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Table s1. Search strategy

Embase <1974 to 2021 March 31>

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to March 31, 2021>

1. exp coronavirus/
2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.
3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw.
4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.
5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.
6. "severe acute respiratory syndrome*".ti,ab,kw.
7. exp Coronavirus Infections/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. limit 8 to yr="2019 -Current"
10. exp Chloroquine/
11. exp hydroxychloroquine/
12. (Hydroxychloroquine or chloroquine or chlorochin or hydroxychlorochin or Aralen or Plaquenil or Resochin or Dawaquin or Lariago or Hydroquin or Axemal or Dolquine or Quensyl or Quinori).ti,ab,kw.
13. exp Azithromycin/
14. (Azithromycin or Sumamed or Zithromax or Zmax or Z-Pak).ti,ab,kw.
15. exp Lopinavir/
16. lopinavir.ti,ab,kw.
17. exp Receptors, Interleukin-6/ai [Antagonists & Inhibitors]
18. exp interleukin 6 antibody/ use oemezd
19. (anti-IL-6 or (IL-6 adj2 inhibitor*) or (Anti-IL6 adj2 antibod*)).ti,ab,kw.
20. exp tocilizumab/ use oemezd
21. exp sarilumab/ use oemezd
22. exp siltuximab/ use oemezd
23. (tocilizumab or sarilumab).mp. or siltuximab.ti,ab,kw. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
24. exp Plasma/ use ppez
25. exp plasma transfusion/ use oemezd
26. convalescent plasma.ti,ab,kw.
27. exp Adrenal Cortex Hormones/ use ppez
28. exp Pregnenediones/ use ppez
29. exp corticosteroid/ use oemezd

30. corticosteroid*.ti,ab,kw.
31. glucocorticoid*.ti,ab,kw.
32. methylprednisolone*.ti,ab,kw.
33. exp Anti-Inflammatory Agents, Non-Steroidal/ use ppez
34. exp nonsteroid antiinflammatory agent/ use oemezd
35. (nsaid* or (anti-inflammator* adj2 non-steroid*) or (antiinflammator* adj2 nonsteroid*)).ti,ab,kw.
36. exp Ribavirin/
37. (Ribavirin or Copegus or Ribasphere or Rebetol).ti,ab,kw.
38. exp Oseltamivir/
39. (Oseltamivir or Tamiflu).ti,ab,kw.
40. exp Immunoglobulins, Intravenous/ use ppez
41. exp immunoglobulin/iv [Intravenous Drug Administration]
42. (ivig or (intravenous* adj2 immunoglobulin*) or Flebogamma or Gamunex or Privigen or Octagam or Gammagard).ti,ab,kw.
43. exp Interferon-beta/ use ppez
44. exp beta interferon/ use oemezd
45. (interferon adj2 beta).ti,ab,kw.
46. exp remdesivir/ use oemezd
47. (GS-5734 or remdesivir).ti,ab,kw.
48. exp famotidine/ use oemezd
49. famotidine.ti,ab,kw.
50. antibodies, monoclonal/ or monoclonal antibod*.ti,ab,kw.
51. exp Heparin/ or heparin.mp.
52. exp Heparin, Low-Molecular-Weight/
53. (LMWH or LMWHs or low molecular weight heparin).mp.
54. exp ivermectin/
55. ivermectin.ti,ab,kw.
56. exp neutralizing antibody/
57. neutralizing antibod*.ti,ab,kw.
58. (Bamlanivimab or LY-CoV555).ti,ab,kw.
59. exp casivirimab/
60. exp imdevimab/
61. (casivirimab or imdevimab).ti,ab,kw.
62. exp baricitinib/
63. baricitinib.ti,ab,kw.
64. exp favipiravir/
65. favipiravir.ti,ab,kw.
66. exp ritonavir/
67. ritonavir.ti,ab,kw.
68. exp anakinra/
69. anakinra.ti,ab,kw.
70. exp eculizumab/
71. eculizumab.ti,ab,kw.
72. exp Sofosbuvir/

73. Sofosbuvir.ti,ab,kw.
74. exp Ruxolitinib/
75. Ruxolitinib.ti,ab,kw.
76. exp Daclatasvir/
77. Daclatasvir.ti,ab,kw.
78. exp Leflunomide/
79. Leflunomide.ti,ab,kw.
80. exp Bromohexine/
81. Bromohexine.ti,ab,kw.
82. exp Colchicine/
83. Colchicine.ti,ab,kw.
84. exp lenzilumab/
85. lenzilumab.ti,ab,kw.
86. auxora.ti,ab,kw.
87. vilobelimab.ti,ab,kw.
88. exp complement component C5a/
89. complement component C5a.ti,ab,kw.
90. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89
91. 8 and 90
92. limit 91 to yr="2019 -Current"

Table s2. Best practices and suggestions for research of treatments for patients with COVID-19

Protocol	Favor study designs that may optimize rapid accrual (e.g., multicentric)
Registration/ IRB-IEC	All RCTs must still be registered at clinicaltrials.gov. All studies must follow Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki, including IRB approval. IRBs should increase resources to facilitate and accelerate study protocol review.
Critical elements to define *a priori*	
Study design	Although RCTs are the favored study designs to evaluate new interventions, other study designs have value especially when data needs to be evaluated quickly: -non-randomized controlled studies (especially cohort studies) -single-arm studies (prospective outcome registries), especially to identify harm
Participants	Depending on the aim of the study, different populations may be included: Aiming to evaluate efficacy: strict inclusion/exclusion criteria (excluding patients with comorbidities and comedications), smaller sample size. This design decreases variability but can increase the risk of slow accrual rate and results can be less generalizable. Aiming to evaluate impact in real-life scenarios: broader population (including special populations such as patients with immunosuppression, HIV, cardiovascular comorbidities and pregnancy). This design increases variability but makes results more generalizable to the general population with better evaluation of drug-drug interactions and harms.
Laboratory-confirmed	Standardized laboratory-confirmation should be based on NAT (nucleic acid testing) for SARS-CoV-2 on respiratory specimen rather than relying on radiological suspicion on imaging studies which are much less specific.
Clinical syndrome	Distinguish between asymptomatic carrier state, upper respiratory tract infection and lower respiratory tract infection
Disease severity	Use standardized definitions, for example as per WHO-China Joint Mission[1]: -mild-to-moderate: non-pneumonia and mild pneumonia -severe defined as tachypnoea[2], oxygen saturation ≤93% at rest, or PaO_2/FiO_2 ratio <300 mm Hg -critical respiratory failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care Despite these standardized criteria, disease severity should focus on objective readily available clinical criteria, like the degree of respiratory failure using Sa02 or FiO2:PaO2 ratios, as opposed to location-based severity determinations such as ICU admission, which can lead to bias based on resource limitations (i.e. bed availability) or regional/institutional practice patterns.
Interventions	Studied interventions should be detailed in terms of dose, interval, duration and timing of administration according to clinical status.
Outcomes	Efficacy as well as harms should be reported. Outcomes should focus on patient-important outcomes (clinical improvement rather than improvement in inflammatory markers such as CRP or procalcitonin). Outcomes should be objectively measured especially if the study is not blinded. Preferably, avoid outcomes that are participant-or observer-reported involving judgement that reflect decision made by the intervention providers which can be influenced by the clinical context (for example, mortality and clinical improvement based on Sa02 or Fi02:Pa02 ratios should be selected as important outcomes rather than duration of mechanical ventilation or ICU stay). Also, the timing at which the outcomes will be measured should be decided *a priori*. In absence of directly measurable outcomes (especially if events are rare), surrogates can be used. If surrogates are used, select those which are the most closely associated with the outcome of interest

	(e.g. select the oxygen requirement in L/min rather than radiological improvement or reduction in viral load as a surrogate for clinical improvement).
Avoid biases	
Selection bias	Define early stoppage criteria before the onset of the study
Information bias	Blinding the participants and the clinicians will not always be possible due to the urgency of the situation, in which case, at minimum and in order to reduce information bias, outcome assessors should be blinded.
Confounders	Multiple cointerventions (such as antivirals, corticosteroids, immunomodulators) are used. Protocolize their use to ensure that studied groups received the same cointerventions and timing of administrations. If not possible, adjust the analysis for potential confounders (including time-varying confounding) and explore for interactions.
Avoid imprecision	
Sample size	Because the a priori estimation of efficacy may be unknown, it is important to readjust sample sizes prior to stopping recruitment as new evidence emerges.
Submission	
Peer-review	Peer-review remains crucial in the process. Journals should add resources to expedite reviews by increasing the number of editors and reviewers, shorten the review process, favor statistical review and adhere to reporting guidelines (i.e., CONSORT for RCTs or STROBE for non-randomized studies at equator-network.org)[3,4,5]

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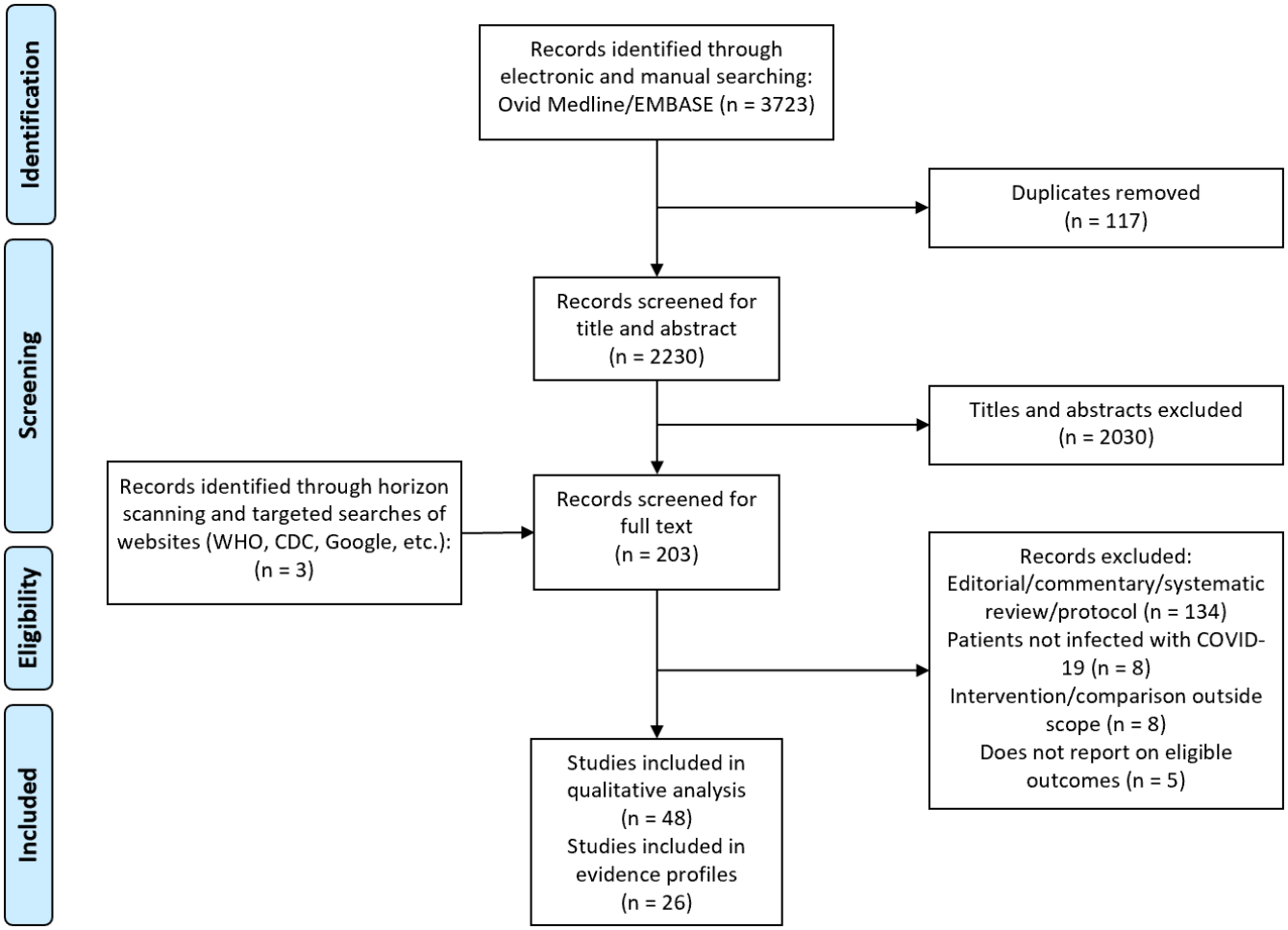
2. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med **2020**.
3. Equator Network. Reporting guidelines for main study types. Available at: http://www.equator-network.org.
4. Hopewell S, Collins GS, Boutron I, et al. Impact of peer review on reports of randomised trials published in open peer review journals: retrospective before and after study. BMJ **2014**; 349: g4145.
5. Keserlioglu K, Kilicoglu H, Ter Riet G. Impact of peer review on discussion of study limitations and strength of claims in randomized trial reports: a before and after study. Res Integr Peer Rev **2019**; 4: 19.

Figure s1. PRISMA Flow Diagram



Hydroxychloroquine/Chloroquine; Hydroxychloroquine/Chloroquine plus Azithromycin

Table s3a. Should hospitalized patients with severe COVID-19 receive treatment with hydroxychloroquine vs. no hydroxychloroquine?

Study/ Year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Cavalcanti /2020	Brazil/ 55 hospitals	RCT	667 (217/221/227)	41.7	Mean: 50.3 (14.6)	Hospitalized with suspected or confirmed Covid-19 with 14 or fewer days since symptom onset	HCQ + AZ: HCQ 400 mg twice daily + AZ 500 mg once daily x 7 days	(1) HCQ (2) SoC	Glucocorticoids, other immunomodulators, antibiotic agents, antiviral agents	Mortality at day 15 Not hospitalized with no limitations on activities Duration of hospital stay (days) Hospitalized and receiving mechanical ventilation	Coalition Covid-19 Brazil EMS Pharma

										Adverse events	
Chen J/2020	China/ Shanghai Public Health Clinical Center	RCT	30 (15/15)	N/A	N/A	N/A	HCQ 400mg daily x 5 days	(1) SoC	Both groups received conventional treatment: bed rest, oxygen inhalation, symptomatic supportive treatment, use of antiviral drugs if necessary and if necessary antibacterial drugs All patients received nebulized alpha-interferon	Viral clearance on day 7 Duration from hospitalization to virus nucleic acid negative conservation Body temperature normalization days after hospitalization Adverse Events	N/A

Chen Z/2020	China/ Renmin Hospital of Wuhan University	RCT	62 (31/31)	53.20	Mean: 44.7 (15.3)	Diagnosis based on China National Health Commission criteria: RT-PCR positive for SARS-CoV-2; chest CT pneumonia, SaO_2/SPO_2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg under hospital room air conditions	HCQ 400mg daily x 5 days	(1) SoC	Oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids	Progressed to severe illness Fever remission time (days) Cough remission time (days) Adverse Events	Epidemiological Study of COVID-19 Pneumonia to Science and Technology Department of Hubei Province
Horby/ 2020	UK/ 176 hospitals	RCT	4,716 (1561/3155)	38.0	Mean: 65.3 (15.3)	Hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection and	HCQ loading dose of 4 tablets (800 mg) at zero and 6 hours, followed by 2 tablets (400 mg) starting at 12 hours after the	(1) SoC	N/A	All-cause mortality at day 28 Discharged by day 28	UK Research and Innovation/ National Institute for Health Research (NIHR)

						no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	initial dose and then every 12 hours for the next 9 days or until discharge (whichever occurred earlier)			Invasive mechanical ventilation Time until discharge alive (days) Adverse events	NIHR Oxford Biomedical Research Centre Wellcome The Bill and Melinda Gates Foundation Department for International Development Health Data Research UK Medical Research Council Population Health Research Unit NIHR Health Protection Unit in

											Emerging and Zoonotic Infections NIHR Clinical Trials Unit Support Funding
Pan/2020	30 countries/ 405 hospitals	RCT	2771 (1399/1372)	38.0	N/A	≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's	Lopinavir/ritonavir 400/200mg orally every 12 hrs x 14 days	(1) SoC	N/A	Mortality Ventilation	N/A

						view, with no contra-indication to any study drug					
Self/2020	USA/ 34 hospitals	RCT	479 (242/237)	44.3	Median: 57 (44-68)	Hospitalized patients with ≥ 1 symptom of respiratory illness (cough, fever, sore throat, or shortness of breath, defined as respiratory rate ≥ 22/min, SpO_2 >92% on RA, or new supplemental O_2 requirement) for less than 10 days	HCQ 400mg twice daily for 1 day, followed by 200mg twice daily for 4 days	(1) SoC	Allowed at discretion of provider, included: azithromycin, remdesivir, corticosteroids	Mortality at day 14 and 28 Clinical status at day 14 Time to recovery Adverse events	National Heart, Lung, and Blood Institute National Center for Advancing Translational Sciences Harvard Catalyst/ Harvard Clinical and Translational Science Center Sandoz (provided study drug and placebo)

Tang/2020	China/ 16 government-designated COVID-19 treatment centers	RCT	150 (75/75)	45.3	Mean: 46.1 (14.7)	Hospitalized patients Disease severity determined by chest CT examination	HCQ loading dose of 200mg daily x 3 days followed by maintained dose of 800mg daily for remaining days (2 weeks for mild/moderate, 3 weeks for severe patients)	(1) SoC	SoC aligning indications from the updating National clinical practice guidelines for COVID-19 in China	Mortality Negative conversion rate of SARS-CoV-2 Time to negative conversion (days) Time to alleviation of clinical symptoms (days) Adverse events	Emergent Projects of National Science and Technology National Natural Science Foundation of China National Jet Research and Development Program of China Shanghai Municipal Key Clinical Specialty Shanghai Key Discipline for Respiratory Diseases

											National Major Scientific and Technological Special Project for Significant New Drugs Development Key Projects in the National Science and Technology Pillar Program
Ulrich/ 2020	USA/ NYU Langone Health (3 hospitals), NYC Health and Hospitals	RCT	128 (67/61)	40.6	Mean: 66.2 (16.2)	Hospitalized patients with ≥ 1 symptom associated with COVID-19 infection, but not in the ICU, on	HCQ 400mg twice daily for 1 day, followed by 200mg twice daily for 4 days	(1) SoC	Concomitant antibacterial therapy and off-label agents with SARS-CoV-2 were allowed at discretion of	Mortality at day 30 Progression to severe disease Change in clinical status	New York University Grossman School of Medicine NYU CTSA grant from National

	Bellevue Hospital Center, State University of New York Downstate Medical Center					mechanical ventilation, ECMO, or receiving vasopressors			providers (included zinc, corticosteroids, tocilizumab, lopinavir/ritonavir, remdesivir), as well as co-enrollment in other COVID-19 therapeutic trials (included convalescent plasma, clazakizumab, remdesivir)	Length of hospitalization Viral clearance Adverse events	Center for Advancing Translational Sciences
Arshad /2020	USA/ Henry Ford Health System (6 hospitals)	Retrospective cohort	2,541 (783/409/1202/147)	48.9	Mean: 63.7 (16.5) Median: 64 (53-76)	Patients with a COVID-related admission in health system; COVID-related admission defined as	HCQ + AZ: HCQ 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2–5 + AZ 500 mg once daily on day 1	(1) SoC (2) HCQ (3) AZ	Adjunctive immunomodulatory therapy with corticosteroids and tocilizumab	In-hospital mortality Mechanical ventilation Length of hospital stay Total ICU days	N/A

						hospitalization during which the patient had a positive SARS-CoV-2 test	followed by 250 mg once daily for the next 4 days				
Geleris/ 2020	USA/ New York–Presbyterian Hospital (NYP)–Columbia University Irving Medical Center (CUIMC)	Retrospective cohort	1446 (811/635) *1376 patients included in analysis*	43.2	N/A	Moderate-to-severe respiratory illness, defined as resting SpO_2 of less than 94% while breathing ambient air. Diagnosis confirmed RT-PCR[Error! Bookmark not defined.] positive test for SARS-CoV-2	HCQ 600mg twice on day 1 and 400mg once daily from days 2-5	(1) SoC	AZ at dose of 500mg day 1 and 250mg for 4 more days was additional suggested therapeutic option	Intubation or Death Respiratory Failure Development (reported as total not based on treatment group) Respiratory failure reported as hazards ratio	Supported in part by grants from the National Institutes of Health

Ip/ 2020	USA/ 13 hospitals in Hackensack Meridian Health network	Retrospective cohort	2512 (1914/598)	37.6	Median: 64 (52-76)	Hospitalized with positive SARS-CoV-2 diagnosis by RT-PCR, did not die during first day of hospitalization, and Were not discharged to home within 24h	HCQ (doses not specified)	(1) HCQ + AZ (2) SoC	N/A	Unadjusted 30-day mortality Association between survival and treatment (hazards ratio) Adverse events	N/A
Magan oli/ 2020	USA/ All Veterans Health Administration medical centres	Retrospective Cohort	807 (198/215/395) Subcohort of 425 (114/148/163) had dispositions of death or discharge by end of	N/A	N/A	Hospitalization with positive SARS-CoV-2 laboratory test	HCQ	(1) HCQ + AZ (2) SoC	ACE inhibitors, angiotensin II receptor blockers, mechanical ventilation	Mortality Discharged Risk of ventilation (adjusted hazards ratio) Length of hospital stay (days)	University of Virginia Strategic Investment Fund

			study period								
Mahévas/ 2020	France/ 4 tertiary care centers providing care to patients with COVID-19	Retrospective cohort	181 (84/181)	29.9	Median: 60 (52-68)	Adults with SARS-CoV-2 pneumonia and requiring oxygen ≥ 2 L/min (required oxygen by mask or nasal prongs)	HCQ 600mg daily; first dose provided within 48h of admission	(1) SoC (HCQ not given within 48h of admission)	17 received concomitant AZ and 64 received concomitant amoxicillin and clavulanic acid in treatment group	Mortality at day 7 Death or transfer to ICU Occurrence of ARDS Adverse Events	No financial support
Rosenberg/2020	USA/25 hospitals	Retrospective cohort	1438 (735/271/211/221)	40.3	N/A	Information collected on COVID-19 diagnosis, patient demographics, pre-existing medical conditions, initial vital signs and laboratory test results within 24	HCQ Investigators recorded the first three prescriptions for each medication. The majority of patients received HCQ dose of 200 mg, 400 mg, or 600	(1) SoC (2) HCQ + AZ (3) AZ The majority of patients received AZ dose of	Patients receiving neither drug received few other abstracted medications; the most common were aspirin (19.8%) and lisinopril (6.7%)	Mortality Abnormal ECG findings Risk of cardiac arrest Adverse events	N/A

						hours of admission, and chest imaging findings	mg once or twice a day	200 mg, 250 mg, 400 mg, or 500 mg once, once a day or twice a day			

Yu/ 2020	China/Tongji Hospital	Retrospective cohort	550 (48/502)	37.5	Median: 68 (59-77)	Critically ill patients had to meet one of the following criteria: (i) patients had respiratory failure and needed mechanical ventilation; (ii) patients had septic shock during hospitalization; (iii) patients with other organ failures that required monitoring and treatment by ICU	HCQ 200 mg tablet twice daily x 7 to 10 days	(1) SoC	antiviral drugs (Lopinavir and Ritonavir, Entecavir hydrate, or Ribavirin), intravenous immunoglobulin, antibiotics, immunoenhancer, oxygen therapy	Mortality Average length of hospital stay (days) Hospital stay time before death (days) IL-6 levels in plasma after treatment	Ministry of Science and Technology of China National Natural Science Foundation of China Emergency Project Fund of Chinese Academy of Sciences Chinese Academy of Engineering Ma Yun Foundation

SpO_2: oxygen saturation; **CQ**: chloroquine; **IV**: intravenous; **AZ**: azithromycin; **HCQ**: hydroxychloroquine; **SoC**: standard of care; **RT-PCR**: reverse transcription polymerase chain reaction; **PaO_2/FIO_2**: ratio of arterial oxygen partial pressure to fractional inspired oxygen; **CT**: computerized tomography; **ECG**: electrocardiogram; **ICU**: intensive care unit; **IL-6**: interleukin 6

Table s3b. Should hospitalized patients with severe COVID-19 receive treatment with hydroxychloroquine/azithromycin vs. no hydroxychloroquine/azithromycin?

Study / year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Cavalcanti /2020	Brazil/ 55 hospitals	RCT	667 (217/221/227)	41.7	Mean: 50.3 (14.6)	Hospitalized with suspected or confirmed Covid-19 with 14 or fewer days since symptom onset	HCQ + AZ: HCQ 400 mg twice daily + AZ 500 mg once daily x 7 days	(1) HCQ (2) SoC	Glucocorticoids, other immunomodulators, antibiotic agents, antiviral agents	Mortality at day 15 Not hospitalized with no limitations on activities Duration of hospital stay (days) Hospitalized and receiving mechanical ventilation Adverse events	Coalition Covid-19 Brazil EMS Pharma

Arshad /2020	USA/ Henry Ford Health System (6 hospitals)	Retrospective cohort	2,541 (783/409/1202/147)	48.9	Mean: 63.7 (16.5) Median: 64 (53-76)	Patients with a COVID-related admission in health system; COVID-related admission defined as hospitalization during which the patient had a positive SARS-CoV-2 test	HCQ + AZ: HCQ 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2–5 + AZ 500 mg once daily on day 1 followed by 250 mg once daily for the next 4 days	(1) SoC (2) HCQ (3) AZ	Adjunctive immunomodulatory therapy with corticosteroids and tocilizumab	In-hospital mortality Mechanical ventilation Length of hospital stay Total ICU days	N/A
Cipriani /2020	Italy/ Azienda Ospedaliera - Università di Padov	Retrospective case-control	22	18.0	Median: 64 (56-70)	Non-critically ill patients affected by COVID-19; SARS-Cov-2 infection was diagnosed according to the WHO	HCQ + AZ: HCQ 200 mg twice daily + AZ 500 mg once daily	N/A	N/A	Mortality Arrythmias Heart Rate QT interval	N/A

						guidance, after positive results of RT-PCR assay of nasal and pharyngeal swabs					
Chorin /2020	USA/ NYU Langone medical center	Retrospective cohort	84 (84/84)	26.0	Mean: 63 (15)	hospitalized with a positive SARS-CoV-2 diagnosis	HCQ + AZ	N/A	N/A	Mortality New severe QTc prolongation of > 500ms Average time of ECG follow-up Maximal value of QTc interval prolongation (ms)	No financial disclosures

Gautret/ 2020	France/ University Hospital Institute Méditerranée Infection	Retrospective cohort	80 (80/80)	46.2	Median: 52.5 (42-62)	PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample and CT chest for pneumonia compatibility	HCQ + AZ given to all participants: HCQ 200mg three times a day x 10 days + AZ 500mg on day 1 and 250mg daily days 2-5	N/A	Broad spectrum antibiotic (ceftriaxone) and oxygen added as needed	Mortality Hospital Discharge Time from treatment to discharge (days) Length of stay in infectious diseases ward (days) Adverse Events	French Government under the Investments for the Future program managed by the Agence Nationale de la Recherche
Ip/ 2020	USA/ 13 hospitals in Hackensack Meridian Health network	Retrospective cohort	2512 (1914/598)	37.6	Median: 64 (52-76)	Hospitalized with positive SARS-CoV-2 diagnosis by RT-PCR, did not die during first day of hospitalization, and Were not discharged to	HCQ + AZ (doses not specified)	(1) HCQ (2) SoC	N/A	Unadjusted 30-day mortality Association between survival and treatment (hazards ratio)	N/A

						home within 24h				Adverse events	
Maganoli/ 2020	USA/ All Veterans Health Administration medical centers	Retrospective Cohort	807 (198/215/395) Subcohort of 425 (114/148/163) had dispositions of death or discharge by end of study period	N/A	N/A	Hospitalization with positive SARS-CoV-2 laboratory test	HCQ	(1) HCQ + AZ (2) SoC	ACE inhibitors, angiotensin II receptor blockers, mechanical ventilation	Mortality Discharged Risk of ventilation (adjusted hazards ratio) Length of hospital stay (days)	University of Virginia Strategic Investment Fund
Molina/ 2020	France/ Saint-Louis Hospital *assumed based	Prospective cohort	11	57.1	Mean: 58.7 (SD not reported)	Patients hospitalized for COVID-19	HCQ + AZ: -HCQ 600mg daily x 10 days -AZ 500mg day 1 then 250mg daily on days 2-5	N/A	10/11 had fever and received nasal oxygen therapy, 8 had comorbidities that they were likely	Mortality Positive for SARS-CoV2 RNA 5/6 days after treatment initiation	N/A

	on author info at bottom*								receiving treatment for as well	Adverse Events	
Rosenberg/2020	USA/ 25 hospitals	Retrospective cohort	1438 (735/271/211/221)	40.3	N/A	Information collected on COVID-19 diagnosis, patient demographics, pre-existing medical conditions, initial vital signs and laboratory test results within 24 hours of admission, and chest imaging findings	HCQ + AZ *patients were given different dosages (details in supplemental table)	(1) HCQ (2) AZ (3) SoC	Patients receiving neither drug received few other abstracted medications; the most common were aspirin (19.8%) and lisinopril (6.7%)	Mortality Abnormal ECG findings Risk of cardiac arrest Adverse events	N/A

RT-PCR: reverse transcriptase polymerase chain reaction; **HCQ**: hydroxychloroquine; **AZ**: azithromycin; **QTc**: corrected QT interval; **CT**: computerized tomography; **PCR**: polymerase chain reaction; **WHO**: World Health Organization; **CQ**: chloroquine; **SoC**: standard of care; **ECG**: electrocardiogram

Figure s2a. Forest plot for the outcome of mortality point estimate demonstrating increased risk with hydroxychloroquine treatment (RR: 1.08; 95% CI: 0.99, 1.19)

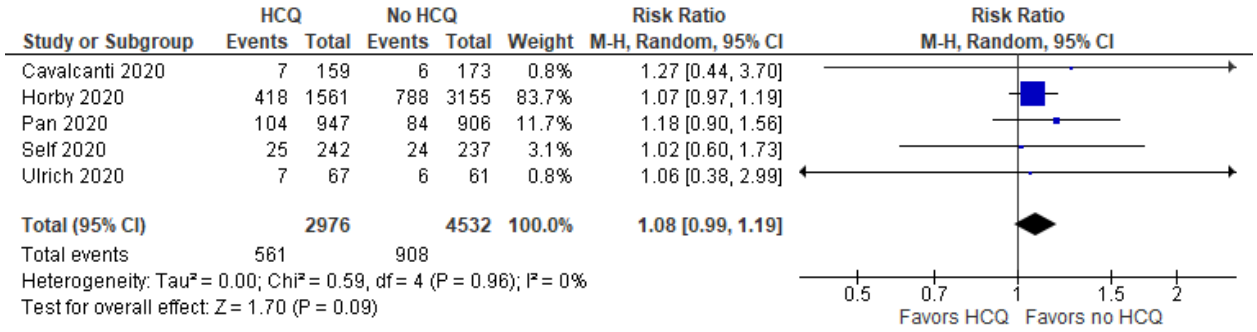


Figure s2b. Forest plot for the outcome of progression to mechanical ventilation demonstrating increased risk with HCQ treatment (RR: 1.10; 95% CI: 0.92, 1.31)

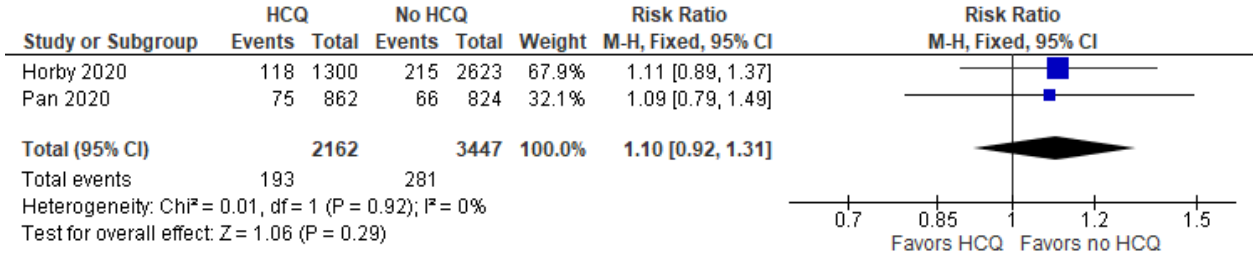


Figure s2c. Forest plot for the outcome of adverse events demonstrating increased risk with hydroxychloroquine treatment (RR: 2.36; 95% CI: 1.49, 3.75)

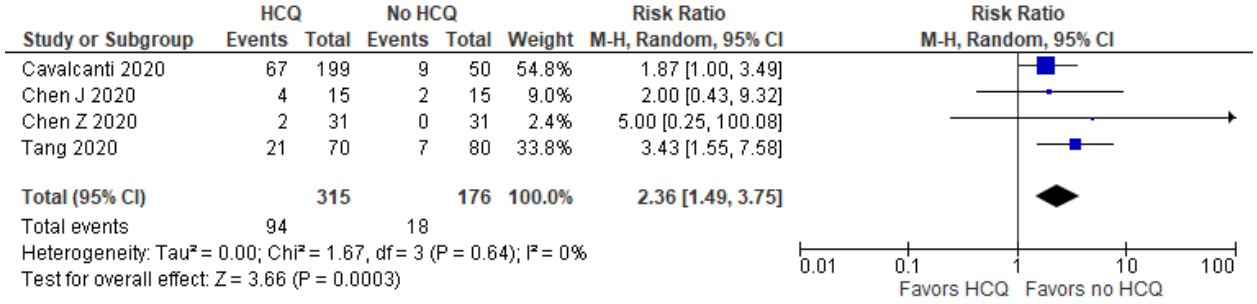


Figure s2d. Forest plot for the outcome of QT prolongation demonstrates increased risk with hydroxychloroquine treatment (RR: 2.89; 95% CI: 1.62, 5.16)

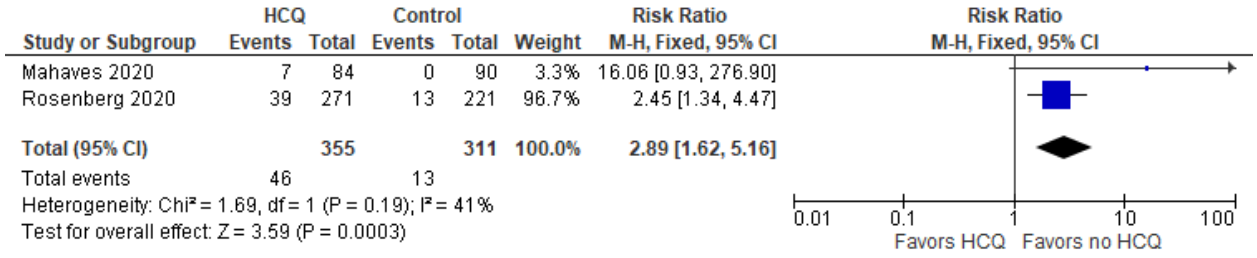


Table s4a. Risk of bias for randomized controlled studies (hydroxychloroquine ± azithromycin vs. no hydroxychloroquine ± azithromycin)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cavalcanti 2020 [1]							
Chen J 2020 [2]							
Chen Z 2020 [3]							
Horby 2020 [4]							
Pan 2020 [5]							
Self 2020 [6]							
Tang 2020 [7]							
Ulrich 2020 [8]							

Low	High	Unclear

References

1. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med **2020**.
2. Chen J, LIU D, LIU L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Journal of Zhejiang University (Medical Sciences) **2020**; 49(1): 0-.
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4. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv **2020**.
5. Pan H, Peto R, Karim Q, et al. Repurposed antiviral drugs for COVID-19-interim WHO SOLIDARITY trial results. MedRxiv **2020**
6. Self WH, Semler MW, Leither L, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: A randomized clinical trial. JAMA **2020**
7. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. bmj **2020**; 369.
8. Ulrich RJ, Troxel AB, Carmody E, et al. Treating COVID-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind Randomized Controlled Trial in Hospitalized Patients. Open Forum Infect Dis **2020**

Table s4b. Risk of bias for non-randomized studies (hydroxychloroquine ± azithromycin vs. no hydroxychloroquine ± azithromycin)

Study	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Arshad 2020 [1]							
Geleris 2020 [2]							
Ip 2020 [3]							
Maganoli 2020 [4]							
Mahévas 2020 [5]							
Rosenberg 2020 [6]							
Yu 2020 [7]							

Low	Moderate	Serious	Critical

References

1. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis **2020**; 97: 396-403.
2. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med **2020**.
3. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients-An Observational Study. medRxiv **2020**.
4. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med **2020**.
5. Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. MedRxiv **2020**.

6. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. Jama **2020**.
7. Yu B, Li C, Chen P, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. Sci China Life Sci **2020**.

Hydroxychloroquine for prophylaxis

Table s5. Should persons exposed to COVID-19 receive post-exposure hydroxychloroquine?

Study/year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Barnabas/ 2021	US/ Nationwide outreach from 7 institutional centers	RCT	689 (353/336)	60	Median: 39 (24)	Asymptomatic patients with negative SARS-CoV-2 test at baseline, who had close contact with person with recent COVID-19 infection within 96 hours	Hydroxychloroquine 400 mg daily for 3 days, followed by 200 mg daily for 11 days	Placebo (ascorbic acid 500 mg daily for 3 days, followed by 250 mg daily for 11 days	None	Symptomatic COVID-19 disease through day 14 PCR-confirmed SARS-CoV-2 infection through day 14 Safety	Bill & Melinda Gates Foundation

Boulware / 2020	US (Nationwide) Canada (Quebec, Manitoba, Alberta)	RCT	821 (414/407)	51.6	Median: 40 (17)	Asymptomatic patients with negative SARS-CoV-2 test at baseline, who had close contact with person with confirmed COVID-19 infection within 4 days	Hydroxychloroquine 800 mg once, followed by 600 mg 6-8 hours later, followed by 600 mg daily for 4 days	Placebo	None	Mortality Hospitalizations Symptomatic COVID-19 disease through day 14 PCR-confirmed SARS-CoV-2 infection through day 14 Safety	David Baszucki and Jan Ellison Baszucki Minnesota Chinese Chamber of Commerce University of Minnesota Clinical Practice Assessment Unit of the McGill University Health Centre McGill Interdisciplinary Initiative in Infection and Immunity Emergency Covid-19 Research

											Funding Program Manitoba Medical Service Foundation Research Manitoba Northern Alberta Clinical Trials Research Centre Covid-19 Clinical Research Grant
Mitjà/ 2020	Spain (Catalonia)	RCT	2313 (1115/1198)	73	Mean: 48.6 (19)	Asymptomatic patients with close contact with person with confirmed COVID-19 infection	Hydroxychloroquine 800 mg on day 1, followed by 400 mg daily for 6 days	None	None	PCR-confirmed, symptomatic COVID-19 infection within 14 days Incidence of COVID-19 infection (PCR	YoMeCorono crowdfunding campaign Generalitat de Catalunya Zurich Seguros

						within 7 days				detection or symptoms compatible with COVID-19) Safety	Synlab Diagnósticos Laboratorios Rubió Laboratorios Gebro Pharma

Figure s3a. Forest plot for the outcome of SARS-CoV-2 infection at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

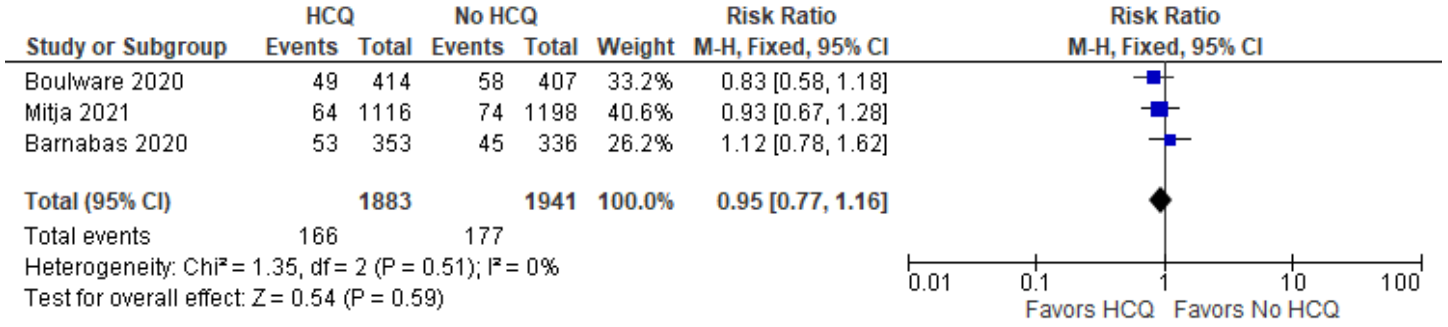

Figure s3b. Forest plot for the outcome of hospitalization at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

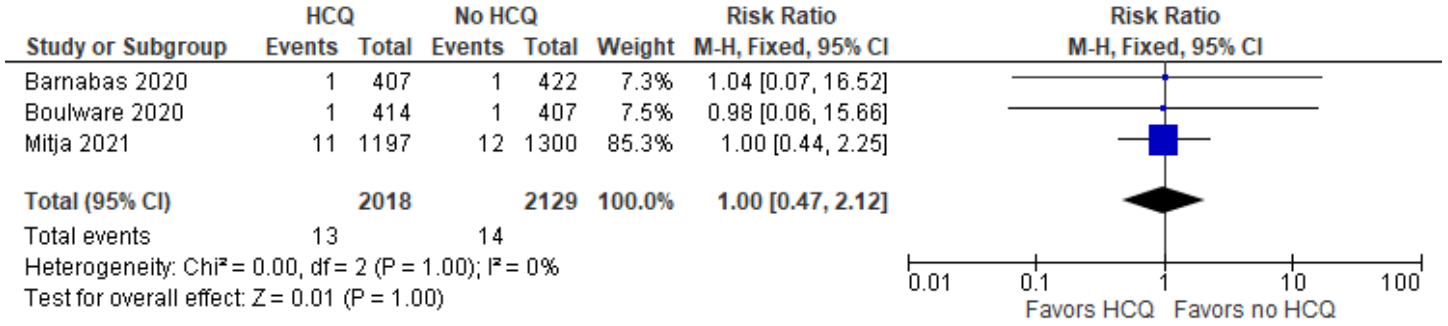

Figure s3c. Forest plot for the outcome of mortality at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

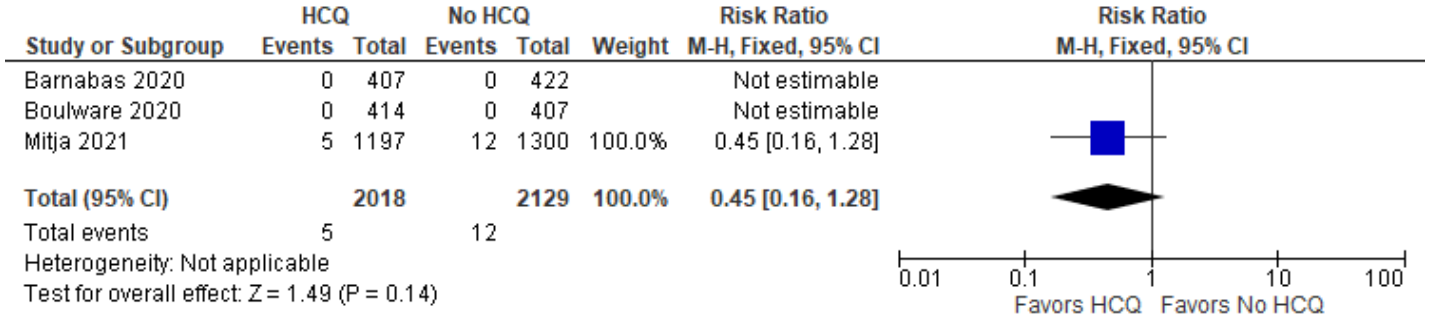

Figure s3d. Forest plot for the outcome of serious adverse events at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

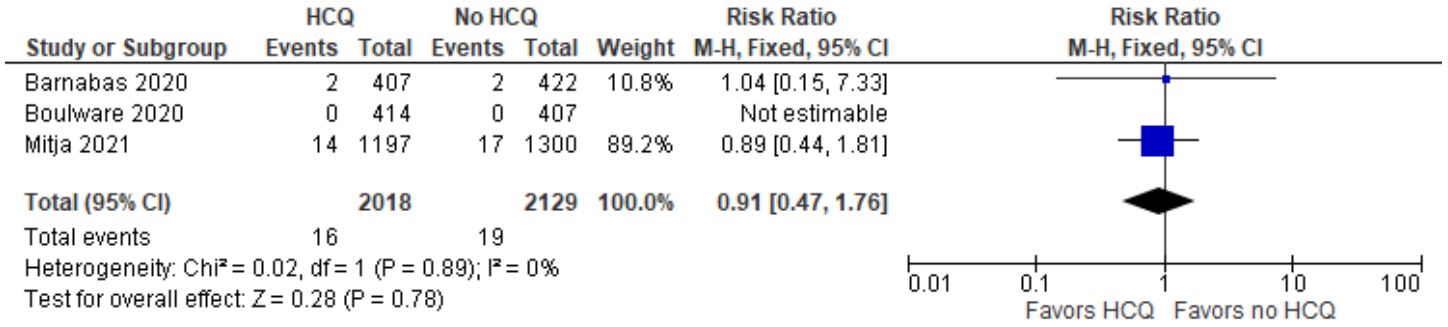

Table s6. Risk of bias for randomized control studies (hydroxychloroquine as post-exposure prophylaxis vs. no hydroxychloroquine for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Barnabas 2021 [1]							
Boulware 2020 [2]							
Mitjà 2020 [3]							

Low	High	Unclear

References

1. Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as Postexposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection : A Randomized Trial. Ann Intern Med **2021**; 174(3): 344-52.
2. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med **2020**; 383(6): 517-25.
3. Mitja O, Corbacho-Monne M, Ubals M, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. N Engl J Med **2021**; 384(5): 417-27.

Lopinavir/Ritonavir

Table s7. Should hospitalized patients with severe COVID-19 receive treatment with lopinavir/ritonavir vs. no lopinavir/ritonavir?

Study/ year	Country/Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Cao/2020	China/ Jin Yin-Tan Hospital	RCT	199 (99/100)	39.7	Median: 58 (49-68)	Severe COVID: had pneumonia confirmed by chest imaging, and had oxygen saturation of 94% or less while breathing ambient air or a ratio of partial pressure of oxygen to the fraction of inspired	Lopinavir/ritonavir 400/100mg orally twice daily x 14 days	(1) SoC	N/A	Mortality at day 28 Clinical improvement at days 7, 14, 28 Adverse events	Major Projects of National Science and Technology on New Drug Creation and Development The Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 National Science

						oxygen at or below 300 mg Hg					Grant for Distinguished Young Scholars
Horby/ 2020 (RECOVERY)	United Kingdom/ 176 hospitals	RCT	5040 (1616/3424)	N/A	N/A	Clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial	Lopinavir/ritonavir 400/100mg orally every 12 hrs x 10 days or until discharge	(1) SoC	N/A	Mortality at day 28 Discharged from hospital within 28 days Invasive mechanical ventilation Adverse events	UK Research and Innovation and NIHR NIHR Oxford Biomedical Research Centre Wellcome The Bill & Melinda Gates Foundation UK Department for International Development Health Data Research UK

											Medical Research Council (MRC) Population Health Research Unit NIHR Health Protection Unit in Emerging and Zoonotic Infections NIHR Clinical Trials Unit Support Funding
Pan/2020	30 countries/ 405 hospitals	RCT	2771 (1399/1372)	38.0	N/A	≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug,	Lopinavir/ritonavir 400/200mg orally every 12 hrs x 14 days	(1) SoC	N/A	Mortality Ventilation	N/A

						without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug					

SoC: standard of care

Figure s4a. Forest plot for the outcome of mortality at 28 days for lopinavir-ritonavir vs. no lopinavir-ritonavir in hospitalized patients with severe COVID-19

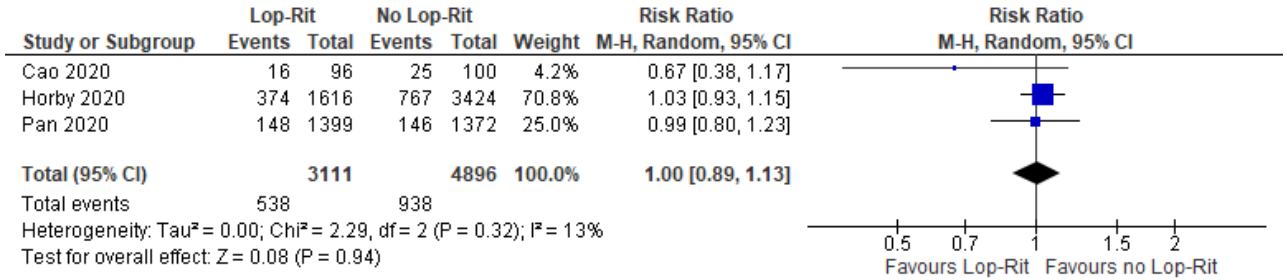

Figure s4b. Forest plot for the outcome of invasive mechanical ventilation for lopinavir-ritonavir vs. no lopinavir-ritonavir in hospitalized patients with severe COVID-19

Table s8. Risk of bias for randomized controlled studies (lopinavir-ritonavir vs. no lopinavir-ritonavir)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cao 2020 [1]							
Pan 2020 (SOLIDARITY) 2							
Horby 2020 (RECOVERY Collaborative Group) [3]							

Low	High	Unclear

References

1. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med **2020**.
2. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results. MedRxiv **2020.** Available at: https://doi.org/10.1101/2020.10.15.20209817 [Preprint 15 October 2020].
3. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet **2020**; 396(10259): 1345-52.

Glucocorticoids

Table s9. Should hospitalized patients with severe COVID-19 receive treatment with corticosteroids vs. no corticosteroids?

Study / year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Horby /2020	UK/ 176 NHS hospital organizations	RCT	6425 (2104/4321)	36.4	Mean (SD): 66.9 (15.4) in intervention/ 65.8 (15.8) in comparator)	Hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate Treatment (at baseline): 24% did not receive any O_2, 61% received O_2 only and 15 % received invasive mechanical ventilation.	Dexamethasone 6 mg once daily for up to 10 days (median treatment duration was 6 days) (median time to steroid treatment from symptom onset of 8 (5-13) days)	(1) SoC	AZ (24%) HCQ, lopinavir-ritonavir, interleukin-6 antagonists (in very few patients)	Mortality (Day 28) Hospital discharge within day 28 Risk of invasive mechanical ventilation or death Median duration of hospitalization (days) Receipt of renal hemodialysis or hemofiltration Major cardiac arrhythmia	Medical Research Council and National Institute for Health Research

						Comparator (at baseline): 24% did not receive any O_2, 60% received O_2 only and 16% received invasive mechanical ventilation				Receipt and duration of ventilation	
Cruz/ 2020	Spain/ Hospital Puerta de Hierro-Majadahonda	Retrospective cohort	463 (396/67)	31.5	Mean (SD): 65.4 (12.9) in intervention/ 68.1 (15.7) in comparator	Adult patients diagnosed with COVID-19 pneumonia according to WHO interim guidance, and complicated with ARDS and/or an hyperinflammatory syndrome	IV methylprednisolone or equivalent 1 mg/kg/day (78.3%), or IV methylprednisolone pulses (21.7%, for a median of 3 pulses) (median time to steroid treatment from symptom onset of 10 (8-13) days)	(1) SoC	HCQ, AZ, Lopinavir/Ritonavir, Interferon, TCZ, Anakinra, ritonavir-boosted darunavir/doxycycline/clarithromycin and other antibiotics	Mortality	N/A

Fadel/ 2020	USA/five hospitals in southeast and south-central Michigan	Quasi-experimental	213 (132/81)	48.8	Median (IQR): 62 (51-62)	18 years of age or older, had confirmed COVID-19 infection, with radiographic evidence of bilateral pulmonary infiltrates, and required oxygen by nasal cannula, HFNC or mechanical ventilation Treatment (at baseline): 9.1% required mechanical ventilation Comparator (at baseline): 12.3% required mechanical ventilation	Methylprednisolone 0.5 to 1mg/kg twice daily divided into 2 doses 3 days for patients with moderate COVID 3 to 7 days for ICU patients (median time to steroid treatment from symptom onset of 8 days)	(1) SoC: with or without a combination of lopinavir/ritonavir and ribavirin or HCQ	HCQ 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2-5 SoC: supplemental oxygen, HFNC, invasive ventilation, antibiotic agents, antiviral agents, vasopressor support, and renal-replacement therapy	Mortality Respiratory failure requiring mechanical ventilation ARDS Length of hospital stay (days) Duration of mechanical ventilation (days) Shock AKI Adverse Events	N/A

Corral-Gudino/ 2020	Spain/ 5 hospitals	RCT with additional patients preferentially assigned to the treatment arm by investigators	85 (56/29)	42.4	Mean (SD): 69(12)	Hospitalized patients with a laboratory confirmed diagnosis of SARS-CoV2 infection; additional criteria: symptom duration of at least 7 days, radiological evidence of lung disease in chest X-ray or CT scan, moderate-to-severe disease with abnormal gas exchange (PaO2/FiO2 <300 or SaO2/FiO2 < 400), and laboratory parameters suggesting a hyperinflammatory state (serum CRP >15 mg/dl, D-dimer > 800 mg/dl, ferritin > 1000 mg/dl or IL-6 levels > 20 pg/ml)	Methylprednisolone 40 mg intravenously every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (median time to steroid treatment from symptom onset not reported)	(1) SoC	Acetaminophen, oxygen therapy, thrombosis prophylaxis with low molecular weight heparin, and antibiotics for co-infection AZ, HCQ, lopinavir plus ritonavir	Composite endpoint (in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation) Biomarkers levels Adverse events	N/A

Lu/ 2020	China/ Tongji Hospital	Retrospective cohort	244 (151/93)	48.0	Median (IQR): 62 (50-71)	Critically ill patients: those who were admitted to intensive care wards and required mechanical ventilation (either invasive or non-invasive), or with ARDS (PaO_2/FIO_2 ≤300mmHg; when PaO_2 is not available, SpO_2/FiO_2 ≤315 suggests ARDS), or sepsis with acute organ dysfunction Treatment (at baseline): 52% received mechanical ventilation Comparator (at baseline): 4% received mechanical ventilation	Steroids: hydrocortisone-equivalent dosage range: 100-800mg/day (median (IQR) administration duration of 8 days (4-12)) (median time to steroid treatment from symptom onset not reported)	(1) SoC	Antiviral therapy (oseltamivir, arbidol, lopinavir/ritonavir, ganciclovir, interferon-a), antibacterials, gamma globulin, mechanical ventilation, muscle relaxant, HFNC	Mortality at day 28 Overall cohort mortality (odds ratio) Adverse events	Supported by the National Key R&D Program of China, the National Natural Science Foundation of China, the "Double First-Class" University Project, the China Postdoctoral Science Foundation, the Science Foundation of Jiangsu Commission of Health, and the Emergency Project for the Prevention and Control of the Novel Coronavirus Outbreak in Suzhou.

Salton /2020	Italy/ 14 Respiratory High Dependency Units	Observational longitudinal	173 (83/90)	30.6	Mean (SD): 64.4 (10.7) in intervention / 67.1 (8.2) in comparator	Hospitalized patients with SARS-CoV-2 positive (on swab or bronchial wash), PaO2:FiO2 <250 mmHg, bilateral infiltrates, CRP >100 mg/L, and/or diagnosis of ARDS	Methylprednisolone loading dose of 80 mg/kg iv at study entry, followed by an infusion of 80 mg/day in 240 mL normal saline at 10 mL/h until achieving either a PaO2:FiO2 > 350 mmHg or a CRP < 20 mg/L. After which, oral administration at 16 mg or 20 mg iv twice daily until CRP reached < 20% of normal range or a PaO2:FiO2 > 400 (alternative	(1) SoC	N/A Use of tocilizumab or other experimental treatment was considered an exclusion criterion	Mortality Transfer to ICU Duration of invasive mechanical ventilation (days) Risk of composite primary endpoint Adverse events	Supported with the resources and use of facilities at the University Hospital of Trieste and Memphis VA Medical Center

							SatHbO2 ≥ 95% on room air) (median time to steroid treatment from symptom onset not reported)				
Wang /2020	China/ Union Hospital of Huazhong University of Science and Technology	Retrospective cohort	46 (26/20)	43.0	Median: 54 (48-64)	Severe COVID: resp rate≥ 30, in resting rate SpO_2 ≤93%, PaO_2/FIO_2 ≤ 300mmHg, other conditions such as 60+ with complication of hypertension, diabetes, coronary disease, cancer, pulmonary heart disease, structural lung disease and immunosuppressed	Methylprednisolone1-2mg/kg/day once a day x 5-7 days (median time to steroid treatment from symptom onset not reported)	(1) SoC	Oxygen therapy, antiviral therapy (a-interferon, lopinavir/ritonavir), immunoenhancement therapy (thymosin), prevention of bacterial infection, relieving cough eliminating	Mortality Hospital Discharge Number of days for no fever Use of supplemental oxygen therapy	Natural Science Foundation of China

									phlegm and nutritional support		
Yuan/ 2020	China / Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology	Retrospective Cohort	132 (74/58)	57.6	Median (IQR): 43.7 (3.0-56.3 in intervention / 52.0 (31.8-67.0) in comparator	diagnosed as non-severe COVID-19 pneumonia and discharged with recovered symptoms or developed to severe cases in the hospitalization were included	Matched corticosteroid therapy maximum dose: 50.6 (40.0-50.0) and median duration of therapy: 10.7 (8-12.3) (median time (IQR) to steroid treatment from symptom onset of 8.3 (5.0-10.0) days)	(1) SoC	Ribavirin, lopinavir/ritonavir and arbidol	Progressing to Severe Cases Secondary Infection Time for Fever Hospital Stay Duration of Viral Shedding After Illness Onset	N/A

CRP: C-reactive protein; NHS: National Health Service; **AZ**: azithromycin; **HCQ**: hydroxychloroquine; **RT-PCR**: reverse transcription polymerase chain reaction; **SpO_2**: oxygen saturation; **TCZ**: tocilizumab; **HFNC**: high-flow nasal cannula; **ICU**: intensive care unit; **SoC**: standard of care; **WHO**: World Health Organization; **ARDS**: acute respiratory distress syndrome; **NCP**: novel coronavirus pneumonia

Table s10. Risk of bias for randomized controlled studies (glucocorticoids vs. no glucocorticoids)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Horby 2020 [1]							

Low	High	Unclear

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Tocilizumab

Table s11. Should hospitalized patients with severe COVID-19 receive treatment with tocilizumab vs. no tocilizumab?

Study/year	Country/Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Gordon / 2021	113 sites open to randomization to sarilumab and/or tocilizumab domain: UK (98) Netherlands (7) Australia (3) New Zealand (2) Ireland (2)	RCT	353 tocilizumab/ 48 sarilumab/ 402 control	27.4	Mean age: Tocilizumab: 61.5 (12.5) Sarilumab: 63.4 (13.4) Control: 61.1 (12.8)	Critically ill patients admitted to an intensive care unit and receiving respiratory or cardiovascular organ support. Respiratory support defined as invasive or non-invasive mechanical ventilation, including high flow nasal cannula with flow rate >30 L/min and FiO_2 >0.4 Cardiovascular support defined as IV infusion of any vasopressor or inotrope	Tocilizumab: 8mg/kg infusion (maximum of 800mg) administered as IV infusion over 1 hour; dose could be repeated after 12-24 hours at discretion of treating clinician Sarilumab: 400mg IV infusion once	(1) SoC	Standard of care at trial site, could also be randomized to another domain of investigational treatments in REMAP-CAP. Most patients enrolled after results of the RECOVERY trial published, which then allowed corticosteroids as standard of care. 79.8% of patients in the immune modulation domain	Organ-support free days 90-day survival Time to ICU and hospital discharge World Health Organization ordinal scale for clinical status at day 14 Adverse events	Platform for European Preparedness Against (Re-) emerging Epidemics consortium by the European Union Rapid European COVID-19 Emergency Research response consortium by the European Union's Horizon 2020 research and innovation programme Australian National Health and Medical

	Saudi Arabia (1)								(690/865) received corticosteroids overall. Remdesivir use recorded in 32.8% of patients (265/807)		Research Council Health Research Council of New Zealand Canadian Institute of Health UK National Institute for Health Research Health Research Board of Ireland UPMC Learning While Doing Program Breast Cancer Research Foundation French Ministry of Health Minderoo Foundation and Wellcome Trust
Hermine/2020	France/ 9 hospitals	RCT	131 (63/67)	32.0	Median (IQR): 64.0	Patients were included in the CORIMUNO-19 cohort if they had	TCZ (8 mg/kg infusion, maximum 800 mg) *administration of an additional	(1) SoC	Antibiotic agents, antiviral agents,	Mortality (Day 28)	Ministry of Health, Programme Hospitalier de

					(57.1-74.3)	confirmed SARS-CoV-2 infection (positive on rRT-PCR and/or typical chest computed tomographic [CT] scan) with moderate, severe, or critical pneumonia (O2 >3 L/min, WHO Clinical Progression Scale [WHO-CPS] score ≥5	fixed dose of TCZ, 400 mg IV, on day 3 was recommended if oxygen requirement was not decreased by more than 50%, but decision was left to the treating physician.		corticosteroids, vasopressor support, anticoagulants	Mechanical ventilation or death (Day 14) Adverse events	Recherche Clinique Foundation for Medical Research AP-HP Foundation The Reacting program
Horby/ 2021	United Kingdom/National Health Service (NHS) hospitals	RCT	N = 4116 (2022/2094)	33%	Mean (SD): 63.6 (13.7)	Up to 21 days after the main randomization and regardless of treatment allocation, participants with clinical evidence of progressive COVID (Sa02 < 92% on RA or receiving oxygen therapy and CRP ≥ 75) could be considered for randomization to	Tocilizumab x 1 dose; A second dose could be given 12-24 hours at the discretion of the attending clinician. Tocilizumab dosing was weight based: > 90 KG (800 mg) >65- ≤ 90 KG (600 mg)	Usual care	Co-interventions according to main randomization and use of steroids were permitted; 82% of participants in each arm received systemic corticosteroids	Mortality at day 28 Receipt of mechanical ventilation or death Successful cessation of invasive mechanical ventilation	UK Research and Innovation (Medical Research Council) and National Institute of Health Research

						tocilizumab or usual care	> 40 ≤ 65 (400 mg				
Rosas/ 2020	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, US/ Multicenter	RCT	438 (294/144)	N/A	N/A	Severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or computed tomography were enrolled. Eligible patients had blood oxygen saturation ≤93% or partial pressure of oxygen/fraction of inspired oxygen <300 mm/Hg	TCZ (8 mg/kg infusion, maximum 800 mg)	(1) SoC	Antiviral treatments, low-dose steroids, CP, supportive care	Mortality (Day 28) Incidence of mechanical ventilation among patients not on mechanical ventilation at randomization Primary endpoint: clinical status based on 7-category ordinal scale at day 28, median (95% CI) Time to hospital discharge or "ready to discharge"(day	F. Hoffmann-La Roche Ltd. Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response Biomedical Advanced Research and Development Authority

										s) Median/95% CI" Adverse Events	
Salama /2020	US, Mexico, Kenya, South Africa, Peru Brazil/ Global study sites	RCT	389 (249/128)	40.8	Mean (SD): 55.9 (14.4)	Patients hospitalized with COVID-19 pneumonia confirmed by a positive polymerase chain reaction test and radiographic imaging were eligible. Patients had a blood oxygen saturation <94% on ambient air but were excluded if they required continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation	TCZ (8 mg/kg infusion, maximum 800 mg) *if patient's clinical signs or symptoms worsened or did not improve (reflected by sustained fever or worsening status on the 7-category ordinal scale), an additional infusion could be administered 8 to 24 hours after the first	(1) SoC	Corticosteroids, antivirals, dexamethasone, remdesivir	Cumulative proportion (95% CI) of patients requiring mechanical ventilation or who had died by Day 28 Time to hospital discharge or ready for discharge (days) Time to improvement in ordinal clinical status to Day 28 (days) Adverse events	Genentech

Salvarani/2020	Italy/24 hopsitals	RCT	126 (60/66)	38.9	Median (IQR): 60.0 (53.0-72.0)	Hospitalized patients with instrumental diagnosis of COVID-19 pneumonia confirmed by positive reverse-transcriptase polymerase chain reaction as- say for SARS-CoV-2 in a respiratory tract specimen. Other inclusion criteria were the presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) ratio between 200 and 300 mm/Hg, an inflammatory phenotype defined by a temperature	TCZ (8 mg/kg infusion, maximum 800 mg) followed by a second dose after 12 hours	(1) SoC	HCQ, heparin and LMWH, antiretrovirals, AZ	Mortality (Day 30) Clinical worsening at day 14 Discharge at day 30 Admissions to ICU Day 30 Adverse Events	Italian Ministry of Health "Fondi Ricerca Corrente – Linea 1, progetto 4" Roche provided the drug and its distribution to the centers

						greater than 38 °C during the last 2 days, and/or serum C-reactive protein (CRP) levels of 10 mg/dL or greater and/or CRP level increased to at least twice the admission measurement					
Stone/2020	USA/ 7 hospitals	RCT	243 (161/82)	42	Median (IQR): 59.8 (45.3-69.4)	SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM anti- body assay. Patients had to have at least two of the following signs: fever (body temperature >38°C) within 72 hours before enrollment, pulmonary infiltrates, or a need for supplemental oxygen in order to maintain	TCZ (8 mg/kg infusion, maximum 800 mg)	(1) SoC	Remdesivir, antiviral therapy, HCQ, glucocorticoids	Mortality (Day 28) Ventilation Clinical worsening on ordinal scale Hospital Initial Discharge Adverse Events	Genentech

						an oxygen saturation higher than 92%. At least one of the following laboratory criteria also had to be fulfilled: a C-reactive protein level higher than 50 mg per liter, a ferritin level higher than 500 ng per milliliter, a d-dimer level higher than 1000 ng per milliliter, or a lactate dehydrogenase level higher than 250 U per liter					
Veiga/2020	Brazil/9 hospitals	RCT	129	32	Mean (SD): 57 (14)	Severe or critical COVID-19 adult patients with a positive RT-PCR with symptoms for 3 or more days; with evidence of pulmonary infiltrates confirmed by chest CT or x-ray and	TCZ (8 mg/kg infusion, maximum 800 mg)	SOC	Co treatments or previous treatments could include, hydroxychlroroquine, azithromycin, steroids, other	Mortality at day 28 In hospital mortality Clinical status at day 15 and day 29 on 7-level ordinal scale;	Beneficência Portuguesa de São Paulo

						receiving supplemental 02 to maintain 02 > 93% or had been on MV for < 24 hours before analysis			immunosuppressants, heparin; remdesivir was not available	composite of death or mechanical ventilation Duration of hospital stay Ventilator free days within 29 days Time to independence from supplemental oxygen	

RT-PCR: reverse transcriptase polymerase chain reaction; **TCZ:** tocilizumab; **SoC**: standard of care; **CP:** convalescent plasma

Figure s5a. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab

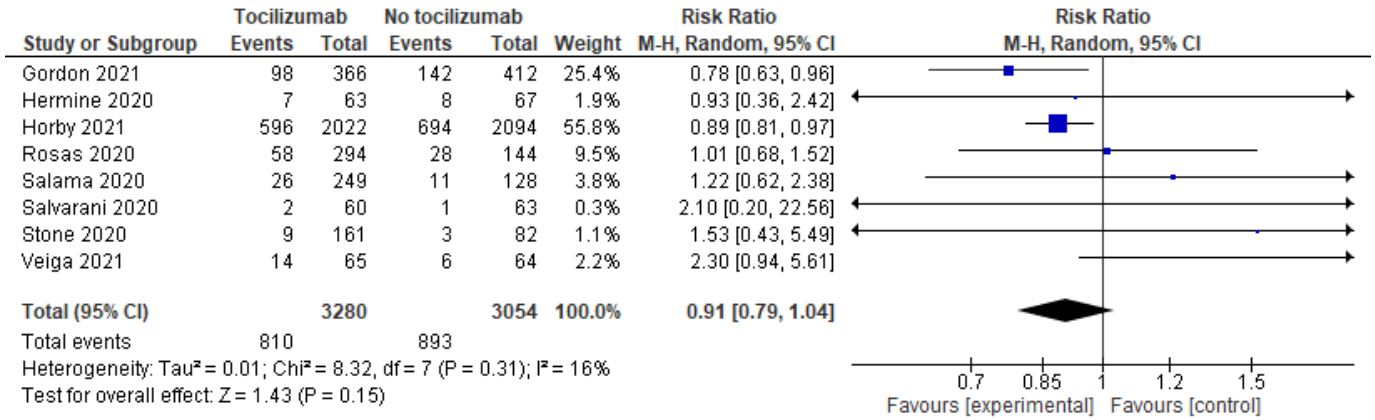
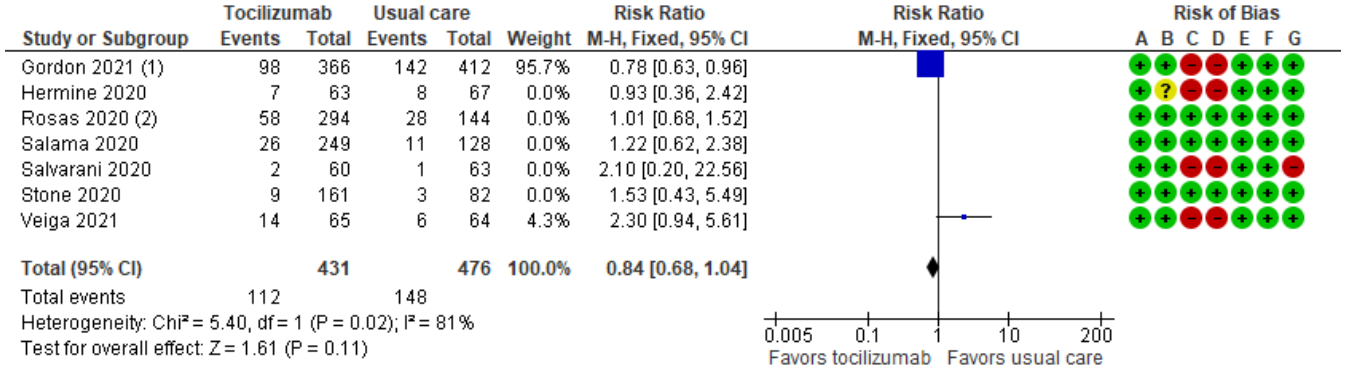


Figure s5b. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab (sensitivity analysis for patients on mechanical ventilation for <24 hours)



Footnotes

(1) Gordon allowed for ventilated patients to be included at randomization

(2) Rosas allowed for ventilated patients to be included at randomization

Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Figure s5c. Forest plot for the outcome of clinical deterioration for tocilizumab vs. no tocilizumab

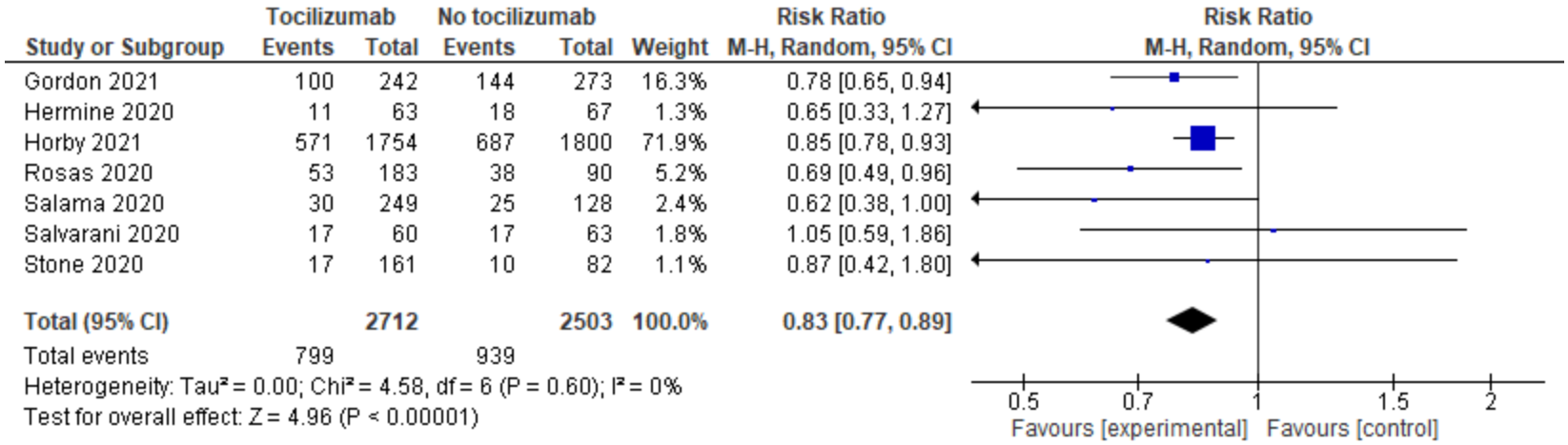
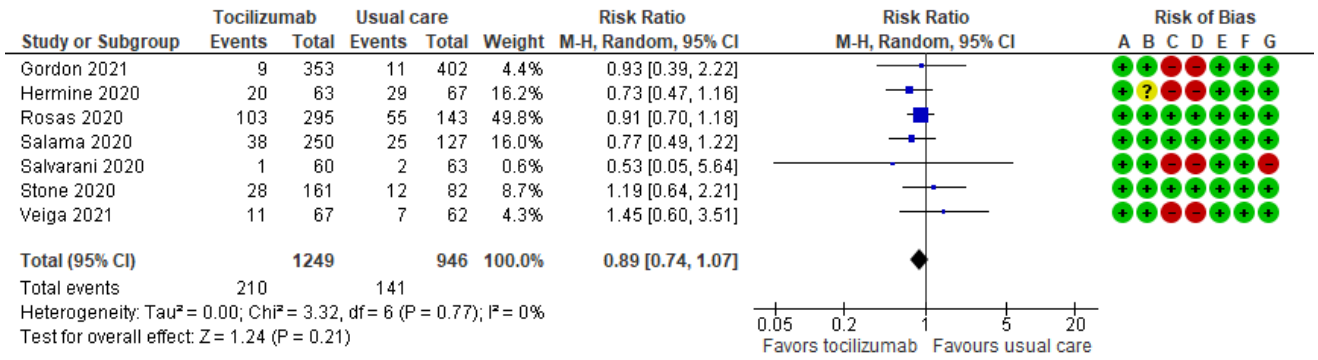


Figure s5d. Forest plot for the outcome of severe adverse events for tocilizumab vs. no tocilizumab



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Table s12. Risk of bias for randomized controlled studies (tocilizumab vs. no tocilizumab)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Gordon 2021							
Hermine 2020							
Horby 2021							
Rosas 2020							
Salama 2020							
Salvarani 2020							
Stone 2020							
Veiga 2021							

Low	High	Unclear

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Convalescent Plasma

Table s13. Should hospitalized patients with severe COVID-19 receive treatment with convalescent plasma vs. no convalescent plasma?

Study /year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Agarwal/ 2020	India/ 39 tertiary care hospitals	RCT	464 (235/229)	23.7	Median: 52 (42-60)	Hospitalized patients with moderate disease defined as having PaO_2/FiO_2 between 200-300 mmHg, or respiratory rate > 24/min with SpO_2 < 94% on RA	CP: 2 units of ABO-compatible CP, 200 mL each, infused 24 hours apart	(1) SoC	Antivirals, broad spectrum antibiotics, immunomodulators, other supportive management per institutional protocol, dictated by best available evidence at the time and guidance issued by Indian government	Composite of progression to severe disease or all-cause mortality at day 28 Symptom resolution Oxygen requirement Duration of respiratory support Clinical status Biomarker levels Adverse events	Indian Council of Medical Research
AlQahtani/ 2020	Bahrain/ 2 medical centers	RCT	40 (20/20)	20.0	Intervention: Mean of 52.6 (14.9)	Hospitalized patients with hypoxia (SpO_2 ≤ 92% on air, or PaO_2 < 60	CP: 2 units of ABO-compatible CP, 200 mL each, infused over 2 successive days	(1) SoC	Standard supportive treatment, including antipyretics, antivirals, tocilizumab,	Invasive or non-invasive ventilation Duration of ventilation	Ministry of Health Bahrain College of Surgeons in

					Control: Mean of 50.7 (12.5)	mmHg, or $PaO_2/FiO_2 \leq$ 300 mmHg) and receiving supplemental oxygen Excluded patients receiving invasive or non-invasive ventilation			and antibacterial medication	Biomarker levels Adverse events	Ireland-Bahrain
Avendano-Sola/ 2020	Spain/ 14 hospitals	RCT	81 (38/43)	45.7	Median: 59.0 (49.0-74.0)	Hospitalized patients with radiographic evidence of pulmonary infiltrates or clinical evidence plus $SpO_2 \leq$ 94% on RA Excluded patients on mechanical ventilation or high flow oxygen	CP: 1 unit, 250-300 mL	(1) SoC	Supportive therapy and specific therapy with off-label marketed medications according to local or national guidelines	Mortality at day 15 and 29 Clinical status at day 15 Length of hospitalization Days free from mechanical ventilation or oxygen support Adverse events	Government of Spain, Ministry of Science and Innovation European Regional Development Fund
Balcells/2020	Single center, Santiago, Chile	RCT	58 (28/30)	50	Mean age: 65.8 (range: 27-92)	Hospitalized patients > 18 years old who are less than 7 days from symptom	Early convalescent (initiated at enrollment) plasma: 2 units (200ml each)	Deferred convalescent plasma only if a pre-specified worsening	Antivirals, antibiotics, heparin thromboprophylaxis, and immunomodulators	Composite of In-hospital mortality, mechanical ventilation, or	Fondo de Adopción Tecnológica SiEmpre, SOFOFA Hub, and Ministerio de

						onset with positive SARS CoV-2 PCR or pending PCR results with imaging consistent with COVID-19 pneumonia and confirmed COVID-19 close contact and CALL score ≥ 9 points and baseline ECOG performance status of 0-2	separated by 24 hours	respirator function (Pa02/Fi02 < 200) or if still in hospital for > 7 days after enrollment; 2 units (200ml each) separated by 24 hours		hospital stay > 14 days 30 day mortality Days of mechanical ventilation, high flow nasal cannula Viral clearance Time to respiratory failure development Serious adverse events TRAILI	Ciencia, Tecnología, Conocimiento e Innovación, Chile
Gharbaran/ 2020	Netherlands/ 14 secondary and academic hospitals	RCT	86 (43/43)	N/A	Median: 63 (56-74)	Eligible patients were at least 18 years, admitted to a study site for COVID-19 and had clinical COVID-19 disease	CP: 300ml of plasma with anti-SARS-CoV-2 neutralizing antibody titers of at least 1:80; "Patients without a clinical response and a persistently	(1) SoC	Off-label use of EMA-approved drugs (e.g. chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra)	Mortality Improvement in WHO COVID-19 disease severity score on day 15 Time to discharge Hazard ratio/95% CI	Erasmusfoundation

						proven by a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test in the previous 96 hours	positive RT-PCR could receive a second plasma unit after five days."				
Horby /2021	United Kingdom /National Health Service (NHS) hospitals	RCT	N= 11558 (5795/5763)	36	Mean: 63.5 (14.7)	Hospitalized patients of any age with clinical suspected or laboratory confirmed SARS CoV-2	Usual care plus convalescent plasma, first unit of 275ml convalescent plasma given as soon as possible after randomization and a second unit of 275ml the following day (at least 12 hours after the first)	Usual care	Co-interventions according to main randomization and use of steroids were permitted; 93% of participants in the CP arm received steroids vs 92% of usual care partcipants	Mortality at day 28 Time to hospital discharge Receipt of mechanical ventilation or death Transfusion elated adverse events at 72 hours Cause-specific mortality Major cardiac arrhythmia	UK Research and Innovation (Medical Research Council) and National Institute of Health Research

Li/ 2020	China/ 7 medical centers	RCT	103 (52/51)	41.7	Median: 70 (62-78)	Hospitalized patients with severe and/or life-threatening COVID-19: Severe: respiratory distress (≥30 breaths/min ; in resting state, SpO_2 of 93% or less on room air; or PaO_2/FIO_2 of 300 or less; Life-threatening: respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring ICU monitoring	CP: transfusion dose approximately 4 to 13 mL/kg; approximately 10 mL for the first 15 minutes, which was then increased to approximately 100 mL per hour with close monitoring	(1) SoC	Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications	Mortality at day 28 Clinical improvement at day 28 Time to clinical improvement (days) Time from hospitalization to discharge Adverse events	Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences

Libster / 2021	Argentina/ 13 centers	RCT	160 (80/80)	62.5%	77.2 (8.6)	Ambulatory patients 65 or older with at least one of each sign or symptom in the following two categories for less than 48 hours: temp > 37.5, unexplained sweating, or chills; and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, or rhinorrhea.	Convalescent Plasma 250 ml with IgG titer > 1:1000 against SARS-CoV-2 x 1 dose	Placebo	None	Mortality Development of severe respiratory disease at day 15 Life-threatening respiratory disease Critical systemic illness	Bill and Melinda Gates Foundation Fundación INFANT Pandemic Fund
O'Donnell/2020	5 hospitals in New York City (USA) and Rio de Janeiro (Brazil)	RCT	223 (150/73)	34	Median age: 61 years	Hospitalized patients ≥ 18 years with positive SARS-CoV-2 within 14 days of randomization, with infiltrates	A single unit of convalescent plasma given over 2 hours	Control	Patients could receive steroids, remdesivir, hydroxychloroquine, and antibacterial agents	Time to clinical improvement Clinical status at day 28 Adverse events throughday 28	Amazon Foundation

						on chest imaging and oxygen saturation ≤ 94% on RA on oxygen, mechanical ventilation, or ECMO					
Ray/ 2020	India/ ID & BG Hospital, Kolkata	RCT	80 (40/40)	28.8	Female: Mean of 61.4 (11.3) Male: Mean of 61.4 (12.2)	Hospitalized patients with severe disease (fever or suspected respiratory infection plus one of the following: respiratory rate > 30/min, severe respiratory distress, or SpO_2 < 90% on RA) with mild-moderate ARDS (PaO_2/FiO_2 100-300mmHg) not on mechanical ventilation	CP: 2 units of ABO-matched CP, 200 mL each, administered on 2 successive days	(1) SoC	Most patients received hydroxychloroquine for 5 days, azithromycin for 5 days, ivermectin for 5 days, and doxycycline for 10 days. Standard of care at trial site for patients with ARDS also included: corticosteroids and anticoagulation in addition to indicated supportive therapy. Several patients also received remdesivir and one patient received tocilizumab.	30-day mortality SpO_2/FiO_2 ratio over 10 days Length of hospitalization Biomarker levels	Council of Scientific Industrial Research, Government of India Fondation Botnar

Simonovich/ 2020	Argentina/ 12 clinical sites	RCT	334 (228/105)	32.3	Median: 62 (52-72)	Hospitalized patients with at least one of the following: SaO_2 < 93% on RA, PaO_2/FiO_2 < 300 mmHg, SOFA or mSOFA score 2 or more points above baseline status Excluded patients on mechanical ventilation or multiorgan failure	CP: IV 5-10 mL/kg with limit of 400 mL for those with body weight < 70 kg and limit of 600 mL for those with body weight > 70 kg SARS-CoV-2 IgG antibody titer > 1:800	(1) SoC	Allowed to receive antiviral agents, glucocorticoids, or other therapies for COVID-19 according to standard of care at institution	Clinical status at day 7, 14, and 30 (including mortality) Time to hospital discharge Time to discharge from ICU Adverse events	Research Council of the Hospital Italiano de Buenos Aires
Joyner, Senefeld et al. /2020	USA/2807 acute care facilities in the US and territories	Open-label, Expanded Access Program	35,322	39.7	N/A	Hospitalized with a laboratory confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and	IV Minimum of one unit approximately 200 mL = one unit (Low IgG, Medium IgG and High IgG)	N/A	angiotensin receptor blocker, ACE inhibitor, AZ, remdesivir, steroids, chloroquine, HCQ	Mortality at Day 7 (Days to Transfusion <= 3 days and 4+ Days) Mortality at Day 30 Days to Transfusion <= 3 days and 4+ Days)	Department of Health and Human Services Office of the Assistant Secretary Preparedness and Response Biomedical Advanced Research and Development

						had (or were judged by a healthcare provider to be at high risk of progression to) severe or life-threatening COVID-19					National Center for Advancing Translational Sciences (NCATS) grant National Heart, Lung, and Blood Institute (NHLBI) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Natural Sciences and Engineering Research Council of Canada (NSERC) National Institute of Allergy and Infectious Disease (NIAID) National Heart Lung and Blood Institute National Institute on Aging (NIA)

											Schwab Charitable Fund (Eric E Schmidt, Wendy Schmidt donors) United Health Group National Basketball Association (NBA) Millennium Pharmaceuticals Octapharma USA, Inc The Mayo Clinic
Joyner /2020	USA/ Over 2,000 acute care facilities registered	Retrospective cohort	5000	36.5	Median: 62.3 (18.5-97.8)	Severe or life-threatening COVID-19 or judged by a healthcare provider to be at high risk of progression to severe or life-threatening COVID-19 Severe or life-	IV 200-500 mL ABO-compatible COVID-19 CP	N/A	N/A	Mortality over first 7 days after CP transfusion Adverse events	Mayo Clinic Biomedical Advanced Research and Development Authority National Center for Advancing Translational Sciences National Heart, Lung, and Blood Institute National Institute of

						threatening COVID-19 is defined by one or more of the following: dyspnea, respiratory frequency ≥ 30 breaths/min, SpO_2 ≤ 93%, lung infiltrates >50% within 24-28h of enrollment, respiratory failure, septic shock, and multiple organ dysfunction or failure					Diabetes and Digestive and Kidney Diseases Natural Sciences and Engineering Research Council National Institute of Allergy and Infectious Diseases Schwab Charitable Fund United Health Group National Basketball Association (NBA) Millennium Pharmaceuticals, Octopharma USA, Inc
Liu/ 2020	USA/ The Mount Sinai Hospital	Retrospective cohort with matching	39	36.0	Mean: 55 (13)	Hospitalized patients; disease severity assessed by O_2 supplementation required	CP 2 units of ABO-type matched CP once, each unit 250mL infused over 1 to 2 hrs	(1) SoC	Antimicrobial agents (AZ), broad spec antibiotics, HCQ; investigational antivirals); therapeutic anticoagulation	Mortality Worsened clinical condition by day 14 Follow-up time	N/A

						and laboratory parameters			; anti-inflammatory agents	Hazard ratio for plasma	

SpO_2: oxygen saturation; **PaO_2/FIO_2**: ratio of arterial oxygen partial pressure to fractional inspired oxygen; **CP**: convalescent plasma; **WHO**: World Health Organization; **SaO_2**: oxygen saturation; **SoC**: standard of care; **AZ**: azithromycin; **HCQ**: hydroxychloroquine; **TCZ**: tocilizumab; **SOFA:** sequential organ failure assessment; **mSOFA**: modified sequential organ assessment; **RA:** room air; **PaO2**: arterial oxygen partial pressure; **ARDS:** acute respiratory distress syndrome

Figure s6a. Forest plot for the outcome of mortality for convalescent plasma vs. no convalescent plasma

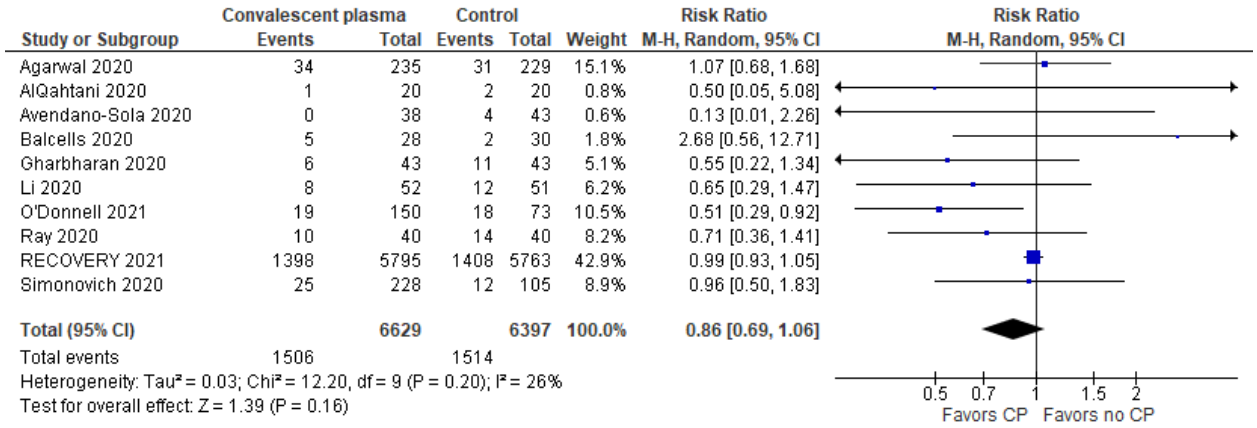


Figure s6b. Forest plot for the outcome of mechanical ventilation for convalescent plasma vs. no convalescent plasma

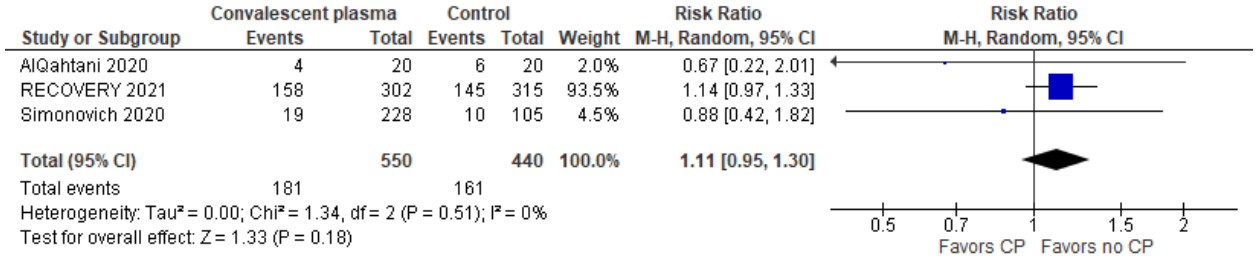


Figure s6c. Forest plot for the outcome of adverse events (mild-to-severe) for convalescent plasma vs. no convalescent plasma

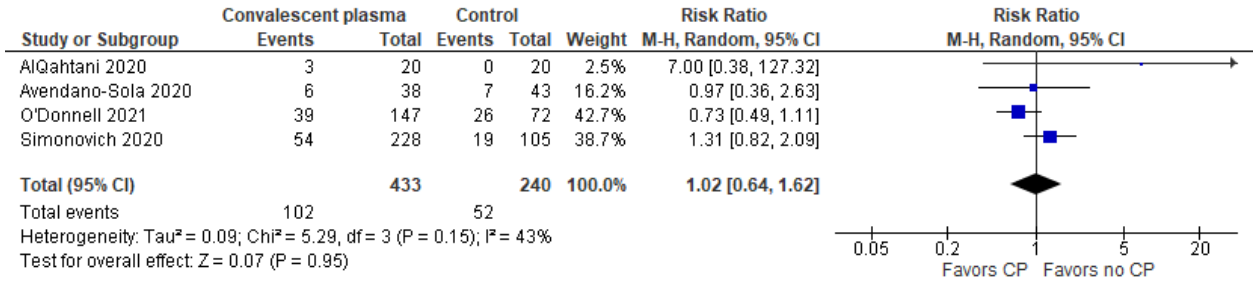


Table s14a. Risk of bias for randomized controlled studies (convalescent plasma vs. no convalescent plasma)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Balcells 2021 [1]							
Li 2020 [2]							
Gharbharan 2020 [3]							
Horby 2021 [4]							
O'Donnell 2021 [5]							
Simonovich 2021 [6]							
Agarwal 2020 [7]							
AlQahtani 2020 [8]							
Avendana-Sola 2020 [9]							
Libster 2020 [10]							
Ray 2020 [11]							

Low | **High** | **Unclear**

References

1. Balcells ME, Rojas L, Le Corre N, et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. PLoS Med **2021**; 18(3): e1003415.
2. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA **2020;** 324(5): 460-70.

3. Gharbharan A, Jordans CC, GeurtsvanKessel C, et al. Convalescent Plasma for COVID-19. A randomized clinical trial. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.07.01.20139857 [Preprint 3 July 2020].
4. Horby PW, Estcourt L, Peto L, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.03.09.21252736 [Preprint 10 March 2021].
5. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized, double-blind, controlled trial of convalescent plasma in adults with severe COVID-19. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.03.12.21253373 [Preprint 13 March 2021].
6. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med **2021**; 384(7): 619-29.
7. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ **2020**; 371: m4232.
8. AlQahtani M, Abdulrahman A, AlMadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.11.02.20224303 [Preprint 4 November 2020].
9. Avendaño-Solà C, Ramos-Martinez A, Muñez-Rubio E, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.08.26.20182444 [Preprint 29 September 2020].
10. Libster R, Marc GP, Wappner D, et al. Prevention of severe COVID-19 in the elderly by early high-titer plasma. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.11.20.20234013 [Preprint 21 November 2020].
11. Ray Y, Paul SR, Bandopadhyay P, et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.11.25.20237883 [Preprint 29 November 2020].

Table s14b. Risk of bias for non-randomized studies (convalescent plasma vs. no convalescent plasma)

Study + Overall RoB Judgement	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Duan 2020 [1]							
Joyner, Senefeld, et al. 2020 [2]							
Joyner, Wright et al. 2020 [3]							
Liu 2020 [4]							

Low	Moderate	Serious	Critical

References

1. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A **2020**; 117(17): 9490-6.
2. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. medRxiv **2020**.
3. Joyner M, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. medRxiv **2020**.
4. Liu ST, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: A matched control study. medRxiv **2020**.

Remdesivir

Table s15. Should hospitalized patients with severe COVID-19 receive treatment with remdesivir vs. no remdesivir?

Study /year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Beigel/2020	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore/ 60 trial sites and 13 subsites	RCT	1062 (541/521)	35.6	Mean: 58.9 (15)	Met one of the following criteria suggestive of lower respiratory tract infection at the time of enrollment: radiographic infiltrates by imaging study, SpO_2 ≤94% on room air, or requiring supplemental oxygen,	Remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10	(1) Placebo 200mg once day 1, 100mg once daily days 2-10	Supportive care according to the standard of care for the trial site hospital; if a hospital had a written policy or guideline for use of other treatments for COVID-19, patients could receive those treatments	Mortality at day 14 Number of recoveries Time to recovery (days) Hazard ratio of mortality Hospital discharge Adverse Events	National Institute of Allergy and Infectious Diseases National Institutes of Health, Bethesda, MD Governments of Japan, Mexico, Denmark, and Singapore. Seoul National University Hospital.

						mechanical ventilation, or extracorporeal membrane oxygenation					United Kingdom Medical Research Council

Goldman/ 2020	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan/ 55 hospitals	RCT	397 (200/197)	N/A	N/A	Radiographic evidence of pulmonary infiltrates and either had SpO_2 of 94% or less while they were breathing ambient air or were receiving supplemental oxygen	Remdesivir (5-Day Group) 200mg once daily day 1, 100mg once daily days 2-5	(1) Remdesivir (10-Day Group): 200mg once daily day 1, 100mg once daily days 2-10	Supportive therapy received at the discretion of the investigator	Mortality at day 14 Clinical improvement (days 5, 7, 11, 14) Duration of hospitalization among patients discharge on or before day 14 Time to recovery Adverse Events	Gilead Sciences
Pan/ 2020	30 countries	RCT	11266 (total) (Remdesivir 2743/2708)	38.0	N/A	Age ≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any	Remdesivir 200 mg once daily day 0, 100 mg once daily days 1-9	(1) SoC	Corticosteroids, convalescent plasma, anti-IL-6 drug, non-trial interferon, non-trial antiviral	Mortality at day 28 Ventilation in those not already being ventilated at the time of randomization	Participating countries covered almost all local costs and WHO covered all other study costs,

						study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contraindication to any study drug					receiving no extra funding
Spinner/2020	United States, Europe, and Asia/ 105 hospitals	RCT	584 (193/191/200)	N/A	N/A	Moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation	Remdesivir (5-Day Group) 200mg once daily day 1, 100mg once daily days 2-5 via IV	(1) Remdesivir (10-Day Group): 200mg once daily day 1, 100mg once daily days 2-10 via IV	Steroids, HCQ, Lopinavir-ritonavir, TCZ, AZ	Day 11 clinical status on 7-point scale, No. (%) (Includes Mortality at Day 11) Clinical improvement	Gilead Sciences

						>94% on room air)		(2) SoC		(at Day 5, 7, 11, 14, 28) Recovery (at Day 5, 7, 11, 14, 28) Adverse Events	
Wang /2020	China/ 10 hospitals	RCT	237 (158/78)	N/A	Median: 65 (56-71)	Hospitalized patients with pneumonia confirmed by chest imaging, $SpO_2 \leq 94\%$ on room air, $PaO_2/FIO_2 \leq$ 300mmHg	Remdesivir 200mg infusion once on day 1, 100mg daily on days 2-10	(1) Placebo infusions 200mg day 1, 100mg days 2-10	Lopinavir/ritonavir, interferons, and corticosteroids	Mortality on day 28 Clinical improvement (days 7, 14, 28) Duration of invasive mechanical ventilation (days) Hospitalization days	Chinese Academy of Medical Sciences Emergency Project of COVID-19 National Key Research Development Program of China

										Adverse events leading to treatment discontinuation	Beijing Science and Technology Project

PaO_2/FIO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; **SpO_2**: oxygen saturation

Figure s7a. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients with moderate disease

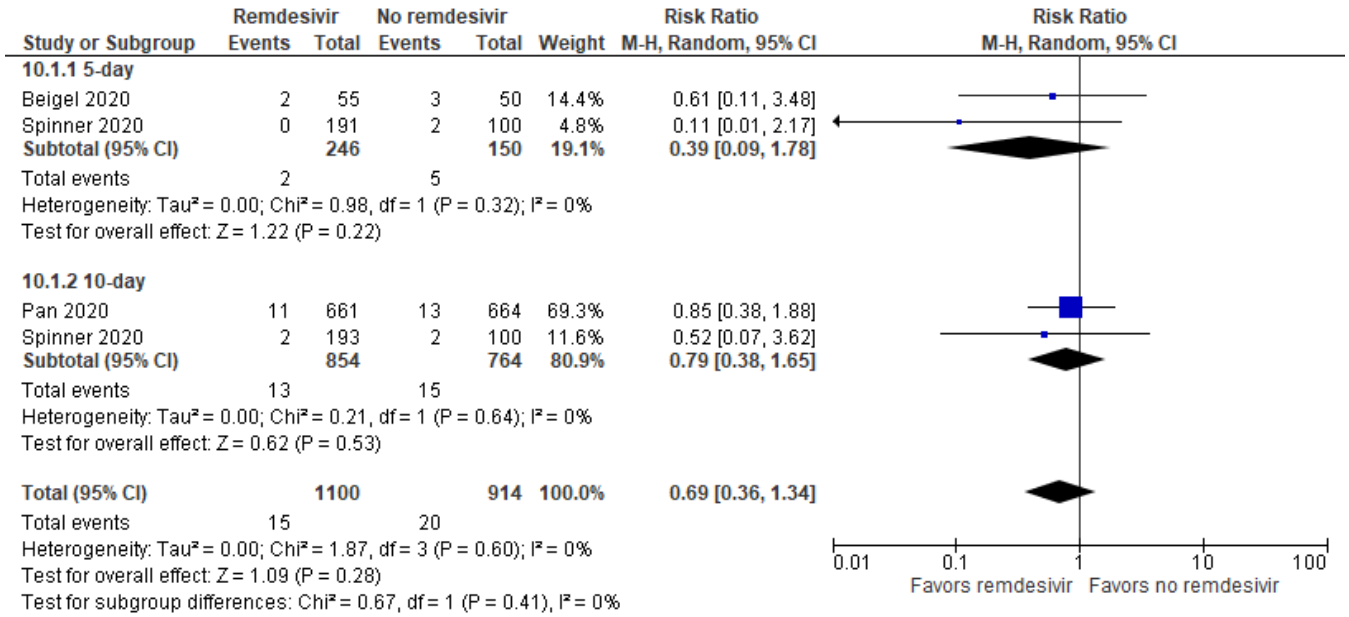


Figure s7b. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients with moderate disease

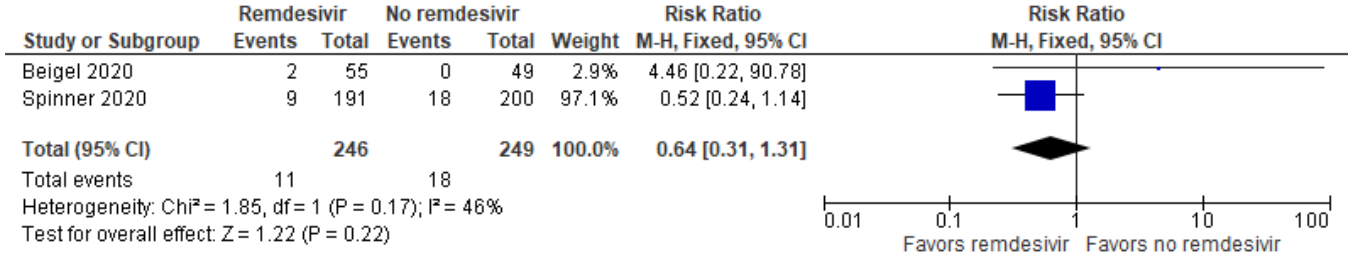


Figure s7c. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients with severe disease

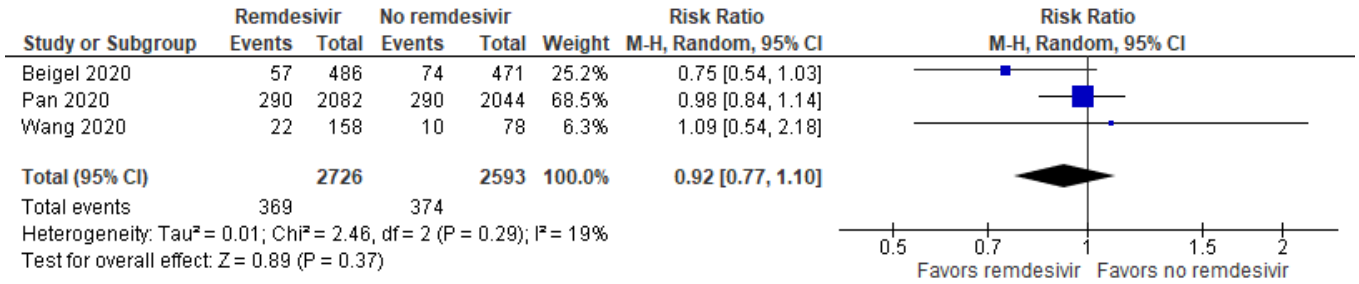


Figure s7d. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients with severe disease

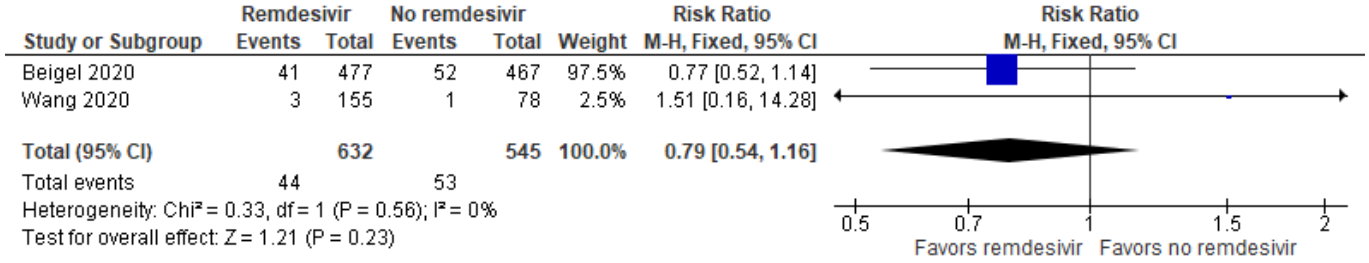


Figure s7e. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

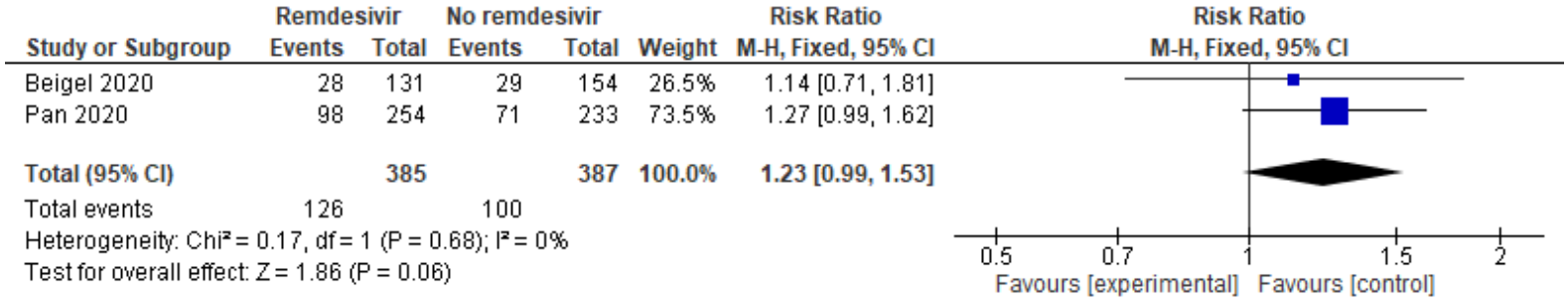


Figure s7f. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

Table s16. Risk of bias for randomized controlled studies (remdesivir vs. no remdesivir)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Beigel 2020 [1]							
Goldman 2020 [2]							
Pan 2020 [3]							
Spinner 2020 [4]							
Wang 2020 [5]							

Low	High	Unclear

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med **2020**.
2. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med **2020**.
3. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results. medRxiv **2020**. Available at: https://doi.org/10.1101/2020.10.15.20209817 [Preprint 15 October 2020]
4. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA **2020**.
5. 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**; 395(10236): 1569-78.

Famotidine

Table s17. Should hospitalized patients with severe COVID-19 receive treatment with famotidine vs. no famotidine?

Study/year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Freedberg/ 2020	USA/ Columbia University Irving Medical Center; Allen Pavilion	Retrospective cohort with matching	1620 (84/1536)	N/A	N/A	Admitted and tested positive for SARS-CoV-2 by nasopharyngeal polymerase chain reaction at presentation or within no more than 72h following admission	Famotidine: median dose of 136 mg (63 – 233 mg) given for median 5.8 days; received within 24 hours of hospital admission	(1) SoC	N/A	Death or intubation Median ferritin (ng/mL) Association between use of famotidine with risk for death or intubation (hazards ratio)	N/A

SoC: standard of care

Table s18. Risk of bias for non-randomized studies (famotidine vs. no famotidine)

Study	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Freedberg 2020[1]							

Low	Moderate	Serious	Critical

Reference

1. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Gastroenterology **2020**.

Neutralizing Antibodies for Prophylaxis

Table s19. Should persons exposed to COVID-19 who are at high risk of progression to severe disease receive post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab?

Study/year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
O'Brien/2021 Part A	United States (110 sites) Romania (1 site) Moldova (1 site)	RCT	1505 (753/752)	54.1	Mean: 42.9 (range of 12-92)	Previously and currently uninfected (RT-PCR negative) household contacts of persons with SARS CoV-2 infection	REGEN-COV 1200 mg (casirivimab 600 mg /imdevimab 600 mg) x 1 subcutaneous injection	Placebo	None	Symptomatic RT-PCR confirmed SARS-CoV-2 infection within 28 days Symptomatic and asymptomatic RT-PCR confirmed infection within 28 days Number of weeks of symptoms present Number of weeks of high viral load COVID-19 related hospitalization or ER visit Safety	Regeneron Pharmaceuticals F. Hoffman-La Roche COVID-19 Prevention Network grant, which is funded by cooperative awards from National Institute of Allergy and Infectious Diseases and National Institutes of Health

O'Brien/2021 Part B	United States (110 sites) Romania (1 site) Moldova (1 site)	RCT	314 (155/156)	55	Mean: 40.9 (18)	RT-PCR positive for SARS CoV-2 and asymptomatic	REGEN-COV 1200 mg (casirivimab 600 mg /imdevimab 600 mg) x 1 subcutaneous injection	Placebo	None	Proportion of patients who developed signs and symptoms of COVID-19 within 14 days of positive RT-PCR Number of weeks of symptomatic SARS CoV-2 infection Number of weeks of high viral load over 28 days COVID-19 related hospitalization or ER visit Safety	Regeneron Pharmaceuticals F. Hoffman-La Roche COVID-19 Prevention Network grant, which is funded by cooperative awards from National Institute of Allergy and Infectious Diseases and National Institutes of Health

Table s20. Risk of bias for randomized controlled studies (post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab for persons exposed to COVID-19 at risk of progression to severe disease)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
O'Brien 2021 (Part A) [1]							
O'Brien 2021 (Part B) [2]							

Low	High	Unclear

References

1. O'Brien MP, Eduardo Forleo-Nato, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med **2021**. Available at: https://doi.org/10.1056/nejmoa2109682 [Epub ahead of print 4 August 2021].
2. O'Brien MP, Eduardo Forleo-Nato, Sarkar N, et al. Subcutaneous REGEN-COV antibody combination in early SARS-CoV-2 infection. medRxiv **2021**. Available at: https://doi.org/10.1101/2021.06.14.21258569. [Preprint 14 June 2021].

Neutralizing Antibodies for Treatment

Table s21. Should ambulatory and hospitalized patients with COVID-19 receive neutralizing antibodies [a,b,c] vs. no neutralizing antibodies?

a. Bamlanivimab/etesevimab
b. Casirivimab/imdevimab
c. Bamlanivimab monotherapy

Study/year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Chen/ 2020	US/ 41 centers	RCT	452 (309/143)	N/A	Study population who received bamlanivimab : Median (range): 45 years (18-86 years) Study population who received placebo: Median (range): 46 years (18-77 years)	All the patients had positive results on testing for SARS-CoV-2 and presented with one or more mild or moderate symptoms	LY-CoV55 intravenously once at a dose of one of following: 700 mg, 2800 mg, 7000 mg	(1) Placebo	N/A	Change from baseline in the viral load at day 11 Change from baseline in the viral load at days 3, 7 Hospitalization at day 29 Adverse events	Eli Lilly

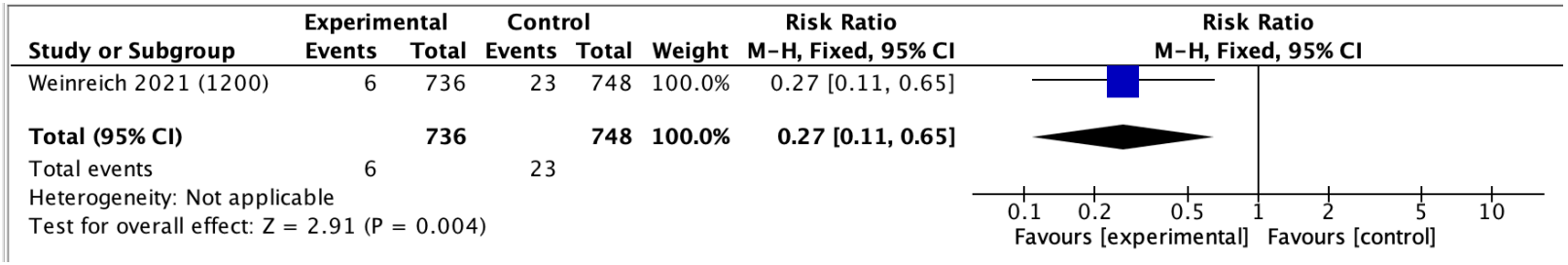
ACTIV-3/TICO LY-CoV555 Study Group /2020	USA (23) Denmark (7) Singapore (1)	RCT	163/151	44	Median (IQR): 61 (49-71)	Hospitalized patients within 12 of illness onset. Included patients with no oxygen requirements and on supplemental oxygen (including noninvasive ventilation). Excluded patients on invasive ventilation or ECMO.	LY-CoV555 (bamlanivimab) 7000 mg once, by intravenous infusion over 1 hour	Placebo plus standard of care	Remdesivir (95%), glucocorticoids (49%), heparinoids (51%)	Pulmonary status at day 5 Sustained recovery Mortality Hospital discharge Adverse events	US Operation Warp Speed National Institute of Allergy and Infectious Diseases Leidos Biomedical Research for the INSIGHT Network National Heart, Lung, and Blood Institute Research Triangle Institute for the PETAL Network US Department of Veterans Affairs Grants from governments of Denmark, Australia, United Kingdom
Dougan/ 2021	US (131 centers)	RCT	1035 (518/517)	52%	Mean (SD): 53.8 years (16.8)	Adult patients with mild to moderate COVID-19 (diagnosed with	Bamlanivimab 2800 mg/Etesevimab 2800 mg x one	Placebo	None	Mortality Acute care hospitalization ≥ 24 hours	Eli Lilly

						positive antigen or RT-PCR)	dose infused over 1 hour			Proportion of patients with persistently high viral load at day 7 (PHVL) SAEs	
Gupta/ 2021	37 study sites in 4 countries (US, Canada, Brazil, Spain)	RCT	583 (291/292)	54	Median 53 years (18-96)	Mild-moderate COVID-19 infection (symptomatic, but no dyspnea at rest, respiratory distress, or supplemental oxygen) and at high risk of progression (age ≥ 55 or at least 1 of following risk factors: diabetes, obesity, chronic kidney disease, congestive heart failure, chronic obstructiv	Sotrovimab 500mg IV infused over 1 hour	Placebo	None	Day 29 all-cause mortality Hospitalization Emergency room visits Patient-reported outcomes Viral load Progression to supplemental oxygen Adverse events	Vir Biotechnology GlaxoSmith Kline

						e pulmonary disease, moderate-severe asthma)					
Weinreich/2021	US (27 centers)	RCT	4519 (2676/1843)	51%	Median (IQR): -2.4 g: 50 (39:60) - 1.2 g 48.5 (37:57.5) Concurrent placebo: 50 (37:58)	Adult, non-hospitalized patients with a positive SARS-CoV-2 result no more than 72 hours before randomization and symptoms onset less than 7 days before randomization	REGN-COV2 - 2.4 g x 1 dose - 1.2 g x 1 dose	Placebo	N/A	Mortality At least one COVID-19 related medically attended visit through day 29 (included telemedicine, in-person visits, urgent care/ER visits, and hospitalizations). Adverse events	Regeneron Pharmaceuticals and Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services
Weinreich/2020	US (27 centers)	RCT	275 (182/93)	51%	Median (IQR): 44 (35-52)	Adult, non-hospitalized patients with a positive SARS-CoV-2 result no more than 72 hours before randomization and symptoms onset less than 7	REGN-COV2 - 8.0 g (high dose) x 1 dose, - 2.4 g (low dose) x 1 dose	Placebo	N/A	Change from baseline in the viral load at day 7 At least one COVID-19 related medically attended visit through day 29 (included telemedicine, in-person visits, urgent care/ER	Regeneron Pharmaceuticals and Biomedical and Advanced Research and Development Authority of the Department of Health and Human Services

						days before randomization				visits, and hospitalizations). Adverse events	

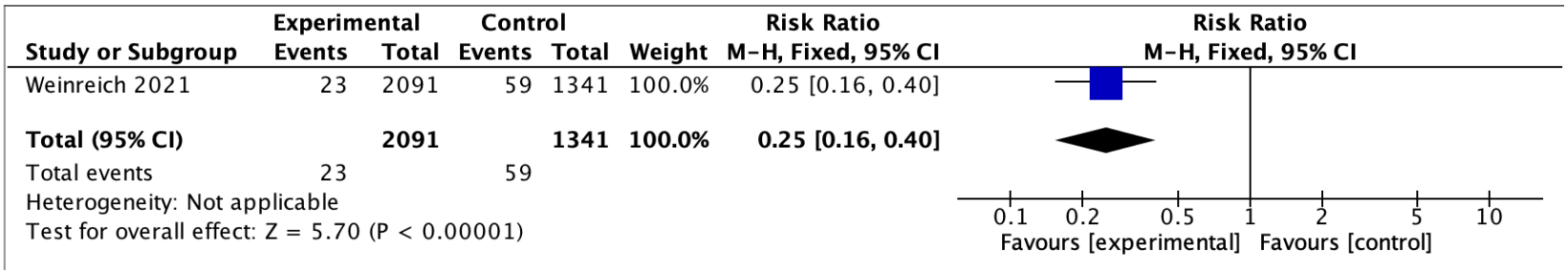
Figure s8a. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (data for 1200-mg dose only) [1]



Reference

1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

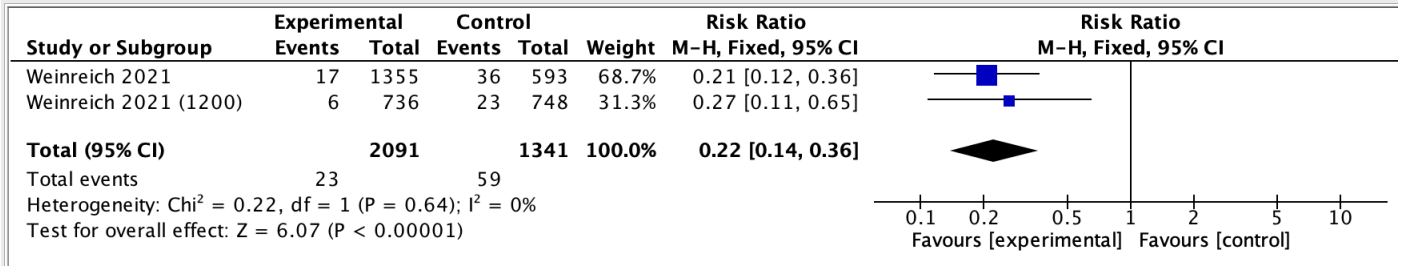
Figure s8b. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (combining data for 2400-mg dose and 1200-mg dose) [1]



Reference

1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

Figure s8c. Forest plot for the outcome of hospitalizations for casirivimab/imdevimab vs. no casirivimab/etesevimab (pooling data for 2400-mg dose and 1200-mg dose) [1]



Reference

1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

Table s22. Risk of bias for randomized controlled studies (bamlanivimab/etesevimab vs. no bamlanivimab/etesevimab; casirivimab/imdevimab vs. no casirivimab/imdevimab; bamlanivimab monotherapy vs. no bamlanivimab monotherapy)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Chen 2020 [1]							
ACTIV-3/TICO LY-CoV555 Study Group 2020 [2]							
Dougan 2021 [3]							
Gupta 2021 [4]							
Weinreich 2021 [5]							
Regeneron Pharmaceuticals, Inc. 2021 [6]							

Low	High	Unclear

Reference

1. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 229-37.
2. ACTIV-3/TICO LY-CoV555 Study Group, Grund B, Barkauskas CE, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med **2020**: [Epub ahead of print 22 December 2020].
3. Dougan M, Nirula A, Azizad M, et al. The Impact of Bamlanivimab + Etesevimab Neutralizing Antibody Combination Treatment on Hospitalization Rates and Deaths Among High-Risk Patients Presenting With Mild-to-Moderate COVID-19 Illness. **2021**: [Under review].
4. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab. medRxiv **2021**: Available at: https://www.medrxiv.org/content/10.1101/2021.05.27.21257096v1. [Preprint 28 May 2021].
5. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med **2021**; 384(3): 238-51.

6. Regeneron Pharmaceuticals, Inc. Phase 3 Trial Shows Regen-CoV™ (Casirivimab with Imdevimab) Antibody Cocktail Reduced Hospitalization or Death by 70% in NonHospitalized COVID-19 Patients. Available at: https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody. Accessed 9 April 2021.

Janus Kinase Inhibitors (Baricitinib and Tofacitinib)

Table s23. Should hospitalized patients with severe COVID-19 receive treatment with remdesivir plus baricitinib vs. remdesivir alone?

Study/ year	Country/ hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Ely/ 2021	18 institutions in 4 countries (Argentina, Brazil, Mexico, United States)	RCT	101 (51/50)	45.5	Mean: 58.6 (13.8)	Invasive mechanical ventilation or extracorporeal membrane oxygenation at randomization with at least one elevated marker of inflammation	Baricitinib 4mg daily (or 2mg daily if eGFR ≥ 30 to < 60 mL/min/1.73 m2) crushed and given via nasogastric tube (or by mouth when feasible) for 14 days or until discharge plus SoC	SoC	SoC based on clinical practice at trial hospital, including use of corticosteroids, antivirals, VTE prophylaxis, or other treatments	Mortality at day 28 and day 60	Ely/ 2021
Kalil/ 2020	United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), United Kingdom	RCT	1033 (515/518)	36.9	Mean : 55.4 (15.7)	Met at least one of the following criteria suggestive of lower respiratory tract infection at enrollment: radiographic	Baricitinib 4mg daily (or 2mg daily if eGFR < 60 mL/min) for 14 days or until discharge plus remdesivir	Remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10 or until discharge and matching	Supportive care according to the standard of care for the trial site hospital; if a hospital had a written policy or guideline for use of other treatments for COVID-19,	Mortality at day 14 and day 28 Time to recovery (days) Clinical status at day 15 Hazard ratio of mortality	National Institute of Allergy and Infectious Diseases National Institutes of Health, Bethesda, MD

	(1), Denmark (1)					infiltrates by imaging study, SpO_2 ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation	200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10 or until discharge	placebo tablets	patients could receive those treatments. All patients without contraindications received VTE prophylaxis. In absence of policy, other specific treatments for COVID-19 prohibited, including corticosteroids, which were permitted only for other standard indications in that case.	Incidence of death or invasive ventilation Adverse events	Governments of Japan, Mexico, Singapore, and Denmark Seoul National University Hospital United Kingdom Medical Research Council
Marconi/ 2021	101 centers from 12 countries (Argentina, Brazil, Germany, India, Italy, Japan, South Korea, Mexico, Russia, Spain, United Kingdom, United States)	RCT	1525 (764/761)	36.9	Mean: 57.6 (14.1)	Hospitalized with evidence of pneumonia or active, symptomatic COVID-19, and had ≥ 1 elevated inflammatory marker (C reactive protein, D-dimer, lactate dehydrogenase, ferritin)	Baricitinib 4mg by mouth daily (or 2mg daily for eGFR < 60 mL/min/1.73m^2) for up to 14 days or until hospital discharge plus standard of care	Standard of care plus matching placebo tablets	Standard of care according to local clinical practice, and could include: corticosteroids (including dexamethasone), antibiotics, antivirals (including remdesivir), antifungals, and antimalarials. VTE prophylaxis required unless contraindicated	Mortality at day 28 Disease progression by day 28 Time to recovery (days) Clinical improvement on disease severity scale Length of hospitalization Ventilator-free days Adverse events	Eli Lilly and Company

Table s24. Risk of bias for randomized control studies (baricitinib plus remdesivir vs. remdesivir alone)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ely 2021 [1]							
Kalil 2020 [2]							
Marconi 2021 [3]							
Marconi 2021 [4]							

Low	High	Unclear

Reference

1. Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomised, Placebo-Controlled Trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.10.11.21263897 [Preprint 12 October 2021]
2. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med **2021**; 384: 795-807
3. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med **2021**: S2213-600(21)00331-3 [Epub ahead of print 31 August 2021].
4. Marconi, VC, Ramanan, AV, de Bono, S, et al. Baricitinib plus Standard of Care for Hospitalized Adults with COVID-19. medRxiv **2021**. Available at: https://doi.org/10.1101/2021.04.30.21255934 [Preprint 3 May 2021].

Table s25. Should hospitalized patients with COVID-19 receive tofacitinib vs. no tofacitinib?

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Guimaraes/ 2021	15 study sites in Brazil	RCT	289 (144/145)	34.9%	Mean: 56 (14)	Patients ≥ 18 with RT-PCR positive for SARS-CoV-2 with evidence of COVID-19 pneumonia on radiographic imaging and who had been hospitalized for < 72 hours.	Tofacitinib 10 mg twice daily for up to 14 days or until hospital discharge	Placebo	Patients treated according to local standards which included glucocorticoids, antibiotic agents, anticoagulants, and antiviral agents	Death or respiratory failure through day 28 Clinical deterioration Avoidance of mechanical ventilation or ECMO at day 14 and day 28 Scores on the NIAID ordinal scare of disease severity at day 14 and day 28	Pfizer

										Adverse events	

Table s26. Risk of bias for randomized control studies (tofacitinib vs. no tofacitinib)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Guimaraes 2021 [1]							

Low	High	Unclear

Reference

1. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med **2021**; 385(5): 406-15.

Ivermectin

Table s27. Should hospitalized patients with severe COVID-19 receive ivermectin vs. no ivermectin?

Study/year	Country/ Hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Ahmed/ 2020	Bangladesh	RCT	68: ivermectin alone vs. ivermectin plus doxycycline vs. placebo (22/23/23)	54	Mean: 42	Hospitalized with a fever, cough, or sore throat	Ivermectin alone (12mg once daily for 5 days) Ivermectin plus doxycycline combination therapy (12mg ivermectin single dose plus doxycycline 200mg once, followed by 100mg twice daily for 4 days)	Placebo	N/A	Length of hospitalization Incidence of hypoxia Time to virologic clearance Biomarker levels Adverse events	Beximco Pharmaceutical Limited
Bukhari/ 2021	Pakistan/ Combined Military Hospital Lahore	RCT	86 (41/45)	15.1	Mean age: Intervention: 42.2 ± 12.0 Comparator: 39.0 ± 12.6	Mild-moderate disease. Mild disease defined as clinical symptoms ,excluding dyspnea or gasping, with no imaging findings of pneumonia. Moderate disease defined as fever,	Ivermectin 12mg once plus standard of care	(1) SoC	Standard of care, which consisted of Vitamin C 500mg daily, Vitamin D3 50,000 units weekly, and paracetamol 500mg as needed.	Negative PCR test by day 3, 7 and 14 Adverse reactions	None

						respiratory symptoms, and imaging findings of pneumonia.					
Chachar/2020	Pakistan/ FatimaMemorial Hospital	RCT	50 (25/25)	38%	Mean: 41.84 (15.7)	Outpatients with positive RT-PCR	Ivermectin 12mg every 12 hours x 3 doses total	No ivermectin	Symptomatic treatment	Symptom improvement at day 7 Rate of heartburn	N/A
Chaccour/2020	Spain/ Clínica Universidad de Navarra	RCT	24 (12/12)	50%	Median (IQR) Ivermectin: 26 years (19-36) Placebo: 26 years (21-44)	RT-PCR positive for SARS-CoV-2 and non-severe symptoms compatible with COVID-19 and symptom onset <72 hours	Ivermectin 400 mcg/kg x one dose	Placebo (not matched)	Symptomatic treatments	Mortality Viral clearance at day 7 Progression to severe disease Viral load at days 4, 7, 14, and 21 Symptom resolution at days 4, 7, 14, and 21 Seroconversion day 21	ISGlobal and University of Navarra
Gorial/ 2020	Iraq/ Al Sharif Hospital	Case control	87 (16/71)	28	Mean (SD; range) Patients receiving ivermectin: 44.87 years (10.64; 28-60) Patients not receiving ivermectin: 45.23 (18.47; 8-80)	Hospitalized patients with mild-moderate disease. Mild disease defined as symptomatic infection without evidence of pneumonia or hypoxia. Moderate disease defined as having clinical signs of pneumonia (fever, cough, dyspnea, tachypnea),	Ivermectin 200mcg/kg single dose	(1) SoC	Hydroxychloroquine 400mg twice a day on day 1, followed by 200mg twice daily for 5 days plus azithromycin 500mg once, followed by 250mg daily for 5 days	Mortality Clinical cure, defined as resolution of symptoms and viral clearance Length of hospitalization Adverse events	None

						without severe pneumonia, including SpO2 ≥ 90% on RA					
Hashim/ 2020	Iraq/ Alkarkh and Alforat hospitals	RCT	140 (70/70)	48	Range: Total population: 16-86 Mean (SD): Patients receiving ivermectin/doxy: 50.1 (9.3) Patients not receiving ivermectin: 47.2 (7.8)	Mild, moderate, severe, or critical disease defined according to WHO guidelines	Ivermectin 200 mcg/kg daily for 2 days, with a possible 3rd dose 7 days after the first dose based on clinical improvement, plus doxycycline 100mg twice daily for 5-10 days, based on clinical improvement	(1) SoC	Standard of care, according to clinical status of the patients, which could include: acetaminophen as needed, Vitamin C, zinc, Vitamin D3, azithromycin, dexamethasone, oxygen therapy/mechanical ventilation if needed	Mortality Disease progression after 3 days Time to recovery	Baghdad-Alkarkh General Directorate of Health
Kirti/ 2021	India/ All India Institute of Medical Sciences	RCT	112 (55/57)	27.7	Mean age: 52.5 ± 14.7	Mild-moderate disease. Mild defined as having no evidence of breathlessness or hypoxia. Moderate defined as breathlessness and/or hypoxia (90-95% SpO2 on room air), respiratory rate >23, no features of severe disease.	Ivermectin 12mg daily for 2 days	Placebo	Hydroxychloroquine, corticosteroids, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab	In-hospital mortality PCR positivity rate at day 6 Symptom resolution Discharge by day 10 Admission for ICU Mechanical ventilation	All India Institute of Medical Sciences
López-Medina/ 2021	Columbia/ Centro de	RCT	398 (200/198)	58	Median (IQR): 37 (29-48)	Mild disease (Home or hospitalized but not	Ivermectin 300 µg/kg/day for 5 days	Placebo	N/A	Mortality Time to symptom resolution	Grant from Centro de Estudios en

	Estudios en Infectología Pediátrica					receiving high-flow nasal oxygen or mechanical ventilation) within 5 days of illness onset				Clinical deterioration Hospitalization Oxygen supplementation Adverse events	Infectología Pediátrica
Mohan/ 2021	India/ All India Institute of Medical Sciences	RCT	Ivermectin 24mg vs 12mg vs placebo: mITT population (40/40/45)	11.2	Mean: 35.3 (10.4)	Non-severe COVID-19 (SpO2 on room air > 90%, no hypotension, no mechanical ventilation)	Ivermectin elixir at a dose of 12mg or 24mg once	Placebo	Hospital standard protocol, which included some patients receiving hydroxychloroquine, favipiravir, remdesivir, dexamethasone, dalteparin, antibiotics	Reduction in viral load Conversion to negative PCR by day 5 Time to clinical resolution Clinical status on day 14 on WHO ordinal scale Hospital-free days on day 28 Adverse effects	Research grant from Department of Science and Technology, Government of India
Podder/ 2020	Bangladesh/ Debidwar Upazila Health Complex	RCT	62 (32/30)	29%	Mean (SD) Total enrolled population: 39.16 (12.07) Ivermectin: 38.41 (11.02) Control: 39.97 (13.24)	Positive RT-PCR with mild (no evidence of pneumonia and SpO2 > 93% on RA) to moderate COVID-19 (signs of pneumonia with SpO2 > 90%)	Ivermectin 200 mcg/kg on day 1	SOC	Symptomatic treatment with doxycycline 100 mg every 12 hours for 7 days	Viral clearance at day 10 Duration of symptoms Time to resolution of symptoms	None
Pott-Junior/ 2021	Brazil/ Federal University of São Carlos	RCT	31: Ivermectin 100µg/kg vs 200µg/kg vs 400µg/kg vs SoC (6/14/7/4)	54.8	Mean (SD): 49.4 (14.6)	Hospitalized patients with mild disease, defined as a National Early Warning Score of 0-4.	Ivermectin 100µg/kg or 200µg/kg or 400µg/kg plus SoC	SoC	VTE prophylaxis, glucocorticoids	Viral clearance by day 7 Mean change in PCR cycle threshold values Adverse events	Federal University of São Carlos, Brazil
Rajter JC/2020	Florida, US (4	Retrospective cohort	280 (173/107)	45.4	Mean (SD):	Hospitalized patients with positive RT-	Ivermectin 200 mcg/kg and usual care;	SOC	Co-treatments up to the discretion of	Mortality	N/A

	hospitals)				59.6 (17.9)	PCR for SARS-CoV-2	second dose of ivermectin could be given at day 7 of treatment		treating clinicians which could include hydroxychloroquine, azithromycin, steroids, or other medications	Extubation rates for intubated patients Length of stay	
Abd-Elsalam/ 2021	Egypt/ 2 hospitals	RCT	164 (82/82)	50	Intervention: Mean of 42.4 (16) Control: Mean of 39.4 (16.9)	Hospitalized mild-moderate disease (no definition given)	Ivermectin 12 mg by mouth every day for 3 days and SoC	SoC	Paracetamol, oseltamivir, hydrocortisone	Mortality at one month Length of hospital stay Progression to mechanical ventilation Safety	None
Biber/ 2021	Israel/ hotels in 3 cities designated as isolation areas	RCT	89 (47/42)	21.6	Median: 35 (20-71)	Mild-moderate disease (non-hospitalized and not requiring oxygen)	Ivermectin 12 mg (40-69 kg) or 15 mg (≥ 70 kg) by mouth every day for 3 days	Placebo	None	Proportion with viral clearance at day 6 Culture viability days 2-6 Safety	None
Gonzales/ 2021	Mexico/ Hospital Centenario Miguel Hidalgo	RCT	106 (33 hydroxychloroquine/ 36 ivermectin/ 37 placebo)	37.8	Mean: 53.8 (16.9)	COVID-19 pneumonia requiring hospitalization and recently established hypoxemic respiratory failure or acute worsening of pre-existing lung or heart disease, but not requiring mechanical ventilation	Ivermectin 12 mg (<80 kg) or 18 mg (>80 kg) by mouth once Hydroxychloroquine 400 mg by mouth every 12 hours on day 1, followed by 200 mg every 12 hours for 4 days Both groups in addition to SoC	SoC	Dexamethasone, pharmacologic thromboprophylaxis	In-hospital mortality Length of hospital stay Discharge without respiratory deterioration or death Time to respiratory deterioration or death	Aguascalienes State Health Institute

Krolewiecki /2021	Argentina/ 4 hospitals	RCT	45 (30/15)	44	Intervention: Mean of 38.1 (11.7) Control: Mean of 42.3 (12.8)	Hospitalized but not receiving intensive care	Ivermectin 600 mcg/kg by mouth every day for 5 days	SoC	None	Proportion with viral clearance at day 5 Clinical evolution at day 7 and 30 Safety	Grant from Agencia Nacional de Promoción de la Investigación, Argentina
Mahmud/2021	Bangladesh/ Dhaka Medical College	RCT	400 (200/200)	41	Mean: 40	Mild-moderate disease (patients excluded if: >30 breaths/min, <90% SpO2 or requiring supplemental oxygenation, admitted to intensive care)	Ivermectin 12 mg by mouth every day for 5 days and doxycycline 100mg twice a day for 5 days in addition to SoC	SoC	Antihistamines, paracetamol, vitamins, low molecular weight heparin, remdesivir, "other antiviral drugs"	Mortality Disease progression Time to clinical recovery Proportion with positive test on day 14 Safety	None
Samaha/2021	Lebanon / Rayak Hospital	RCT	100 (50/50)	50	Intervention: Mean of 31.8 (7.9) Control: Mean of 31.6 (7.7)	Asymptomatic with with positive RT-PCR for SARS-CoV-2	Ivermectin weight-based dosing at 9 mg, 12 mg, or 150 mcg/kg as a single dose	Placebo	Zinc, vitamin C	Hospitalization at day 3 Clinical symptoms at day 3 Change in viral PCR CT values at day 3	None
Vallejos/2021	Argentina	RCT	501 (250/251)	47	Intervention: Mean of 42.6 (15.3) Control: Mean of 42.4 (15.8)	RT-PCR positive and non-hospitalized and not requiring home oxygen	Ivermectin weight-based dosing at 12 mg, 18 mg, or 24 mg every day for 2 days, plus SoC	SoC	Supplements including zinc and vitamin c	Mortality All-cause hospitalization Mechanical ventilation Proportion with viral clearance at day 12 Adverse Events	None

Figure s9a. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among hospitalized patients (from RCTs)

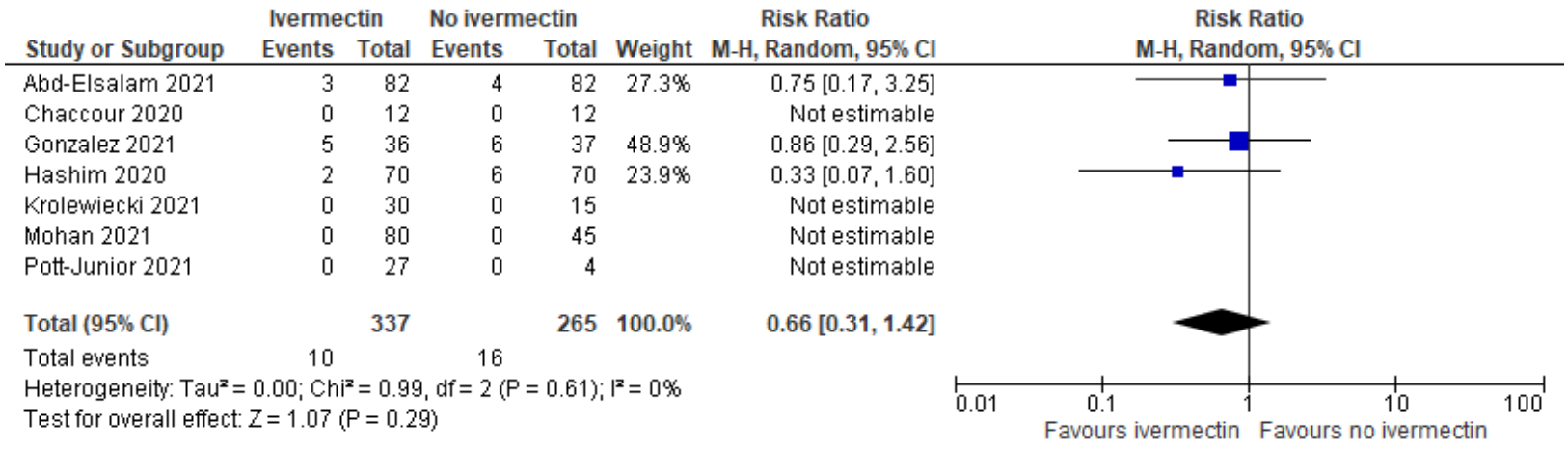


Figure s9b. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among hospitalized patients (from non-randomized studies)

Figure s9c. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (all studies)

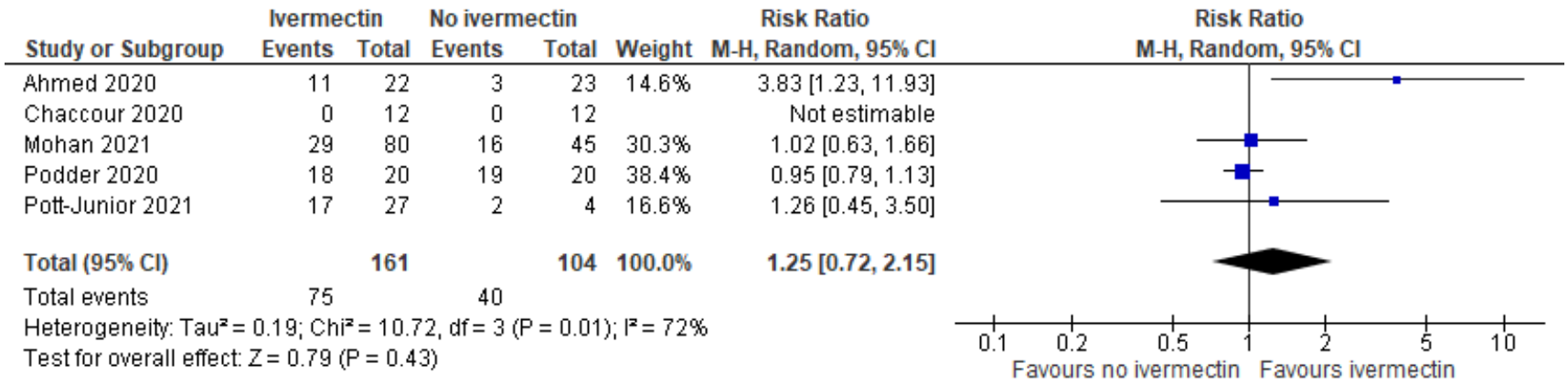


Figure s9d. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (without Ahmed 2020)

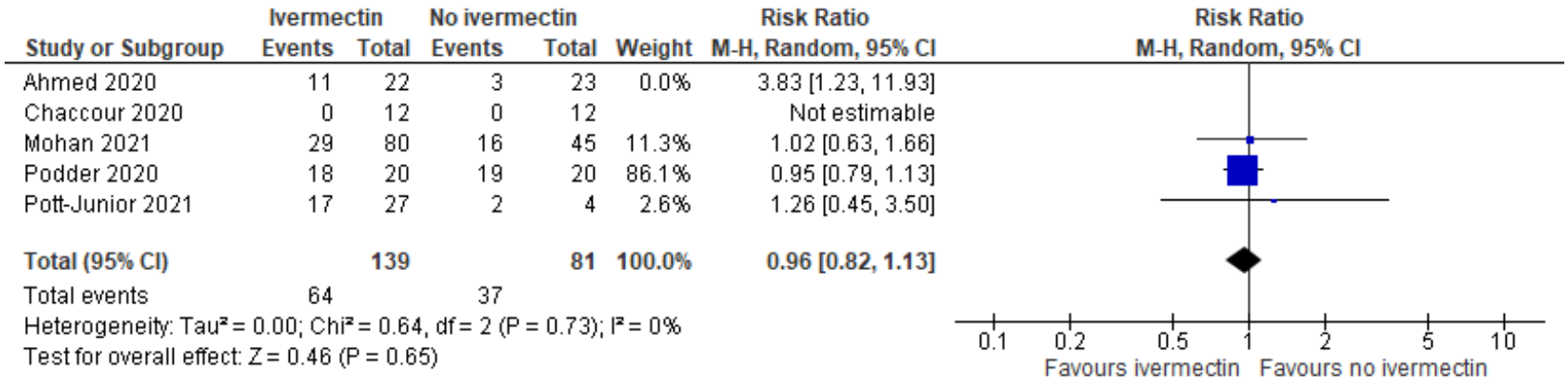


Figure s9e. Forest plot for the outcome of adverse events for ivermectin vs. no ivermectin among hospitalized patients

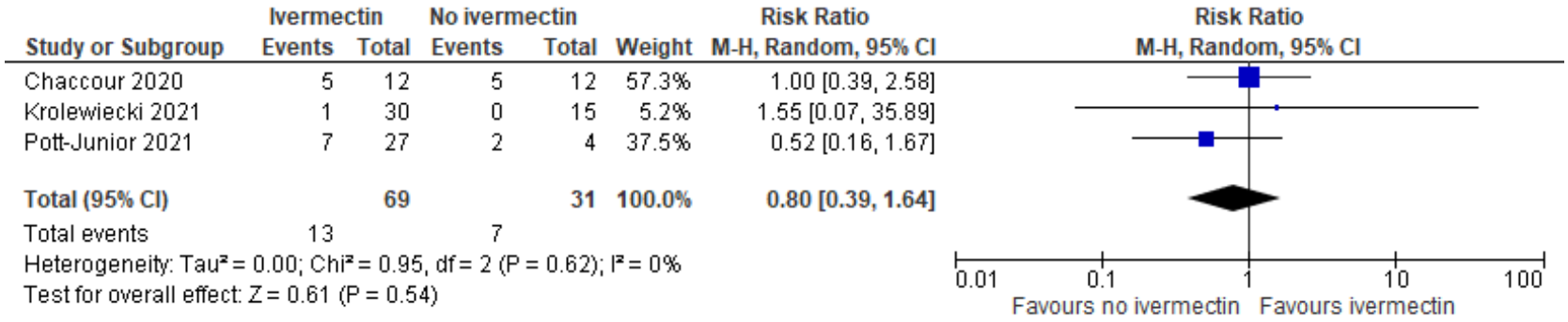


Figure s9f. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among ambulatory patients

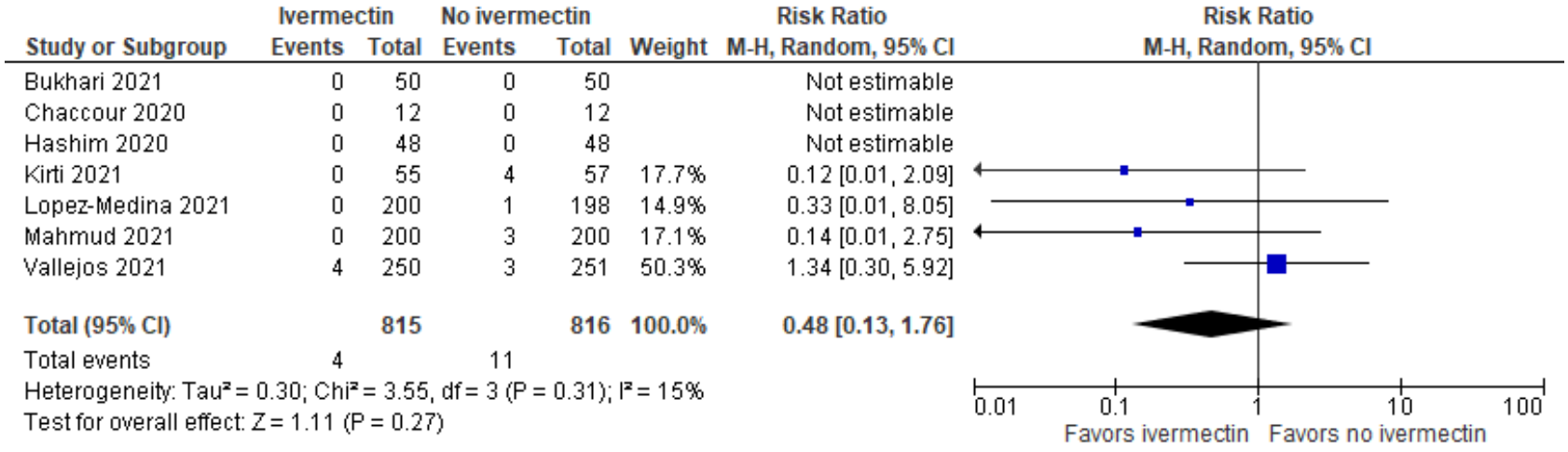


Figure s9g. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among ambulatory patients (sensitivity analysis excluding studies combining ivermectin plus doxycycline)

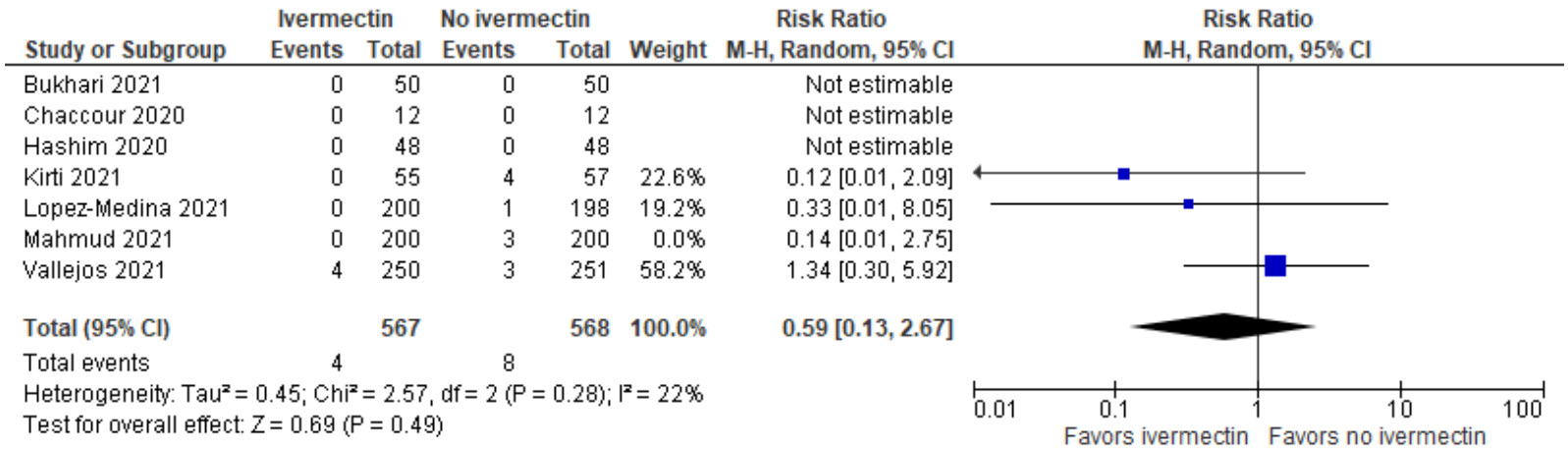


Figure s9h. Forest plot for the outcome of progression to severe disease for ivermectin vs. no ivermectin among ambulatory patients

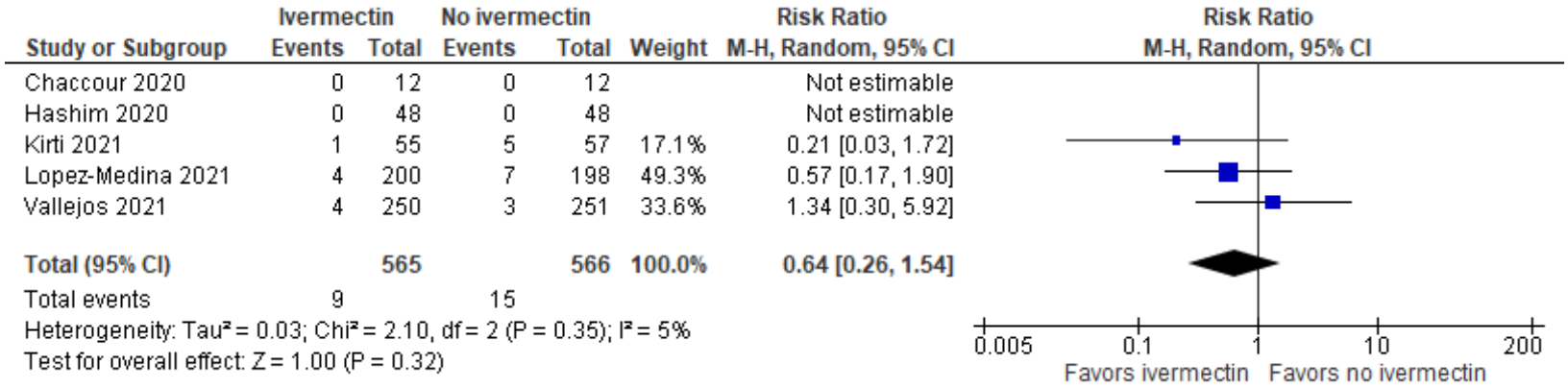


Figure s9i. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among ambulatory patients

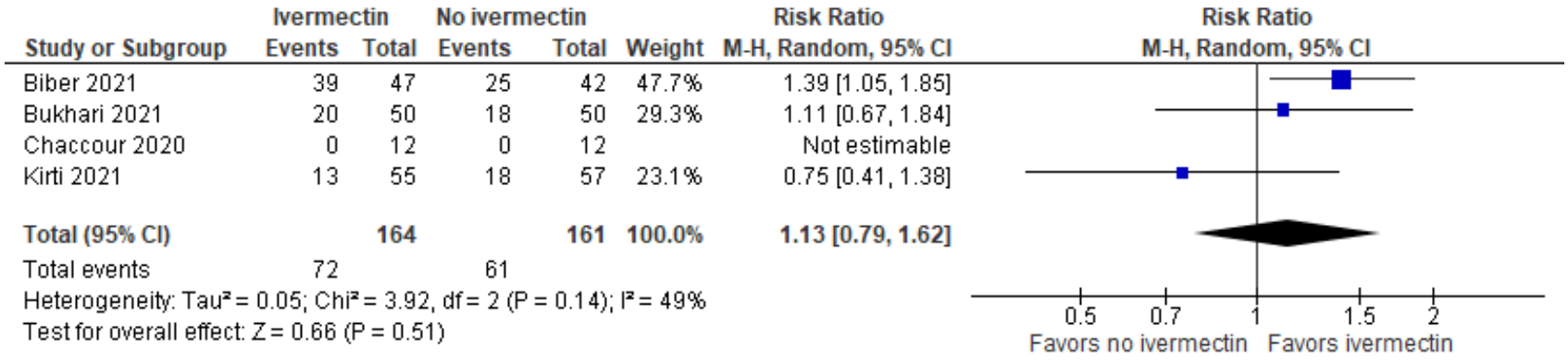


Figure s9j. Forest plot for the outcome of time to recovery for ivermectin vs. no ivermectin among ambulatory patients

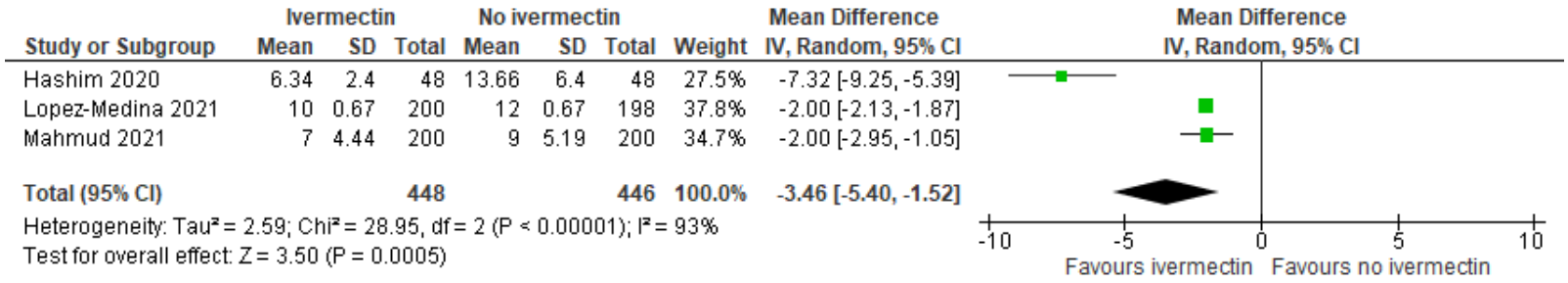


Table s28a. Risk of bias for randomized control studies (ivermectin vs. no ivermectin)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ahmed 2020[1]							
Bukhari 2021[2]							
Chaccour 2020[3]							
Chachar 2020[4]							
Hashim 2020[5]							
Ravikirti 2021[6]							
López-Medina 2021[7]							
Mohan 2021[8]							
Podder 2020[9]							
Pott-Junior 2021[10]							
Abd-Elsalam 2021[11]							
Biber 2021[12]							
Gonzalez 2021[13]							
Krolewiecki 2021[14]							
Mahmud 2021[15]							

Samaha 2021[16]							
Vallejos 2021[17]							

Low	High	Unclear

References

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Table s28b. Risk of bias for non-randomized control studies (ivermectin vs. no ivermectin)

Study + Overall RoB Judgement	Bias due to confounding	Selection Bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Gorial 2020 [1]							
Rajter 2020 [2]							

Low	Moderate	Serious	Critical

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Fluvoxamine

Table s29. Should ambulatory patients with COVID-19 receive fluvoxamine vs. no fluvoxamine?

Study/year	Country/ Hospital	Study design	N subjects (intervention/comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Lenze/2020	US/ St. Louis greater metropolitan area	RCT	152 (80/72)	71.7	Mean: 46 (13)	Outpatients with positive SARS-CoV-2 test within 7 days of enrollment and symptoms of COVID-19, who were not severe enough at baseline to meet trial's clinical worsening criteria (dyspnea and/or hospitalization for shortness of breath or pneumonia in addition to oxygen saturation	Fluvoxamine 50 mg by mouth for 1 day, followed by 100 mg by mouth twice a day for 2 days as tolerated, followed by 100 mg by mouth three times a day as tolerated through day 15	Placebo	None	Proportion of patients with clinical deterioration	Taylor Family Institute for Innovative Psychiatric Treatment at Washington University COVID-19 Early Treatment Fund Center for Brain Research in Mood Disorders at Washington University Bantly Foundation National Institutes of Health Grant

						<92% or on supplemental O2)					
Reis/ 2021	Brazil/ 11 cities in state of Minas Gerais	RCT	1472 (739/733)	57.5	Median: 50 (18)	Outpatients with positive SARS-CoV-2 test and symptoms consistent with COVID-19 within 7 days of trial enrollment, who were considered at high-risk of disease progression	Fluvoxamine 100mg twice a day for 10 days	Placebo	None	All-cause mortality	FastGrants The Rainwater Foundation

Figure s10a. Forest plot for the outcome of mortality for fluvoxamine vs. no fluvoxamine

Study or Subgroup	Fluvoxamine Events	Fluvoxamine Total	No fluvoxamine Events	No fluvoxamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lenze 2020	0	80	0	72		Not estimable
Reis 2021	17	741	25	756	100.0%	0.69 [0.38, 1.27]
Total (95% CI)		**821**		**828**	**100.0%**	**0.69 [0.38, 1.27]**
Total events	17		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)

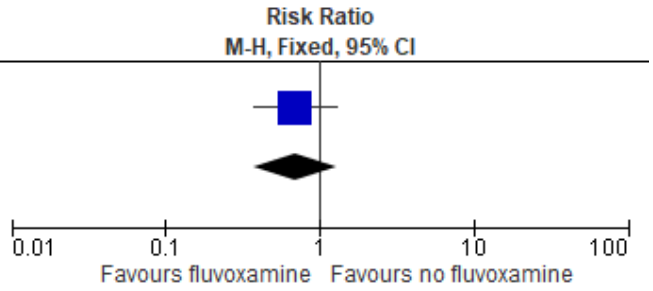

Figure s10b. Forest plot for the outcomes of hospitalization, emergency room visits (>6 hours), or oxygen saturation <92% for fluvoxamine vs. no fluvoxamine

Study or Subgroup	Fluvoxamine Events	Fluvoxamine Total	No fluvoxamine Events	No fluvoxamine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lenze 2020	0	80	6	72	5.5%	0.07 [0.00, 1.21]
Reis 2021	79	741	119	756	94.5%	0.68 [0.52, 0.88]
Total (95% CI)		**821**		**828**	**100.0%**	**0.64 [0.50, 0.84]**
Total events	79		125			

Heterogeneity: $Chi^2 = 2.47$, df = 1 (P = 0.12); $I^2 = 60\%$
Test for overall effect: Z = 3.28 (P = 0.001)

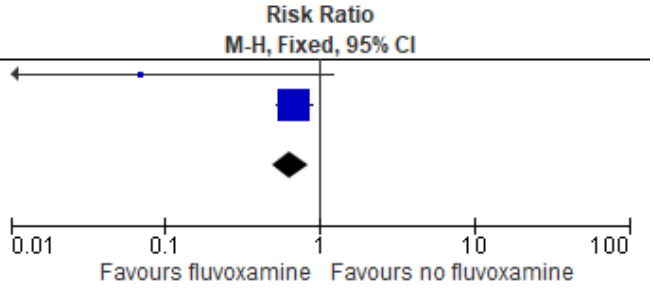

Figure s10c. Forest plot for the outcome of hospitalization for fluvoxamine vs. no fluvoxamine

Figure s10d. Forest plot for the outcome of serious adverse events for fluvoxamine vs. no fluvoxamine

Table s30. Risk of bias for randomized control studies (fluvoxamine vs. no fluvoxamine)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lenze 2020 [1]							
Reis 2021 [2]							

Low	High	Unclear

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