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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. (molnupiravir or mk-4482).ti,ab,kw.
91. upamostat.ti,ab,kw.
92. 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 or 90 or 91
93. 8 and 92
94. limit 93 to yr="2019 -Current"

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

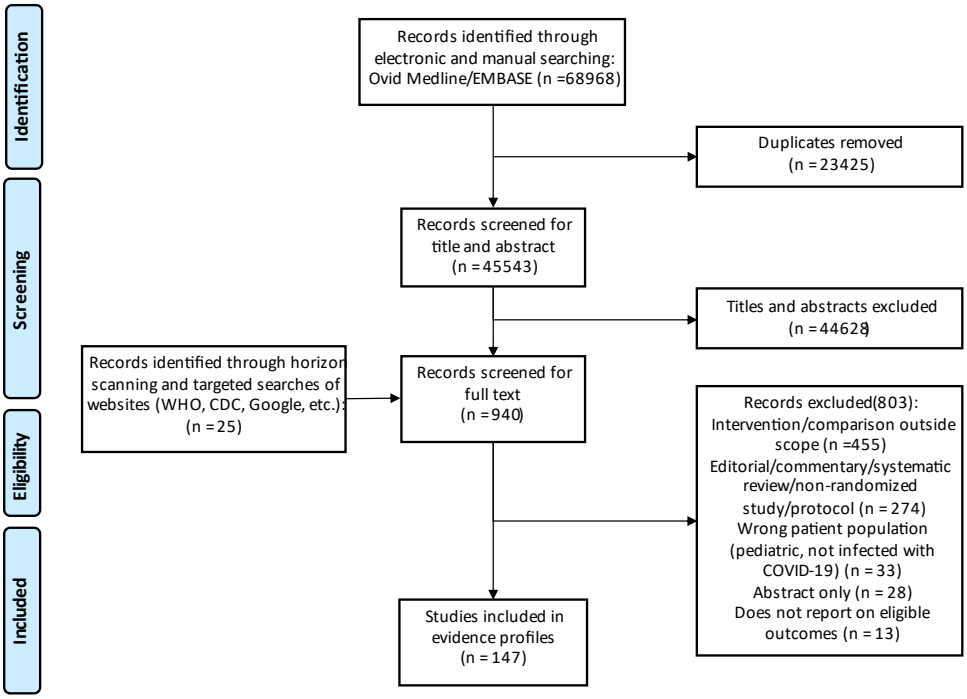
Protocol	**Favor study designs that may optimize rapid accrual (e.g., multicentric)**
Registration/ IRB-IEC	All RCTs must still be registered at clinicaltrials.gov. All studies must follow Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki, including IRB approval. IRBs 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 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]

References

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), **2020** 28 February.
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**; 180(7): 934-43.
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
Arshad / 2020 [1]	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
Cavalcanti/ 2020 [2]	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

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
										Adverse events	
Chen J/ 2020 [3]	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 [4]	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	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

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
						> 93% or PaO2/FIO2 ratio > 300 mmHg under hospital room air conditions					
Geleris / 2020 [8]	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 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

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[9]	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 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	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 initial dose and then every 12 hours for the next 9 days or until discharge (whichever occurred earlier)	(1) SoC	N/A	All-cause mortality at day 28 Discharged by day 28 Invasive mechanical ventilation Time until discharge alive (days) Adverse events	UK Research and Innovation/ National Institute for Health Research (NIHR) 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

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
											and Zoonotic Infections NIHR Clinical Trials Unit Support Funding
Ip/ 2020 [10]	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 [11]	USA/ All Veterans Health Administration	Retrospective Cohort	807 (198/215/395) Subcohort of 425 (114/148/163)	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	University of Virginia Strategic Investment Fund

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
	medical centres		had dispositions of death or discharge by end of study period							Risk of ventilation (adjusted hazards ratio) Length of hospital stay (days)	
Mahévas/ 2020 [12]	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 [14]	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 Investigators recorded the first three prescriptions for each medication. The majority of patients received HCQ dose of 200 mg, 400 mg, or 600 mg once or twice a day	(1) SoC (2) HCQ + AZ (3) AZ The majority of patients received AZ dose of 200 mg, 250 mg, 400 mg, or 500 mg once, once a day or twice a day	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

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
Self/ 2020 [15]	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 [16]	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

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
											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 [17]	USA/ NYU Langone Health (3 hospitals), NYC Health and Hospitals Bellevue Hospital	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 mechanical ventilation, ECMO, or	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 providers (included zinc, corticosteroids	Mortality at day 30 Progression to severe disease Change in clinical status Length of hospitalization	New York University Grossman School of Medicine NYU CTSA grant from National Center for Advancing

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
	Center, State University of New York Downstate Medical Center					receiving vasopressors			, tocilizumab, lopinavir/ritonavir, remdesivir), as well as co-enrollment in other COVID-19 therapeutic trials (included convalescent plasma, clazakizumab, remdesivir)	Viral clearance Adverse events	Translational Sciences
WHO Solidarity Trial Consortium/ 2021 [18]	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 view, with no contra-indication to any study drug	Lopinavir/ritonavir 400/200mg orally every 12 hrs x 14 days	(1) SoC	N/A	Mortality Ventilation	N/A
Yu/ 2020 [19]	China/	Retrospectiv	550 (48/502)	37.5	Median: 68 (59-77)	Critically ill patients had to meet one of the following	HCQ 200 mg tablet twice	(1) SoC	antiviral drugs (Lopinavir and Ritonavir, Entecavir	Mortality	Ministry of Science and

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
	Tongji Hospital	e cohort				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	daily x 7 to 10 days		hydrate, or Ribavirin), intravenous immunoglobuli n, antibiotics, immunoenhan cer, oxygen therapy	Average length of hospital stay (days) Hospital stay time before death (days) IL-6 levels in plasma after treatment	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
Arshad /2020 [1]	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
Cavalcanti /2020 [2]	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

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
										Adverse events	
Chorin/ 2020 [5]	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
Cipriani/ 2020 [6]	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 guidance, after positive results of RT-PCR assay of nasal and pharyngeal swabs	HCQ + AZ: HCQ 200 mg twice daily + AZ 500 mg once daily	N/A	N/A	Mortality Arrythmias Heart Rate QT interval	N/A

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
Gautret/ 2020 [7]	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 [10]	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 + AZ (doses not specified)	(1) HCQ (2) SoC	N/A	Unadjusted 30-day mortality Association between survival and treatment (hazards ratio) Adverse events	N/A
Magan oli/ 2020 [11]	USA/ All Veterans	Retrospective Cohort	807	N/A	N/A	Hospitalization with positive	HCQ	(1) HCQ + AZ	ACE inhibitors, angiotensin II receptor blockers,	Mortality Discharged	University of Virginia Strategic

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
	Health Administration medical centers		(198/215/395) Subcohort of 425 (114/148/163) had dispositions of death or discharge by end of study period			SARS-CoV-2 laboratory test		(2) SoC	mechanical ventilation	Risk of ventilation (adjusted hazards ratio) Length of hospital stay (days)	Investment Fund
Molina / 2020 [13]	France/ Saint-Louis Hospital *assumed based on author info at bottom*	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 receiving treatment for as well	Mortality Positive for SARS-CoV2 RNA 5/6 days after treatment initiation Adverse events	N/A
Rosenberg/ 2020 [14]	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	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	Mortality Abnormal ECG findings Risk of cardiac arrest	N/A

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
						conditions, initial vital signs and laboratory test results within 24 hours of admission, and chest imaging findings			common were aspirin (19.8%) and lisinopril (6.7%)	Adverse events	

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)

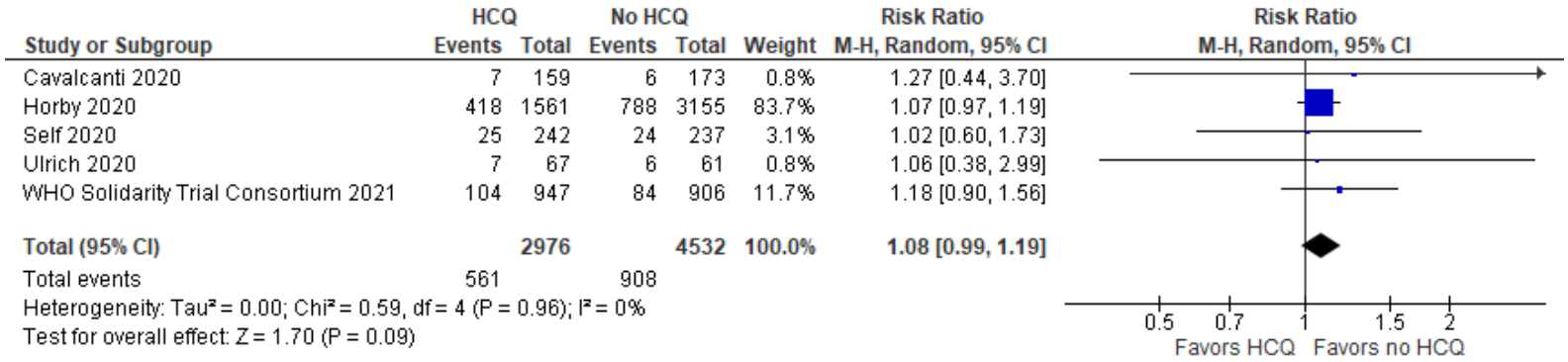


Figure s2b. Forest plot for the outcome of progression to mechanical ventilation demonstrating increased risk with HCQ treatment (RR: 1.10; 95% CI: 0.92, 1.31)

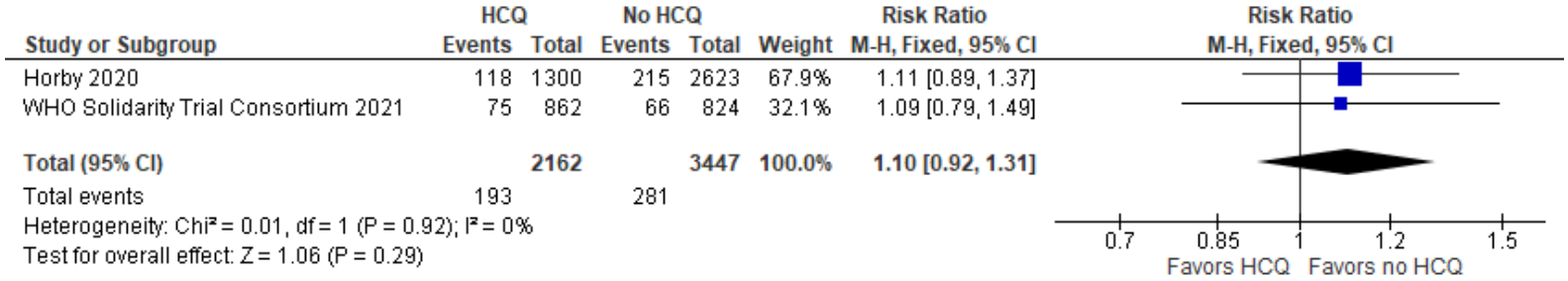


Figure s2c. Forest plot for the outcome of adverse events demonstrating increased risk with hydroxychloroquine treatment (RR: 2.36; 95% CI: 1.49, 3.75)

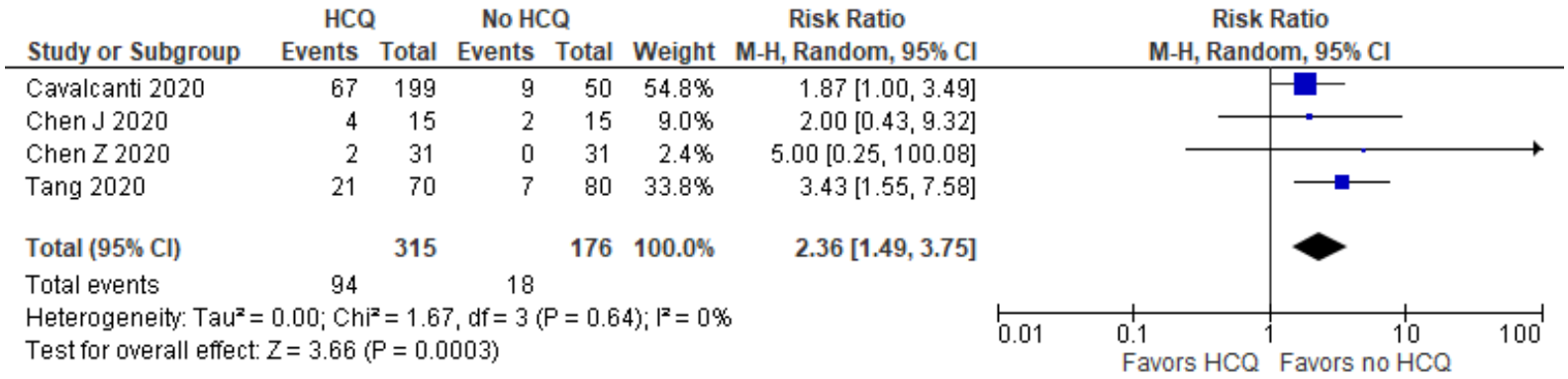


Figure s2d. Forest plot for the outcome of QT prolongation demonstrates increased risk with hydroxychloroquine treatment (RR: 2.89; 95% CI: 1.62, 5.16)

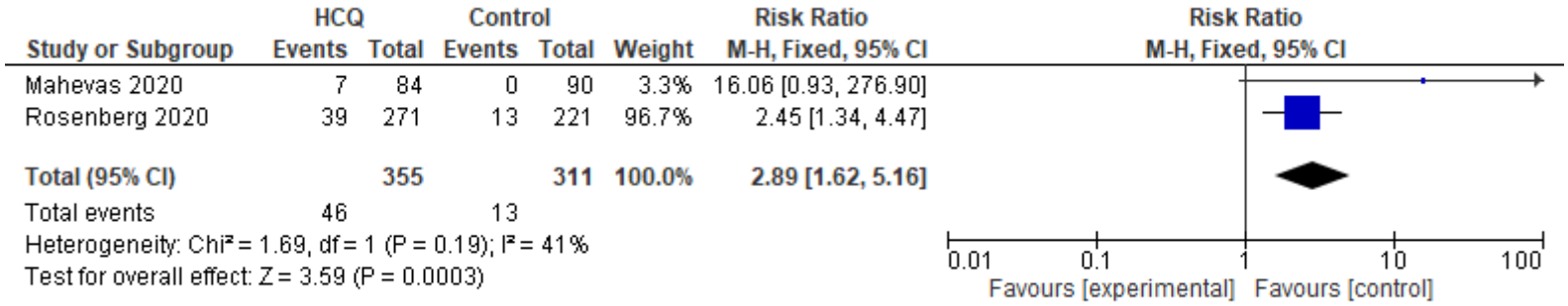


Table s4a. Risk of bias for randomized controlled studies (hydroxychloroquine ± azithromycin vs. no hydroxychloroquine ± azithromycin)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cavalcanti 2020 [2]							
Chen J 2020 [3]							
Chen Z 2020 [4]							
Horby 2020 [9]							
Self 2020 [15]							
Tang 2020 [16]							
Ulrich 2020 [17]							
WHO Solidarity Trial Consortium (Pan) 2020 [18]							

Low	High	Unclear

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 [8]							
Ip 2020 [10]							
Maganoli 2020 [11]							
Mahévas 2020 [12]							
Rosenberg 2020 [14]							
Yu 2020 [19]							

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. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med **2020**; 383: 2041-52.
3. 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(2): 215-9.
4. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv **2020**; Available at: https://doi.org/10.1101/2020.03.22.20040758 [Preprint 10 April 2020].
5. Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv **2020**; Available at: https://doi.org/10.1101/2020.04.02.20047050 [Preprint 3 April 2020].
6. Cipriani A, Zorzi A, Ceccato D, et al. Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin. Int J Cardiol **2020**; 316: 280-4.
7. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis **2020**; 34: 101663.
8. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med **2020**; 382(25): 2411-8.
9. 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**: Available at: https://doi.org/10.1101/2020.07.15.20151852 [Preprint 15 July 2020].
10. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients-An Observational Study. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.05.21.20109207 [Preprint 25 May 2020].
11. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.04.16.20065920 [Preprint 23 April 2020].
12. Mahévas 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**; Available at: https://doi.org/10.1101/2020.04.10.20060699 [Preprint 14 April 2020].
13. Molina JM, Delaugerre C, Goff J, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses **2020**; 50(4): 384.

14. 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**; 323(4): 2493:502.
15. 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**; 324(21): 2165-76.
16. 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: m1849.
17. 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**; 7(10): ofaa446.
18. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384(6): 497-511.
19. 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**; 63(10): 1515-21.

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 [1]	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 [2]	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

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
											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
Mitijà / 2020 [3]	Spain (Catalonia)	RCT	2313 (1115/1198)	73	Mean: 48.6 (19)	Asymptomatic patients with close contact with person with confirmed COVID-19 infection within 7 days	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 detection or symptoms compatible with COVID-19) Safety	YoMeCorono crowdfunding campaign Generalitat de Catalunya Zurich Seguros Synlab Diagnósticos Laboratorios Rubió

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
											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

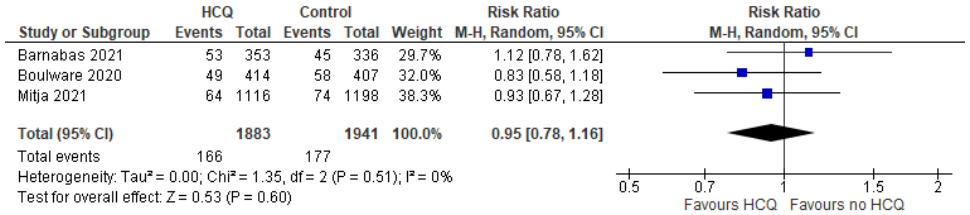


Figure s3b. Forest plot for the outcome of hospitalization at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

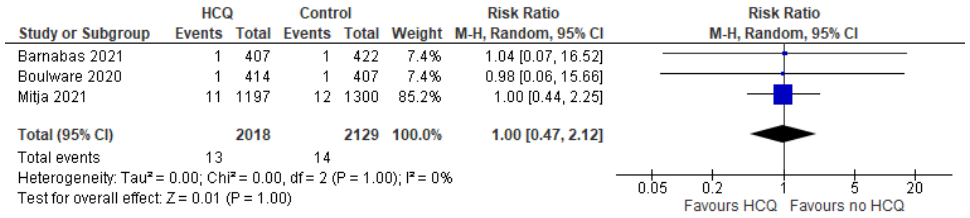


Figure s3c. Forest plot for the outcome of mortality at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

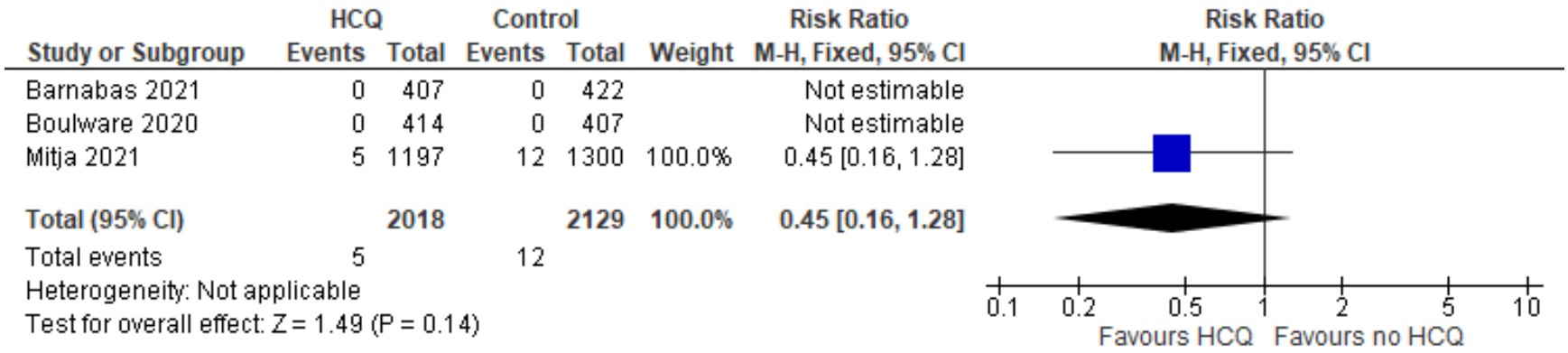


Figure s3d. Forest plot for the outcome of serious adverse events at 14 days for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19

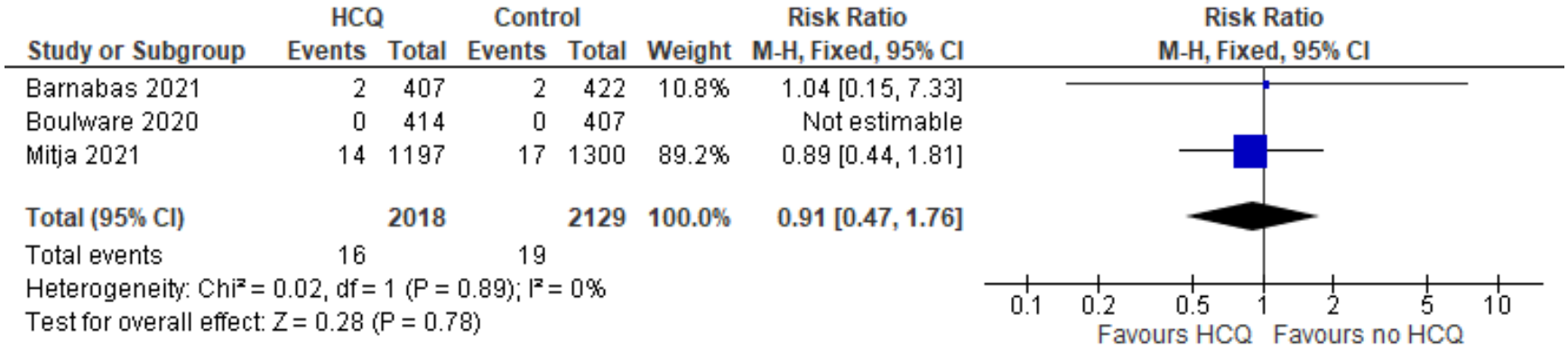


Table s6. Risk of bias for randomized control studies (hydroxychloroquine as post-exposure prophylaxis vs. no hydroxychloroquine for post-exposure hydroxychloroquine vs. no hydroxychloroquine for persons exposed to COVID-19)

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]							
Mitijà 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 persons exposed to or with 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 [1]	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 oxygen at or below 300 mg Hg	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 Grant for Distinguished Young Scholars
Labhardt / 2021 [2]	Brazil and Switzerland/4 centers	RCT	318 (209/109)	49.4	Median: 39 (28-50)	Asymptomatic with documented exposure as a close contact with a person with confirmed	Lopinavir 400 mg/ritonavir 100 mg twice daily for 5 days	Surveillance and no PeP	None	Incidence of COVID-19 at day 21 Severity of COVID-19	Swiss National Science Foundation Private Foundation of Geneva

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
						SARS CoV-2 infection				Serious adverse events Acceptability of PeP Adherence Drug levels at day 5	University Hospitals
RECOVERY Collaborative Group (Horby)/ 2020 [3]	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)

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
											Population Health Research Unit NIHR Health Protection Unit in Emerging and Zoonotic Infections NIHR Clinical Trials Unit Support Funding
Reis/ 2021 [4]	Brazil/10 cities	RCT	685 (244/227) Additional 214 patients randomized to HCQ alone	55%	Median: 53 (18-94)	Adults with symptom onset of flu-like symptoms within 8 days or CT chest consistent with COVID-19 AND one criterion for high risk to progression to severe disease	Lopinavir 800 mg/ritonavir 200 mg, then lopinavir 400 mg/ritonavir 100 mg every 12 hours for an additional 9 days	Placebo	None	Mortality COVID-associated hospitalization Hospital admissions Proportion of patients with negative swab at days 3, 7, and 14 Treatment-emergent adverse events	Bill and Melinda Gates Foundation
WHO Solidarity Trial Consorti	30 countrie	RCT	2771 (1399/1372)	38.0	N/A	≥18 years, hospitalized with a diagnosis of COVID-19,	Lopinavir/ritonavir 400/200mg	(1) SoC	N/A	Mortality Ventilation	N/A

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
um (Pan)/ 2020 [5]	s/ 405 hospitals					not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug	orally every 12 hrs x 14 days				

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

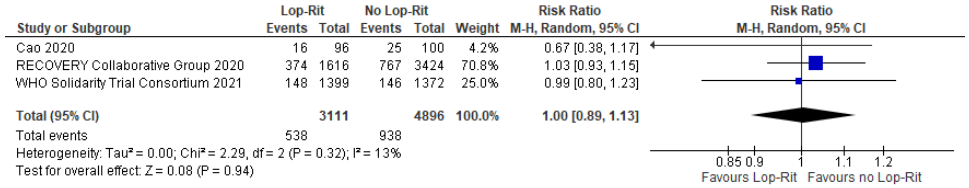


Figure s4b. Forest plot for the outcome of invasive mechanical ventilation for lopinavir/ritonavir vs. no lopinavir/ritonavir in hospitalized patients with severe COVID-19

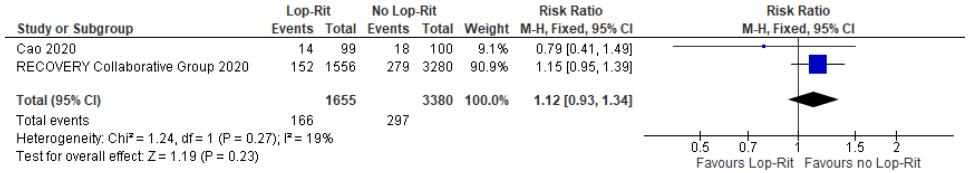


Table s8. Risk of bias for randomized controlled studies (lopinavir/ritonavir vs. no lopinavir/ritonavir)

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]							
Labhardt 2021 [2]							
RECOVERY Collaborative Group (Horby) 2020 [3]							
Reis 2021 [4]							
WHO Solidarity Trial Consortium (Pan) 2020 [5]							

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**; 382(19): 1787-99.
2. Labhardt ND, Smit M, Petignat I, et al. Post-exposure Lopinavir-Ritonavir Prophylaxis versus Surveillance for Individuals Exposed to SARS-CoV-2: The COPEP Pragmatic Open-Label, Cluster Randomized Trial. EClinicalMedicine **2021**; 42: 101188.
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.
4. Reis G, Moreira Silva E, Medeiros Silva DC, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA Netw Open **2021**; 4(4): e216468.
5. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.

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
Corral-Gudino/ 2020 [1]	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-CoV-2 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
Fadel/ 2020 [2]	USA/five hospitals in southeast and south-	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	Methylprednisolone 0.5 to 1mg/kg twice daily divided into 2 doses	(1) SoC: with or without a combination of lopinavir/ritonavir and	HCQ 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice	Mortality Respiratory failure requiring	N/A

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
	central Michigan					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	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)	ribavirin or HCQ	daily on days 2-5 SoC: supplemental oxygen, HFNC, invasive ventilation, antibiotic agents, antiviral agents, vasopressor support, and renal-replacement therapy	mechanical ventilation ARDS Length of hospital stay (days) Duration of mechanical ventilation (days) Shock AKI Adverse events	
Fernandez-Cruz/ 2020 [3]	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	(1) SoC	HCQ, AZ, Lopinavir/Ritonavir, Interferon, TCZ, Anakinra, ritonavir-boosted darunavir/doxycycline/clarithromycin and other antibiotics	Mortality	N/A

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
							of 10 (8-13) days)				
Horby / 2021 [4]	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. Comparator (at baseline): 24% did not receive any O_2, 60% received O_2 only and 16% 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 Receipt and duration of ventilation	Medical Research Council and National Institute for Health Research
Lu/ 2020 [5]	China/	Retrospective cohort	244 (151/93)	48.0	Median (IQR): 62 (50-71)	Critically ill patients: those who were admitted to intensive care wards and	Steroids: hydrocortisone-equivalent dosage range:	(1) SoC	Antiviral therapy (oseltamivir, arbidol,	Mortality at day 28	Supported by the National Key R&D Program of

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
	Tongji Hospital					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	100-800mg/day (median [IQR] administration duration of 8 days [4-12]) (median time to steroid treatment from symptom onset not reported)		lopinavir/ritonavir, ganciclovir, interferon-a), antibacterials, gamma globulin, mechanical ventilation, muscle relaxant, HFNC	Overall cohort mortality (odds ratio) Adverse events	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 [6]	Italy/ 14 Respiratory High	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	Methylprednisolone loading dose of 80 mg/kg iv at study entry, followed by an	(1) SoC	N/A Use of tocilizumab or other experimental	Mortality Transfer to ICU Duration of invasive	Supported with the resources and use of facilities at the

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
	Dependency Units					infiltrates, CRP >100 mg/L, and/or diagnosis of ARDS	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 SatHbO2 ≥ 95% on room air) (median time to steroid treatment from symptom onset not reported)		treatment was considered an exclusion criterion	mechanical ventilation (days) Risk of composite primary endpoint Adverse events	University Hospital of Trieste and Memphis VA Medical Center
Wang/ 2020[7]	China/ Union Hospital of Huazhong	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+	Methylprednisolone1-2mg/kg/day once a day x 5-7 days	(1) SoC	Oxygen therapy, antiviral therapy (a-interferon, lopinavir/rito	Mortality Hospital Discharge	Natural Science Foundation of China

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
	University of Science and Technology					with complication of hypertension, diabetes, coronary disease, cancer, pulmonary heart disease, structural lung disease and immunosuppressed	(median time to steroid treatment from symptom onset not reported)		navir), immunoenhancement therapy (thymosin), prevention of bacterial infection, relieving cough eliminating phlegm and nutritional support	Number of days for no fever Use of supplemental oxygen therapy	
Yuan/ 2020[8]	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 [4]							

Low	High	Unclear

References

1. Corral-Gudino L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.06.17.20133579 [Preprint 18 June 2020].
2. Fadel R, Morrison AR, Vahia A, et al. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. Clin Infect Dis **2020**; 71(16): 2114-20.
3. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, et al. Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality: A retrospective controlled cohort study. **2020**: Available at: https://doi.org/10.1101/2020.05.22.20110544 [Preprint 26 May 2020].
4. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.06.22.20137273 [Preprint 22 June 2020].
5. Lu X, Chen T, Wang Y, et al. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.04.07.20056390 [Preprint 11 April 2020].
6. Salton F, Confalonieri P, Santus P, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.06.17.20134031 [Preprint 25 June 2020].
7. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.03.06.20032342 [Preprint 12 March 2020].
8. Yuan M, Xu X, Xia D, et al. Effects of Corticosteroid Treatment for Non-Severe COVID-19 Pneumonia: A Propensity Score-Based Analysis. Shock **2020**; 54(5): 638-43.

Inhaled Corticosteroids

Table s11. Should ambulatory patients with mild-to-moderate COVID-19 receive treatment with **i**nhaled corticosteroids compared to no inhaled 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
ACTIV-6/ 2022 [1]	United States/9 3 sites	RCT	1277 (656/621)	63.2	Mean age: 47 (12)	Non-hospitalized adults aged ≥30 years, experiencing ≥2 symptoms of acute infection for ≤7 days	Inhaled fluticasone furoate 200 µg once daily	Placebo	Not specified	Time to recovery Hospitalization or death by day 28 Time unwell with ongoing symptoms COVID-19 clinical progression scale on days 7, 14, 28 Mortality though day 28 Urgent care visit, emergency department visit, or hospitalization through day 28	National Center for Advancing Translational Sciences Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority
Agusti/ 2022 [2]	Spain, Argentin a	RCT	120 (58/62)	52.9	Mean age: 51.1 (13.7)	PCR-confirmed SARS-CoV-2 infection, with radiological evidence (plain chest radiography) of pneumonia	Inhaled budesonide 400 µg/12 h via Pulmicort Turbuhaler	SoC	Not Specified	Proportion of patients with disease progression Adverse events	AstraZeneca GlaxoSmithKlin e Menarini Chiesi

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
											Sanofi Novartis Boehringer Ingelheim
Clemency/ 2021 [3]	U.S./ 10 centers	RCT	400 (197/203)	55.3	Mean age: 43.3 (16.9)	Positive SARS-CoV-2 antigen test within 72 hours, non-hospitalized, not hypoxic, with at least 1 symptom of COVID-19 (fever, cough, dyspnea)	Ciclesonide MDI 160 mcg/actuation, 2 puffs twice daily plus standard supportive care for 30 days	(1) SoC	Supportive care at discretion of treating provider (4 patients received antivirals, 1 patient monoclonal antibodies)	Time to alleviation of all COVID-19 symptoms ED visits Hospitalizations All-cause mortality Proportion of patients with alleviation of COVID-19 symptoms Adverse events	Covis Pharma GmbH National Center for Advancing Translational Sciences National Heart, Lung, and Blood Institute
Duvignaud/ 2022 [4]	France/14 trial centres	RCT	217 (110/107)	51.2%	Median (range): 63 (50-86)	COVID-19 with first symptoms ≤7 days earlier; positive SARS-CoV-2 nasopharyn-geal RT-PCR or antigen test	10-day treatment with ALVESCO 160 mg, two puffs twice a day using an inhalation chamber (640 mg of ciclesonide per day)	Control: 10-day treatment with a combination of vitamins and trace elements (Azinc Vitality, 2 pills per day).	Not specified	Grade 3-4-5 adverse events. Hospitalization Death Adverse events of any grade WHO Ordinal Scale for Clinical Improvement	French Ministry of Health French National Research Agency University of Bordeaux Inserm/REACTing

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
Ezer/ 2021 [5]	Canada/ Centers across 3 provinces (Quebec, Ontario, British Columbia)	RCT	203 (105/98)	53.7	Median age: 35 (27-47)	Positive SARS-CoV-2 PCR test within 5-6 days, unvaccinated, non-hospitalized, with at least 1 symptom of fever, cough, or shortness of breath	Inhaled ciclesonide 600 mcg twice daily plus intranasal ciclesonide 200 mcg/day for 14 days	Placebo	Not specified	Proportion with resolution of fever and respiratory symptoms at day 7 Hospitalizations COVID-19 mortality Resolution of fever and respiratory symptoms at day 14 Improvement in overall feeling at day 7 and 14 Adverse events	McGill University Health Centre Foundation McGill Interdisciplinary Initiative in Infection and Immunity
Ramakrishnan/ 2021 [6]	Oxfordshire, United Kingdom	RCT	139 (70/69)	57.6	Mean age: Intervention: 44 (No SD reported) Control: 46 (No SD reported)	Onset of COVID-19 symptoms within 7 days of trial enrollment and non-hospitalized	Budesonide dry powder inhaler 400 mcg/actuation, 2 puffs twice daily plus supportive care per NHS guidelines until patient felt better or the primary outcome was achieved	Supportive care	Not specified	COVID-19 related urgent care visit, ER visit, or hospitalization Time to symptom resolution Viral symptoms measure by Common Cold Questionnaire Influenza Patient-reported Outcome questionnaire Oxygen saturation Body temperature	National Institute for Health Research Biomedical Research Centre AstraZeneca

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
										Viral load Adverse events	
Song/ 2021 [7]	South Korea/ 6 hospitals	RCT	61 (35/26)	53	Median age: 53 (35-61)	Hospitalized patients with positive SARS-CoV-2 PCR within 3 days of diagnosis or 7 days from symptom onset, with mild-moderate disease (National Early Warning Score of 0-4 and O_2 sat ≥95% on RA)	Ciclesonide 320 mcg inhaler twice daily for 14 days plus standard of care	(1) SoC	Hydroxychloroquine 400mg daily for 14 days (8 patients in ciclesonide group)	SARS-CoV-2 eradication rate based on qRT-PCR on day 14 SARS-CoV-2 eradication rate at day 7 and 10 Rate of clinical improvement at day 7, 10, 14 Rate of clinical failure within 28 days Adverse events	National Research Foundation of Korea Korea University Guro Hospital
Yu/ 2021 [8]	United Kingdom	RCT	1959 (833/1126)	51.8	Mean age: 64.2 (7.6)	Patients in the community age ≥ 65 or ≥ 50 with comorbidities with suspected or confirmed COVID-19 within 14 days with ongoing symptoms (fever, cough, or loss of taste or smell)	Budesonide 800 mcg inhaler twice daily for 14 days plus standard of care	(1) SoC	None	COVID-19 related hospital admission or death within 28 days Time to first reported recovery Time to sustained recovery Time to alleviation of symptoms Oxygen use ICU admission	National Institute of Health Research United Kingdom Research Innovation

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
										Mechanical ventilation WHO-5 Wellbeing Index New household infections Adverse events	

Figure s5a. Forest plot for the outcome of mortality for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

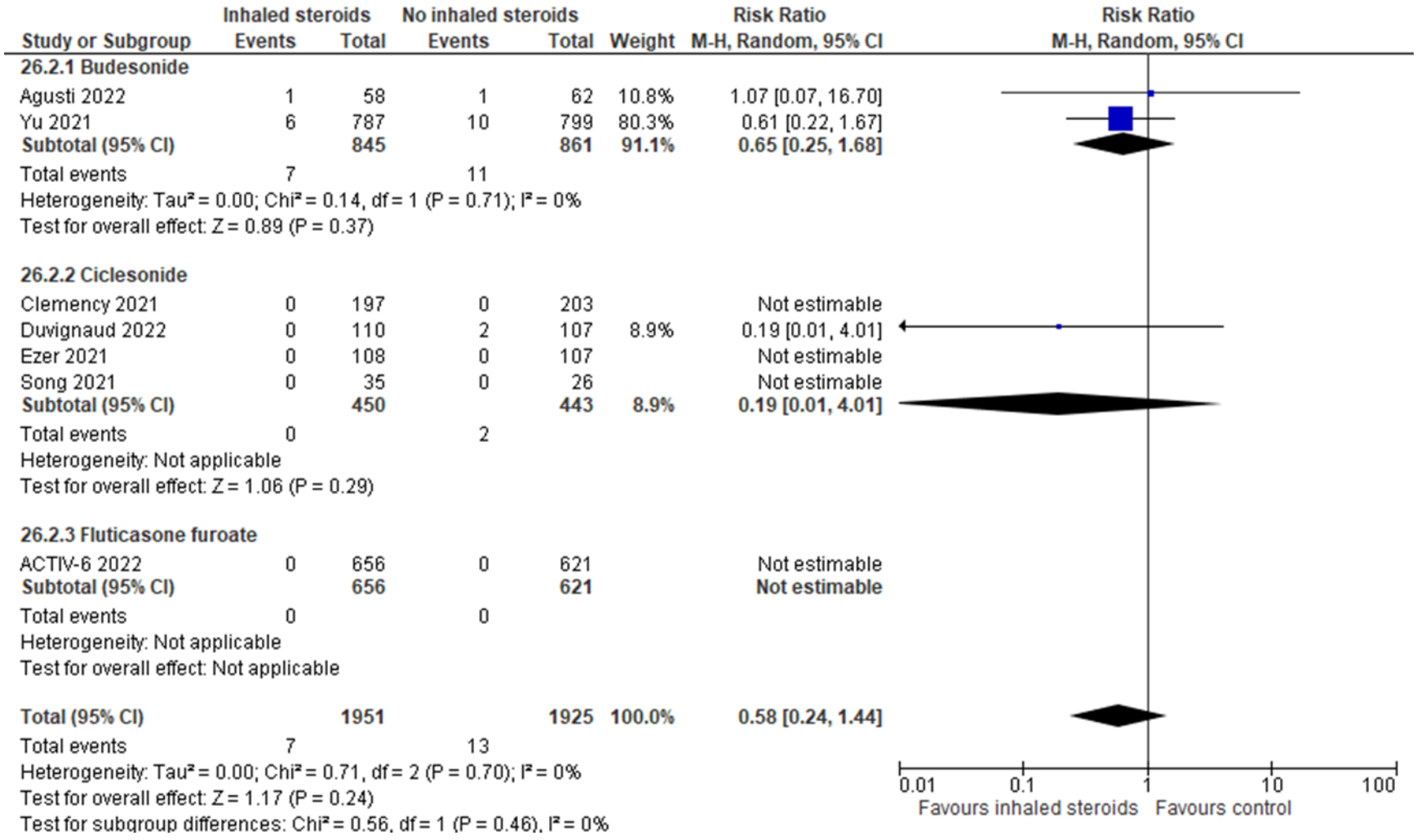


Figure s5b. Forest plot for the outcome of hospitalization for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

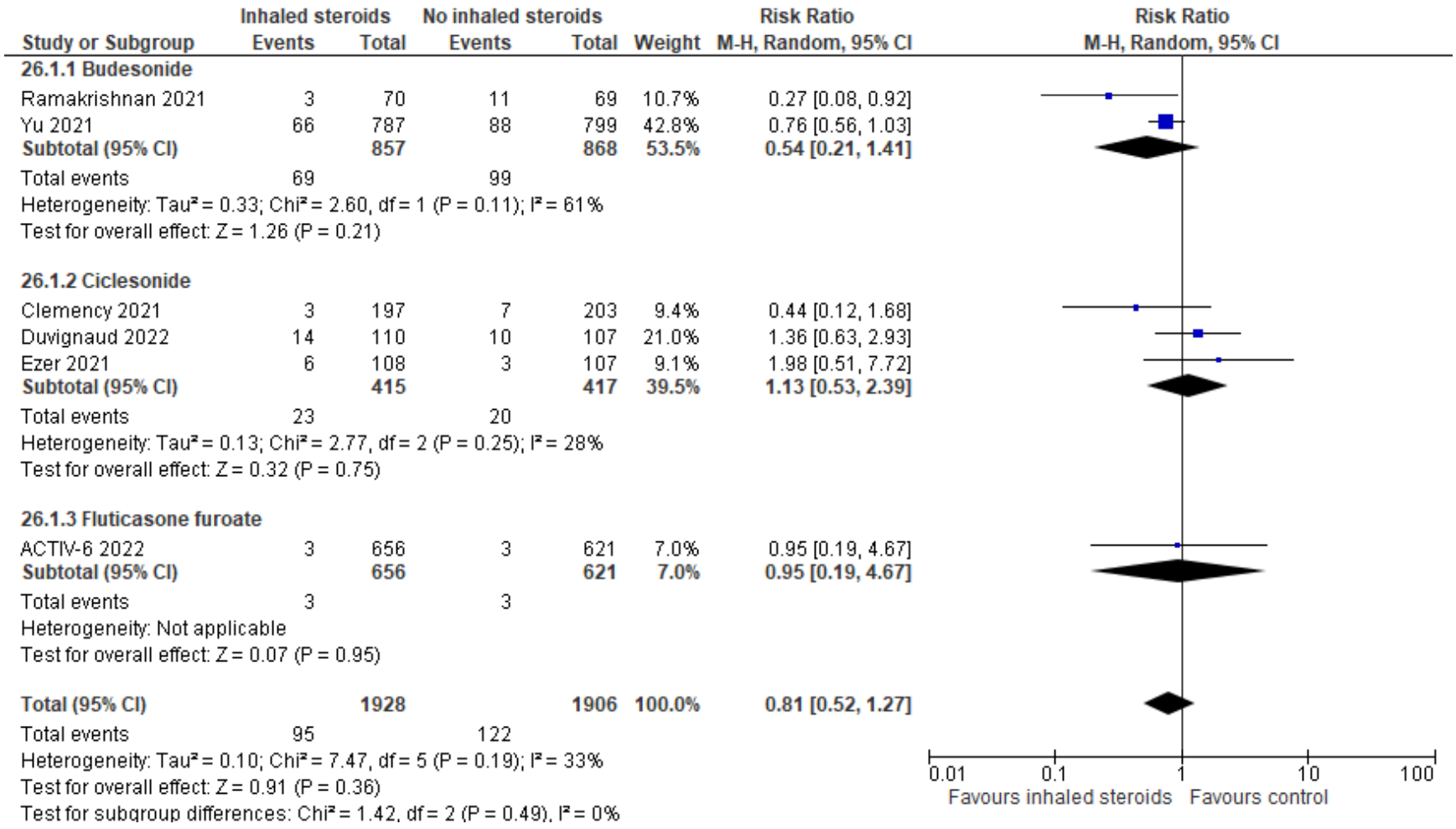


Figure s5c. Forest plot for the outcome of serious adverse events for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

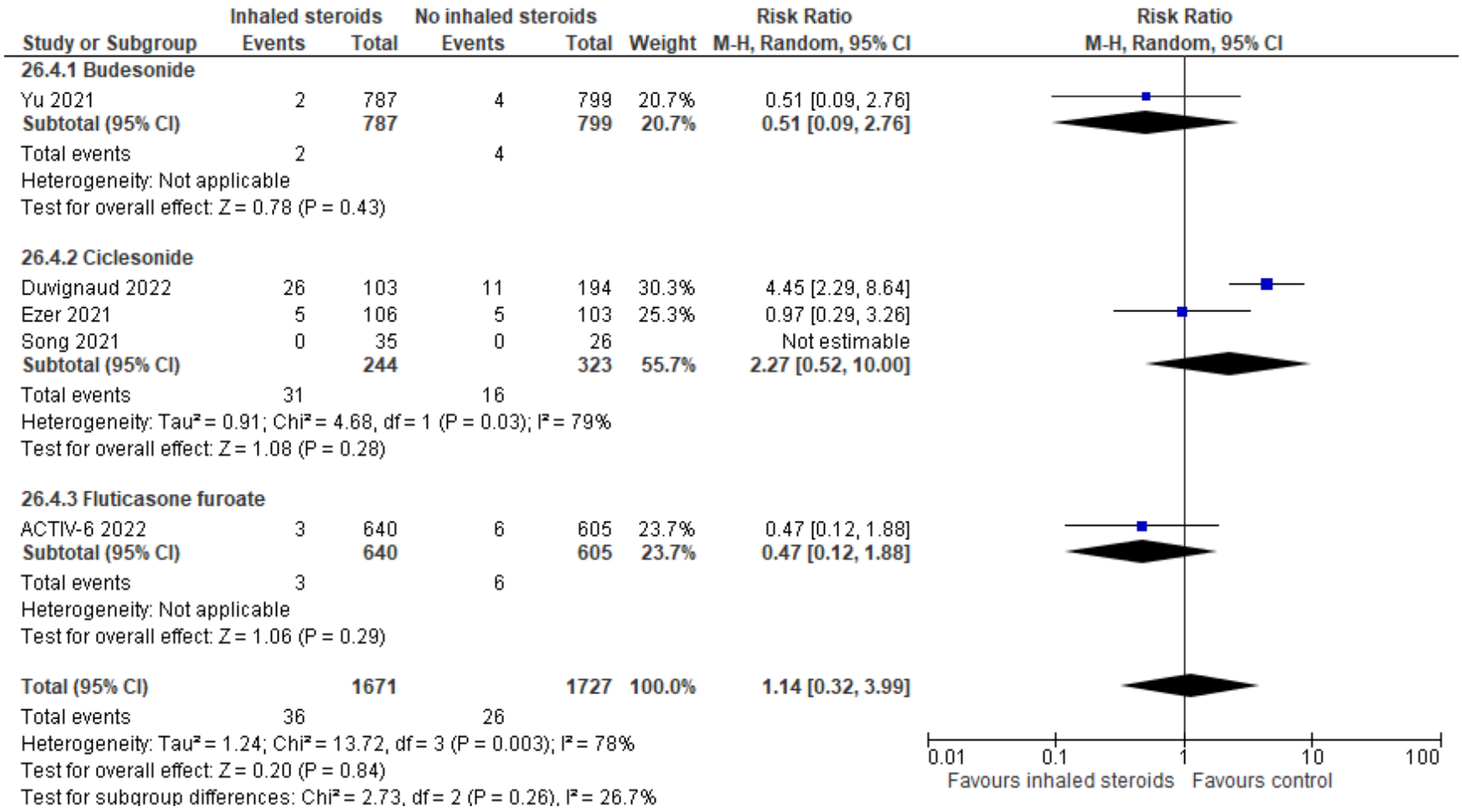


Table s12. Risk of bias for randomized controlled studies (inhaled corticosteroids vs. no inhaled corticosteroids)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ACTIV-6 2022[1]							
Agusti 2022[2]							
Clemency 2021[3]							
Duvignaud 2022[4]							
Ezer 2021[5]							
Ramakrishnan 2021[6]							
Song 2021[7]							
Yu 2021[8]							

Low	High	Unclear

References

1. Accelerating Covid-19 Therapeutic I, Vaccines -6 Study G, Naggie S. Inhaled Fluticasone for Outpatient Treatment of Covid-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial. medRxiv **2022**.
2. Agusti A, De Stefano G, Levi A, et al. Add-on inhaled budesonide in the treatment of hospitalised patients with COVID-19: a randomised clinical trial. Eur Respir J **2022**; 59(3).
3. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA Intern Med **2022**; 182(1): 42-9.
4. Duvignaud A, Lhomme E, Onaisi R, et al. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). Clin Microbiol Infect **2022**; 28(7): 1010-6.
5. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. BMJ **2021**; 375: e068060.
6. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med **2021**; 9(7): 763-72.
7. Song JY, Yoon JG, Seo YB, et al. Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial. J Clin Med **2021**; 10(16): 3545.
8. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet **2021**; 398(10303): 843-55.

Interleukin-6 Inhibitors (Tocilizumab)

Table s13. 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
Hermine/ 2020 [1]	France/9 hospitals	RCT	131 (63/67)	32.0	Median (IQR): 64.0 (57.1-74.3)	Patients were included in the CORIMUNO-19 cohort if they had 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	TCZ (8 mg/kg infusion, maximum 800 mg) *administration of an additional 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.	(1) SoC	Antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants	Mortality (Day 28) Mechanical ventilation or death (Day 14) Adverse events	Ministry of Health, Programme Hospitalier de Recherche Clinique Foundation for Medical Research AP-HP Foundation The Reacting program
Horby/ 2021 [2]	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	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	Usual care	Co-interventions according to main randomization and use of steroids were permitted; 82% of participants in each arm received	Mortality at day 28 Receipt of mechanical ventilation or death Successful cessation of invasive	UK Research and Innovation (Medical Research Council) and National Institute of Health Research

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
						and CRP ≥ 75) could be considered for randomization to tocilizumab or usual care	mg) > 40 ≤ 65 (400 mg		systemic corticosteroids	mechanical ventilation	
REMAP-CAP Investigators/ 2021 [3]	113 sites open to randomization to sarilumab and/or tocilizumab domain: UK (98) Netherlands (7) Australia (3) New Zealand (2) Ireland (2) Saudi Arabia (1)	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 (690/865) received	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 Research Council Health Research Council of New Zealand

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
									corticosteroids overall. Remdesivir use recorded in 32.8% of patients (265/807)		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
Rosas/ 2020[4]	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	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	F. Hoffmann-La Roche Ltd. Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response

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
						patients had blood oxygen saturation ≤93% or partial pressure of oxygen/fraction of inspired oxygen <300 mm/Hg				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"(days) Median/95% CI" Adverse events	Biomedical Advanced Research and Development Authority
Salama /2021 [5]	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	TCZ (8 mg/kg infusion, maximum 800 mg) *if patient's clinical signs or symptoms worsened or did not improve (reflected by	(1) SoC	Corticosteroids, antivirals, dexamethasone, remdesivir	Cumulative proportion (95% CI) of patients requiring mechanical ventilation or who had died by Day 28	Genentech

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
						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	sustained fever or worsening status on the 7-category ordinal scale), an additional infusion could be administered 8 to 24 hours after the first			Time to hospital discharge or ready for discharge (days) Time to improvement in ordinal clinical status to Day 28 (days) Adverse events	
Salvarani/ 2020 [6]	Italy/24 hospitals	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	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

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
						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 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 [7]	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	TCZ (8 mg/kg infusion, maximum 800 mg)	(1) SoC	Remdesivir, antiviral therapy, HCQ, glucocorticoids	Mortality (Day 28) Ventilation Clinical worsening on ordinal scale	Genentech

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
						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 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				Hospital initial discharge Adverse events	
Veiga/ 2021 [8]	Brazil/ 9 hospitals	RCT	129	32	Mean (SD): 57 (14)	Severe or critical COVID-19 adult patients with a positive RT-PCR	TCZ (8 mg/kg infusion,	SOC	Co treatments or previous treatments	Mortality at day 28	Beneficência Portuguesa de São Paulo

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
						with symptoms for 3 or more days; with evidence of pulmonary infiltrates confirmed by chest CT or x-ray and receiving supplemental 02 to maintain 02 > 93% or had been on MV for < 24 hours before analysis	maximum 800 mg)		could include, hydroxychloroquine, azithromycin, steroids, other immunosuppressants, heparin; remdesivir was not available	In hospital mortality Clinical status at day 15 and day 29 on 7-level ordinal scale; 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 s6a. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	No tocilizumab Events	No tocilizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
Hermine 2020	7	63	8	67	1.9%	0.93 [0.36, 2.42]
Horby 2021	596	2022	694	2094	55.8%	0.89 [0.81, 0.97]
REMAP-CAP Investigators 2021	98	366	142	412	25.4%	0.78 [0.63, 0.96]
Rosas 2020	58	294	28	144	9.5%	1.01 [0.68, 1.52]
Salama 2021	26	249	11	128	3.8%	1.22 [0.62, 2.38]
Salvarani 2020	2	60	1	63	0.3%	2.10 [0.20, 22.56]
Stone 2020	9	161	3	82	1.1%	1.53 [0.43, 5.49]
Veiga 2021	14	65	6	64	2.2%	2.30 [0.94, 5.61]
Total (95% CI)		**3280**		**3054**	**100.0%**	**0.91 [0.79, 1.04]**
Total events	810		893			

Heterogeneity: Tau² = 0.01; Chi² = 8.32, df = 7 (P = 0.31); I² = 16%
Test for overall effect: Z = 1.43 (P = 0.15)

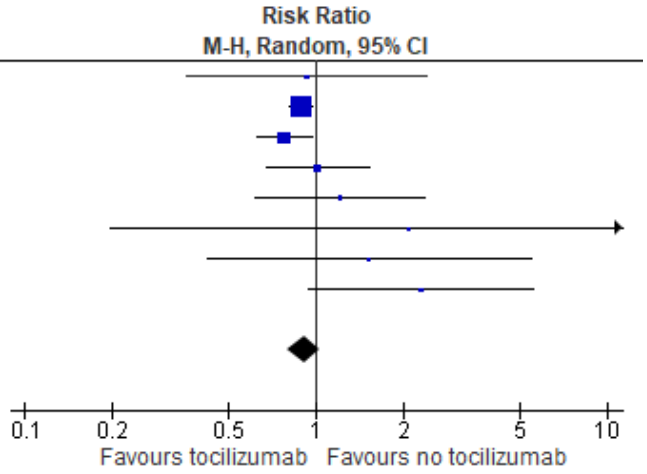


Figure s6b. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab (sensitivity analysis for patients on mechanical ventilation for <24 hours)

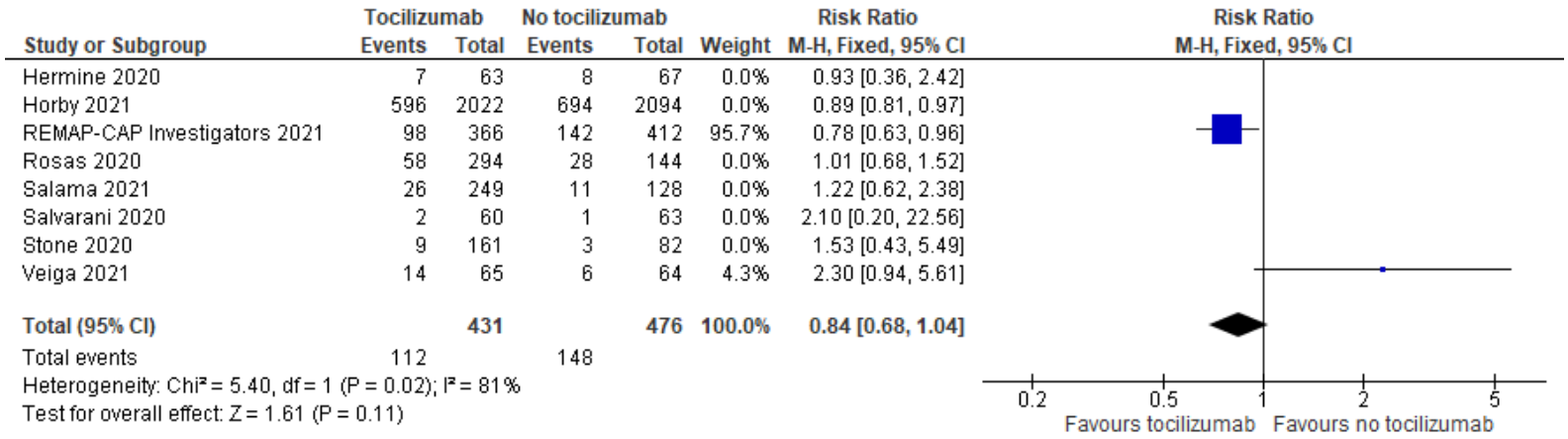


Figure s6c. Forest plot for the outcome of clinical deterioration for tocilizumab vs. no tocilizumab

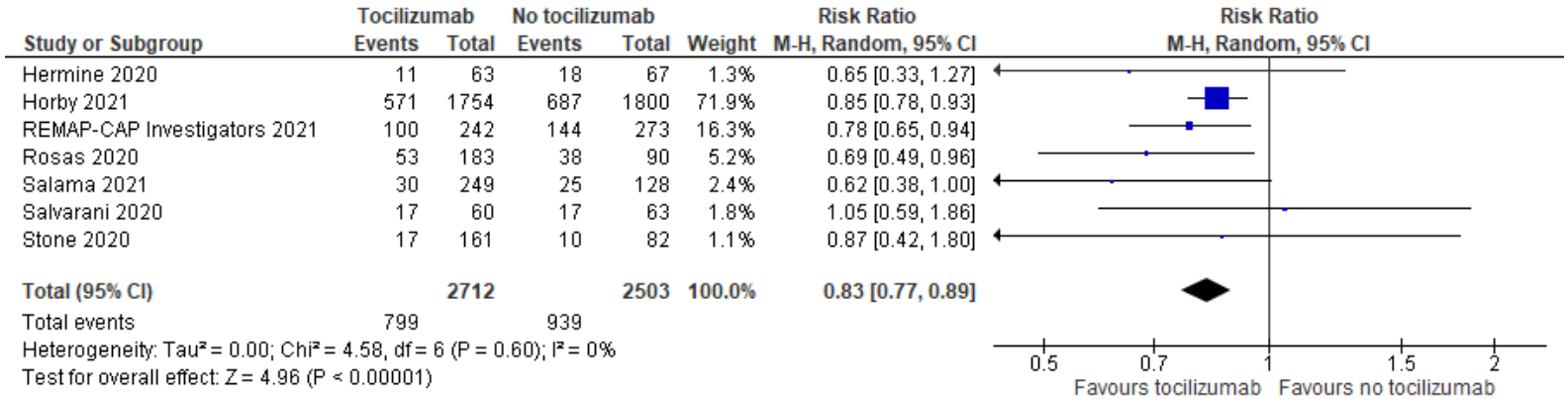


Figure s6d. Forest plot for the outcome of severe adverse events for tocilizumab vs. no tocilizumab

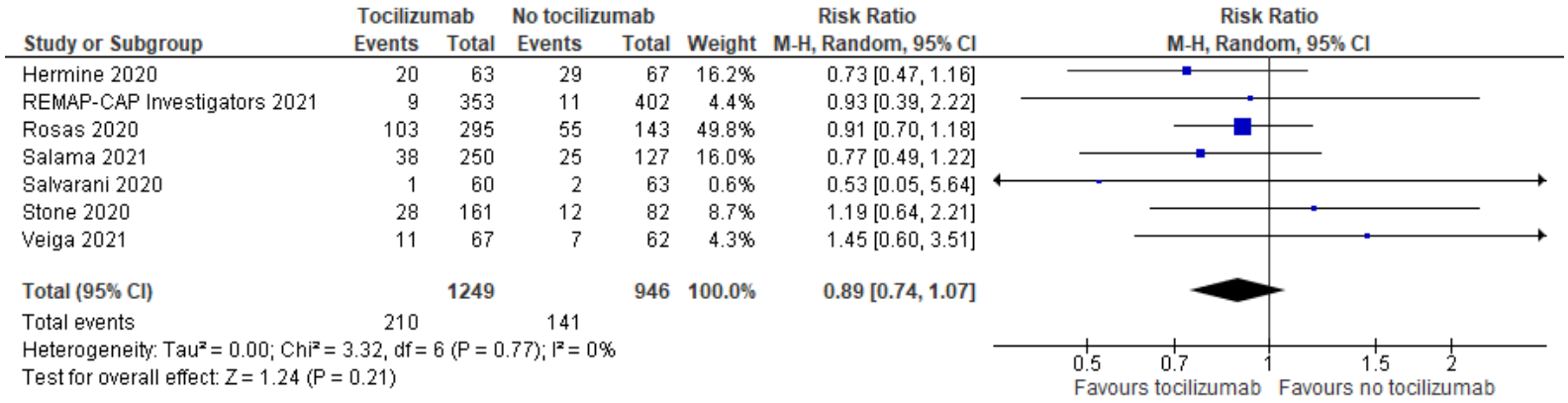


Table s14. Risk of bias for randomized controlled studies (tocilizumab vs. no tocilizumab)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Hermine 2020 [1]							
Horby 2021 [2]							
REMAP-CAP Investigators 2021 [3]							
Rosas 2020 [4]							
Salama 2021 [5]							
Salvarani 2020 [6]							
Stone 2020 [7]							
Veiga 2021 [8]							

Low	High	Unclear

References

1. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med **2020**; 181(1): 32-40.
2. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. Lancet **2021**; 397(10285): 1637-45.
3. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med **2021**; 384(16): 1491-502.
4. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.08.27.20183442 [Preprint 12 September 2020].
5. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med **2021**; 384(1): 20-30.
6. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med **2020**; 181(1): 24-31.
7. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med **2020**; 383: 2333-44.
8. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ **2021**; 372: n84.

Convalescent Plasma

Table s15. Should patients (hospitalized or ambulatory) with 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 [1]	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/ 2021 [2]	Bahrain/ 2 medical centers	RCT	40 (20/20)	20.0	Intervention: Mean of 52.6 (14.9)	Hospitalized patients with hypoxia ($SpO_2 \leq$ 92% on air, or $PaO_2 <$ 60 mmHg, or $PaO_2/FiO_2 \leq 300$	CP: 2 units of ABO-compatible CP, 200 mL	(1) SoC	Standard supportive treatment, including antipyretics, antivirals,	Invasive or non-invasive ventilation Duration of ventilation	Ministry of Health Bahrain College of Surgeons in

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
					Control : Mean of 50.7 (12.5)	mmHg) and receiving supplemental oxygen Excluded patients receiving invasive or non-invasive ventilation	each, infused over 2 successive days		tocilizumab, and antibacterial medication	Biomarker levels Adverse events	Ireland-Bahrain
Avendaño-Solà/ 2021 [3]	Spain/ 14 hospitals	RCT	350 (179/171)	34.6	Median : 62.0 (53.0-75.0)	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/2021 [4]	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 onset with positive SARS-CoV-2 PCR or	Early convalescent (initiated at enrollment) plasma: 2 units (200ml each)	Deferred convalescent plasma only if a pre-specified worsening respirator function	Antivirals, antibiotics, heparin thromboprophylaxis, and immunomodulators	Composite of In-hospital mortality, mechanical ventilation, or hospital stay > 14 days	Fondo de Adopción Tecnológica SiEmpre, SOFOFA Hub, and Ministerio de Ciencia,

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
						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	(Pa02/Fi02 < 200) or if still in hospital for > 7 days after enrollment; 2 units (200ml each) separated by 24 hours		30 day mortality Days of mechanical ventilation, high flow nasal cannula Viral clearance Time to respiratory failure development Serious adverse events TRAILI	Tecnología, Conocimiento e Innovación, Chile
Bégin/ 2021 [5]	Canada (47 sites) US (3 sites)	RCT	938 (625/313)	40.9	Median : 69 (58-79)	Hospitalized patient with confirmed COVID-19 infection on supplemental oxygen, and within 12 days of symptom onset	1 unit of 500 mL of ABO-compatible CP from one donor, or 2 units of 250 mL of CP from two donors	SoC	None	All-cause mortality within 30 days Intubation or death within 30 days Time to intubation or death Ventilator-free days Length of stay Need for organ support QALY	Canadian Institutes of Health Research Ontario COVID-19 Rapid Research Fund Toronto COVID-19 Action Initiative 2020

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
										Adverse effects	Fondation du CHU Ste-Justine Ministére de l'Economie et de l'Innovation du Québec Fonds de Recherche du Québec University Health Network Emergent Access Innovation Fund University Health Academic Health Science Centre Alternative Funding Plan

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
											Saskatchewan Ministry of Health University of Alberta Hospital Foundation Alberta Health Services COVID-19 Foundation Competition Sunnybrook Health Sciences Centre Foundation Fondation du CHUM Ottawa Hospital Academic Medical Organization Ottawa Hospital Foundation

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
											COVID-19 Research Fund Sinai Health System Foundation McMaster University
Bennett-Guerrero/ 2021 [6]	US/ Stony Brook University Hospital	RCT	74 (59/15)	40.5	Intervention: Mean of 67 (15.8) Control: Mean of 64 (17.4)	Patients hospitalized with positive SARS-CoV-2 PCR test	2 units of ABO-compatible CP (about 480 mL). Each unit infused over 2-14 hours	2 units of standard plasma	Therapies for COVID-19 treatment at discretion of providers, including glucocorticoids, remdesivir, hydroxychloroquine, tocilizumab, sarilumab	All-cause mortality at 90 days Ventilator-free days at day 28 WHO clinical severity scale Antibody levels Adverse effects	Stony Brook Medicine
Denkinger/ 2023 [7]	Germany	RCT	134 (68/66)	32.1	Mean (SD): 68.5 (11.3)	PCR-confirmed infection with SARS-CoV-2 in a respiratory tract sample Oxygen saturation on ambient air of	Received two units of ABO-compatible plasma (238–337 ml each from two different donors) on the day of	None (delayed intervention)	Anti-inflammatories, antiviral, antibiotics, anticoagulants, other concomitant	Clinical improvement assessed using a seven-point ordinal scale Time to discharge	Federal Ministry of Education and Research, Germany (emergency

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
						≤94% or a partial oxygen pressure – inspired oxygen fraction ratio of <300 mmHg Meeting at least one high-risk criterion to define the patient group (see the study protocol described in the Supplementary Information): Group 1 (cancer): patients with pre-existing or concurrent hema tological cancer and/or receiving active cancer therapy for any cancer (including chemotherapy, radiotherapy and surgical treat ments) within the past 24 months Group 2 (immunosuppressi on): patients experiencing chronic	randomization (day 1) and on a later day intravenously		medications not detailed	Overall survival Adverse Events	research funding FKZ)

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
						immunosuppression, either pharmacological or due to underlying diseases not meeting group 1 criteria Group 3 (lymphopenia/elevated d-dimers): patients aged >50 years and ≤75 years and not meeting group 1 or 2 criteria who had lym- phopenia (<0.8 × 10^9 cells per liter) and/or d-dimers (>1 μg ml^{-1}) Group 4 (age >75 years): patients aged >75 years and not meeting group 1, 2 or 3 criteria					
Gharbharan/ 2021 [10]	Netherlands/ 14 secondary and academi	RCT	86 (43/43)	28	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 proven by	CP: 300ml of plasma with anti-SARS-CoV-2 neutralizing antibody titers of at	(1) SoC	Off-label use of EMA-approved drugs (e.g., chloroquine, azithromycin, lopinavir/ritonav	Mortality Improvement in WHO COVID-19 disease severity score on day 15	Erasmusfoundation

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
	c hospitals					a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test in the previous 96 hours	least 1:80; "Patients without a clinical response and a persistently positive RT-PCR could receive a second plasma unit after five days."		ir, tocilizumab, anakinra)	Time to discharge Hazard ratio/95% CI	
Joyner, Senefeld, et al/ 2020 [11]	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 SARS-CoV-2, and had (or were judged by a healthcare provider to be at high risk of progression to) severe or life-threatening COVID-19	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 National Center for

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
											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

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
											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

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
											Octapharma USA, Inc The Mayo Clinic
Joyner, Wright, et al/ 2020 [12]	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-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,	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 Diabetes and Digestive and Kidney Diseases

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
						respiratory failure, septic shock, and multiple organ dysfunction or failure					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

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
Kirenga/ 2021 [13]	Uganda/ Mulago National Referral Hospital	RCT	136 (69/67)	28.7	Median : 50 (38.5-62)	Patients with positive SARS-CoV-2 PCR test	2 units of ABO-compatible CP infused over 2-3 hours at a rate of 1.4 to 2 mL/min, with 3 hours between infusions.	SoC (Ugandan National Guidelines)	Most recent Uganda National Treatment Guidelines available (last updated April 2020) include hydroxychloroquine, vitamin C, zinc, thiamine, empiric antibiotics, heparin, and statins	Time to viral clearance Time to symptom resolution Clinical status on WHO ordinal scale Progression to severe/critical condition (SpO_2 <93% or needing supplemental O_2) Adverse events	Makerere University Research and Innovation Fund
Korley/ 2021 [14]	USA/ 48 Emergency departments across 21 states	RCT	511 (257/254)	54	Median : 54 (41-62)	Positive SARS-CoV-2 NAAT, symptom onset within 7 days of enrollment, and either greater than 50 years old or have at least 1 risk factor for disease progression	1 unit of high-titer ABO-compatible CP	Placebo	None	All-cause mortality within 30 days Disease progression within 15 days WHO illness severity scale Time until worsening of symptoms	National Heart, Lung, and Blood Institute National Institute of Neurological Disorders and Stroke Biomedical Advanced Research and Development

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
										Hospital-free days within 15 days Adverse events	Authority Operation Warp Speed
Körper/ 2021 [15]	Germany (13 hospitals)	RCT	105 (53/52)	26.7	Median: 60 (53-66)	Patients with a positive SARS-CoV-2 PCR test between 18-75 years old, with severe COVID-19 disease (RR ≥30 on ambient air, requirement of any respiratory support, or need of ICU treatment)	One unit of CP given on day 1, 3, and 5. CP collected from donors had a 50% plaque reduction neutralization test titer of at least 1:20.	SoC	Other antiviral treatments and/or supportive treatments according to institutional protocols	Mortality Treatment success day 21 (survival, no ventilation support, no ICU treatment, and RR <30) Time to clinical improvement of ≥2 points on an ordinal severity scale Duration of ventilatory support Length of hospitalization Time to ICU discharge Time until negative SARS-CoV-2 PCR Adverse events	German Federal Ministry of Health

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
Lacombe/ 2022 [16]	France	RCT	120 (60/60)	37	Median (IQR): Convalescent plasma: 64.5 (55.7-76.6) Usual care: 67.0 (58.3-78.9)	Positive SARS-CoV-2 nasopharyngeal PCR and/or CT scan prior to randomization, onset of symptoms <9 days Illness of mild or moderate severity according to the WHO clinical progression scale (CPS) (hospitalized, mild disease: no oxygen need; hospitalized, moderate disease: oxygen needed)	4 units of plasma over 2 days (≈ 840 ml) After the first 3 patients received 2 units of ABO-compatible CCP as per protocol, all subsequent patients randomized to the CCP arm received 4 units of CCP (200-220 ml/unit, 2 units/day over 2 consecutive days) provided by different donors	None	Usual care: the use of dexamethasone, tocilizumab, supportive care including supplemental oxygen, antivirals, and antibiotics	Proportion of patients with a WHO-Clinical Progression Score (CPS) ≥6 on the 10-point scale on day 4 Survival without ventilation or additional immunomodulatory treatment by day 14 WHO-Clinical Progression Score (CPS) at 4, 7 and 14 days after randomization, Overall survival at 14 and 28 days after randomization Time to discharge Time to oxygen supply independency Evolution of a series of biological parameters at days	Programme Hospitalier de Recherche Clinique / DGOS; Fondation pour la Recherche Médicale ; Sorbonne Université Paris; Emergency support instrument, DG Santé, European Commission

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
										4, 7 and 14 after randomization	
Li/ 2020 [17]	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

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
Liu/ 2020 [18]	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 and laboratory parameters	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; anti-inflammatory agents	Mortality Worsened clinical condition by day 14 Follow-up time Hazard ratio for plasma	N/A
Libster/ 2021 [19]	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

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'Donnell/ 2021 [20]	5 hospitals in New York City (USA) and Rio de Janeiro (Brazil)	RCT	223 (150/73)	34	Median age: 61 years	Hospitalize d patients ≥ 18 years with positive SARS-CoV-2 within 14 days of randomization, with infiltrates on chest imaging and oxygen saturation ≤ 94% on RA on oxygen, mechanical ventilation, or ECMO	A single unit of convalescent plasma given over 2 hours	Control	Patients could receive steroids, remdesivir, hydroxychloroq uine, and antibacterial agents	Time to clinical improvement Clinical status at day 28 Adverse events through day 28	Amazon Foundation
Pouladzadeh / 2021 [21]	Iran/ Ravi Hospital, Ahvaz	RCT	60 (30/30)	45	Interve ntion: Mean of 53.5 (10.3) Control : Mean of 57.2 (17)	Patients with a positive SARS-CoV-2 PCR test, positive changes on CT scan, were within 7 days of symptom onset, SpO2 <94% on room air, and WHO severity score > 4	One unit of CP given within 4 hours of admission. Second unit given at discretion of physician if no improvement	SoC	SoC included chloroquine phosphate and lopinavir/ritonav ir	2-month mortality Length of hospitalization Improvement in WHO severity score Change in cytokine levels Adverse effects	Ahvaz University of Medical Sciences

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
Ray/ 2020 [22]	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

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
RECOVERY Collaborative Group (Horby)/ 2021 [23]	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 participants	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
Sekine/ 2021 [24]	Brazil/ Hospital de Clínicas de Porto Alegre	RCT	160 (80/80)	41.9	Median : 60.5 (48-68)	Patients with positive SARS-CoV-2 PCR test and within 15 days of symptom onset, with severe disease (RR > 30 breaths/min, SpO2 ≤ 93% in RA, PaO2/FIO2 ≤ 300, supplemental oxygen)	2 infusions 48 hours apart of 300 mL of CP	SoC	Glucocorticoids, "other immunomodulators", antibiotics, antivirals	All-cause mortality at 14 and 28 days Proportion with clinical improvement at 28 days RT-PCR for SARS-CoV-2	Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul Fundação de Amparo à Pesquisa do Estado de São Paulo

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
										Clinical status using a 6-level ordinal scale Time to hospital discharge Days free from oxygen support SOFA and NEWS 2 scores Length of ventilator support Adverse events	Instituto Cultural Floresta
Simonovich/ 2021 [25]	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	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	(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

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
						ventilation or multiorgan failure	SARS-CoV-2 IgG antibody titer > 1:800				
Sullivan 2021 [26]	US/23 sites	RCT	1225 (592/589)	57%	CP: 42 (31.5-54) Control: 44 (33-55)	Adult patients who were positive for SARS CoV-2 who within 8 days of symptom onset	Convalescent plasma with minimum titers of ≥ 1:320	Control plasma	Allowed to receive steroids. Monoclonals prior to plasma were not permitted however were allowed after plasma receipt.	COVID-19 related hospitalization at day 28 Mortality SAEs	US Department of Defense Defense Health Agency Bloomberg Philanthropies State of Maryland NIH/NIAID NCATS Moriah Fund Octapharma HealthNetwork Foundation Shear Family Foundation

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
Writing Committee for the REMAP-CAP Investigators (Estcourt), et al/ 2021 [27]	Australia , Canada, UK, US	RCT	1987 (1078/909)	32.3	CP: Median 61 (52-69) SoC: 61 (52-70)	Adult, hospitalized patient with confirmed SARS-CoV-2 infection with moderate or severe illness	CP: High titer, ABO compatible	SoC	Standard of care at trial site, could also be randomized to another domain of investigational treatment in REMAP-CAP. 94% of patients were treated with glucorticoids 45% of patients received remdesivir	In hospital mortality, day 28 and 90 day mortality, Respiratory and cardiovascular organ-free support days by day 21 Progression to invasive mechanical ventilation, ECMO, or death ICU and hospital length of stay WHO ordinal scale at day 14 VTE at day 90 and SAEs	Monash University Utrececht Medical Center St. Michaels Hospital Global Coalition for Adaptive Research Platform for European Preparedness Against (Re-) emerging Epidemics Australian National Health and Medical Research Council Health Research

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
											Council of New Zealand Canadian Institute of Health National Institute For Health Research The EU programme Emergency Support Instrument UPMC Learning While Doing Program Breast Cancer Research Foundation French Ministry of Health Minderoo Foundation

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
											Wellcome Trust

Figure s7a. Forest plot for the outcome of mortality for convalescent plasma vs. no convalescent plasma in hospitalized patients

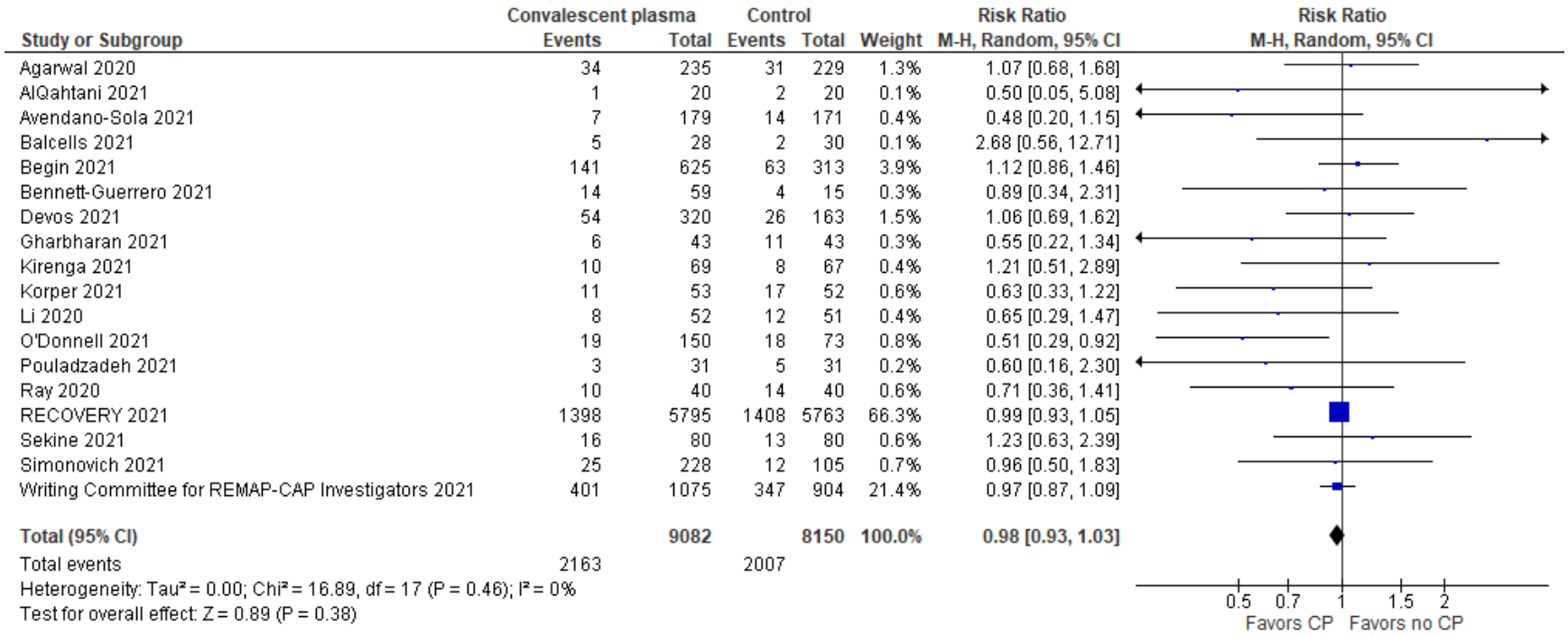


Figure s7b. Forest plot for the outcome of mechanical ventilation for convalescent plasma vs. no convalescent plasma in hospitalized patients

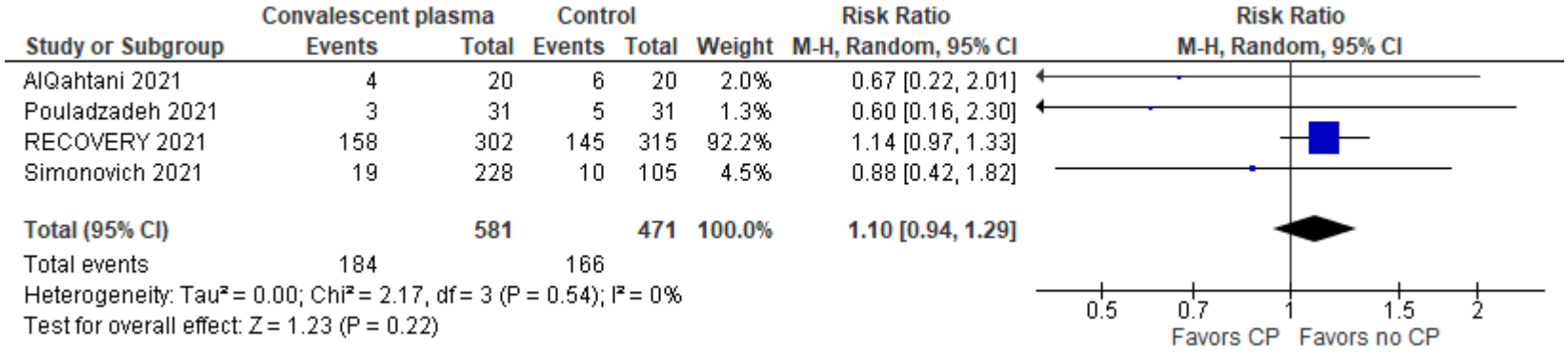


Figure s7c. Forest plot for the outcome of adverse events (mild to severe) for convalescent plasma vs. no convalescent plasma in hospitalized patients

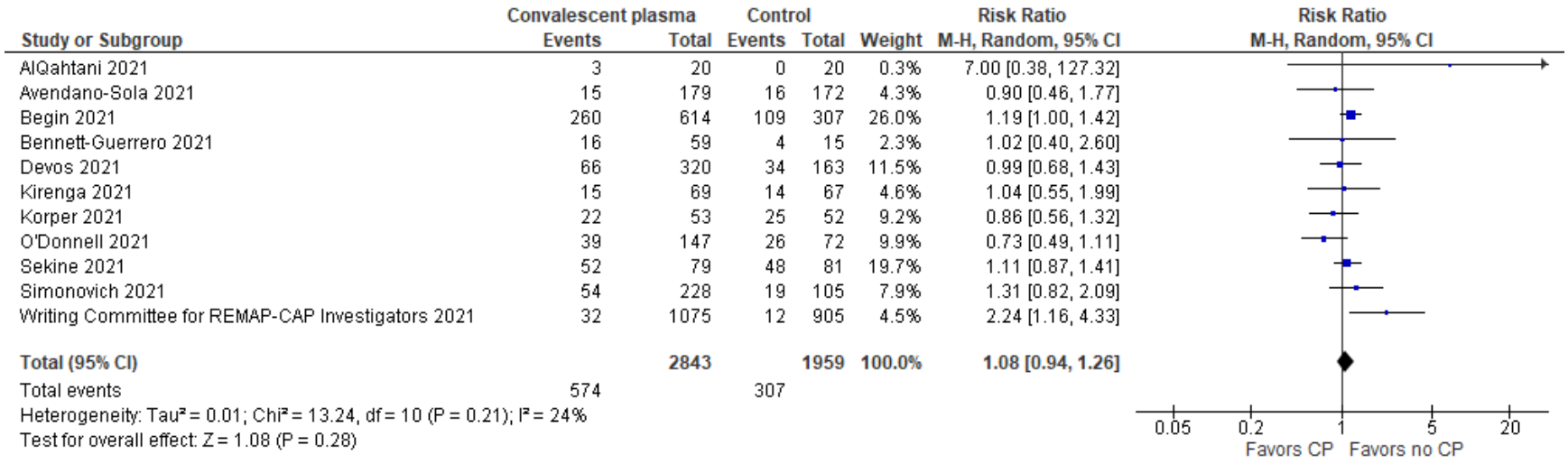


Figure s7d. Forest plot for the outcome of mortality for convalescent plasma vs. no convalescent plasma in ambulatory patients

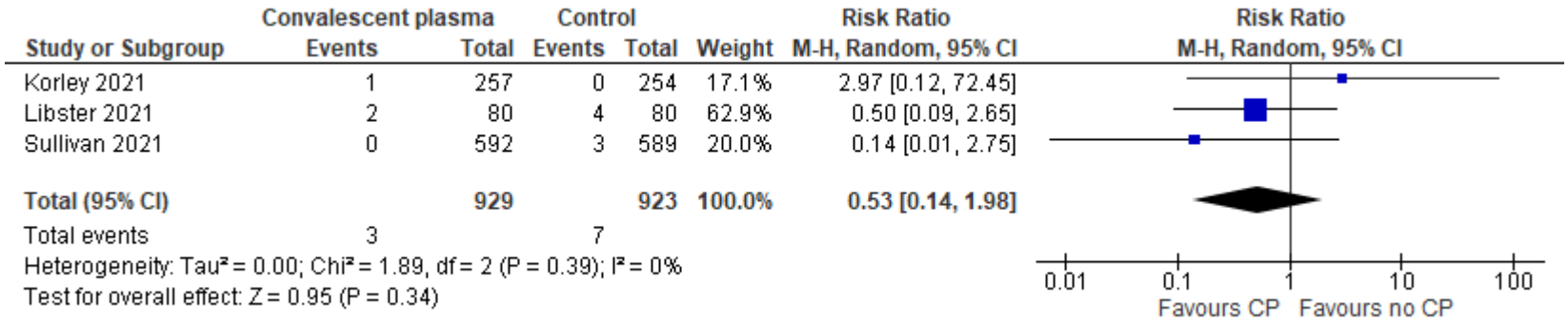


Figure s7e. Forest plot for the outcome of COVID-19-related hospitalizations for convalescent plasma vs. no convalescent plasma in ambulatory patients

Figure s7f. Forest plot for the outcome of all-cause hospitalizations for convalescent plasma vs. no convalescent plasma in ambulatory patients

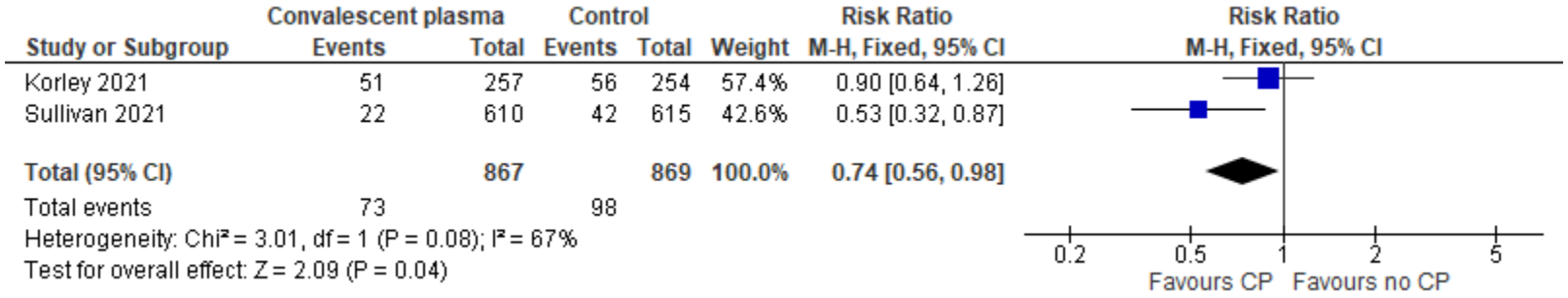


Figure s7g. Forest plot for the outcome of serious adverse events for convalescent plasma vs. no convalescent plasma in ambulatory patients

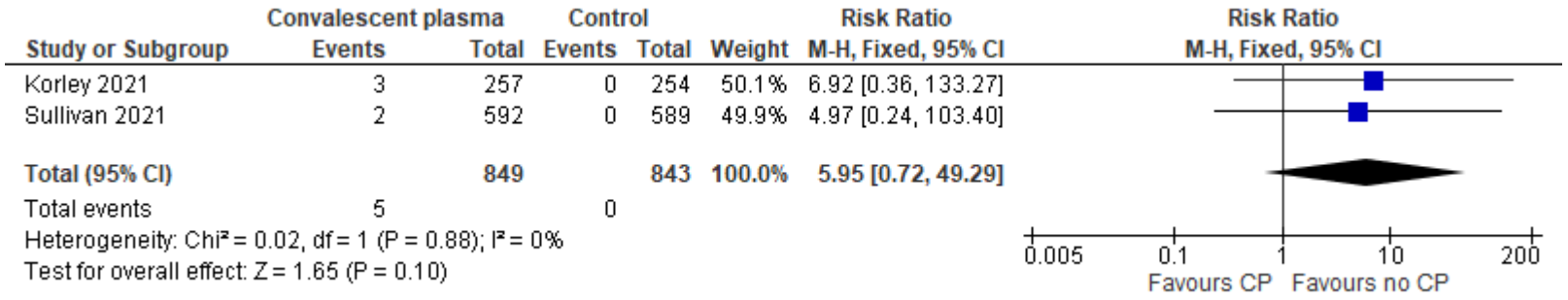


Figure s7h. Forest plot for the outcome of adverse events for convalescent plasma vs. no convalescent plasma in ambulatory patients

Figure s7i. Forest plot for the outcome of mortality for convalescent plasma vs. no convalescent plasma in hospitalized immunocompromised patients

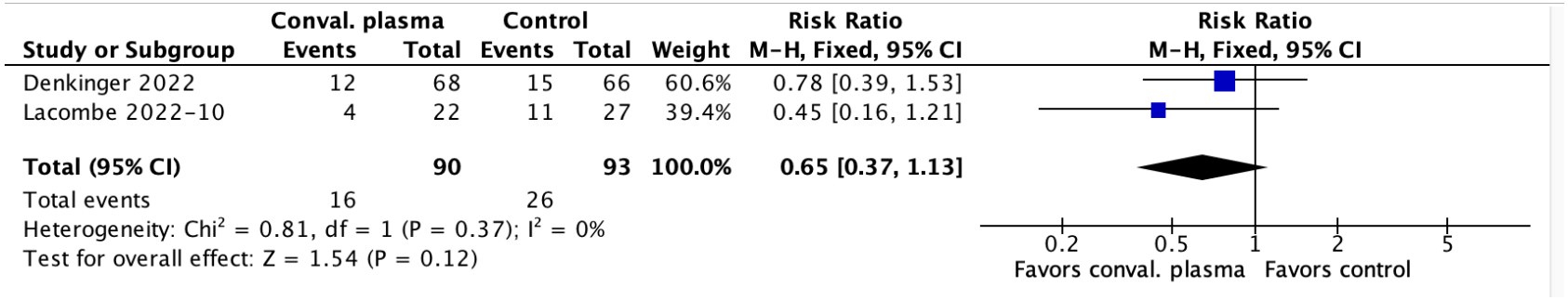


Figure s7j. Forest plot for the outcome of SAEs for convalescent plasma vs. no convalescent plasma in hospitalized immunocompromised patients

Study or Subgroup	Conval. plasma Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denkinger 2022	0	68	0	66		Not estimable
Lacombe 2022-10	30	46	26	48	100.0%	1.20 [0.86, 1.68]
Total (95% CI)		**114**		**114**	**100.0%**	**1.20 [0.86, 1.68]**
Total events	30		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)

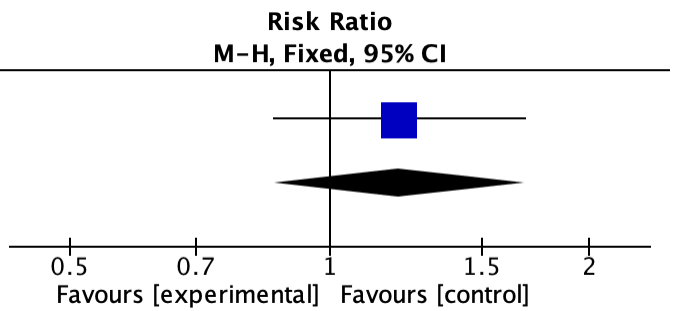


Table s16a. Risk of bias for randomized controlled studies (convalescent plasma vs. no convalescent plasma)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Agarwal 2020 [1]							
AlQahtani 2021 [2]							
Avendaño-Solà 2021 [3]							
Balcells 2021 [4]							
Bégin 2021 [5]							
Bennett-Guerrero 2021 [6]							
Denkinger 2023 [7]							
Devos 2021 [8]							
Gharbharan 2021 [10]							
Kirenga 2021 [13]							
Korley 2021 [14]							
Körper 2021 [15]							
Lacombe 2022 [16]							
Li 2020 [17]							
Libster 2021 [19]							
O'Donnell 2021 [20]							

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Pouladzadeh 2021 [21]							
Ray 2020 [22]							
RECOVERY Collaborative Group (Horby) 2021 [23]							
Sekine 2021 [24]							
Simonovich 2021 [25]							
Sullivan 2021 [26]							
Writing Committee for the REMAP-CAP Investigators (Estcourt) 2021 [27]							

Low	High	Unclear

Table s16b. Risk of bias for non-randomized studies (convalescent plasma vs. no convalescent plasma)

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
Duan 2020 [9]							
Joyner, Senefeld, et al 2020 [11]							
Joyner, Wright, et al 2020 [12]							
Liu 2020 [17]							

Low	Moderate	Serious	Critical

References

1. 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.
2. 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. Sci Rep **2021**; 11: 9927.
3. Avendaño-Solà C, Ramos-Martinez A, Munez-Rubio E, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. J Clin Invest **2021**; 131(20).
4. 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.
5. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med **2021**: Available at: https://doi.org/10.1038/s41591-021-01488-2 [Epub ahead of print 9 September 2021].
6. Bennett-Guerrero E, Romeiser JL, Talbot LR, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease **2019** Infected Hospitalized Patients in New York: A Double-Blind Randomized Trial. Crit Care Med **2021**; 49(7): 1015-25.
7. Denkinger CM, Janssen M, Schakel U, et al. Anti-SARS-CoV-2 antibody-containing plasma improves outcome in patients with hematologic or solid cancer and severe COVID-19: a randomized clinical trial. Nat Cancer **2023**; 4(1): 96-107.
8. Devos T, Van Thillo Q, Compernolle V, et al. Early high antibody-titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma. Eur Respir J **2021**: 2101724.
9. 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.
10. Gharbharan A, Jordans CC, Geurts van Kessel C, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun **2021**; 12(3189).
11. 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**: Available at: https://doi.org/10.1101/2020.08.12.20169359 [Preprint 12 August 2020].
12. Joyner M, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest **2020**; 130(9): 4791-7.
13. Kirenga B, Byakika-Kibwika P, Muttamba W, et al. Efficacy of convalescent plasma for treatment of COVID-19 in Uganda. BMJ Open Respir Res **2021**; 8(1): e001017.
14. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early Convalescent Plasma for High-Risk Outpatients with Covid-19. N Engl J Med **2021**; 385(21): 1951-60.

15. Körper S, Weiss M, Zickler D, et al. High Dose Convalescent Plasma in COVID-19: Results from the randomized Trial CAPSID. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.05.10.21256192 [Preprint 10 May 2021].
16. Lacombe K, Hueso T, Porcher R, et al. COVID-19 convalescent plasma to treat hospitalised COVID-19 patients with or without underlying immunodeficiency. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.08.09.22278329 [Preprint 27 October 2022].
17. 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.
18. Liu ST, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nat Med **2020**; 26(11): 1708-13.
19. Libster R, Perez Marc G, Wappner D, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med **2021**; 384(7): 610-8.
20. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest **2021**; 131(13): e150646.
21. Pouladzadeh M, Safdarian M, Eshghi P, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. Intern Emerg Med **2021**; 16(8): 2181-91.
22. 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].
23. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet **2021**; 397(10289): 2049-59.
24. Sekine L, Arns B, Fabro BR, et al. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. Eur Respir J **2021**; 58(5): 2101471.
25. 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.
26. Sullivan DJ, Gebo KA, Shoham S, et al. Randomized Controlled Trial of Early Outpatient COVID-19 Treatment with High-Titer Convalescent Plasma. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.12.10.21267485 [Preprint 21 December 2021].
27. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, et al. Effect of Convalescent Plasma on Organ Support-Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA **2021**; 326(17): 1690-702.

Remdesivir

Table s17. 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 [1]	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, mechanical ventilation, or extracorporeal membrane oxygenation	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. United Kingdom Medical Research Council

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
Goldman/ 2020 [2]	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

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
Spinner/ 2020 [4]	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 >94% on room air)	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 (2) SoC	Steroids, HCQ, Lopinavir-ritonavir, TCZ, AZ	Day 11 clinical status on 7-point scale, No. (%) (Includes Mortality at Day 11) Clinical improvement (at Day 5, 7, 11, 14, 28) Recovery (at Day 5, 7, 11, 14, 28) Adverse Events	Gilead Sciences
Wang / 2020 [5]	China/ 10 hospitals	RCT	237 (158/78)	N/A	Median: 65 (56-71)	Hospitalized patients with pneumonia confirmed by chest imaging, SpO_2 ≤ 94% on room air, PaO_2/FIO_2 ≤ 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

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
										Adverse events leading to treatment discontinuation	Beijing Science and Technology Project
WHO Solidarity Trial Consortium (Pan)/ 2021 [6]	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 study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contraindication to any study drug	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, receiving no extra funding

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

Table s18. Should ambulatory patients with 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
Gottlieb/ 2021 [3]	64 sites in US, Spain, Denmark, and UK	RCT	562 (279/283)	47.9	50 (15)	SARS CoV-2 PCR positive within 4 days prior to screening with at least one symptom and symptom onset for ≤7 days	Remdesivir 200 mg x 1 day, then 100 mg daily for 2 days	Placebo	None	Mortality All cause hospitalization COVID-19 related hospitalization COVID-19 related medically attended visits Change in nasopharyngeal viral load Serious adverse events	Gilead

Figure s8a. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients with severe disease

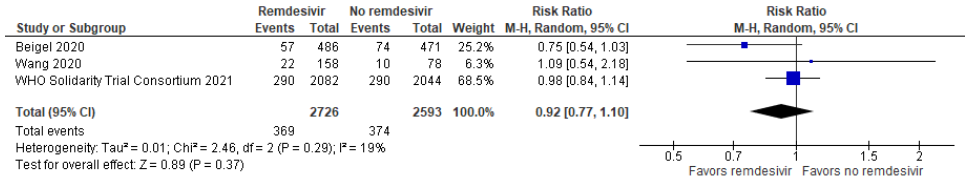


Figure s8b. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients with severe disease

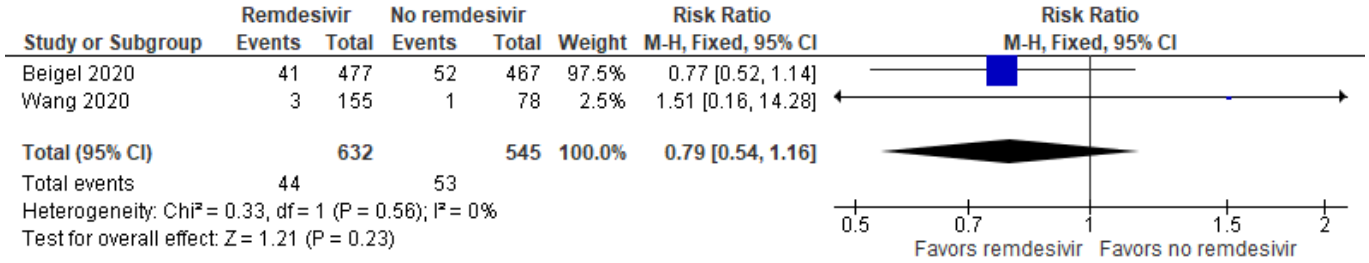


Figure s8c. Forest plot for the outcome of mortality for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

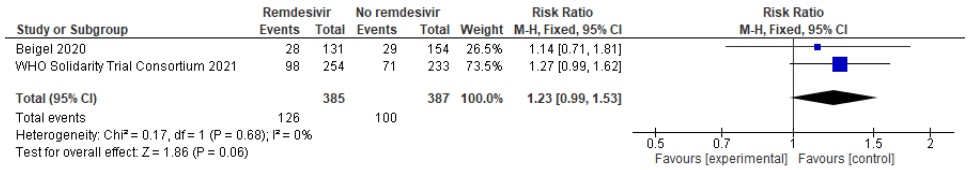


Figure s8d. Forest plot for the outcome of serious adverse events (grade 3/4) for remdesivir vs. no remdesivir in hospitalized patients on invasive ventilation and/or ECMO

Table s19. 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]							
Gottlieb 2021 [3]							
Spinner 2020 [4]							
Wang 2020 [5]							
WHO Solidarity Trial Consortium (Pan) 2021 [6]							

Low	High	Unclear

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med **2020**; 383(19): 1813-26.
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**; 383: 1827-37.
3. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med **2021**: Available at: https://doi.org/10.1056/nejmoa2116846 [Epub ahead of print 22 December 2021].
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**; 324(11): 1048-57.
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.
6. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.

Famotidine

Table s20. Should patients with COVID-19 (ambulatory with mild-to-moderate disease, hospitalized with severe disease) 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
Brennan/ 2022 [1]	U.S./ Northwell Health; New York City Health and Hospitals Corporation	RCT	55 (27/28)	63.6	Median age: 35.0 (15-50)	Unvaccinated adults with a positive SARS-CoV-2 PCR test within 72 hours and a minimum of three symptoms of moderate severity for 1-7 days	Famotidine 80 mg by mouth three times a day for 14 days	Placebo	None	Time to symptom resolution (symptom score ≤ 3 and no individual symptoms >1 for 2 consecutive days) Decreasing rate of symptom resolution from day 0 to 28 Cumulative incidence of symptom resolution (symptom score	Pershing Square Foundation Emergent Ventures Fast Grant Dr. Lee MacCormick Edwards Charitable Foundation Cancer Centre Support Grant

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
										decreased to ≤ 1 for 2 consecutive days) of each individual symptom that is >1 at baseline Relative change in CRP, ferritin Adverse events	
Pahwani/ 2022 [2]	Pakistan / Jinnah Sindh Medical University	RCT	178 (89/89)	39.3	Mean: Intervention: 52 (11) Control: 51 (12)	Patients 18-65 hospitalized with PCR-confirmed COVID-19 infection	Famotidine 40mg daily plus standard of care	Standard of care	None	Mortality Need for ICU care Need for mechanical ventilation	None

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
										Length of hospitalization Time to resolution of symptoms	

Table s21. Risk of bias for randomized controlled studies (famotidine vs. no famotidine)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Brennan 2022 [1]							
Pahwani 2022 [2]							

Low	High	Unclear

References

1. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial. Gut **2022**; 71(5): 879-88.
2. Pahwani S, Kumar M, Aperna F, et al. Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2. Cureus **2022**; 14(2): e22404.

Janus Kinase Inhibitors (Baricitinib and Tofacitinib)

Table s22. 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 [1]	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/ 2021 [2]	United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), United Kingdom (1), Denmark (1)	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 infiltrates by imaging study, SpO_2 ≤ 94% on room air, requiring	Baricitinib 4mg daily (or 2mg daily if eGFR < 60 mL/min) for 14 days or until discharge plus remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10 or until discharge	Remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10 or until discharge and matching placebo tablets	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. All patients	Mortality at day 14 and day 28 Time to recovery (days) Clinical status at day 15 Hazard ratio of mortality Incidence of death or invasive ventilation	National Institute of Allergy and Infectious Diseases National Institutes of Health, Bethesda, MD Governments of Japan, Mexico, Singapore, and Denmark Seoul National University Hospital

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
						supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation			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.	Adverse events	United Kingdom Medical Research Council
Marconi/ 2021 [3]	101 centers from 12 countries (Argentina, Brazil, Germany, India, Italy, Japan, South Korea, Mexico, Russia, Spain, United Kingdom,	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	Mortality at day 28 Disease progression by day 28 Time to recovery (days) Clinical improvement on disease severity scale	Eli Lilly and Company

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
	United States)								required unless contraindicated	Length of hospitalization Ventilator-free days Adverse events	
RECOVERY Collaborative Group/ 2022 [4]	United Kingdom (156 hospitals)	RCT	8156 (4148/4008)	34.1	Mean: 58.1 (15.5)	Patients at least 2 years old admitted to the hospital with clinically suspected or laboratory confirmed SARS-CoV-2	Baricitinib 4mg daily for 10 days or until discharge plus standard of care (or 2mg daily if eGFR ≥ 30 to < 60 mL/min/1.73 m^2, 2mg every other day if eGFR ≥ 15 to < 30 mL/min/1.73 m^2, or 2mg every other day for pediatric patients if eGFR ≥ 30 to < 60 mL/min/1.73 m^2)	SoC	Tocilizumab in 23% patients at randomization Also eligible for other platform trial treatments - colchicine, aspirin, dimethyl fumarate, casirivimab/ imdevimab, empagliflozin	Mortality at day 28 Time to hospital discharge Composite of mechanical ventilation or death Adverse events	UK Research and Innovation National Institute of Health Research

Table s23. 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]							
RECOVERY Collaborative Group 2022 [4]							

Low	High	Unclear

Table s24. 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 [5]	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 Adverse events	Pfizer

Table s25. 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 [5]							

Low	High	Unclear

References

Baricitinib

1. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med **2022**; 10(4): 327-36.
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**; 9(12): 1407-18.
4. RECOVERY Collaborative Group, Horby PW, Emberson JR, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.03.02.22271623 [Preprint 3 March 2022].

Tofacitinib

5. 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 s26. Should ambulatory or hospitalized patients with 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
Abbas/ 2022 [1]	China/ China University of Medical Sciences hospitals	RCT	202 (99/103)	42	Mean: Intervention: 38.33 (6.84) Control: 37.33 (5.84)	Patients age 18-50 years old with COVID-19	Ivermectin 300 mcg/kg/day divided into 2 doses by mouth for 5 days	Placebo	None	All-cause mortality Time to complete symptom resolution Deterioration of WHO clinical status scale by 2 or more points Development of fever Escalation of care Adverse events	Unspecified
Abd-Elsalam/ 2021 [2]	Egypt/ 2 hospitals	RCT	164 (82/82)	50	Intervention: Mean of 42.4 (16) Control: Mean of	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	None

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
					39.4 (16.9)					Progression to mechanical ventilation Safety	
ACTIV-6/ 2022 [3]	USA	RCT	1591 (817/774)	58.6	Median: 47.0 (39.0-56.0)	Patients ≥30 years old with confirmed SARS-CoV-2 infection within 10 days, and experiencing ≥2 symptoms of acute COVID-19 for ≤7 days from enrollment	Ivermectin 400 µg/kg for 3 days	Placebo	N/A	Time to sustained recovery Hospitalization pr death by day 28 COVID clinical progression scale on days 7, 14 and 28 Mortality Hospitalization, urgent care, or emergency department visit Adverse events	National Center for Advancing Translational Sciences
Ahmed/ 2020 [4]	Bangladesh	RCT	68: ivermectin alone vs. ivermectin plus doxycycline	54	Mean: 42	Hospitalized with a fever, cough, or sore throat	Ivermectin alone (12mg once daily for 5 days) Ivermectin plus doxycycline combination	Placebo	N/A	Length of hospitalization Incidence of hypoxia	Beximco Pharmaceutical Limited

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
			vs. placebo (22/23/23)				therapy (12mg ivermectin single dose plus doxycycline 200mg once, followed by 100mg twice daily for 4 days)			Time to virologic clearance Biomarker levels Adverse events	
Angkasekwinai/ 2022 [5]	Thailand/ Siriraj Hospital	RCT	1000 (500/500)	57.4	Mean (SD): 38.4 (12.1)	Suspected of having SARS-CoV-2 infection because of respiratory tract symptoms or because had a history of contact with a confirmed COVID-19 patient (also had documented positive or negative test for SARS-CoV-2 (RT-PCR) from a nasopharyngeal swab sample taken on the enrollment day)	Ivermectin 400-600 µg/kg/day	Placebo	None	Proportion of patients with positive RT-PCR within 14 days after enrollment among those with negative RT-PCR result at enrollment Proportion of patients with oxygen desaturation (oxygen saturation <96% or decreased from baseline ≥3% after exertion) Changes in the WHO 10-point clinical progression	Siriraj Foundation, Faculty of Medicine Siriaj Hospital, Mahidol University

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
										score on Day 3, Day 7, and Day 14 Absence of all symptoms at Day 3, Day 7, and Day 14 Hospitalization within 14 days 28-day mortality Adverse effects	
Beltran Gonzalez/ 2021 [6]	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	Aguascalientes State Health Institute

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
Biber/ 2021 [7]	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
Bramante/ 2022 [8]	United States/ 6 institutions	RCT	1431 (1431 metformin analysis/880 ivermectin analysis/721 fluvoxamine analysis)	56.0	Median: 46 (37-55)	SARS-CoV-2 infection within the past 3 days; and an onset of symptoms within 7 days before randomization	Ivermectin 390-470 µg/kg per day for 3 days Immediate release metformin with increase in dose over 6 days to 1500 mg/d for 14 days Fluvoxamine 50 mg BID for 14 days	Placebo	None	Severe COVID-19 through 14 days (composite of hypoxemia, emergency department visit, hospitalization, or death) Daily symptom severity Total symptom score Drug discontinuations	Parsemus Foundation Rainwater Charitable Foundation Fast Grants UnitedHealth Group Foundation
Bukhari/ 2021 [9]	Pakistan / Combined Military	RCT	86 (41/45)	15.1	Mean age: Intervention: 42.2 ± 12.0	Mild-moderate disease. Mild disease defined as clinical symptoms ,excluding dyspnea or	Ivermectin 12mg once plus standard of care	(1) SoC	Standard of care, which consisted of Vitamin C 500mg daily, Vitamin D3 50,000 units	Negative PCR test by day 3, 7 and 14 Adverse reactions	None

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
	Hospital Lahore				Comparator: 39.0 ± 12.6	gasping, with no imaging findings of pneumonia. Moderate disease defined as fever, respiratory symptoms, and imaging findings of pneumonia.			weekly, and paracetamol 500mg as needed.		
Buonfrate/ 2022 [10]	Italy/ 4 outpatient centers	RCT	87 (30 high-dose/28 low-dose/29 placebo)	41.9	Median: 47 (31-58)	Adult outpatients with newly diagnosed SARS-CoV-2 infection by RT-PCR not requiring supplemental oxygen or hospitalization	Ivermectin 1200 mcg/kg/day for 5 days OR Ivermectin 600 mcg/kg/day for 5 days	Placebo	Unspecified therapies related to COVID-19 treatment (61.3% overall)	Change in viral load at day 7 Severe adverse drug reactions Trend in quantitative viral load Proportion of patients with virologic clearance day 14 and 30 Hospitalizations COVID-19 severity score day 14 and 30	Italian Ministry of Health

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
Chaccour/ 2021 [11]	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
Chachar / 2020 [12]	Pakistan /Fatima Memorial 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
Elshafie 2022 [13]	Egypt	RCT	303 (104 ivermectin/87 HCQ/102 placebo)	47.5	Mean (SD): Patients receiving ivermectin: 59.84 (16.3)	Hospitalized moderate to severe COVID-19 patients	Ivermectin orally 36 mg dose on day 1, 3, 6	Placebo HCQ orally 400 mg loading dose on day 1, followed by a 200 mg	All patients who required supplemental oxygen received steroids in the form of dexamethas	Recovery (hospital discharge or improvement in clinical condition by 2 WHO ordinal scales)	None

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
					Patients receiving HCQ: 61.13 (18.8) Patients receiving placebo: 59.06 (16.7)			maintenance dose on day 2 until day 5	one 6 mg IV for 10 days or solumedrol 1– 2 mg/kg/day IV infusion in severe cases complicated with adult respiratory distress syndrome Antibiotics were given to cases clinically diagnosed with secondary bacterial infection based on radiological and laboratory findings Enoxaparin with prophylactic dose was	Mortality Adverse events	

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
									used in all patients unless there were indications for therapeutic dose		
George/ 2022 [14]	India/Christian Medical College	RCT	112 (38 ivermectin 12 mg/35 ivermectin 24 mg/39 SoC)	29	Median (range): Patients receiving ivermectin 12 mg: 38.5 (6-70) Patients receiving ivermectin 24 mg: 42.3 (4-73) Standard of care: 43.2 (3-77)	Patients with hematological disorders with positive rRT-PCR for SARS CoV-2 (asymptomatic, mild, or moderate COVID-19 illness as per the interim WHO definitions in May 2020)	Ivermectin 12mg x one dose Ivermectin 24 mg x one dose	SoC	None	Proportion of patients negative for SARS-CoV-2 RNA by rRT-PCR on day 7 post-treatment Viral load on days 3, 5 and 7 post treatment Proportion of patients with symptom progression as judged by the WHO ordinal scale Incidence of adverse events attributable to ivermectin	COVID grant from the Science and Engineering Board [SERB], Department of Science and Technology, Government of India

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
										All-cause mortality at discharge from COVID ward	
Hashim/ 2020 [15]	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
Krolewiecki/ 2021 [16]	Argentina/ 4 hospitals	RCT	45 (30/15)	44	Intervention: Mean of 38.1 (11.7)	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	Grant from Agencia Nacional de Promoción de la Investigació

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
					Control: Mean of 42.3 (12.8)					Clinical evolution at day 7 and 30 Safety	n, Argentina
Lim/ 2022 [17]	Malaysia (20 hospitals, 1 quarantine center)	RCT	490 (241/249)	54.5	Mean: 62.5 (8.7)	Mild-moderate disease (at least 1 symptom but not on supplemental oxygen) within 7 days of laboratory-confirmed SARS-CoV-2 infection, considered high risk for progression (≥ 50 years old with ≥ 1 comorbidity)	Ivermectin 0.4 mg/kg/day for 5 days plus standard of care	Standard of care	Therapies considered standard of care per Malaysia guidelines (steroids, tocilizumab, convalescent plasma, anticoagulants)	28-day in-hospital all-cause mortality Proportion of patients progressing to severe COVID-19 Time of progression to severe disease Mechanical ventilation rate ICU admissions Length of hospitalization Adverse events	Institute for Clinical Research, Ministry of Health Malaysia
López-Medina/ 2021 [18]	Columbia/ Centro de Estudios en Infectol	RCT	398 (200/198)	58	Median (IQR): 37 (29-48)	Mild disease (Home or hospitalized but not receiving high-flow nasal oxygen or mechanical	Ivermectin 300 µg/kg/day for 5 days	Placebo	N/A	Mortality Time to symptom resolution	Grant from Centro de Estudios en Infectología Pediátrica

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
	ogía Pedíatrica					ventilation) within 5 days of illness onset				Clinical deterioration Hospitalization Oxygen supplementation Adverse events	
Mahmud/ 2021 [19]	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
Manomaipiboon / 2022 [20]	Thailand/ Vajira Hospital	RCT	72 (36/36)	62.5	Mean age: 48.57 (14.8)	Patients age 18-80 years with mild (cough, runny nose, anosmia, fever, or diarrhea, without dyspnea or tachycardia) or moderate (pneumonia	Ivermectin 12mg by mouth once daily for 5 days plus standard of care	SoC	Favipiravir, andrographolide, cetirizine	All-cause mortality Viral clearance on day 7 and 14 Length of hospitalization	Grant from Navamindradhiraj University

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
						with oxygen saturation > 90%) COVID-19				Frequency of clinical worsening Mechanical ventilation Adverse events	
Mirahmadizadeh/ 2022 [21]	Iran/ 14 specialized COVID-19 outpatient treatment centres	RCT	393 (131 single dose ivermectin/131 double dose ivermectin/131 placebo)	45.8	Median (IQR): Single dose: 39.5 (16.5) Double dose: 39 (17) Placebo: 39.5 (17.5)	Mild symptomatic COVID- 19 confirmed by RT-PCR test, had symptom onset-to-visit interval of less than 48 h, were aged 18–80 years and had oxygen saturation levels of at least 93% in room air	Single dose ivermectin: 3 mg tablet x 4 tablets + placebo tablets x 4, at the second day Double dose ivermectin: 3 mg tablet x 4 tablets x 2 days	Placebo	None	Proportion of subjects who required hospitalization up to 28 days follow-up Proportion of subjects with resolution of symptoms, required machine ventilation or deceased, as well as time to resolution of symptoms Trend of change in severity scale Adverse events	Shiraz University of Medical Sciences

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
Mohan/ 2021 [22]	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 [23]	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 SpO_2 >93% on RA) to moderate COVID-19 (signs of pneumonia with SpO_2 >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

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
Ravikirti / 2021 [24]	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% SpO_2 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
Reis/ 2022 [25]	Brazil/ 12 public health clinics	RCT	1358 (679/679)	58.2	Median: 49 (38-57)	Adult outpatients not requiring hospitalization with laboratory-confirmed SARS- CoV-2 infection within 7 days with ≥1 risk factor for progression	Ivermectin 400 mcg/kg/day for 3 days plus standard of care	Standard of care	None specified	All-cause mortality Hospitalization or ED visit by day 28 due to COVID-19 SARS-CoV-2 viral clearance Length of hospitalization	FastGrants Rainwater Charitable Foundation

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
										Mechanical ventilation Health-related quality of life Adverse reactions	
Rezai/ 2022 [26]	Iran/ 6 trial sites	RCT	891 (447/444)	35.7	Mean (SD): 53.79 (15.3)	Patients with positive diagnostic by RT-PCR assay for SARS-CoV-2 using a nasopharyngeal swab ≤ 4 days prior to screening or positive rapid COVID-19 test, without evidence of viral pneumonia or hypoxia	Ivermectin 0.4 mg/kg x 3 days	Placebo	None	Time to resolution of symptoms Time to recovery including complete recovery and relative recovery Progression (needing hospitalization) Negative RT-PCR result at 5 days ICU admission Drug-induced adverse events Death	

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
Vallejos/ 2021 [27]	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)

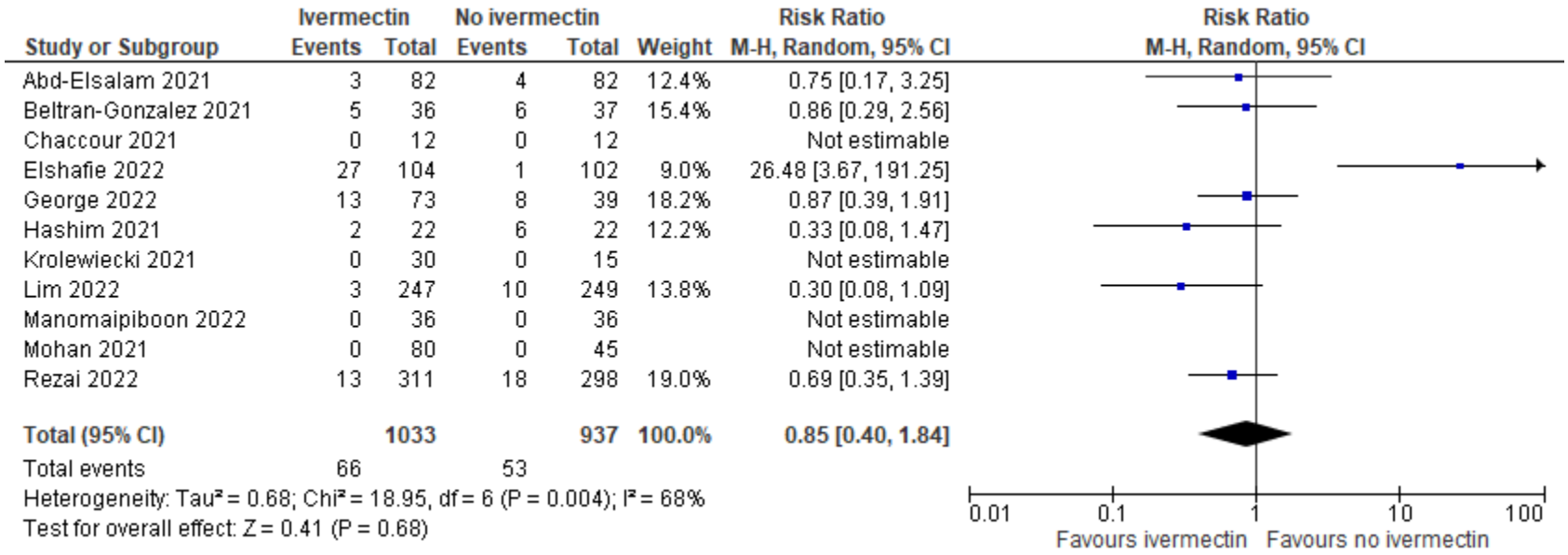


Figure s9b. Forest plot for the outcome of need for mechanical ventilation for ivermectin vs. no ivermectin among hospitalized patients

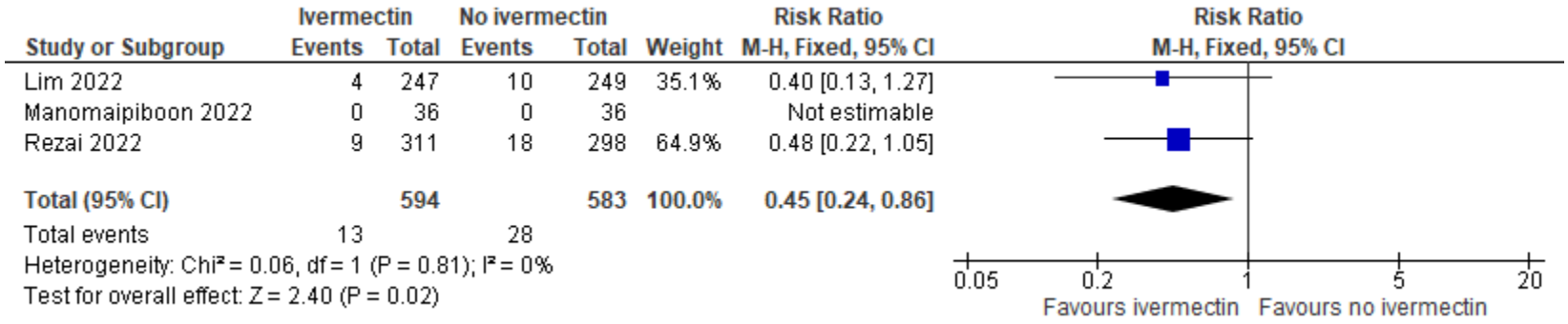


Figure s9c. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (all studies)

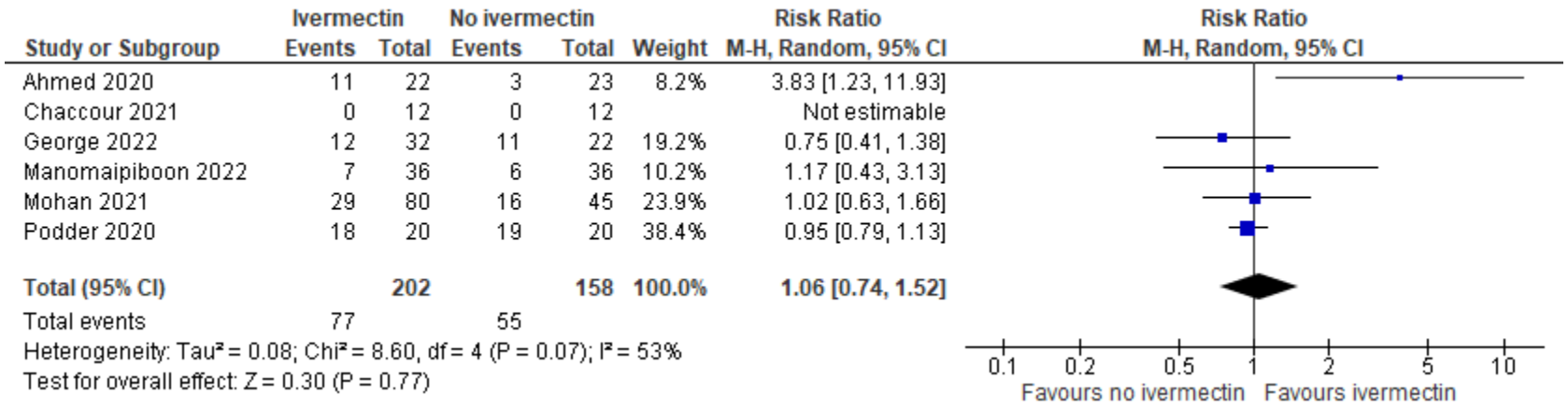


Figure s9d. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (without Ahmed 2020)

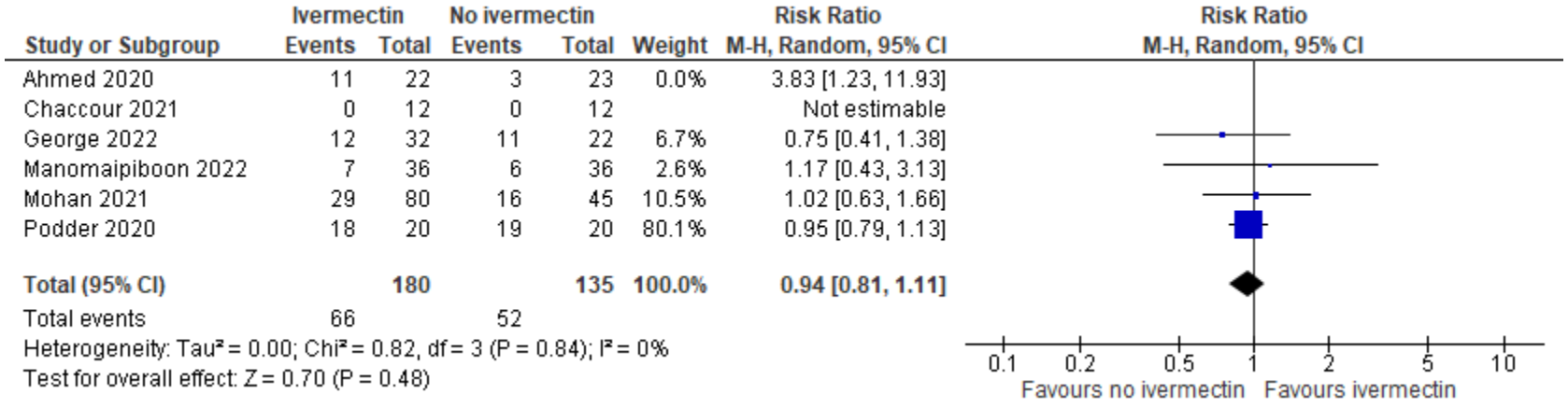


Figure s9e. Forest plot for the outcome of serious adverse events for ivermectin vs. no ivermectin among hospitalized patients

Study or Subgroup	Ivermectin Events	Ivermectin Total	No ivermectin Events	No ivermectin Total	Weight	Risk Ratio M-H, Random, 95% CI
Chaccour 2021	0	12	0	12		Not estimable
Elshafie 2022	33	104	51	102	67.8%	0.63 [0.45, 0.89]
Krolewiecki 2021	1	30	0	15	11.6%	1.55 [0.07, 35.89]
Lim 2022	4	241	1	249	20.5%	4.13 [0.47, 36.71]
Manomaipiboon 2022	0	36	0	36		Not estimable
Rezai 2022	0	311	0	298		Not estimable
Total (95% CI)		**734**		**712**	**100.0%**	**1.03 [0.32, 3.34]**
Total events	38		52			

Heterogeneity: Tau² = 0.50; Chi² = 3.15, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.06 (P = 0.95)

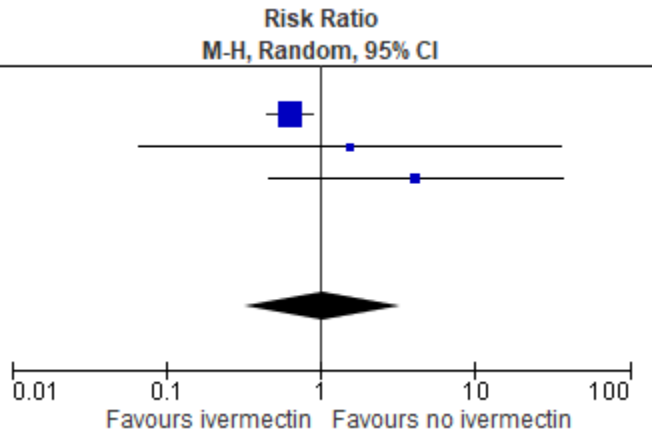


Figure s9f. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among ambulatory patients

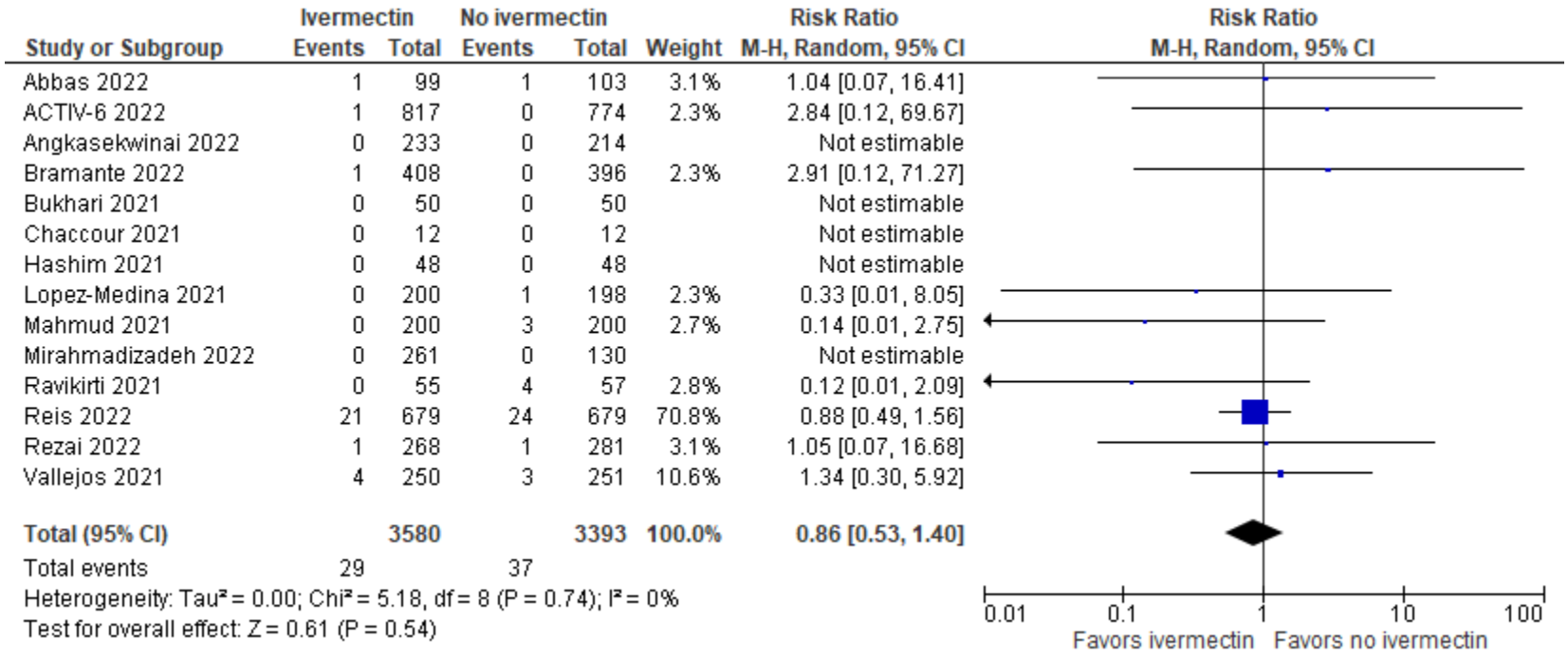


Figure s9g. Forest plot for the outcome of progression to severe disease for ivermectin vs. no ivermectin among ambulatory patients

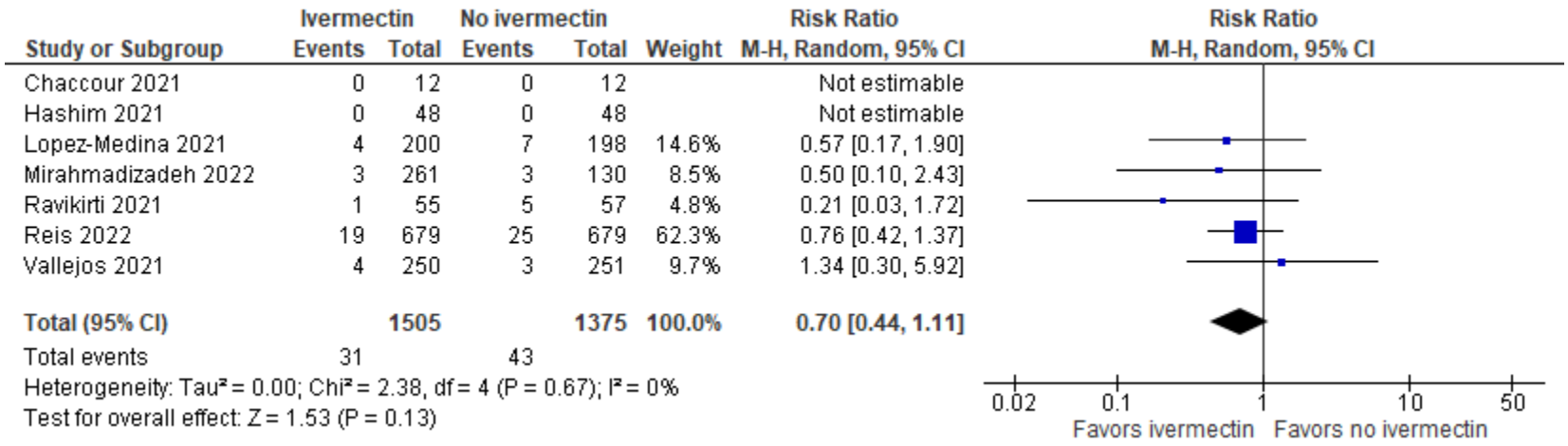


Figure s9h. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among ambulatory patients

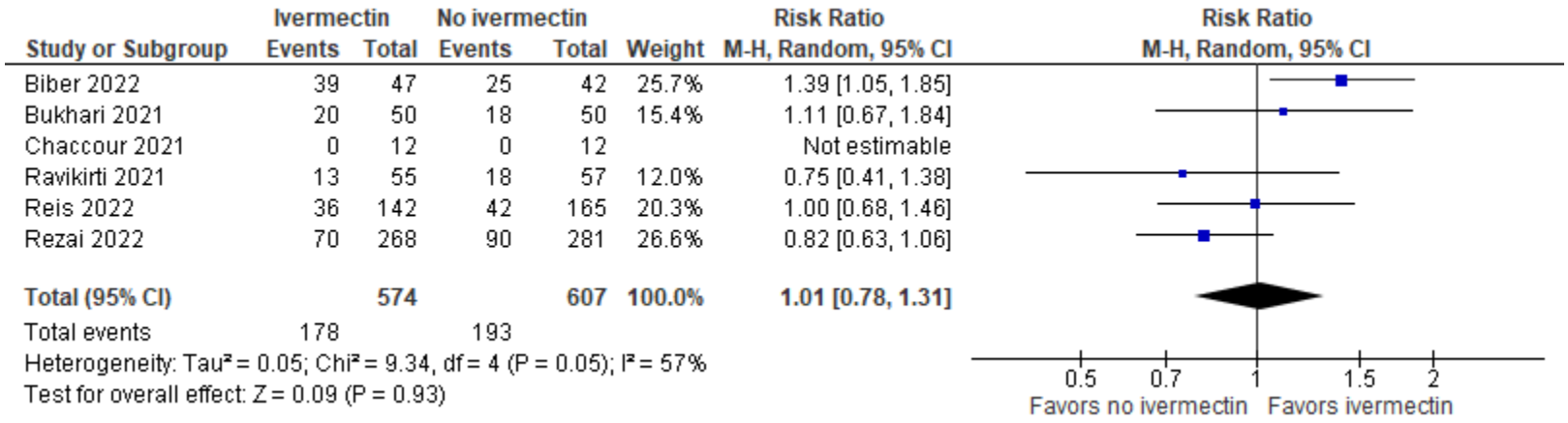


Figure s9i. Forest plot for the outcome of time to recovery for ivermectin vs. no ivermectin among ambulatory patients

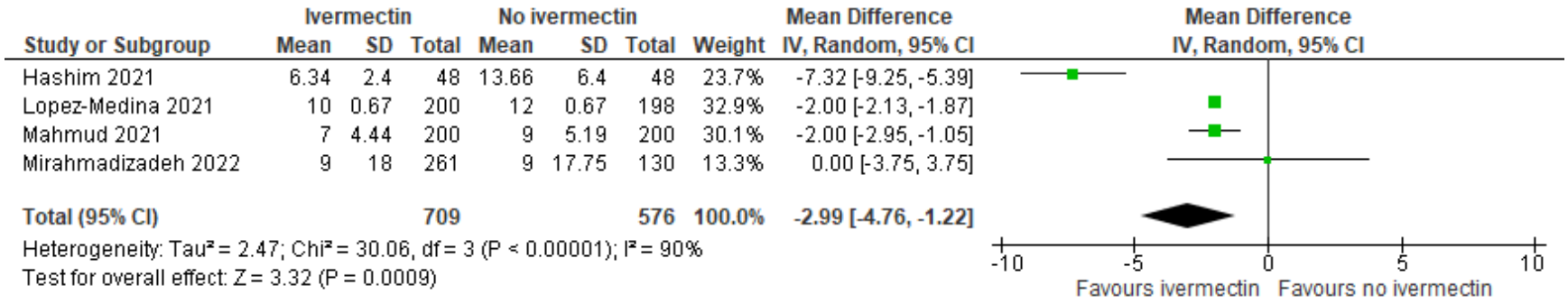


Figure s9j. Forest plot for the outcome of hospitalization for ivermectin vs. no ivermectin among ambulatory patients

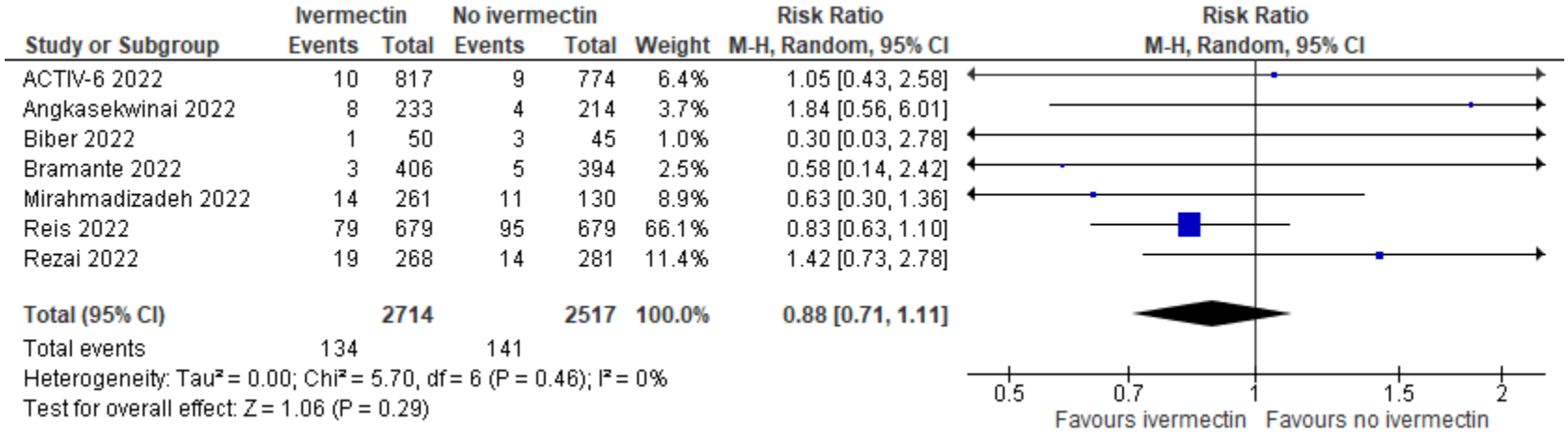


Figure s9k. Forest plot for the outcome of serious adverse events for ivermectin vs. no ivermectin among ambulatory patients

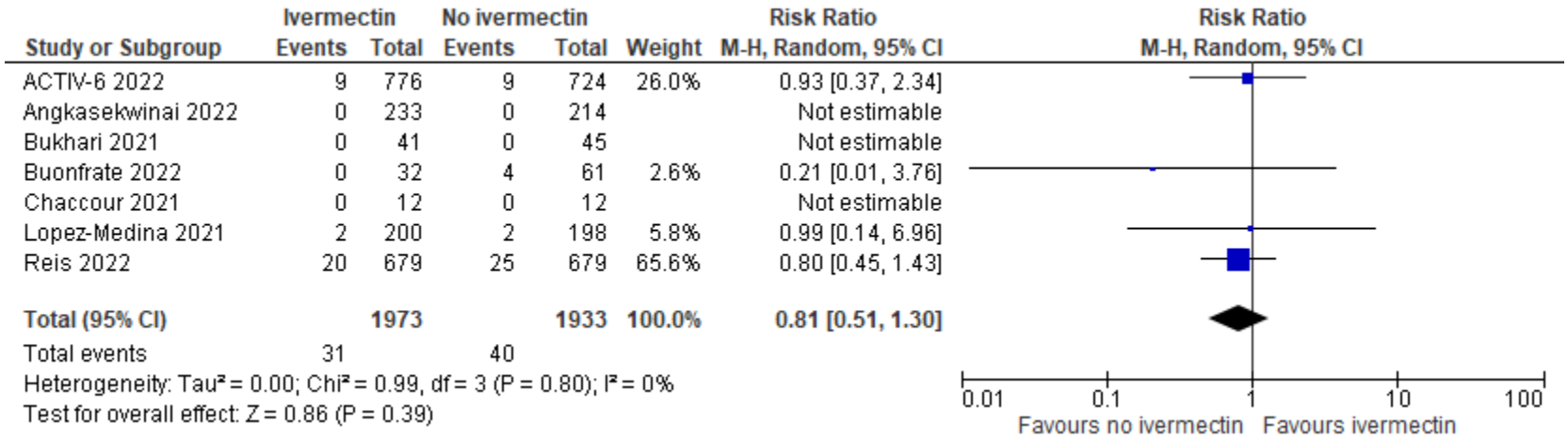


Table s27. Risk of bias for randomized controlled studies (ivermectin vs. no ivermectin)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abbas 2022 [1]							
Abd-Elsalam 2021 [2]							
ACTIV-6 2022 [3]							
Ahmed 2020 [4]							
Angkasekwinai 2022 [5]							
Beltran Gonzalez 2022 [6]							
Biber 2021 [7]							
Bramante 2022 [8]							
Bukhari 2021 [9]							
Buonfrate 2022 [10]							
Chaccour 2021 [11]							
Chachar 2020 [12]							
Elshafie 2022 [13]							
George 2022 [14]							
Hashim 2020 [15]							
Krolewiecki 2021 [16]							
Lim 2022 [17]							
López-Medina 2021 [18]							

Mahmud 2021 [19]							
Manomaipiboon 2022 [20]							
Mirahmadizadeh 2022 [21]							
Mohan 2021 [22]							
Podder 2020 [23]							
Ravikirti 2021 [24]							
Reis 2022 [25]							
Rezai 2022 [26]							
Vallejos 2021 [27]							

Low	High	Unclear

References

1. Abbas KU, Muhammad S, Ding SF. The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19. Indian J Pharm Sci **2022**; 84(1): Spl Issue 87-91.
2. Abd-Elsalam S, Noor RA, Badawi R, et al. Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study. J Med Virol **2021**; 93(10): 5833-8.
3. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group, Naggie S. Ivermectin for Treatment of Mild-to-Moderate COVID-19 in the Outpatient Setting: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.06.10.22276252 [Preprint 12 June 2022].
4. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis **2020**; 103: 214-6.
5. Angkasekwinai N, Rattanaumpawan P, Chayakulkeeree M, et al. Safety and Efficacy of Ivermectin for the Prevention and Treatment of COVID-19: A Double-Blinded Randomized Placebo-Controlled Study. Antibiotics (Basel) **2022**; 11(6).
6. Beltran Gonzalez JL, Gonzalez Gamez M, Mendoza Enciso EA, et al. Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial. Infect Dis Rep **2022**; 14(2): 160-8.
7. Biber A, Harmelin G, Lev D, et al. The effect of ivermectin on the viral load and culture viability in early treatment of nonhospitalized patients with mild COVID-19 - a double-blind, randomized placebo-controlled trial. Int J Infect Dis **2022**; 122: 733-40.
8. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. N Engl J Med **2022**; 387(7): 599-610.
9. Bukhari SKHS, Asghar A, Perveen N, et al. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.02.02.21250840 [Preprint 5 February 2021].
10. Buonfrate D, Chesini F, Martini D, et al. High-dose ivermectin for early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. Int J Antimicrob Agents **2022**; 59(2):106516.
11. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine **2021**; 32: 100720.
12. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. Int J Sci **2020**; 9(09): 31-5.
13. Elshafie AH, Elsawah HK, Hammad M, et al. Ivermectin role in COVID-19 treatment (IRICT): single-center, adaptive, randomized, double-blind, placebo-controlled, clinical trial. Expert Rev Anti Infect Ther **2022**; 20(10): 1341-50.
14. George B, Moorthy M, Kulkarni U, et al. Single Dose of Ivermectin is not Useful in Patients with Hematological Disorders and COVID-19 Illness: A Phase II B Open Labelled Randomized Controlled Trial. Indian J Hematol Blood Transfus **2022**; 38(4): 615-22.

15. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.10.26.20219345 [Preprint 27 October 2020].
16. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. EClinicalMedicine **2021**; 37: 100959.
17. Lim SCL, Hor CP, Tay KH, et al. Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial. JAMA Intern Med **2022**; 182(4): 426-35.
18. López-Medina E, Lopez P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. JAMA **2021**; 325(14): 1426-35.
19. Mahmud R, Rahman MM, Alam I, et al. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. J Int Med Res **2021**; 49(5): 300060521101355.
20. Manomaipiboon A, Pholtawornkulchai K, Pupipatpab S, et al. Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial. Research Square **2022**: Available at: https://doi.org/10.21203/rs.3.rs-1290999/v1 [Preprint 2 February 2022].
21. Mirahmadizadeh A, Semati A, Heiran A, et al. Efficacy of single-dose and double-dose ivermectin early treatment in preventing progression to hospitalization in mild COVID-19: A multi-arm, parallel-group randomized, double-blind, placebo-controlled trial. Respirology **2022**; 27(9): 758-66.
22. Mohan A, Tiwari P, Suri T, Mittal S, Patel AA, Jain A. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. Research Square **2021**: Available at: https://doi.org/10.21203/rs.3.rs-191648/v1 [Preprint 2 February 2021].
23. Podder CS, Chowdhury N, Sina MI, Ul Haque WMM. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC J Med Sci **2020**; 14(2): 11-8.
24. Ravikirti, Roy R, Pattadar C, et al. Ivermectin as a potential treatment for mild to moderate COVID-19–A double blind randomized placebo-controlled trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.01.05.21249310 [Preprint 9 January 2021].
25. Reis G, Silva E, Silva DCM, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med **2022**; 386(18): 1721-31.
26. Rezai S. COVID-19 Update: Ivermectin. Available at: https://rebelem.com/covid-19-update-ivermectin/. Accessed 10 February 2021.
27. Vallejos J, Zoni R, Bangher M, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC Infect Dis **2021**; 21(1): 635.

Fluvoxamine

Table s28. 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 [1]	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 <92% or on SpO_2)	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
Reis/ 2021 [2]	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	Fluvoxamine 100mg twice a day for 10 days	Placebo	None	All-cause mortality	FastGrants The Rainwater Foundation

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
						disease progression					

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

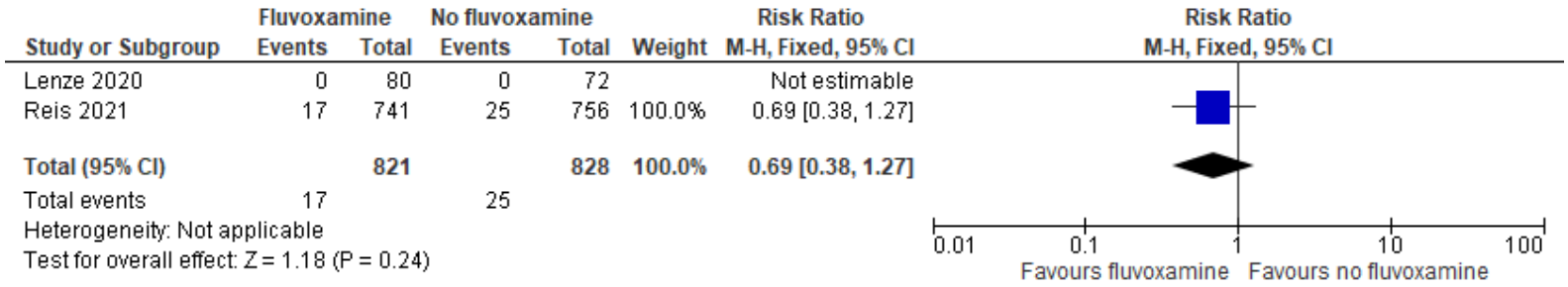


Figure s10b. Forest plot for the outcomes of hospitalization, emergency room visits (>6 hours), or oxygen saturation <92% for fluvoxamine vs. no fluvoxamine

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 s29. 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

References

1. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA **2020**; 324(22): 2292-300.
2. Reis G, dos Santos Moreira Silva EA, Medeiros Silva DC, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet **2021**; S2214-109X(21): 00448-4.

Nirmatrelvir/Ritonavir

Table s30. Should nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir be used for ambulatory or hospitalized patients with mild to moderate COVID-19 at high risk for progression to severe disease?

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
Pfizer-FDA EUA/ 2021 [1]	359 multi-national sites	RCT	2224 (1109/1115)	49	46 years	Ambulatory patients with mild to moderate symptoms at high risk for progression to severe disease who had confirmed SARS CoV-2 infection within 5 days prior to randomization	Nirmatrelvir 300 mg/Ritonavir 100 mg (or renally adjusted for moderate renal disease) every 12 hours for 5 days	Placebo	Neutralizing monoclonal antibody treatments were balanced in each group	Mortality COVID-19 related hospitalization Serious adverse events Proportion of patients requiring discontinuation for adverse events	Pfizer
Liu 2023 [2]	China/ 5 COVID-19-designated hospitals	Parallel RCT	264 (132/132)	46.2	Mean (SD): Paxlovid + standard care: 71.50 (11.61) Standard treatment: 69.20 (14.43)	Hospitalized patients aged from 18 to 90 years old, had severe comorbidities, confirmed SARSCoV-2 infection by positive of real-time PCR within	Received Paxlovid at a dose of 300 mg nirmatrelvir [two tablets] + 100 mg ritonavir [one tablet], orally administered	Standard care including: antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and	Standard care including: antivirus, anticoagulant therapy, prone position ventilation, awake prone	28-day all-cause mortality Risk of death assessed in subgroup participants based	National Natural Science Foundation of China

						the previous 48 h, duration from symptoms onset to hospital admission less than 5 days or the SARS-CoV-2 nucleic acid Ct value ≤ 25 by RT-PCR The severe patients were defined as patients with severity comorbidities, SOFA or Charlson score ≥2. Severe comorbidities were defined as immunosuppressive disease or immunosuppressive status, chronic obstructive pulmonary disease, hypertension complicated with target organ injury, acute and chronic cardiac insufficiency,	every 12 h for 5 days,	nutrient support, etc.	positioning, corticosteroid therapy, and nutrient support, etc.	on the duration since symptoms onset to hospital admission Body mass index Ct value of N and ORF1ab gene The total number of comorbidities Efficacy included in-hospital mortality The proportion of progress to severe COVID-19 within 14 days The proportion of acute	

						chronic renal insufficiency, etc.				exacerbation from the chronic disease within 14 days SARS–CoV-2 RNA clearance within 7 days and 14 days The duration of SARS–CoV-2 RNA clearance, length of hospital and ICU stay, Organ support days to 28 days Adverse events occurring during and after	

										treatment period	

Table s31. Risk of bias for randomized controlled studies (nirmatrelvir/ritonavir vs. no nirmatrelvir/ritonavir in ambulatory patients with mild to moderate COVID-19 at high risk for 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
Pfizer/FDA EUA 2021 [1]							
Liu 2023 [2]							

Low	High	Unclear

References

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid™. Available at: https://www.fda.gov/media/155050/download. Accessed 22 December 2021.
2. Liu J, Pan X, Zhang S, et al. Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. Lancet Reg Health West Pac **2023**; 33: 100694.

Molnupiravir

Table s32. Should ambulatory patients with mild to moderate COVID-19 at high risk for progression to sever disease receive molnupiravir vs. no molnupiravir?

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
Butler 2023 [2]	UK	RCT	25783 (12821/12962)	58.6	Mean (range): 56.6 (18 to 99)	Adults with comorbidities had ongoing symptoms from COVID-19 that had started within the previous five days and a positive polymerase chain reaction (PCR) or rapid antigen SARS-CoV-2 test within the past seven days	Molnupiravir 800mg twice daily for 5 days	Usual care	Usual care	All-cause, non-elective hospital admission and/or death within 28 days of randomization Time to self-reported recovery Time to early sustained recovery (recovered by day 14 and remained recovered until day 28) Time to sustained recovery (date participant first Reported recovery and subsequently remained well until 28 days) Rating from 0-10 of how well participants felt	NIHR

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
										Time to initial alleviation of symptoms (date symptoms first reported as minor or none) Time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remained minor or none until 28 days) Time to initial reduction of severity of symptoms Contacts with health and social services Hospital assessment without admission Oxygen administration New household COVID-19 infections	

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
										Safety outcome measures	
Fisher 2021 [4]	10 sites in US	RCT	202	51.5	Age: Median (range by treatment arm) Molnupiravir 200 mg: 32 (19-65) Molnupiravir 400 mg: 42.5 (19-82) Molnupiravir 800 mg: 42 (18-68) Placebo: 39 (19-71)	Unvaccinated adults if they had a positive test for SARS-CoV-2 infection within 96 hours and had onset of symptoms within 7 days of treatment initiation	Molnupiravir 200 mg every 12 hours x 5 days Molnupiravir 400 mg every 12 hours x 5 days Molnupiravir 800 mg every 12 hours day x 5 days	Placebo	None	Mortality Change in SARS-CoV-2 viral load from baseline Median time to COVID-19 symptom resolution Isolation of infectious virus SAEs	Merck and Ridgeback Biotherapeutics
Jayk 2021 [1]	107 sites in 20 countries	RCT	1433 (716/717)	51.3	43.0 (Range: 18-90)	Ambulatory adults with mild or moderate COVID-19 (at least 1 symptom) with a positive SARS-CoV-2 test within 5 days and at least one risk factor for the development	Molnupiravir 800 mg twice daily for 5 days	Placebo	Standard of care including: antipyretics, anti-inflammatory agents, glucocorticoids)	Mortality Hospitalization Rate of hospitalization Clinical improvement Serious adverse events	Merck

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
						of severe disease					
Khoo 2023 [3]	UK	RCT	180 (90/90)	57.0	Median: 43	Adult out-patients (50/50 vaccinated) with PCR-confirmed SARS-CoV-2 infection within five days of symptom onset	Molnupiravir at 800mg twice daily for 10 doses over 5 days	Matching placebo twice daily for 10 doses over 5 days	Standard of care (symptomatic relief including antipyretics)	Time from randomization to negative PCR with an exploratory virological endpoint of change in viral titer Change in viral titer at day 5 Clinical progression: WHO Clinical Progression Scale for COVID- 19, NEWS2 score (UK Royal College of Physicians measuring acute illness, the FLU-PRO Patient reported outcome measures: presence and severity of influenza-like symptoms across 6 domains of nose, throat, eyes,	Ridgeback Biotherapeutics, UK National Institute for Health and Care Research, Medical Research Council and The Wellcome Trust

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
										chest/respiratory, gastrointestinal and body/system at day 15 and 29 Overall survival (time-to-event) Safety and tolerability	
Zou 2022 [5]	China/Third People's Hospital of Shenzhen	RCT	108 (77/31)	44.4	Median (range) molnupiravir: 39 (20, 63) Median (range) Control: 42 (22, 61)	Adults with mild/moderate COVID-19 who tested positive for SARS-CoV-2 Omicron variant and had initial onset of symptoms for ≤5 days prior to the day of treatment	Molnupiravir (800 mg twice per day) plus basic treatment for 5 days	Basic treatment for 5 days	Basic treatment, which consisted of vitamin C, lianhuaqingwen granule, and nasal irrigation	Time of viral RNA Percentage of patients who were negative for SARS-CoV-2 infectious virus on days 5, 7, and 10 Duration of fever, time of symptom alleviation and laboratory test results (AST, ALT, CK, CK-MB, LDH, IL-6, CRP, Bun, Cr) Serious adverse events	National Key Research and Development Project, Shenzhen Science and Technology Research and Development Project and in part from the National Science and Technology Major Projects

Figure s11a. Forest plot for the outcome of mortality for molnupiravir vs. no molnupiravir

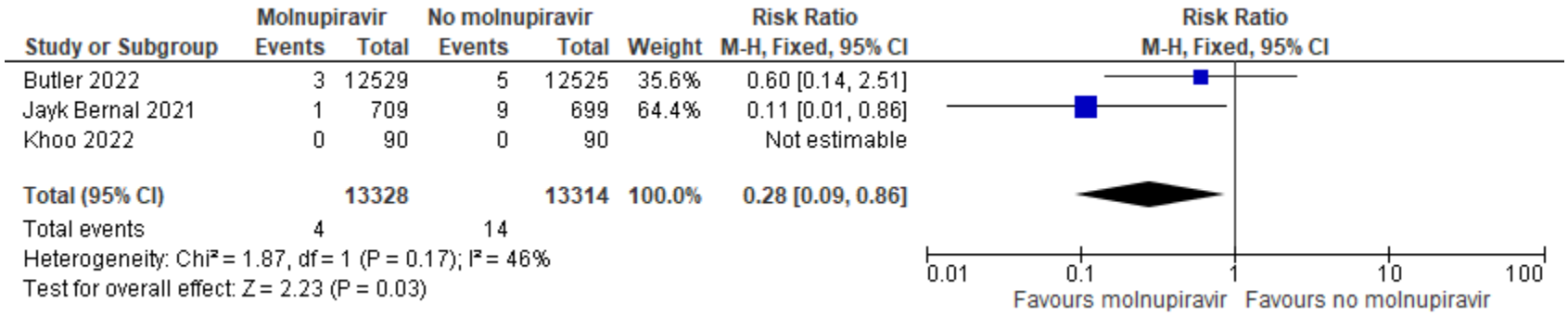


Figure s11b. Forest plot for the outcome of hospitalization for molnupiravir vs. no molnupiravir

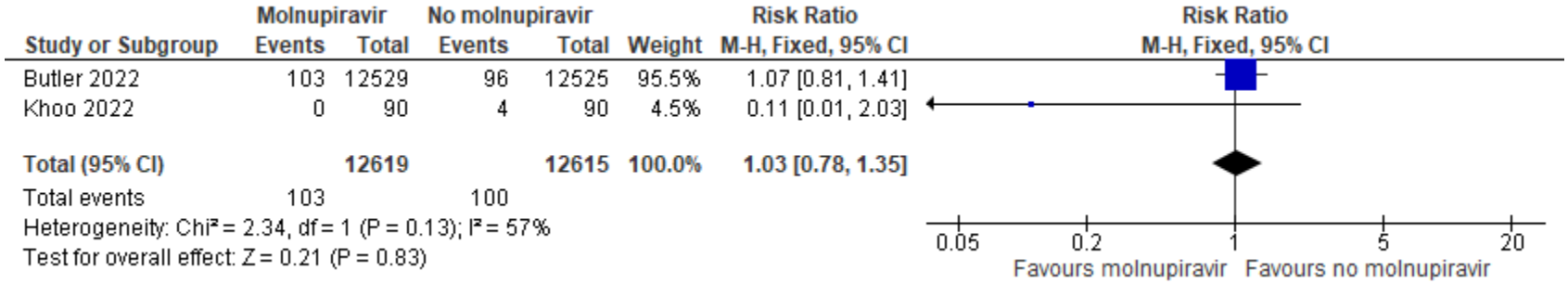


Figure s11c. Forest plot for the outcome of hospitalization or death for molnupiravir vs. no molnupiravir

Figure s11d. Forest plot for the outcome of serious adverse events for molnupiravir vs. no molnupiravir

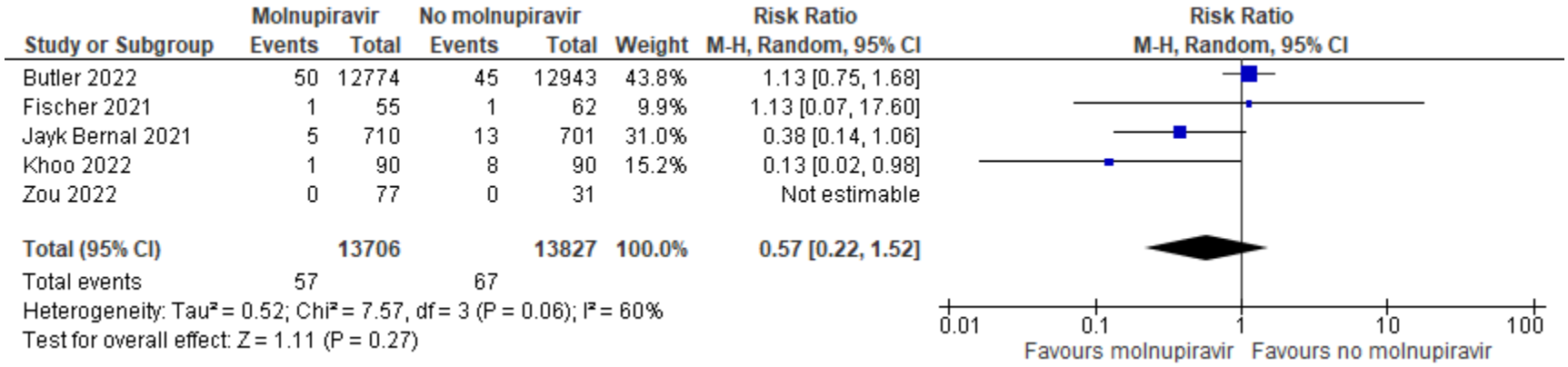


Figure s11e. Forest plot for the outcome of adverse events for molnupiravir vs. no molnupiravir

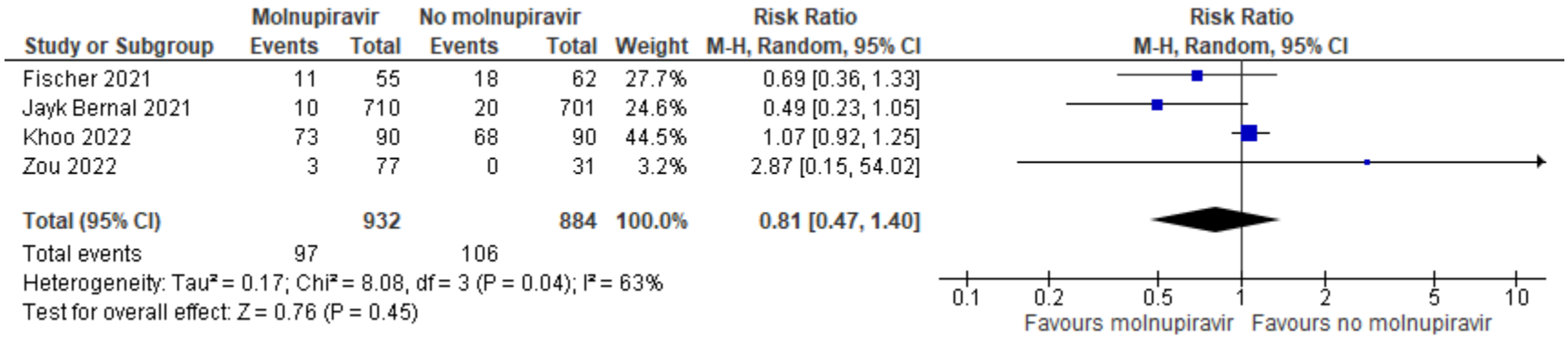


Table s33. Risk of bias for randomized controlled studies (molnupiravir vs. no molnupiravir)

Study	Bias in randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of outcome	Bias in selection of the reported result
Butler 2023 [2]					
Fischer 2021 [4]					
Jayk 2021 [1]					
Khoo 2023 [3]					
Zou 2022 [5]					

Low	High	Some concerns

References

1. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med **2021**: Available at: https://doi.org/10.1056/nejmoa2116044 [Epub ahead of print 16 December 2021].
2. Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet **2023**; 401(10373): 281-93.
3. Khoo SH, FitzGerald R, Saunders G, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis **2023**; 23(2): 183-95.
4. Fischer WA, 2nd, Eron JJ, Jr., Holman W, et al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med **2021**: eabl7430. Available at: https://doi.org/10.1126/scitranslmed.abl7430 [Epub ahead of print 23 December 2021].
5. Zou R, Peng L, Shu D, et al. Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial. Front Pharmacol **2022**; 13: 939573.

Colchicine

Table s34. Should patients (hospitalized and ambulatory) with COVID-19 receive colchicine vs. no colchicine?

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
Absalón-Aguilar 2022 [1]	Mexico/ Instituto Nacional de Ciencias Médicas y Nutrición Salva- dor Zubirán and at Instituto Nacional de Cardiología Ignacio Chávez	RCT	116 (56/60)	34.4	Median (IQR): 53 (44–62)	Hospitalized with severe disease (SpO_2 ≤93%)	(1) Colchicine 1.5 mg PO at baseline (day of recruitment) and then 0.5 mg PO BID for 10 days	(2) Placebo	N/A	Death or progression to critical disease (multiple organ failure, shock, or need for invasive mechanical ventilation) Length of hospital admission Adverse events	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Asultan 2021 [2]	Syria/ Al Assad University Hospital	RCT	49 (14/14/21)	61.2	N/A	Hospitalized with severe disease (SpO_2 ≤93%)	(1) Supportive care plus colchicine (colchicine 1.5 mg PO followed by 0.5 mg after hour in day 1,then 0.5 mg BID for the next 4 days)	(2) Supportive care plus budesonide inhaler (200 mcg BID for 5 days in an inhalation chamber) (3) Supportive care only	All patients received appropriate supportive care with oxygen supplementation, vitamins, anticoagulants, dexamethasone, prone position, noninvasive	Hospitalization days ICU/Death	N/A

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
									ventilation (CPAP or BIPAP), antibiotics, and fluids. Vitamins consist of vitamin C, vitamin D, and zinc. All patients had taken anticoagulants		
Deftereos 2020 [3]	Greece/ 16 tertiary care hospitals	RCT	105 (55/50)	41.9	Median (IQR): 64 (54-76)	Hospitalized with mild to moderate disease (WHO scale 3/4)	(1) Loading dose of colchicine 1.5 mg PO followed by 0.5 mg colchicine 60 minutes later if no adverse gastrointestinal effects were observed, 0.5 mg colchicine BID (reduced to QD among patients with body weight <60 kg) until hospital discharge or a maximum of 21 days In the case of azithromycin coadministration, a single 1.0 mg loading dose of	(2) Medical treatment for COVID-19 per local protocols	Chloroquine or hydroxychloroquine, azithromycin, lopinavir or ritonavir, tocilizumab	2-grade increase on WHO ordinal clinical scale Requiring mechanical ventilation All-cause mortality Adverse events	ELPEN Pharmaceuticals Acarpia Pharmaceuticals Karian Pharmaceuticals

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
							colchicine was administered				
Diaz 2021 [4]	Argentina/ 42 centers	RCT	1279 (640/639)	35.1	Mean (SD): 61.8 (14.6)	Hospitalized with severe disease (SpO_2 ≤93%)	(1) Colchicine loading dose of 1.5 mg PO, followed by 0.5 mg PO within 2 hours of the initial dose, and subsequently 0.5 mg BID for 14 days or discharge, whichever occurred first The colchicine dose was reduced in patients with kidney or liver dysfunction or if drugs that could interact were used concomitantly	(2) usual care	Corticosteroids, anticoagulant drugs, convalescent plasma, ivermectin, antiplatelet drugs, oseltamivir, hydroxychloroquine, lopinavir/ritonavir	Intubation for mechanical ventilation 28-day mortality Adverse events	Population Health Research Institute Fundacion ECLA
Dorward 2021 [5]	UK/ multicentre	RCT	314 (174/140)	53.5	N/A	Ambulatory care	(1) Colchicine 500 µg daily for 14 days	(2) SoC largely focused on managing symptoms with antipyretics and inhaled budesonide on an off-label, case-by-case basis	SoC	Death Hospitalization Duration of hospitalization	UK Research and Innovation Department of Health and Social Care through the National

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
								for people aged ≥65 years or 50-65 with comorbidities		Mechanical ventilation	Institute for Health Research
Gaitán-Duarte 2022 [6]	Colombia/ 6 referral hospitals	RCT	633 (160/153/ 159/161)	32.0	Mean (SD): 55.4 (12.8)	Hospitalized with severe disease (with pneumonia; 85% of patients on non-invasive support or no oxygen, 15% on high-flow cannula or mechanical ventilation)	(1) Emtricitabine/ Tenofovir (200/300 mg PO for 10 days) (2) Colchicine + Rosuvastatin (0.5 mg and 40 mg PO for 14 days) (3) Emtricitabine/ Tenofovir + Colchicine + Rostuvastin (200/300 mg, 0.5 mg and 40 mg PO)	(4) SoC based on the recommendations of the Colombian consensus for hospitalized patients with COVID-19 that included the use of dexamethasone, ivermectin or albendazole as prophylaxis for *Strongyloides* infection, enoxaparin, acetaminophen, oxygen as needed, and mechanical ventilation, or dialysis, if required	SoC	All-cause mortality within 28 days Mechanical ventilation Adverse events	Colombian Ministry of Science and Technology
Gorial 2022 [7]	Iraq/ Alkarkh hospital	RCT	160 (80/80)	46.9	Median (IQR): 49 (37-60.5)	Ambulatory and hospitalized with moderate to severe	(1) Colchicine 0.5 mg tablet BID for 1 week followed by 0.5 mg tablet QD for another week	(2) SoC with acetaminophen 500 mg on need, vitamin c 1000 mg BID, zing 75-125 mg/day, vitamin d3	SoC	Death Adverse events	None

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
						COVID-19 (WHO classification)		5000IU/day, azithromycin 250 mg/day for 5 days, oxygen therapy/C-pap if needed, dexamethasone 6 mg/day or methylprednisolone 40 mg BID, if needed, and mechanical ventilation, if needed			
Lopes 2021[8]	Brazil	RCT	72 (36/36)	54.2	N/A	Hospitalized with severe disease (SpO_2 ≤92%)	(1) Colchicine 0.5 mg PO TID for 5 days, then 0.5 mg BID for 5 days; if body weight ≥80kg, the first dose was 1.0 mg Whether a patient had chronic kidney disease, with glomerular filtration rate under 30mL/min/1.73m2, colchicine dose was reduced to 0.25 mg TID for 5 days, then 0.25 mg	(2) Institutional treatment with azithromycin 500 mg QD for up to 7 days, hydroxychloroquine 400 mg BID for 2 days, then 400 mg QD for up to 8 days and unfractionated heparin 5000 UI TID until the end of hospitalization	Institutional treatment	Time of hospitalization Death rate Adverse events	Fundação de Amparo à Pesquisa do Estado de São Paulo

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
							BID for 5 days, no matter the body weight				
Mareev 2021 [9]	Russia	RCT	43 (21/22)	30.2	N/A	Hospitalized with severe disease (pneumonia + elevated CRP >60 mg/l + fever >37.5°C; persistent cough; dyspnea with the respiratory rate (RR) >20 brpm and / or SaO2 <94% when breathing atmospheric air)	(1) Colchicine 1 mg during first 1-3 days followed by 0.5 mg/day	(2) Control	N/A	Change in SHOCS-COVID score Death Hospitalization duration	MSU Medical Research and Educational Center
Pascual-Figal 2021 [10]	Spain	RCT	103 (52/51)	47.6	Mean (SD): 51.0 (12.0)	Hospitalized with mild to moderate disease (WHO scale 3/4)	(1) Initial load dose of colchicine 1.5 mg PO (1 mg and 0.5 mg two hours after), followed by 0.5 mg every 12 hours during the	(2) SoC: • dexamethasone (6 mg QD for 10 days) for patients who required	SoC	WHO 7-points ordinal clinical scale Death	"Cardiology Research group" at the IMIB-Arrixaca and the University of

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
							next 7 days and 0.5 mg every 24 hours until the completion of 28 days of total treatment The dose was reduced by half in patients receiving ritonavir or lopinavir or with at least one of the following: reduced renal clearance (<50 mL/min/ 1.37m2), weight <70 kg or age >75 years old	supplemental oxygen (WHO scale ≥4) • remdesivir for 5 days (time from symptoms onset <7 days; two or more measurements of oxygen saturation below 94% on room air, respiratory rate >24 breaths/min without supplemental oxygen or Pa02/Fi02<30 • tocilizumab single dose of 600 mg and baricitinib at 4 mg/day for 14 days (need for tocilizumab or baricitinib established according to physician on care criteria)		Mechanical ventilation Adverse events	Murcia, Murcia, Spain Centro Nacional de Investigaciones Cardiovasculares Spanish Ministry of Economy and Competitiveness (MINECO) Pro-CNIC Foundation

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
RECOVERY Collaborative Group 2021 [11]	177 hospitals in UK, 2 hospitals in Indonesia, 2 hospitals in Nepal	RCT	11 340 (5610/5730)	30.3	Mean (SD): 63.4 (13.8)	Hospitalized with severe disease (68% of patients on non or simple oxygen, 27% on non-invasive ventilation, and 5% on invasive mechanical ventilation)	(1) Colchicine 1 mg followed by 500 µg 12 h later and then 500 µg BID orally or by nasogastric tube for 10 days in total or until discharge, whichever occurred first Dose frequency was halved for patients receiving a moderate CYP3A4 inhibitor (eg, diltiazem), those who had renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m2), and patients with an estimated body weight of less than 70 kg	(2) SoC	Corticosteroids, remdesivir	28-day mortality Median time to being discharged alive Discharged from hospital within 28 days Invasive mechanical ventilation Adverse events	UK Research and Innovation (Medical Research Council) National Institute of Health Research Wellcome Trust
Tardif 2021 [12]	Canada/ led by the Montreal	RCT	4488 (2235/2253)	53.9	N/A	Ambulatory care with at least one	(1) 0.5 mg BID for the first 3 days and then QD for 27 days thereafter	(2) Placebo	N/A	Composite of death or hospital	The Government of Quebec, the Bill & Melinda Gates Foundation, the

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
	Heart Institute					high risk characteristic				admission for COVID-19 Need for mechanical ventilation Serious adverse events	National Heart, Lung, and Blood Institute of the US National Institutes of Health, the Montreal Heart Institute Foundation, the NYU Grossman School of Medicine, the Rudin Family Foundation, and philanthropist Sophie Desmarais.

Figure s12a. Forest plot for the outcome of mortality for colchicine vs. no colchicine

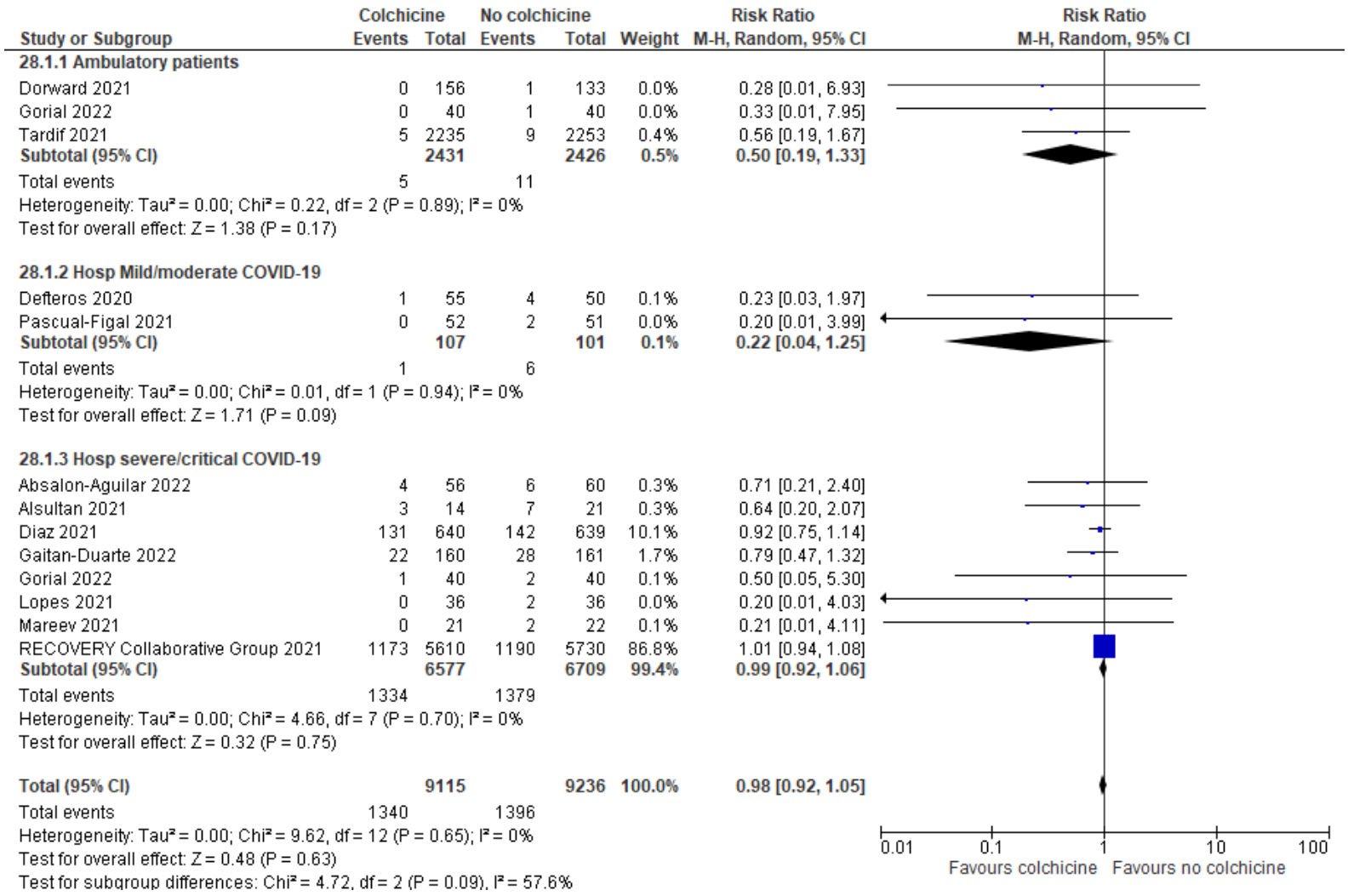


Figure s12b. Forest plot for the outcome of duration of hospitalization for colchicine vs. no colchicine (hospitalized patients)

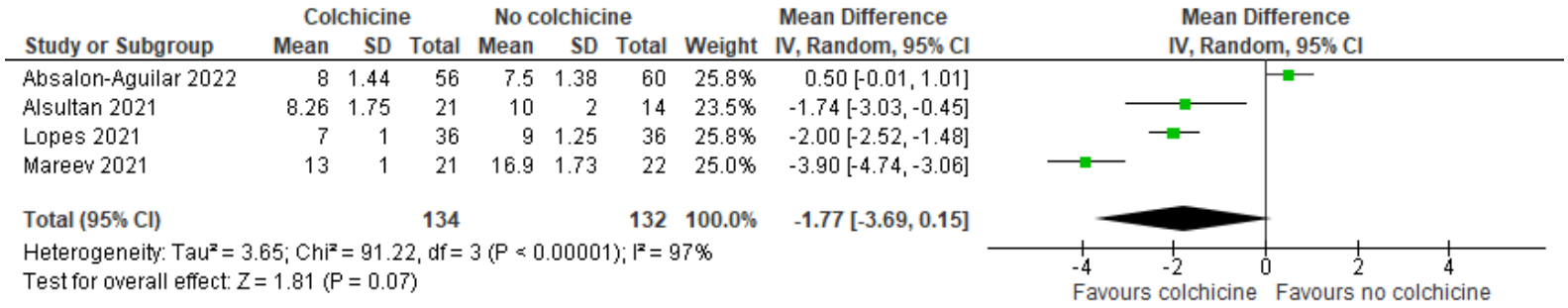


Figure s12c. Forest plot for the outcome of hospitalization for colchicine vs. no colchicine (ambulatory persons)

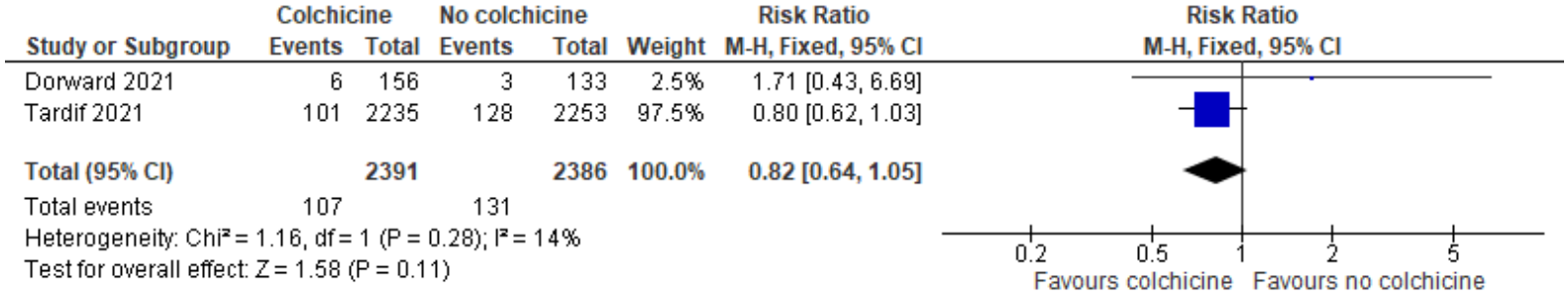


Figure s12d. Forest plot for the outcome of mechanical ventilation for colchicine vs. no colchicine

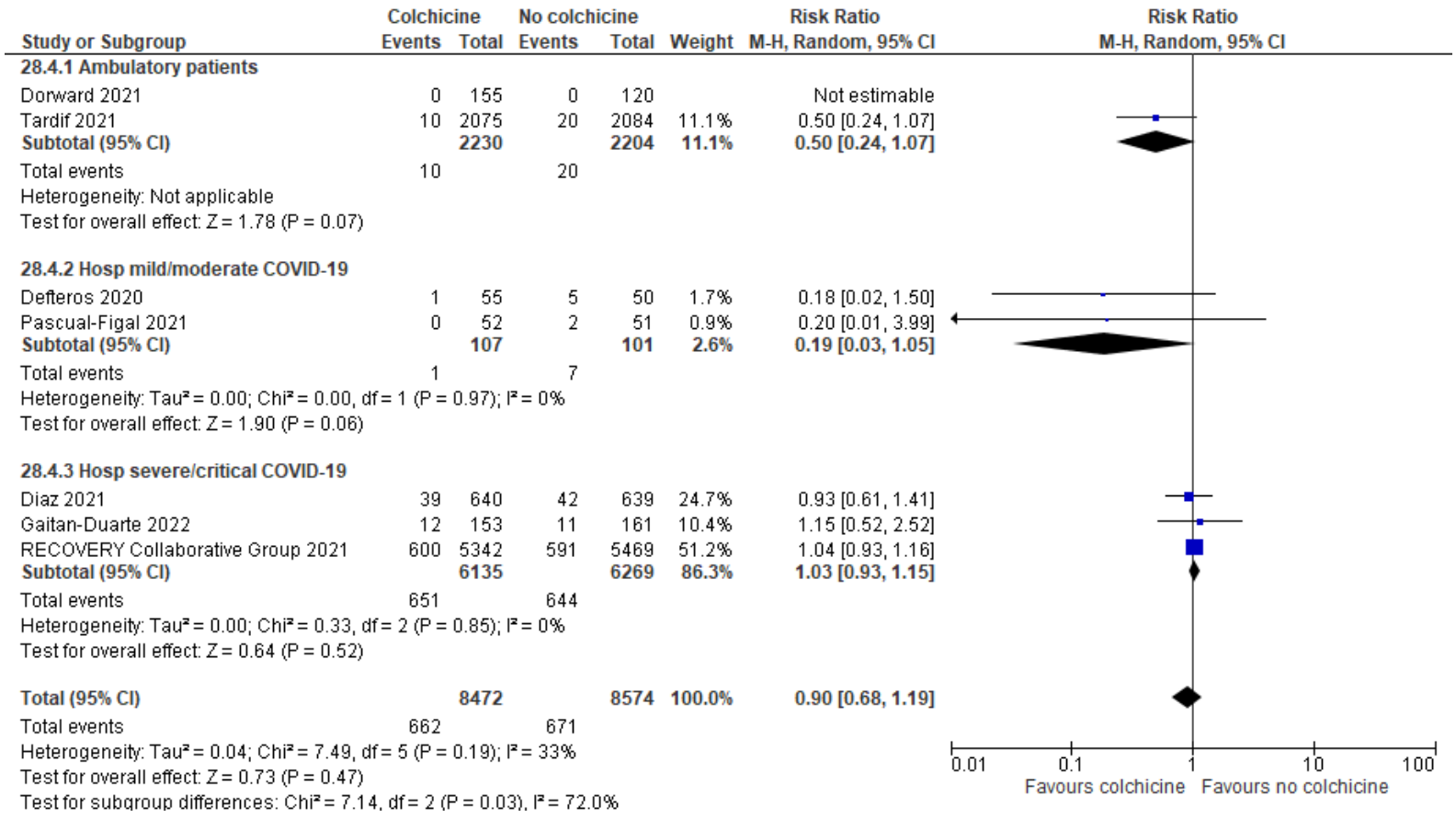


Figure s12e. Forest plot for the outcome of adverse events for colchicine vs. no colchicine (hospitalized patients)

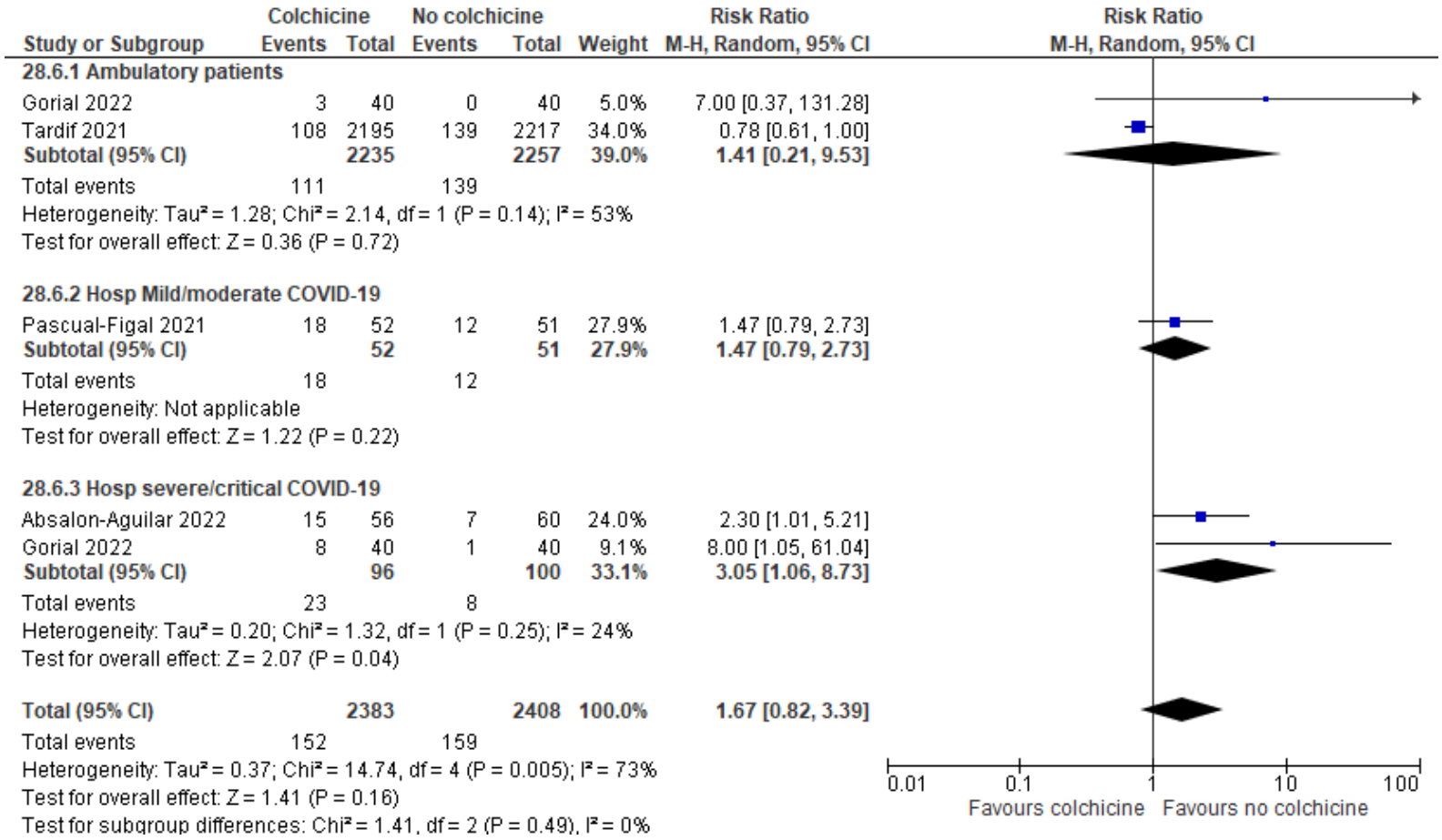


Table s35. Risk of bias for randomized controlled studies (colchicine vs. no colchicine)

Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result
Abalsón-Aguila 2022 [1]					
Alsultan 2021 [2]					
Deftereos 2020 [3]					
Diaz 2021 [4]					
Dorward 2021 [5]					
Gaitan-Duarte 2022 [6]					
Gorial 2022 [7]					
Lopes 2021 [8]					
Mareev 2021 [9]					
Pascual-Figal 2021 [10]					
RECOVERY Collaborative Group 2021 [11]					

Tardif 2021 [12]					

Low Risk	Some Concerns	High Risk

References

1. Absalón-Aguilar A, Rull-Gabayet M, Perez-Fragoso A, et al. Colchicine Is Safe Though Ineffective in the Treatment of Severe COVID-19: a Randomized Clinical Trial (COLCHIVID). J Gen Intern Med **2022**; 37(1): 4-14.
2. Alsultan M, Obeid A, Alsamarrai O, et al. Efficacy of Colchicine and Budesonide in Improvement Outcomes of Patients with Coronavirus Infection 2019 in Damascus, Syria: A Randomized Control Trial. Interdiscip Perspect Infect Dis **2021**; 2021: 2129006.
3. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA Netw Open **2020**; 3(6): e2013136.
4. Diaz R, Orlandini A, Castellana N, et al. Effect of Colchicine vs Usual Care Alone on Intubation and 28-Day Mortality in Patients Hospitalized With COVID-19: A Randomized Clinical Trial. JAMA Netw Open **2021**; 4(12): e2141328.
5. Dorward J, Yu L-M, Hayward G, et al. Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.09.20.21263828 [Preprint 23 September 2021].
6. Gaitán-Duarte HG, Álvarez-Moreno C, Rincón-Rodríguez CJ, et al. Effectiveness of Rosuvastatin plus Colchicine, Emtricitabine/Tenofovir and a combination of them in Hospitalized Patients with SARS Covid-19. EClinicalMedicine **2022**; 43: 101242.
7. Gorial FI, Maulood MF, Abdulamir AS, Alnuaimi AS, Abdulrrazaq MK, Bonyan FA. Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection. Ann Med Surg (Lond) **2022**; 77: 103593.
8. Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. RMD Open **2021**; 7(1): e001455.
9. Mareev VY, Orlova YA, Plisyk AG, et al. Proactive anti-inflammatory therapy with colchicine in the treatment of advanced stages of new coronavirus infection. The first results of the COLORIT study. Kardiologiia **2021**; 61(2): 15-27.
10. Pascual-Figal DA, Roura-Piloto AE, Moral-Escudero E, et al. Colchicine in Recently Hospitalized Patients with COVID-19: A Randomized Controlled Trial (COL-COVID). Int J Gen Med **2021**; 14: 5517-26.
11. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Respir Med **2021**; 9(12): 1419-26.
12. Tardif J-C, Bouabdallaoui N, L'Allier PL, et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.01.26.21250494 [Preprint 27 January 2021].

Anakinra

Table s36. Should hospitalized patients with severe COVID-19 receive anakinra vs. no anakinra?

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
Audemard-Verger 2022 [6]	France/ 20 University and General Hospitals	RCT	71 (37/34)	26.8	Mean (SD): Intervention: 71 (15) Control: 70 (14)	Positive rRT-PCR and/or typical chest or CT scan of COVID 19 pneumonia and required oxygen therapy	Anakinra IV 400 mg/day (100 mg every 6 hrs) x 3 days then 200 mg/day (100 mg ever 12 hrs) x 7 days	SoC	SoC included antiviral drugs, hydroxychloroquine, corticosteroid, anticoagulants, hydration, nutrition, extra-renal purification, oxygen therapy and vasopressive drugs	Treatment success at day 14 (patient being alive and not requiring invasive mechanical ventilation or ECMO) Clinical status (WHO Clinical Progression Scale) National Early Warning Score Biological parameters (lymphocytes count, CRP, ferritin, d-dimers, fibrinogen levels) Overall survival Time to hospital discharge Time to ICU admission	Endowment fund of the university hospital of Tours

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
										Time to ventilatory support Time to oxygen supply withdrawal over 28-day follow-up Adverse and serious adverse events	
CORIMUNO-19 2021 [5]	France/ 16 University hospitals	RCT	116 (59/57)	29.8	Median (IQR): Intervention: 67.0 (55.5-74.3) Control: 64.9 (59.5-78.3)	Mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving at least 3 L/min of oxygen but without ventilation assistance (eg, high-flow oxygen, non-invasive ventilation, or mechanical ventilation	Anakinra IV 200 mg twice a day (total 400 mg) on days 1-3, then 100 mg twice a day on day 4 (total 200 mg), then 100 mg once on day 5 If no improvement was seen on morning of day 4 (reduction in requirement of oxygen of more than 50%, but the decision was left to the treating physician), 3 supplementary days of treatment at 400 mg per day were done on days 4–6, followed by a	SoC	Antibiotic drugs, antiviral drugs, corticosteroid, vasopressor support, anticoagulants	Proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (score of >5 points on WHO-CPS) Survival with no need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14 Clinical status assessed with WHO-CPS at days 4, 7, and 14	The Ministry of Health Programme Hospitalier de Recherche Clinique Foundation for Medical Research AP-HP Foundation

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
							decrease to 200 mg per day on day 7 and 100 mg per day on day 8			Overall survival at days 14, 28, and 90 Time to discharge from hospital Time to oxygen supply independency Biological factors (eg, CRP concentration) Adverse events Time to discharge and at day 28 Time to oxygen supply independency at day 28	
Declercq 2021 [2]	Belgium/ 16 hospitals	RCT	342 (112/230)	N/A	Median (IQR): Intervention: 67 (56-74) Control: 64 (54-72)	Symptoms between 6 and 16 days, PaO_2:FiO_2 < 350 mm Hg on room air or > 280 mm Hg on supplemental oxygen and bilateral pulmonary infiltrates	Anakinra 100 mg once daily SC for 28 days or until hospital discharge	SoC	Antibiotics, remdesivir, HCQ, glucocorticoids, methylprednisolone equivalents	Time to clinical improvement or to discharge from hospital alive Median time until discharge Median time until independence from invasive ventilation	Belgian Health Care Knowledge Center

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
										Median time until first use of high-flow oxygen device Ventilation or death Number of days in hospital Number of days in ICU Number of days in ICU in patients ventilated at day of randomization Number of days in ICU, relative to number of days alive the first 28 days after randomization Number of days without supplemental oxygen use up to 28 days after randomization Number of invasive ventilator days	

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
										Number of invasive ventilator days in patients ventilated at day of randomization Number of invasive ventilator days, relative to number of days alive the first 28 days after randomization Number of invasive ventilator-free days up to 28 days after randomization Number of invasive ventilator-free days up to 28 days after randomization in patients ventilated at day of randomization Death	

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
										Serious adverse events	
Elmekaty 2022 [1]	Qatar/ 3 clinical sites	RCT	80 (40/40)	17.5	Mean (SD): 49.9 (11.7)	Positive SARS-CoV2 PCR test and associated presence of respiratory distress [defined as: $PaO_2/FiO_2 \leq$ 300 mm Hg or respiratory Rate ≥24 breaths/min or $SpO_2 \leq 94\%$ at room air], and signs of cytokine release syndrome	Anakinra 100 mg SC injection evert 12 hrs for 3 days, then 100 mg SC once daily from day 4 to 7	SoC	Remdesivir, favipravir, corticosteroid, convalescent plasma, azithromycin, ceftriaxone, anticoagulants	Treatment success on day 14 (WHO Clinical Progression score of ≤3) Duration of mechanical ventilation in ventilated patients up to 14 days Changes in WHO Clinical Progression Score between day 1 and 7 Viral burden (change in PCR cycle threshold) at day 7 and day 10-14 Time to ICU admission up to 28 days Adverse events	Medical Research Center at Hamad Medical Corporation, Qatar

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
										Length of hospital stay up to 28 days All-cause mortality rate at hospital discharge or at 28 days	
Kharazmi 2022 [4]	Iran/ Imam Hossein Medical Center	RCT	30 (15/15)	36.7	Mean (SD) Intervention: 49.25 (19.12) Control: 59.00 (1.79)	Elevated CRP levels, oxygen saturation ≤ 93% measured using a peripheral capillary pulse oximeter, fever, or cough or shortness of breath, and $PaO_2/FiO_2 < 300$	Anakinra 100 mg IV once daily until discharge or maximum of 14 days	SoC	Remdesivir, lopinavir/ritonavir, interferon, favipiravir, and corticosteroid, oxygen supplementation, ventilation support, fluid, and electrolyte correction, vasoactive agents and antibiotic administration, and renal replacement support if appropriate	Need for endotracheal intubation due to hypoxemia Hospital length of stay ICU length of stay Seven categories ordinal scale (includes hospitalization, mechanical ventilation) Survival on day 14	Not specified
Kyriazopoulou 2021 [3]	Greece	RCT	594 (405/189)	42.1	Mean (SD): 61.9 (12.1)	Confirmed infection by SARS-CoV-2 by molecular test; findings in chest X-ray or chest CT	Anakinra 100 mg SC once daily in for 7–10 days	Placebo	Remdesivir, dexamethasone (severe patients)	Frequencies of the scores from the 11-point WHO-CPS on day 28	Hellenic Institute for the Study of Sepsis

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
						compatible with lower respiratory tract infection; need for hospitalization; and plasma suPAR ≥6 ng ml^{-1}				Changes of WHO-CPS scores at days 14 and 28 from the baseline Change of SOFA score at day 7 from baseline Time until hospital discharge Time of stay in the ICU Comparison of biomarkers	Swedish Orphan Biovitrum

Figure s13a. Outcome of mortality for convalescent plasma vs. no convalescent plasma in hospitalized patients

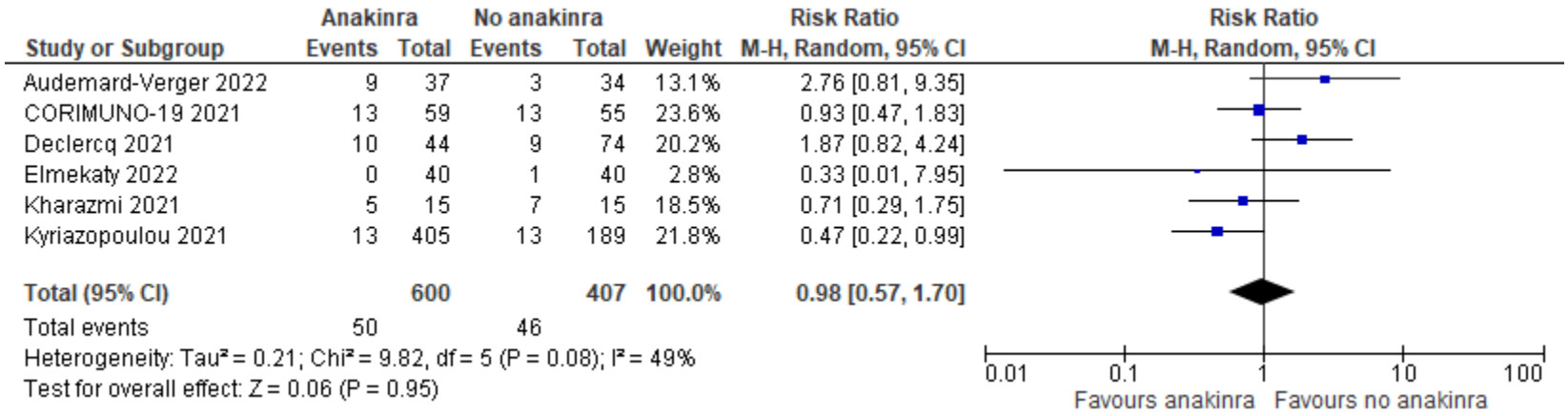


Figure s13b. Outcome of hospitalization duration for anakinra vs. no anakinra in hospitalized patients

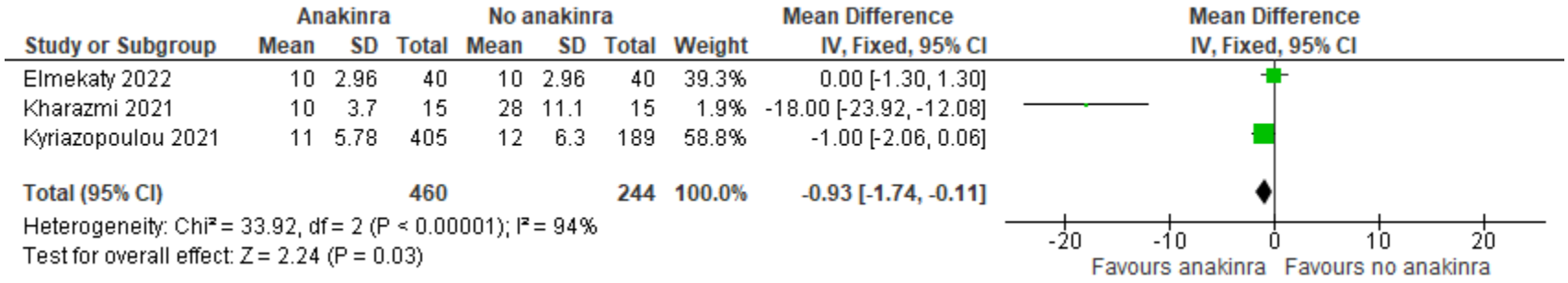


Figure s13c. Outcome of mechanical ventilation for anakinra vs. no anakinra in hospitalized patients

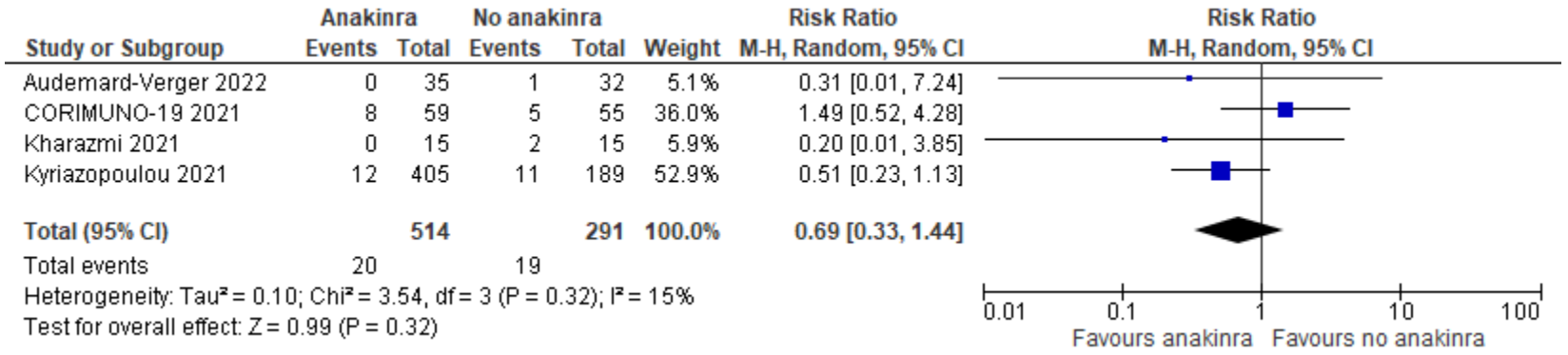


Figure s13d. Outcome of adverse events (mild to severe) for anakinra vs. no anakinra in hospitalized patients

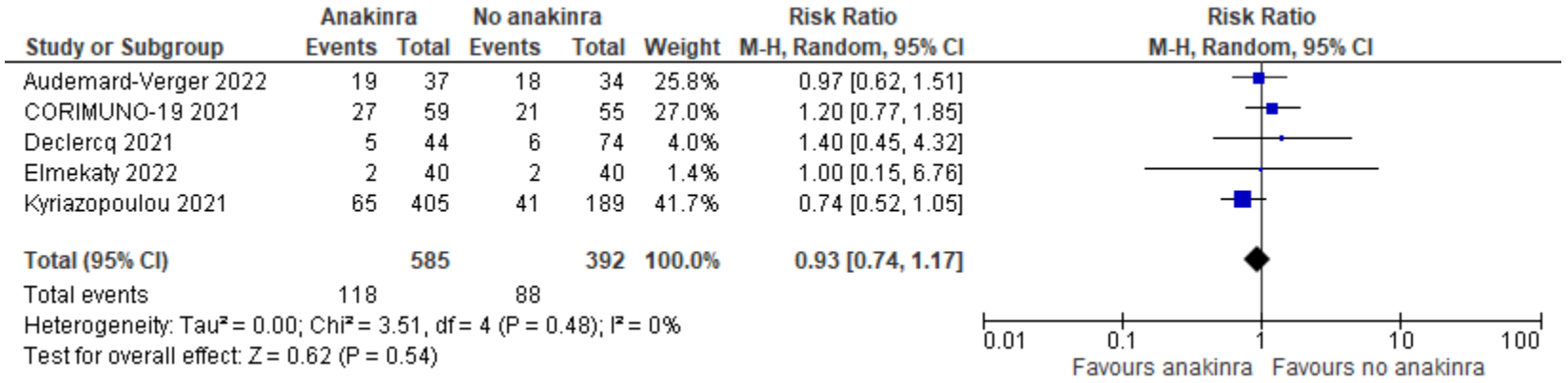


Table s37. Randomized control studies (anakinra vs. no anakinra)

Study	Randomization process	Deviation from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result
Audemard-Verger 2022 [6]					
CORIMUNO-19 2021 [5]					
Declercq 2021 [2]					
Elmekaty 2022 [1]					
Kharazmi 2022 [4]					
Kyriazopoulou 2021 [3]					

Low	High	Some concerns

References

1. Elmekaty E, Maklad A, Abouelhassan R, et al. Efficacy of Anakinra in the Management of Patients with COVID-19 Infection: A Randomized Clinical Trial. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.07.04.22277207 [Preprint 6 July 2022].
2. Declercq J, Van Damme KFA, De Leeuw E, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. Lancet Respir Med **2021**; 9(12): 1427-38.
3. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med **2021**; 27(10): 1752-60.
4. Kharazmi AB, Moradi O, Haghighi M, et al. A randomized controlled clinical trial on efficacy and safety of anakinra in patients with severe COVID-19. Immun Inflamm Dis **2022**; 10(2): 201-8.
5. Corimuno-Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med **2021**; 9(3): 295-304.
6. Audemard-Verger A, Le Gouge A, Pestre V, et al. Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial. PLoS One **2022**; 17(8): e0269065.