i.e. applying a fixed-effects model in the sensitivity analysis where a random-effects model has been used initially and vice versa) (Table S5). We also performed sub-group analyses for each drug category, including single drug sub-groups and stage of disease sub-groups (If there were 3 or more studies)-(Table S4). Data were pooled and the meta-analysis was performed using RevMan version 5. CorelDraw and GraphPad Prism were used for drawing graphs. A p-value equal or less than 0.05 is considered significant.

(1) **Results**

A total of 21,438 articles were collected during the initial search. Among those articles, 10.065 duplicated files were recognized and removed. Then, the title and abstract of articles were screened and a total of 11,293 unrelated articles (i.e. *in vitro* and animal studies, case series, case report, cohort, case-control, cross-sectional, and clinical trials that were not in phase III) were removed (Figure 1). In the next step, 61 RCTs were found suitable for the outcomes of interest including death and the length of hospitalization. After excluding 4 trials, 57 RCTs (72 groups) were included for synthesis of evidence of mortality rate. Furthermore, 37 RCTs (44 groups) were included for the final review and meta-analysis of the

Table 1. Mechanism of action of drugs in the context of COVID-19.

Classification	Drugs	Mechanism	Common use	COVID-19 context	Reference
Antiviral	Ribavirin	A nucleoside incorporates into viral RNA and disrupts the viral genome	MERS-CoV, HCV infection, viral hemorrhagic fevers respiratory syncytial virus	Act against different parts of viruses (proteases and polymerases) and are used for viral infections	[14–16]
	Favipiravir	An inhibitor of viral RNA polymerase	Influenza A H1N1, Ebola, Yellow fever		[14]
	Remdesivir	An inhibitor of viral RNA polymerase	Ebola		[14]
	Darunavir	An inhibitor of protease	HIV		[14]
	Cobicistat	A cytochrome P450 3A4 inhibitor	HIV		[14]
	Lopinavir	An inhibitor of protease	HIV, SARS-, and MERS-CoV		[14]
	Ritonavir	A cytochrome P450 3A4 inhibitor	HIV, SARS-, and MERS-CoV		[14]
	INF-α and β	A stimulator of innate antiviral immunity	T cell lukemia and lymphoma		[14,17]
	Sofosbuvir	A polymerase reaction terminator	Hepatitis C		[18–20]
	Daclatasvir	It binds to the N-terminus of non-structural protein 5A	Hepatitis C		[21,22]
	Triazavirin	An inhibitor of RNA polymerase	Influenza A and B		[23–25]
Antiparasitic	Ivermectin	An inhibitor importin α/β receptor	Parasitic infections (e.g. malaria and helminth infection)	Act against microbes and commonly is used for malarial and parasitic infections. They act through various pathways on whole infection process.	[12,14,26,27]
	Hydroxychloroquine	1- An inhibitor of ACE-II and spike protein by affecting the terminal glycosylation 2- An inhibitor of viral particles release 3- Anti-inflammatory effect	Malaria		[12,14,28]
Anti-inflammatory	Leflunomide	An inhibitor of dihydroorotate dehydrogenase	Rheumatoid arthritis	Inflammatory responses are suppressed through acting on different inflammatory compartments and commonly are used as anti-inflammatory drugs.	[29]
	Hydrocortisone	An inhibitor of various inflammatory factors (phospholipase A2, NF-kappa B, etc.) and upregulating of anti-inflammatory genes	Many (e.g. COPD, autoimmune disease)		[14,30]
	Tocilizumab	Anti-IL-6 antibody	Systemic juvenile, Rheumatoid arthritis		[14,31]
	Sarilumab	Anti-IL-6 antibody	Rheumatoid arthritis		[32,33]
	Pentoxifylline	An inhibitor of phosphodiesterase and downregulator of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6)	Claudication (Sarcoidosis, Venous ulcers, and evere alcoholic hepatitis)		[34–36]
	Dexamethasone	An inhibitor of pro-inflammatory genes	Rheumatoid arthritis		[37,38]
	Colchicine	Decreasing the chemotaxis of neutrophils, inhibiting inflammasome signaling and reducing pro-inflammatory cytokines	Gout and familial Mediterranean fever		[39,40]
	Baricitinib	An inhibitor of JAK 1/2 enzymes (pro-inflammatory cytokines' gene expression) and viral entrance and assemblage	Systemic lupus erythematosus		[14]
	Canakinumab	Anti-IL-1beta antibody	Periodic fever syndrome (serious auto-inflammatory disease)		[41,42]
Antibody	Convalescent plasma	Binds to SARS-CoV-2, blocks infection, binds to infected cells and changes the immune system	Ebola & SARS-CoV	Sole antibodies act through pathogen neutralization and antibody effector activity	[14,43]
	INM005 (polyclonal antibody)	It neutralizes the interaction of SARS-CoV-2 with cellular receptor	Passive immunotherapy		[44]
	LY-CoV555 (monoclonal antibody)	An inhibitor of viral entry and fusion between the virus and membrane of host cell	Passive immunotherapy		[14]
Antibacterial	Azithromycin	Acts on intracellular mitogen-activated protein kinase (extracellular signal-regulated kinases 1/2 and NF-κB pathway)	Bacterial infection	It has immunomodulation effects and benefits secondary bacterial infections. It commonly uses for bacterial infections.	[45]
Other	Telmisartan & Losartan	A blocker of angiotensin receptor (It antagonizes the production of angiotensin 2 and its pro-inflammatory effect through AT1 receptors)	Hypertension	Angiotensin receptor blockers (ARBs) are commonly used as anti-hypertensive drugs. They may act on SARS-COV-2 through several ways.	[46]

length of hospitalization. Descriptive characteristics and reference list of 80 included RCTs are shown in Tables 2 & 3.

Thus, 80 RCTs were included for the assessment of the risk of bias measured by JBI were mostly low to moderate. Among 80 RCTs, one study was high risk, 34 studies were moderate risk, and 45 studies were low risk. Among them, 14 studies were excluded as they had incomplete outcomes. The details are presented in Table S2 and Figure 2.

2.10. Efficacy outcomes

2.10.1. Mortality

Fifty-seven RCTs that reported mortality, were classified into five groups. As shown in Table 1, nine drugs (Hydrocortisone, Pentoxifylline, Dexamethasone (DXM), Baricitinib, Colchicine, Tocilizumab, Sarilumab, Canakinumab and Methylprednisolone) were classified as anti-inflammatory drugs. Three drugs (Ivermectin (IVM), Hydroxychloroquine (HCQ) and Chloroquine) were found as antiparasitic drug. Three drugs (Convalescent plasma (CP), Immunoglobulin and mono/poly-clonal antibody) were indicated as antibodies agents. Eight mix or alone drugs (Remdesivir, Interferon (IFN), Sofosbuvir/Daclatasvir, Sofosbuvir/Velpatasvir, Triazavirin, Lopinavir/Ritonavir (LPV/RTV), Favipiravir and Lopinavir) were found as antiviral drugs. Finally, azithromycin was found in seven studies as an antibacterial agent.

Based on RCTs, mortality of COVID-19 patients was significantly decreased with anti-inflammatory drugs (OR: 0.77, CI: 0.69 to 0.85, P < 0.00001; I^2 = 2%) compared to SOC/control/placebo (Figure 3). Twenty RCTs involving 15,991 hospitalized COVID-19 patients, including 7281 in the intervention groups and 8710 in the SOC/control/placebo groups, were enrolled. Mortality of COVID-19 patients among the intervention groups was 927, which was lower than that in the SOC/control/placebo groups (1551)-(Table 3).

On the other hand, no noticeable beneficial effect was seen in other pharmacological interventions in comparison to SOC/control/placebo in terms of 'mortality' (antibiotics; OR: 0.97, CI: 0.86 to 1.08, P = 0.57; I^2 = 0%, antiparasitic drugs; OR: 1.00, CI: 0.79 to 1.28, P = 0.98; I^2 = 8%, antibodies agents; OR: 1.08, CI: 0.74 to 1.58, P = 0.08; I^2 = 44%, antiviral drugs; OR: 1.01, CI: 0.90 to 1.12, P = 0.92; I^2 = 3%)-(Figure 3).

2.10.2. The length of hospitalization

The average length of hospital stay of COVID-19 patients was significantly reduced with anti-inflammatory drugs (MD: −1.41, CI:-1.75 to −1.07, P < 0.00001; I^2 = 11%) compared to SOC/control/placebo (Figure 4). Furthermore, antiparasitic drugs was shown to be associated with reduced the length of hospital stay (MD: −0.65, CI: −1.26 to −0.03, P = 0.04; I^2 = 77%) in comparison to SOC/control/placebo. However, no evident beneficial effect was seen in other pharmacological interventions in comparison to SOC/control/placebo in the length of hospital stay of COVID-19 patients (antibacterial drugs; MD: −0.09, CI: −1.07 to 0.90, P = 0.86; I^2 = 83%, antibodies agents; MD: 0.92, CI: −0.59 to 2.44, P = 0.23; I^2 = 93%, antiviral drugs; MD: −0.94, CI: −1.99 to 0.12, P = 0.08; I^2 = 63%).

2.10.3. Subgroup analysis

2.10.3.1. Stage of disease sub-group analysis

Four class of drugs, antiviral, anti-parasitic, anti-inflammatory and antibody included in mortality sub-group analysis. The results show that anti-inflammatory drugs could significantly reduce the mortality rate among severe patients (OR = 0.77 [0.59, 1.00], P = 0.05, I^2 = 35%). Antiviral, anti-parasitic and antibody drugs enrolled for LOH sub-group analysis and antibody drugs increased LOH among severe patients (OR = 2.40 [1.19, 3.60], P < 0.0001, I^2 = 7%)- (Table S4).

2.10.3.2. Single drug sub-group analysis

Regarding mortality outcome, all seven drugs, including remdesivir, interferon, lopinavir/ritonavir, hydroxychloroquine, ivermectin, tocilizumab and convalescent plasma, had no significant effect. Out of 5 drugs included in sub-group analysis for LOH outcome (interferon, hydroxychloroquine, ivermectin, tocilizumab and convalescent plasma), ivermectin and tocilizumab could reduce the LOH (Ivermectin: MD = −1.31 [−1.93, −0.68], P < 0.0001, I^2 = 67%; Tocilizumab: MD = −1.64 [−3.08, −0.20], P = 0.03, I^2 = 33%). Table S4 shows the forest and funnel plots of all sub-group analysis.

3. Discussion

In this study, 27 active pharmacologic drugs and their combinations were included in a comprehensive analysis including 29,126 COVID-19 patients. Among different pharmacological interventions, anti-inflammatory drugs showed survival benefits compared to SOC/control/placebo. However, our MA indicated that other pharmacological interventions, such as antiviral, antibody, antiparasitic, and antibiotic were failed to show benefit in mortality rate. Also, we found that anti-inflammatory drugs showed a benefit on the length of hospital stay in patients with COVID-19. Moreover, the antiparasitic drug was associated with reduced the average length of hospital stay in patients with COVID-19. Antiviral drugs, a topic of much deliberation, were not shown to decrease the length of hospital stay in patients with COVID-19. We found that antibiotics and antibodies agents did not show a benefit on the average length of hospital stay.

Inhibition of the inflammatory response and possible cytokine storm with immune-modulatory treatments was suggested as a prospective therapeutic object; our results verify the efficacy of anti-inflammatories. Efficacy of anti-inflammatory drugs (Hydrocortisone, Pentoxifylline, Dexamethasone, Baricitinib, Tocilizumab, Sarilumab, Canakinumab, Methylprednisolone and Colchicine) and unsuccessfulness of antiviral drugs (Remdesivir, Interferon, Sofosbuvir/daclatasvir, Sofosbuvir/velpatasvir, Triazavirin, Lopinavir/Ritonavir, Favipiravir and Lopinavir) in COVID-19 patients advocate that the management of cytokine storm is valuable over pursuing viral replication itself. Our findings broadly support the work of the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. REACT group stated that administration of systemic corticosteroids improved the 28-day all-cause mortality in

Table 2. Descriptive summary of RCTs phase III studies on antiviral drugs, anti-parasitic drugs, antibody drugs and antibiotics that included in the systematic review.

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Pan et al.	Remdesivir: 2743 HCQ: 947 LPV:1399 IFN:2050	2708 906 1372 2050	Remdesivir: 1706/1037 HCQ: 574/373 LPV:851/548 IFN:1303/747	1725/983 532/374 802/570 1278/772			Remdesivir: 200 mg on day 0 and 100 mg on days 1–9 HCQ: 4 tablets at hour 0 and 6, and, starting at hour 12, two tablets BID for 10 days LPV: 2 tablets BID for 14 days IFN: 3 doses over 6 days of 44 µg of subcutaneous IFN beta-1a C: SOC	Remdesivir [Diabetes: 707, Heart disease: 571, Chronic lung disease: 151, Asthma: 139, Chronic liver disease: 36] C [Diabetes: 666, Heart disease: 567, Chronic lung disease: 145, Asthma: 139, Chronic liver disease: 41] HCQ: [Diabetes:199, Heart disease:193, Chronic lung disease: 62, Asthma: 41, Chronic liver disease: 15] C [Diabetes: 205, Heart disease: 194, Chronic lung disease: 66, Asthma: 46, Chronic liver disease: 14] LPV [Diabetes: 341, Heart disease: 289, Chronic lung disease: 95, Asthma: 65, Chronic liver disease: 15] C [Diabetes: 324, Heart disease: 290, Chronic lung disease: 87, Asthma: 56, Chronic liver disease: 23] IFN [Diabetes: 489, Heart disease: 427, Chronic lung disease: 114, Asthma: 75, Chronic liver disease: 11] C: [Diabetes; 537, Heart disease: 456, Chronic lung disease: 109, Asthma: 97, Chronic liver disease: 22]	No drug reduced mortality or reduced initiation of ventilation or length of hospital stay.	Severe, Mild-to-moderate	[6]
Spinner et al.	10-Day remdesivir: 193 5-Day remdesivir: 191	200	10-Day remdesivir: 118/75 5-Day remdesivir: 114/77	125/75	10-Day remdesivir: 56 (45–66) 5-Day remdesivir: 58 (48–66)	57 (45–66)	I: 200 mg Remdesivir on day 1 followed by 100 mg/d for 5 or 10 days C: SOC	10-Day remdesivir [Cardiovascular disease: 111, Hypertension: 85, Diabetes: 85, Asthma: 31] 5-Day remdesivir [Cardiovascular disease: 111, Hypertension: 82, Diabetes: 71, Asthma: 22] C [Cardiovascular disease: 107, Hypertension: 81, Diabetes: 76, Asthma: 28]	10-Day remdesivir: No statistically significant difference in clinical status. 5-Day remdesivir: Statistically significant difference in clinical status.	Moderate	[49]
Wang et al	158	78	89/69	51/27	66 (57–73)	64 (53–70)	I: 200 mg intravenous remdesivir on day 1 and 100 mg on days 2–10 in single daily infusions C: Placebo infusions	I [Hypertension: 72, Diabetes: 40, Coronary heart disease: 15] C [Hypertension: 30, Diabetes: 16, Coronary heart disease: 2]	Remdesivir was not associated with statistically significant clinical benefits.	Severe	. [50]
Beigel et al.	541	521	352/189	332/190	58.6 (14.6)	59.2 (15.4)	I: 200 mg intravenous remdesivir on day 1 and 100 mg on days 2–10 in single daily infusions (or until hospital discharge or death) C: Placebo infusions	I [Hypertension: 231, Obesity: 177, Type 2 diabetes: 144] C [Hypertension: 229, Obesity: 165, Type 2 diabetes: 131]	Remdesivir could reduce the time to recovery and lower respiratory tract infection.	Severe, Mild-to-moderate	[51]

(*Continued*)

Table 2. (Continued).

Authors	Sample size		Sex (Male/Female)		Age		Treatment panel	Comorbidity	Main findings	Stage of disease	References
	I	C	I	C	I	C					
Davoudi et al.	42	39	22/20	22/17	56.50 (47.25–67-25)	61.00 (50.00–70.00)	I: 44-g/ml (12 million IU/ml) dose of IFN −1a 3 times weekly for 2 weeks C: SOC	I [Any comorbidity; 32, Hypertension: 15, Diabetes mellitus: 13, Ischemic heart disease: 11, Endocrine disorder: 6, Malignancy: 4, Neuropsychiatric disorders: 3, Hematologic disorder: 2, Rheumatoid disorder: 1, Renal disease: 1, Liver disease: 1, Rheumatoid arthritis: 1, Asthma: 1, Transplantation: 1] C [Any comorbidity: 31, Hypertension: 16, Diabetes mellitus: 9, Ischemic heart disease: 12, Endocrine disorder: 6, Malignancy: 5, Neuropsychiatric disorders: 2, Rheumatoid disorder: 2, Renal disease: 2, Liver disease: 2, Rheumatoid arthritis: 1, COPD: 1]	Time to the clinical response was not significantly different.	Most of them were mild	[52]
Ader et al.	HCQ:145 LPV/RTN+IFN:145 LPV/RTN:145	148	HCQ:104/41 LPV/RTN +IFN:103/42 LPV/RTN: 106/39	105/43	HCQ: 65 (55–71) LPV/RTN+IFN: 64 (53–71) LPV/RTN: 63 (55–71)	62 (52–71)	HCQ: 400 mg orally, twice on day 1 as a loading dose followed by 400 mg once daily for 9 days LPV/RTN+IFN: 400 mg LPV and 100 mg ritonavir orally twice a day for 14 days+44 mg subcutaneous IFN-b-1a on days 1, 3, and 6 LPV/RTN: 400 mg LPV and 100 mg ritonavir orally twice a day for 14 days C: SOC	HCQ [Chronic cardiac disease:41, Chronic pulmonary disease:19, Chronic kidney disease:stage 1 to 3:10, Mild liver disease:4, Chronic neurological disorder: including dementia:8, Active cancer:11, Autoinflammatory disease:5, Obesity:43, Diabetes mellitus:31, Current smoker:4] LPV/RTN+IFN [Chronic cardiac disease:36, Chronic pulmonary disease:19, Chronic kidney disease:stage 1 to 3:5, Chronic neurological disorder:including dementia:4, Active cancer:6, Autoinflammatory disease:9, Obesity:41, Diabetes mellitus:27, Current smoker:5] LPV/RTN [Chronic cardiac disease:35, Chronic pulmonary disease:19, Chronic kidney disease:stage 1 to 3:2, Mild liver disease:3, Chronic neurological disorder: including dementia:5, Active cancer:8, Autoinflammatory disease:4, Obesity:36, Diabetes mellitus:35, Current smoker:4] C [Chronic cardiac disease:39, Chronic pulmonary disease:31, Chronic kidney disease:stage 1 to 3:7, Mild liver disease:6, Chronic neurological disorder: including dementia:6, Active cancer:10, Autoinflammatory disease:8, Obesity:46, Diabetes mellitus:35, Current smoker:5]	No improvement in clinical status or SARS-CoV-2 clearance	Moderate/Severe HCQ:93/52 LPV/RTN+IFN:91/54 LPV/RTN:94/51 C:94/54	[53]
Rahmani et al.	33	33	20/13	19/14	60 (47–73)	61 (50–71)	I: Daily IFN β-1b 250 mcg subcutaneously for two weeks. C:	I: [Hypertension: 18, Diabetes mellitus: 9, Ischemic heart disease: 7, Asthma: 1, COPD: 2, Malignancy: 1, Transplantation: 1] C: [Hypertension: 19, Diabetes mellitus: 12, Ischemic heart disease: 13, Asthma: 2, COPD: 1, Malignancy: 1]	IFN β-1b could decrease the time to clinical improvement without serious complications.	Severe	[54]

(*Continued*)

Table 2. (Continued).

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Zheng et al.	Novaferon:30 Novaferon + LPV/RTV:30 LPV/RTV:29		Novaferon: 17/13 Novaferon + LPV/RTV:13/17 LPV/RTV:12/17		Novaferon: 46.5 (40.0–63.8) Novaferon + LPV/RTV: 50.0 (37.8–62.8) LPV/RTV: 37.0 (26.0–54.0)		Novaferon: daily injection of 10 mg of protein in 1.0 ml volume per vial LPV/RTV: 200 mg of LPV and 50 mg of Ritonavir	Novaferon [Diabetes:3, Hypertension: 3, Coronary heart disease: 1] Novaferon + LPV/RTV [Diabetes: 3, Hypertension: 2, Coronary heart disease: 1, Chronic hepatitis B: 1, Chronic bronchitis: 1] LPV/RTV [Diabetes: 2, Hypertension: 3, Coronary heart disease: 1, Chronic hepatitis B:1, Chronic bronchitis:1]	Novaferon and Novaferon plus LPV/RTV could significantly increase viral clearance rates compare LPV/RTV alone.	Moderate or severe	[55]
Sadeghi et al.	33	33	20/13	14/19	58 (38–65)	62 (49–70)	I: Single daily oral tablet containing 400 mg sofosbuvir and 60 mg daclatasvir C: SOC	I [Chronic pulmonary disease: 6, Asthma: 1, Diabetes: 17, Heart failure: 3, Hypertension: 12, Malignancy: 1] C [Chronic pulmonary disease: 9, Asthma: 1, Diabetes: 11, Heart failure: 7, Hypertension: 11, Malignancy: 2]	Clinical recovery was not significantly different.	Moderate or severe	[56]
Roozbeh et al	27	28	12/15	14/14	43 (37–52)	47.5 (37–53)	I: single daily oral tablet containing 400 mg sofosbuvir and 60 mg daclatasvir. C: SOC	I: 13 C: 8	Sofosbuvir/daclatasvir did not significantly improve symptoms after 7 days of treatment.	Mild	. [57]
Sayad et al.	40	40	20/20	24/16	53.6 (16.3)	54.6 (19.4)	I: 400 mg sofosbuvir and 100 mg velpatasvir orally once daily for 10 days C: SOC	I [Hypertension: 9, Diabetes: 10, Cardiovascular disease: 4, Pulmonary disorders: 4, Others: 6] C [Hypertension: 15, Diabetes: 6, Cardiovascular disease: 10, Pulmonary disorders: 4, Others: 5]	The 28 day mortality rate in both arms was the same.	Moderate to severe	[58]
Wu et al.	26	26	14/12	12/14	53 (46–62)	59 (51–69)	I: Triazavirin 250 mg orally three/four times a day C: Placebo		No differences in the time to clinical improvement.	Mild and severe	[59]
Li et al.	LPV/RTV: 34 Arbidol: 35	17	LPV/RTV: 17/17 Arbidol: 16/19	7/10	LPV/RTV: 50.7 (15.4) Arbidol: 50.5 (14.6)	44.3 (13.1)	LPV/RTV: LPV:200 mg and ritonavir:50 mg:orally administed, BID, 500 mg, each time for 7–14 days Arbidol: 100 mg: orally administed, 200 mg three times daily for 7–14 days C:None	LPV/RTV [Underlying chronic diseases: 7] Arbidol [Underlying chronic diseases: 5] C [Underlying chronic diseases: 6]	The rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, was similar between groups	Mild/Moderate LPV/RTV: 6/28 Arbidol: 2/33 C: 3/14	[60]
Cao et al.	99	100	61/38	59/41	58.0:50.0–68.0	58.0 (48.0–68.0)	LPV/RTV: 400 mg and 100 mg orally, BID C: SOC	I [Diabetes: 10, Cerebrovascular disease: 5, Cancer: 5] C [Diabetes: 13, Cerebrovascular disease: 8, Cancer: 1]	No difference in the time to clinical improvement.	Severe	[61]

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Table 2. (Continued).

Authors	Sample size		Sex (Male/Female)		Age		Treatment panel	Comorbidity	Main findings	Stage of disease	References
	I	C	I	C	I	C					
Reis et al.	HCQ: 214 LPV/RTV: 244	227	HCQ:92/122 LPV/RTV: 110/134	106/121	HCQ: 53 (18–81) LPV/RTV: 54 (18–94)	53 (18–80)	HCQ: 800 mg loading dose, 400 mg daily for 9 days LPV/RTV: loading dose of 800 mg and 200 mg, respectively, every 12 hours followed by 400 mg and 100 mg, respectively, every 12 hours for the next 9 days C: Placebo	HCQ [Chronic cardiac disease: 6, Hypertension: 101, Chronic pulmonary disease: 7, Asthma: 24, Chronic kidney disease: 1, Rheumatologic disorder: 4, Chronic neurological disorder: 1, Diabetes Type 1: 17, Diabetes Type 2: 24, Obesity: 70, Malignant neoplasm: 2, HIV/AIDS:1, Autoimmune disease: 1, Smoking: 12, Any other risk factor:s: 8] LPV/RTV [Chronic cardiac disease: 13, Hypertension: 128, Chronic pulmonary disease: 4, Asthma: 15, Chronic kidney disease: 1, Rheumatologic disorder: 2, Diabetes Type 1: 13, Diabetes Type 2: 31, Obesity: 83, Malignant neoplasm: 2, Autoimmune disease: 3, Smoking: 12, Any other risk factor:s: 8] C [Chronic cardiac disease: 8, Hypertension: 109, Chronic pulmonary disease: 6, Asthma: 20, Chronic kidney disease: 3, Mild liver disease: 2, Rheumatologic disorder: 3, Diabetes Type 1: 13, Diabetes Type 2: 35, Obesity: 81, Malignant neoplasm: 4, HIV/AIDS: 6, Autoimmune disease: 1, Smoking: 11, Any other risk factor:s: 9]	No significant differences between interventions for COVID-19–associated hospitalization.	Mild	[62]
Arabi et al.	LPV/RTV: 254 HCQ: 50	362	LPV/RTV: 182/72 HCQ: 35/15	252/110	LPV/RTV: 61 (13) HCQ: 56.3 (13)	60.8 (12.9)	LPV/RTV: Lopinavir 400 mg & ritonavir 100 mg BID, 5–14 days HCQ: First, two doses of 800 mg, 6-hour apart, then 6 h later by 400 mg 12 hourly for 12 doses C: No antiviral drug	LPV/RTV: [Diabetes mellitus: 90, Respiratory disease: 62, Kidney disease: 31, Severe cardiovascular disease: 40, Immunosuppressive disease: 5, Chronic immunosuppressive therapy: 14] HCQ: [Diabetes mellitus: 15, Respiratory disease: 9, Kidney disease: 3, Severe cardiovascular disease: 2, Immunosuppressive disease: 2] C: [Diabetes mellitus: 10, Respiratory disease: 6, Kidney disease: 4, Severe cardiovascular disease: 3, Immunosuppressive disease: 1, Chronic immunosuppressive therapy: 1]	Lopinavir-ritonavir, hydroxychloroquine, administration deteriorated outcomes compared to no antiviral therapy in critically ill patients with SARS-COV-2.	Moderate & severe	[63]
Ivashchenko et al.	Lower dose:20 Higher dose:20	20					Lower dose: Favipiravir 1st day 1600 mg BID and 600 mg BID for 13 days Higher dose: Favipiravir 1st day 1800 mg BID and 800 mg BID for 13 days C:SOC		AVIFAVIR demonstrated rapid antiviral response against SARS-CoV-2.	Moderate	[64]

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Table 2. (Continued).

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Udwadia et al.	72	75	51/21	57/18	43.6 (12.2)	43.0 (11.2)	I: Day 1: Favipiravir 1800 mg; Days 2–14: 800 mg C:SOC	I [Comorbidity:19] C [Comorbidity:19]	Median time to cessation of viral shedding was not significantly different.	Mild/Moderate I: 44/28 C: 45/30	[65]
Chen et al.	15	15	9/6	9/6	51.5 (12.2)	42.9 (17.7)	I: Single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat per day for 5 days C: IFN alpha 2b	I [Cardiovascular diseases: 4] C [Cardiovascular diseases: 4, Diabetes: 2]	Five days of darunavir/cobicistat did not increase the proportion of negative conversion.	Mild	[66]
López et al.	200	198	78/122	89/109	37 (29–47.7)	37 (28.7–49.2)	I: IVM, 300 µg/kg:body weight C: Placebo	I [Obesity: 37, Hypertension: 28, Diabetes: 10, Thyroid disease: 7, Respiratory disease: 6, Cardiovascular disease: 4, Any coexisting condition: 44] C [Obesity: 38, Hypertension: 25, Diabetes: 12, Thyroid disease: 8, Respiratory disease: 6, Cardiovascular disease: 3, Any coexisting condition: 38]	Time to improvement of symptoms were not meaningfully different.	Mild	[67]
Ahmed et al.	IVM+DXC:24 IVM:24	24					IVM+ DXC::12 mg IVM and 200 mg stat doxycycline day-1 and 100 mg 12 hrly for 4 days IVM: 12 mg once daily for 5 days C: Placebo		A 5-day course of IVM was found to be safe and effective in treating adult COVID-19 patients with mild stage of disease.	Mild	[68]
Okumuş et al.	30	30	21/9	19/11	58.17 (11.52)	66.23 (13.31)	IVM: 200 microgr/kg/day for 5 days C:SOC	IVM [Diabetes mellitus: 9, Hypertension: 15, Coronary artery disease: 5, Chronic Obstructive Pulmonary Disease: 6] C [Diabetes mellitus: 10, Hypertension: 12, Coronary artery disease: 8, Cardiac failure: 1, Chronic Obstructive Pulmonary Disease: 6, Malignancy: 1, Immunodeficiency: 1]	IVM can accelerate clinical recovery	Severe	[69]
Abd-Elsalam et al	82	82	37/45	45/37	42.38 (16.02)	39.38 (16.92)	IVM: 12 mg once daily for 3 days C:SOC	IVM [Diabetes: 17, Hypertension: 18, Comorbidities: 36] C [Diabetes: 10, Hypertension: 14, Comorbidities: 45]	Mortality, the length of hospital stay, and the need for mechanical ventilation were same in groups.	Mild to moderate	. [70]
Shahbaznejad et al.	35	34	18/17	18/16			IVM: single oral dose:0.2 mg/kg utilizing 3-mg oral tablets C:SOC		Clinical status of COVID-19 was improved	Moderate to severe	[71]

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Table 2. (Continued).

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Mahmud et al	200	200	123/77	112/88	41 (14)	38 (12)	I: Single dose of IVM 12 mg and doxycycline 100 mg, BID for 5 days C:SOC	I [Comorbidities: 19, Hypertension: 29, Diabetes: 24, Asthma: 9, Chronic kidney disease: 3] C [Comorbidities: 22, Hypertension: 28, Diabetes: 29, Asthma: 12, Chronic kidney disease: 5]	The median recovery time was 7 (4–10) days in the treatment group and 9 (5–12) days in the placebo group.	Mild/Moderate I:141/59 C:136/64	. [72]
Vallejos et al.	250	251	139/111	125/126	42.58 (15.29)	42.40 (15.29)	I: 6 mg IVM (according to weight) C: Placebo + SOC	I: [Hypertension: 53, Diabetes mellitus: 21, Smoker: 27, Former smoker: 72, Asthma: 16, COPD: 7, Previous myocardial infarction: 3, Previous coronary angioplasty: 3, Previous stroke: 1, Heart failure: 1, Cancer: 4, Previous cancer: 6, Any comorbidity: 143] C: [Hypertension: 66, Diabetes mellitus: 27, Smoker: 25, Former smoker: 71, Asthma: 20, COPD: 7, Previous myocardial infarction: 6, Previous coronary angioplasty: 1, Previous stroke: 4, Heart failure: 3, Cancer: 2, Previous cancer: 4, Any comorbidity: 149]	Ivermectin administration in patients with mild or moderate COVID-19 had no meaningful effect on preventing hospitalization.	Mild or moderate	[73]
Niaee et al.	Arm1:30 Arm2:30 Arm3:30 Arm4:30	60	Arm1: 12/18 Arm2: 19/11 Arm3: 16/14 Arm4: 13/17	30/30	61 (42, 68) 53 (42, 65) 54 (47, 60) 54 (46, 65)	56.5 (45, 69)	Arm1: Single dose IVM (200 µg/kg) Arm2:Three low interval doses of IVM (200, 200, 200 µg/kg) Arm3: Single dose IVM (400 µg/kg) Arm4: Three high interval doses of IVM (400, 200, 200 µg/kg) C: HCQ 200 mg		Ivermectin as an adjunct reduced the rate of death, time of low O2 saturation, and length of hospitalization in COVID-19 patients.	Mild/Moderate/ Severe Arm1: 8/21/1 Arm2: 2/20/6 Arm3: 4/21/5 Arm4: 2/23/5 C: 9/46/5	[74]
Réa-Neto et al.	53	52	36/17	34/18	54.7 (12.1)	52.8 (12.6)	I: 450 mg once daily from day 1 to 5 and HCQ 400 mg once daily from day 1 to 5 C:SOC	I [Hypertension: 19, Diabetes mellitus: 11, Chronic lung disease: 6] C [Hypertension: 21, Diabetes mellitus: 16, Chronic lung disease: 3]	On the 14/28th day, the proportional odds of being in a worse clinical condition was higher in the Clq/ HClq group.	Severe	[75]
Mitjà et al.	157	136	32/104	54/103	41.7 (12.6)	41.3 (12.4)	I: HCQ 800 mg on day 1 followed by 400 mg once daily for 6 days C: SOC	I [Cardiovascular disease: 15, Respiratory disease: 10, Metabolic disease: 11, Nervous system disease: 21] C [Cardiovascular disease: 20, Respiratory disease: 7, Metabolic disease: 9, Nervous system disease: 19]	In patients with mild COVID-19, no benefit was seen with HCQ beyond the usual care.	Mild	[76]

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Table 2. (Continued).

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Lyngbakken et al	27	26	19/8	16/10	56 (41, 72)	69 (51, 74)	I:400 mg HCQ BID for seven days C:SOC	I [Hypertension: 6, Diabetes mellitus: 4, Coronary heart disease: 3, Obstructive pulmonary disease: 5, Obesity: 5] C [Hypertension: 11, Diabetes mellitus: 5, Coronary heart disease: 2, Obstructive pulmonary disease: 9, Obesity: 11]	No important antiviral effect of HCQ.	Moderately severe	. [77]
Kamran et al.	349	152	328/21	139/13			I: HCQ 400 mg 12 hourly day 0 followed by HCQ 200 mg 12 hourly for next 5 days C:SOC		Neither stops disease progression nor helps in early and sustained viral clearance.	Mild	[78]
Cavalcanti et al	HCQ: 221 HCQ+AZM: 217	227	HCQ: 142 HCQ+AZM: 123	123	HCQ: 51.3 (14.5) HCQ+AZM: 49.6 (14.2)	49.9 (15.1)	HCQ-alone: HCQ at a dose of 400 mg BID for 7 days HCQ+AZM: HCQ at a dose of 400 mg BID +azithro at a dose of 500 mg once a day for 7 days. C: SOC	I [HCQ+AZM: Hypertension: 81, Diabetes: 40, Current or former smoking: 17, Obesity: 29, Cancer: 7, Heart failure: 4, COPD: 4, AIDS: 1, Chronic renal disease: 2, Asthma: 16] HCQ [Hypertension: 94, Diabetes: 47, Current or former smoking: 12, Obesity: 37, Cancer: 4, Heart failure: 3, COPD: 4, Chronic renal disease: 1, Asthma: 9] C [Hypertension: 83, Diabetes: 40, Current or former smoking: 15, Obesity: 37, Cancer: 8, Heart failure: 3, COPD: 4, AIDS: 3, Chronic renal disease: 2, Asthma: 15]	The use of HCQ, alone or with AZM, did not improve clinical status at 15 days as compared with standard care.	Mild-to-moderate	. [79]
Dubée et al.	125	125	65/60	56/69	76 (60–85)	78 (57–87)	I:HCQ:200 mg tablets, orally at a dose of two tablets BID on the first day followed by one tablet BID for 8 days C: Placebo + SOC	I [Chronic respiratory disease: 15, Diabetes: 20, Arterial hypertension: 65, Heart disease: 34, Cerebrovascular disease: 21, Obesity: 25, Active smoker: 3] C [Chronic respiratory disease: 13, Diabetes: 23, Arterial hypertension: 68, Heart disease: 38, Cerebrovascular disease: 22, Obesity: 40, Active smoker:3]	No significant difference in the rate of death or start of mechanical ventilation.	Mild-to-moderate	[80]
Skipper et al.	212	211	89/123	96/115	41 (33–49)	39 (31–50)	I: HCQ 800 mg:4 tablets once, then 600 mg:3 tablets 6 to 8 hours later, then 600 mg:3 tablets once daily for 4 more days. C:Placebo	I [Hypertension: 23, Diabetes: 8, Asthma: 28] C [Hypertension: 23, Diabetes: 7, Asthma: 20]	HCq did not significantly reduce symptom severity in outpatients with early, mild COVID-19.	Mild	[81]
Wesley et al.	242	237	135/107	132/105	58 (45–69)	57 (43–68)	I: HCQ 400 mg BID for 2 doses, then 200 mg BID for 8 doses C: placebo + SOC	I [Hypertension: 136, Diabetes: 88, Chronic kidney disease: 28, Coronary artery disease: 19, Chronic obstructive pulmonary disease: 18] C [Hypertension: 117, Diabetes: 78, Chronic kidney disease: 14, Coronary artery disease: 23, Chronic obstructive pulmonary disease: 21]	Treatment with HCQ did not improve or worsen clinical outcomes.	Mix	[133]

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Table 2. (Continued).

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Abd-Elsalam et al	97	97	56/41	58/39	40.35 (18.65)	41.09 (20.07)	I:HCQ 400 mg BID in day 1 followed by 200 mg tablets BID C: SOC	I [Comorbidities: 15, Renal impairment: 2] C [Comorbidities: 12, Liver diseases: 2, Renal impairment: 4]	Adding HCQ to standard care did not add an extra benefit for the patients.	Moderate	. [82]
Tang et al.	75	75	42/33	40/35	48.0 (14.1)	44.1 (15.0)	I: HCQ loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily C: SOC	I [Diabetes: 12, Hypertension: 6] C [Diabetes: 9, Hypertension: 3]	The probability of negative conversion by 28 days were similar.	Mild or moderated = 148 Severe = 2	[83]
Schwartz et al	111	37	67/46	17/20	46.7 (11.5)	46.9 (11.0)	I: HCQ 800 mg orally on day 1 followed by 200 mg BIDfor 4 days C: Placebo	I [Hypertension: 29, Diabetes: 18, Asthma: 12, Current cigarette smoker: 16] C: [Hypertension: 12, Diabetes: 11, Asthma: 8, Current cigarette smoker: 5]	HCQ could not alleviate symptom duration or prevent severe outcomes in COVID-19 outpatients.	Mild to moderate	. [84]
Pouladzadeh et al.	30	30	16/14	17/13	53.5 (10.3)	57.2 (17)	I: 500 mL convalescent plasma on the admission day C: SOC		CP has a remarkable immunomodulatory and antiviral potential to improve the cytokine storm and disease severity in COVID-19 patients.	Secondary infection phase	[85]
RECOVERY Collaborative Group	5795	5763	3643/2152	3787/1976	63 · 5 (14 · 7)	63 · 4 (14 · 6)	I: Two units (CP):275 ml (200–350) intravenously C: SOC	I [Diabetes: 1535, Heart disease: 1267, Chronic lung disease: 1385, Tuberculosis: 20, HIV: 17, Severe liver disease: 70, Severe kidney impairment: 323] C [Diabetes: 1569, Heart disease: 1309, Chronic lung disease: 1328, Tuberculosis: 23, HIV:19, Severe liver disease: 72, Severe kidney impairment: 293]	There was no significant difference in 28-day mortality between the two groups.	Mix	[86]
Gharbharan et al.	43	43	29/14	33/10	61 (56–70)	63 (55–77)	I: 300 mL CP containing SARS-CoV-2-neutralizing antibodies C: SOC	I [Diabetes mellitus: 8, Hypertension: 11, Cardiac: 11, Pulmonary: 11, Cancer: 3, Immunodeficiency" 6, Chronic kidney disease: 6] C [Diabetes mellitus: 8, Hypertension: 11, Cardiac: 11, Pulmonary: 11, Cancer: 3, Immunodeficiency: 6, Chronic kidney disease: 6, Liver cirrhosis: 1]	There is no overall clinical benefits.	Moderate & severe	[87]
Sekine et al	80	80	49/31	44/36	59.0 (48.0–68.5)	62.0 (49.5–68.0)	I: Two infusions 48 hours apart of CP 300 ml C: SOC	I [Diabetes: 34, Hypertension: 49, Cardiovascular Disease: 19, Chronic Pulmonary Disease: 13, Obesity: 43] C [Diabetes: 29, Hypertension: 49, Cardiovascular Disease: 16, Chronic Pulmonary Disease: 9, Obesity: 38]	CP did not increase proportion of clinical improvement among hospitalized patients.	Severe	. [88]

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Table 2. (Continued).

Authors	Sample size		Sex (Male/Female)		Age		Treatment panel	Comorbidity	Main findings	Stage of disease	References
	I	C	I	C	I	C					
Gottlieb et al.	700 mg:1,012,800 mg:1,077,000 mg:101 Combination treatment:112	156	71/85	700 mg:38/ 632,800 mg:56/ 517,000 mg:43/58 combination treatment:54/ 58	700 mg: 39 (31–58) 2800 mg: 45 (31–56) 7000 mg: 46 (34–55) combination treatment: 44 (30–60)	46 (35–57)	700 mg: Bamlanivimab 2800 mg: Bamlanivimab 7000 mg: Bamlanivimab combination treatment: 2800 mg of bamlanivimab and 2800 mg of etesevimab C: Placebo		Bamlanivimab monotherapy didn't reduce the viral load but combination of bamlanivimab with etesevimab reduced significantly viral load compared to placebo group.	Mild/Moderate 700 mg:83/182,800 mg:79/287,000 mg:70/31 combination treatment:92/20 C: 125/31	[89]
Lopardo et al	118	123	80/38	77/46	54 (43 to 63)	54 (45 to 65)	I: EpAbs: INM005: Two intravenous doses:4 mg/kg of INM005 C: Placebo		Improvement in at least two categories in WHO ordinal clinical scale were not different between groups.	Moderate and severe	. [44]
Lundgren at al.	163	151	97/66	80/71	63 (50–72)	59 (48–71)	I: LY-CoV555: at a dose of 7000 mg C: Placebo	I [Hypertension: 82, Diabetes: 54, Renal impairment: 24, Asthma: 14, Heart failure: 12] C [Hypertension: 72, Diabetes: 36, Renal impairment: 9, Asthma: 14, Heart failure: 1]	Monoclonal antibody LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure.	Mix	[90]
Tabarsi et al.	52	32	40/12	25/7	54.29 (12.85)	52.47 (14.49)	I: Intravenous Immunoglobulin: 400 mg/Kg daily for three doses C: SOC	I [Hypertension: 11, Ischemic heart disease: 3, Chronic obstructive pulmonary disease: 1, Diabetes: 10, Chronic kidney disease: 3, Rheumatoid arthritis: 1] C [Hypertension: 6,Ischemic heart disease: 2, Malignancy: 1, Diabetes: 8,Chronic kidney disease: 1]	There was no significant difference between the two groups in terms of mortality rate and the need for mechanical ventilation.	Severe	[91]
Gharebaghi et al	30	39	21/9	20/9	55.5 (45–60)	56 (47–66)	I: four vials of 5 gm5 Intravenous immunoglobulin daily for 3 days C: Placebo		The administration of IVIg in patients with severe COVID-19 infection who did not respond to initial treatment could improve their clinical outcome and significantly reduce mortality rate.	Severe	. [92]

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Table 2. (Continued).

Authors	Sample size		Sex (Male/Female)		Age		Treatment panel	Comorbidity	Main findings	Stage of disease	References
	I	C	I	C	I	C					
Furtado et al.	214	183	140/74	122/61	59 · 4 (49 · 3–70 · 0)	60 · 2 (52 · 0–70 · 1)	I: AZM group received 500 mg AZM once daily: by oral, nasogastric, or intravenous route for 10 days C: SOC	I [Smoker: 18, Hypertension: 126, Diabetes: 81, Heart failure: 14, Previous stroke: 10, Previous myocardial infarction: 8, Chronic obstructive pulmonary disease: 12, Active cancer: 10, Chronic kidney failure: 26] C [Smoker: 18, Hypertension: 115, Diabetes: 71, Heart failure: 9, Previous stroke: 5, Previous myocardial infarction: 9, Chronic obstructive pulmonary disease: 12, Active cancer: 4, Chronic kidney failure: 18]	In patients with severe COVID-19, adding azithromycin to SOC treatment did not improve clinical outcomes.	Mix	[93]
RECOVERY Collaborative Group	2582	5181	1604/978	3215/1966	65 · 4 (15 · 6)	65 · 2 (15 · 7)	I: AZM 500 mg once a day C: SOC	I [Diabetes: 700, Heart disease: 693, Chronic lung disease: 621, Tuberculosis: 3, HIV: 7, Severe liver disease: 45, Severe kidney impairment: 155, Any of the above: 1507] C [Diabetes: 1433, Heart disease: 1350, Chronic lung disease: 1313, Tuberculosis: 16, HIV:22, Severe liver disease: 65, Severe kidney impairment: 334, Any of the above: 3013]	Azithromycin cannot improve mortality and length of hospitalization.	Mix	[94]
Sekhavati et al.	56	55	28/28	23/32	54.38 (15.92)	59.89 (15.55)	I: AZM 500 mg daily for 5 days C: SOC		Patients received AZM had a significantly shorter length of hospitalization & meaningfuly higher SpO2 and lower respiratory rate at discharge.	N/A	[95]
Hinks et al.	147	148	76/71	76/72	46 · 3 (15 · 5)	45 · 5 (14 · 2)	I: AZM 500 mg once daily orally for 14 days C: SOC	I [Hypertension: 25, Diabetes: 11] C [Hypertension: 27, Diabetes: 14]	AZM plus standard care did not reduce the risk of hospital admission or rate of mortality.	Mild to moderate	[96]
PRINCIPLE Trial Collaborative Group	526	862	224/301	375/486	60.5 (7.8)	60.9 (7.9)	I: AZM 500 mg daily for three days C: SOC	I [Asthma, chronic obstructive pulmonary disease, or lung disease: 193, Diabetes: 90, Heart problem: 86, High blood pressure: 209, Liver disease: 16, Stroke or other neurological problem: 31] C: [Asthma, chronic obstructive pulmonary disease, or lung disease: 329, Diabetes: 162, Heart problem: 126, High blood pressure: 368, Liver disease: 23, Stroke or other neurological problem: 39]	AZM did not decrease time to recovery or risk of hospitalization	Mild	[97]
Oldenburg et al	171	92	51/117	35/57	42 (35–49)	44 (35–51)	I: A single oral 1.2-g dose of AZM C: Placebo	I [Asthma: 21, Hypertension: 20, Diabetes: 5, COPD: 4, Chronic kidney disease: 1, Cancer: 1, Stroke: 1] C [Asthma: 11, Hypertension: 12, Diabetes: 5, Chronic kidney disease: 1, Stroke: 1]	A single dose of AZM did not increase likelihood of being symptom free at day 14	Mild	. [98]

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Table 2. (Continued).

	Sample size		Sex (Male/Female)		Age						
Authors	I	C	I	C	I	C	Treatment panel	Comorbidity	Main findings	Stage of disease	References
Moghadam et al.	30	30	15/15	15/15	57.53 (18.27)	61 (15.90)	I: High dose vitamin C:6 g daily C:SOC	I [Hypertension: 15, Diabetes mellitus:12, Ischemic heart disease: 4, COPD: 3, Thyroid disease: 2] C [Hypertension: 10, Diabetes mellitus: 11, Ischemic heart disease: 7 COPD: 3, Thyroid disease: 3]	No signifcantly better outcomes in the group who were treated with High dose vitamin C in addition to the main treatment regimen at discharge.	Severe	[99]
Geriak et al	16	15	10/6	9/6	59	55	I: Losartan:ARB 12.5 mg orally every 12 h for 10 days	I [Diabetes mellitus: 3, Hypertension: 7, Tobacco use: 4, Cardiovascular disease: 1] C [Diabetes mellitus: 5, Hypertension: 5, Tobacco use: 2]	No clinically significant impacts of ARB therapy in mildly hypoxemic patients hospitalized with COVID-19.	Mild to moderate hypoxia ($SpO_2 \leq$ 96% on $\geq$ 1 L/min O_2 by nasal cannula) but not on mechanical ventilation.	. [100]
Abulmeaty et al	24	20			45.08 (9.19)	52.80 (10.84)	I: Antioxidant Oral Supplements: 1500 ug Vitamin A, 250 mg Vitamin C, 90 mg vitamin E, 15 ug Selenium, and 7.5 mg Zinc C: Placebo			Non-Critically Ill	. [101]
Zarehoseinzade et al.	40	40	40/0	40/0	71 (62 − 81)	72 (65–77)	I: 5 mg finasteride once daily for 7 days. C: SOC	I [Diabetes mellitus: 5, Hypertension: 24, Cardiac disease: 17, Chronic obstructive pulmonary disease: 3] C [Diabetes mellitus: 15, Hypertension: 29, Cardiac disease: 14, Chronic obstructive pulmonary disease: 7]	A short Course of finasteride administration partially improves O_2 saturation but does not influence other outcomes in hospitalized male patients.	Moderate to Severe	[102]
Fan et al.	27	12	11/16	7/5	46.7 (11.9)	45.82 (9.89)	I: Emetine 3.6 mg per os, TID for 10 days C: SOC		Low-dose emetine combined SOC improved clinical symptoms.	Mild & common	[103]
Siami et al.	60	60					I: 12.5 mg Diphenhydramine +125 mg Ammonium Chloride/5 ml syrup C: SOC		Ammonium Chloride adjucent to SOC was not superior to SOC alone in reducing death rate.	N/A	[104]
Duarte et al.	78	80	35/45	49/29	63.7 ± 17.0	66.9 ± 17.2	I: Telmisartan 80 mg BID for 14 days C: SOC	I [Hypertension: 35, COPD: 8, Diabetes: 16, Obesity: 16, Dyslipemia: 14, Stroke: 7, Asthma: 2, Chronic kidney disease: 5] C [Hypertension: 35, COPD: 10, Diabetes: 14, Obesity: 8, Dyslipemia: 12, Stroke: 4, Asthma: 3]	Telmisartan decreased morbidity and mortality in hospitalized patients.	N/A	[105–124]

Abbreviations: I: Intervention, C: Control, SOC: Standard of Care, LPV: Lopinavir, RTV:Ritanavir, IFN: Interferon, IVM: Ivermectin, AZM: Azithromycin, IV: Intravenous, Ig: Immunoglobulin, CP: Convalescent plasma, DXM: Dexamethasone, HCQ: Hydroxychloroquine, BID: Twice a day, DXC: Doxycycline, TID: Three times per day

*All intervention groups recienved same treatment except the main intervention

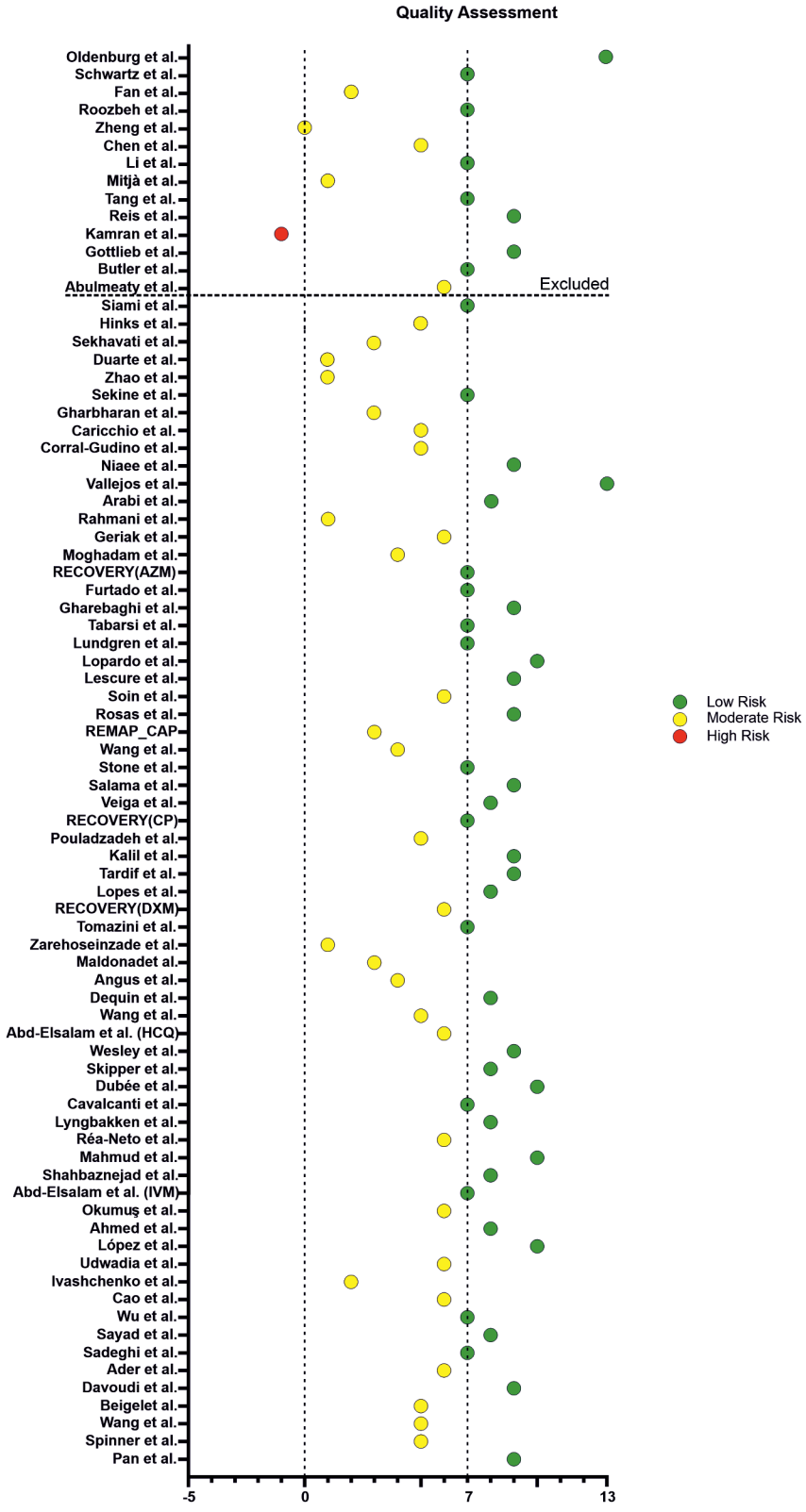

Figure 2. Quality assessment final score base on Joanna Brigs Institute (JBI) checklist (Each 'Yes' answer had a + 1 score, each 'Unclear' answer had a 0 score and each 'No' answer had a − 1 score) .

patients with COVID-19 compared to usual care or placebo [125]. Our findings are also in accordance with recent published review studies [126,127] and the WHO Solidarity Trial Consortium finding that have shown antiviral and antiparasitic drugs were not effective on survival benefit in 11,330 patients at 405 hospitals over 30 countries [128]. Also, previous systematic reviews and meta-analyses have shown that tocilizumab (monoclonal IL-6 receptor antibody) has the potential to reduce mortality in patients with COVID-19 [129–131]. The result of the sub-group analysis

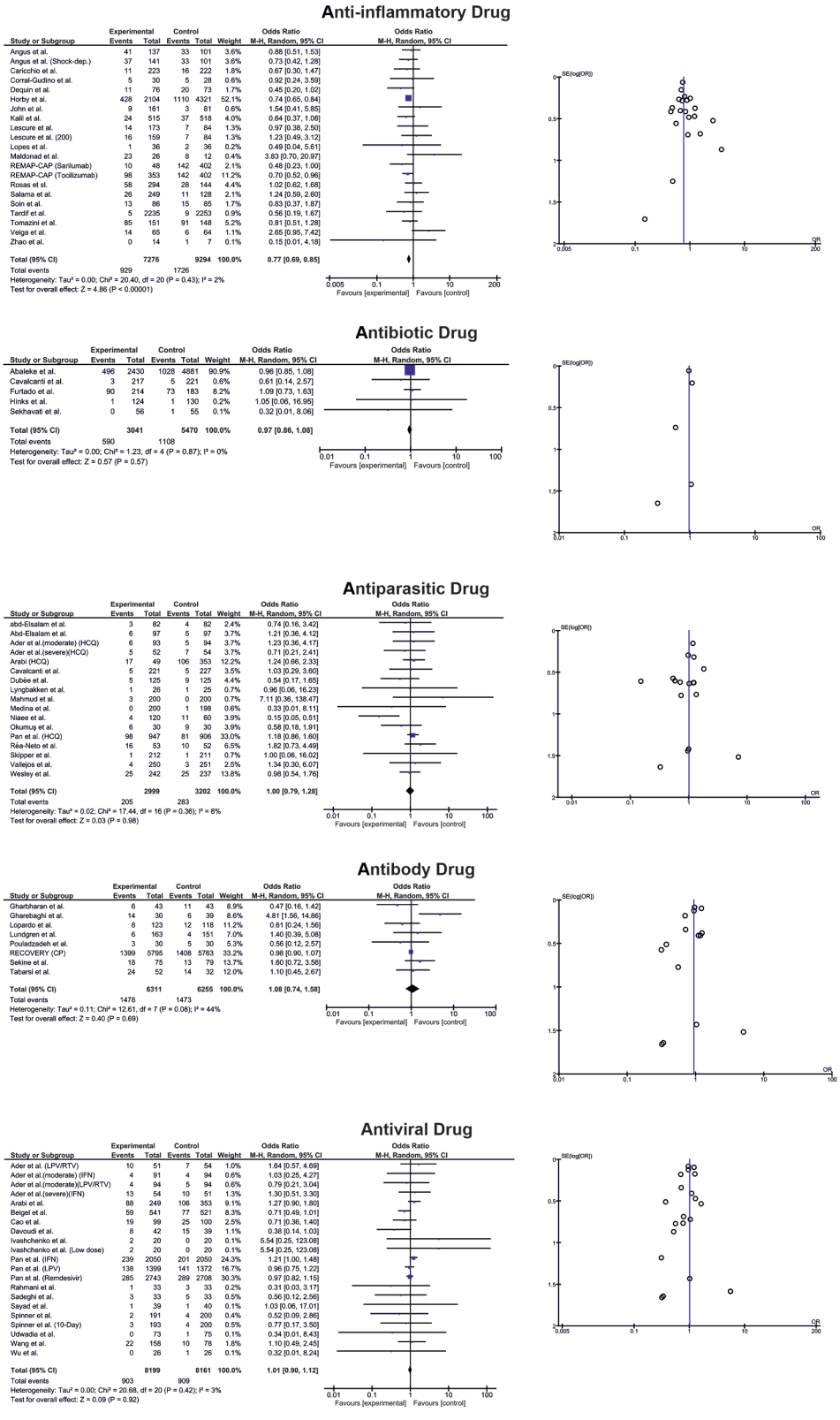

Figure 3. Meta-analysis of intervention versus control on mortality.

on tocilizumab did not show a reduction in mortality; however, it could decrease the LOH. It may be explained by the lack of enough studies.

Following the determination of the effectiveness of antiparasitic drugs against Corona viruses in vitro, studies have evaluated the effect of these drugs on COVID-19 patients in clinical settings [132–134]. The finding of this meta-analysis proposed the application of antiparasitic drugs did not result in mortality rate in patients with COVID-19. Previous systematic reviews and meta-analyses

Table 3. Descriptive summary of RCTs phase III studies on anti-inflammatory drugs included in the systematic review.

Authors	Sample size			Sex (Male/Female)		Age		BMI	
	I	C	Stage of disease	I	C	I	C	I	C
Treatment panel	Comorbidity	Main finding	Country	Study design	Duration of study	Follow-up for death outcome	References		
Wang et al.	26	24	All stages	13/13	9/15	56.0 (43.0-67.3)	55.5 (47.8-66.5)	-	-
Dequin et al.	76	73	Critically ill patients	54/22	50/23	63.1 (51.5-70.8)	66.3 (53.5-72.7)	27.5 (25.3-32.4)	28.4 (26.0-31.2)
Angus et al.	Fixed-dose:137 Shock-dependent:146	101	Severe	Fixed-dose:98/39 Shock-dependent:103/43	72/29	Fixed-dose: 60.4 (11.6) Shock-dependent: 59.5 (12.7)	59.9 (14.6)		
Maldonado et al.	26	12	Moderate or severe	14/12	7/5	55.3 (9.2)	62.3 (15.3)		
Corral-Gudino et al.	35	29	Moderate to severe	23/22	16/13	73 (11)	66 (12)		
Tomazini et al.	151	148	Moderate or Severe	90/61	97/51	60.1 (15.8)	62.7 (13.1)	-	-
RECOVERY Collaborative Group	2104	4321		male:1338/766	2749/1572	66.9 (15.4)	65.8 (15.8)	-	-
Lopes et al.	36	36	moderate to severe	19/17	14/22	54.5 (42.5–64.5)	55.0 (42.0–67.0)	33.5 (28.6–37.8)	29.7 (26.3–36.0)
Tardif et al.	2235	2253		997/1238	1070/1183	53·0 (47·0–61·0)	54·0 (47·0–61·0)	30·0 (6·2)	30·0 (6·3)
Kalil et al	515	518	Moderate/severe I: 358/157 C: 348/170	319/196	333/185	55.0 (15.4)	55.8 (16.0)	32.16	32.25
Caricchio et al.	223	222	Severe						
Veiga et al	65	64	Severe	44/21	44/20	57.4 (15.7)	57.5 (13.5)	-	-
Salama et al.	249	128		150/99	73/55	56.0 (14.3)	55.6 (14.9)	32. (7.9)	33.1 (7.2)
Zhao et al	Favipiravir: 7 Tocilizumab: 5 Favipiravir+ Tocilizumab: 14		Common/Severe/criticsl Favipiravir: 2/5/0 Tocilizumab: 2/3/0 Favipiravir+ Tocilizumab: 8/5/1	Favipiravir: 5/2 Tocilizumab: 3/2 Favipiravir+ Tocilizumab: 6/8		Favipiravir: 71 (48–77) Tocilizumab: 70 (45–89) Favipiravir+ Tocilizumab: 75 (34–81)		Favipiravir: 21.5 Tocilizumab: 21.1 Favipiravir+ Tocilizumab: 24.8	
Stone et al.	161	82	Moderate	96/65	45/37	61.6 (46.4–69.7)	56.5 (44.7–67.8)	29.9	30.2
Wang et al.	34	31	Moderate or severe	18/16	15/16	63.5 (58–71)	63 (54–69)	-	-
Gordon et al.	Tocilizumab: 353 Sarilumab: 48	402	Severe	Tocilizumab: 261/92 Sarilumab: 39/9	283/119	Tocilizumab: 61.5 (12.5) Sarilumab: 63.4 (13.4)	61.1 (12.8)	Tocilizumab: 30.5 (26.9–34.9) Sarilumab: 29.2 (26.0–33.8)	30.9 (27.1–34.9)
Rosas et al	294	144	Severe	205/89	101/43	60.9 (14.6)	60.6 (13.7)	-	-
Soin et al.	91	88	Moderate to severe	76/15	76/12	56 (47–63)	54 (43–63)	27 (22.6-31.4)	26.8 (22.2-31.4)
Lescure et al.	Sarilumab 200 mg: 159 Sarilumab 400 mg: 173	84	Severe	Sarilumab 200 mg: 108/51 Sarilumab 400 mg: 99/74	54/30	Sarilumab 200 mg: 58·0 (51·0–67·0) Sarilumab 400 mg: 58·0 (48·0–67·0)	60·0 (53·0–69·5)	-	-

Abbreviations: Intervention (I), Control (C) *All intervention groups recienved same treatment except the main intervention

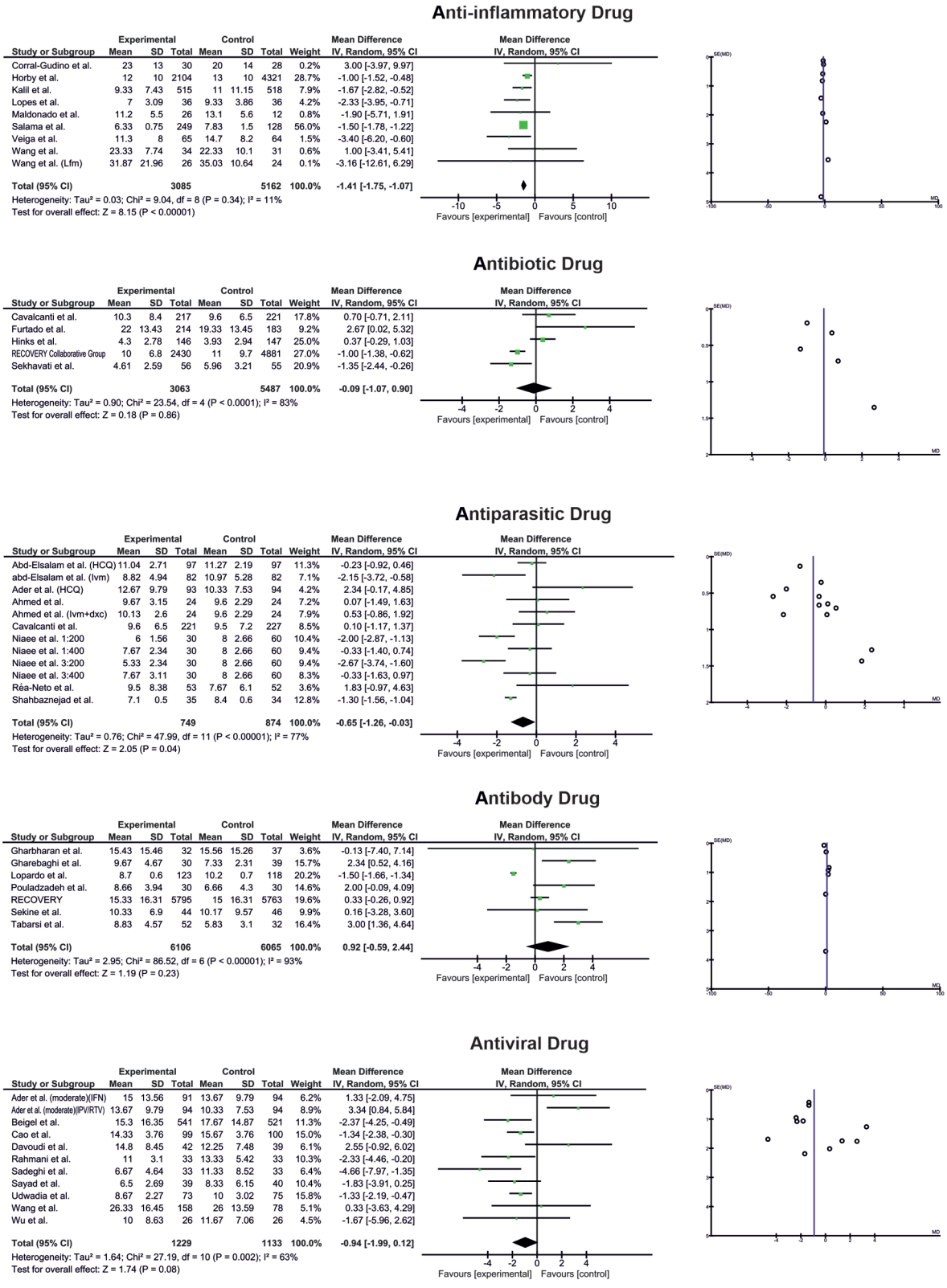

Figure 4. Meta-analysis of intervention versus control on length of hospitalization.

confirmed our findings [135–137]. They found that hydroxychloroquine alone were not associated with reduced mortality in hospitalized COVID-19 patients. However, meta-analyses on ivermectin reported controversial results for mortality outcome [138,139]. On the other hand, our finding showed that antiparasitic drugs were associated with reduced duration of hospital stay of COVID-19 patients. This finding should be interpreted with caution

because the heterogeneity (I^2 = 77%) was high. Sub-group analysis showed that ivermectin could significantly reduce the LOH (I^2 = 67%).

Previous studies reported antibody therapy as a potential anti-COVID-19 treatment [140]. By contrast, the mortality rate and duration of hospital stay of COVID-19 patients among the antibody treated groups were not significantly different from SOC/control/placebo groups.

3.1. Strengths and limitations

Strength of our review is a comprehensive and comparative systematic review that summarizes the main findings in the table formats. This study will help investigators for future studies and clinicians make a good decision for treatment management of COVID-19. We selected the highest-quality literature by our criteria and using the JBI method. To get this point, we excluded observational studies, non-randomized studies and phase I and II clinical trials. Also, we included studies that have at least two arms with only one drug difference. On the other hand, our study had some limitations. First, drugs were administered at different stages of the disease, however, we used odds ratio for reducing the effect of this confounding factor but drugs may have beneficial effects on a specific stage of the disease. Second, the death results were reported in less than 30-days follow up period. Third, some sub-group analysis should be done in future with more studies.

3.2. Future studies

Numerous studies on paraclinical data or time to viral clearance are conducting, a systematic review of these data can get us a big picture to make a precise decision in treatment management. We excluded clinical trials of herbal agents, conducting a robust systematic litterateur review will clear the efficacy of herbal treatment in the course of COVID-19. Although anti-inflammatory drugs were highlighted as effective therapeutic options against COVID-19 here, there are side effects concerns (e.g. more superinfection compared to standard care) related to these drugs; therefore, future studies should focus on side effects of anti-inflammatory drugs administration in COVID-19 patients.

3.3. Conclusion

To summarize, the anti-inflammatory drugs were associated with improved mortality and the average length of hospital stay of COVID-19 patients. Moreover, the length of hospital stay was significantly reduced when patients were treated with antiparasitic drugs. However, no difference was seen in antibiotic drugs, antibodies agents, and antiviral drugs in comparison to SOC/control/placebo in terms of 'mortality' and 'duration of hospital stay.' As a conclusion, summarizing data of different categories of drugs on the mortality and duration of hospital stay may facilitate physicians to properly manage COVID-19 patients.

Funding

This paper was not 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.

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