Supplementary material

Supplementary File 1. Details of search terms

MEDLINE® search string (searches were conducted via PubMed)

Search number	Query	Filters
1	Coronavirus[MeSH] OR Coronavirus[Title/Abstract]	
2	COVID*[Title/Abstract]	
3	#1 OR #2	
4	"covid 19"[Title/Abstract] OR "Covid-19"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "Novel Corona Virus"[Title/Abstract] OR "corona virus disease"[Title/Abstract] OR "Coronavirus disease"[Title/Abstract] OR "Coronavirus disease 2019"[Title/Abstract] OR nCOV[Title/Abstract] OR "n-COV"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "SARS coronavirus 2"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR 2019-nCoV[Title/Abstract]OR "nCoV2019"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARSCoV19"[Title/Abstract] OR "SARS-CoV19"[Title/Abstract] OR "SARS-CoV19"[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR "coronavirus SARSCoV-2"[Title/Abstract] OR Coronavirus[Title/Abstract]	
5	#3 OR #4	
6	Vaccines[MESH]	
7	vaccin*[Title/Abstract] OR prevent*[Title/Abstract] OR prophylaxis[Title/Abstract] OR prophylactic[Title/Abstract]	
8	#6 OR #7	
9	Drug therapy[MeSH]	
10	pharmacotherap*[Title/Abstract] OR treat*[Title/Abstract] OR therap*[Title/Abstract] OR management[Title/Abstract]	
11	#9 OR #10	
12	(drug[Title/Abstract] OR pharmacologic*[Title/Abstract] OR antiviral[Title/Abstract] OR anti-viral[Title/Abstract]) AND (treat*[Title/Abstract] OR therap*[Title/Abstract] OR agent*[Title/Abstract])	
13	#8 OR #11 OR #12	
14	#5 AND #13	
15	#5 AND #13	Other Animals
16	#14 NOT #15	
17	2019/11:2020/07[dp]	
18	animal OR rat* OR mouse OR guinea* OR ferret OR monkey* OR hamster* OR pig OR pigs OR rabbit OR chimpanzee* OR rodent OR mammal* OR ape OR rodent* OR mammal* OR ape OR apes	
19	#16 AND #17	
20	human* OR patient* OR men OR women OR volunteer*	

21	#18 AND #20	
22	#19 AND (#21 OR #20)	
23	#19 AND (#21 OR #20)	Case Reports
24	#19 AND (#21 OR #20)	Review
25	#23 OR #24	
26	#22 NOT #25	
27	#22 NOT #25	English

Embase search string

Search number	Query
1	'coronavirus'/exp
2	covid*:ab,ti
3	#1 OR #2
4	'covid 19':ab,ti OR 'covid-19':ab,ti OR 'corona virus':ab,ti OR 'novel corona virus':ab,ti OR 'corona virus disease':ab,ti OR 'coronavirus disease':ab,ti OR 'coronavirus disease 2019':ab,ti OR 'ncov':ab,ti OR 'n-cov':ab,ti OR covid19:ab,ti OR 'sars coronavirus 2':ab,ti OR '2019ncov':ab,ti OR '2019 ncov':ab,ti OR 'ncov2019':ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti OR 'sars-cov-2':ab,ti OR 'sarscov-2':ab,ti OR 'sars-cov2':ab,ti OR 'sarscov19':ab,ti OR 'sars-cov19':ab,ti OR 'hcov-19':ab,ti OR 'wn-cov':ab,ti OR 'coronavirus sarscov-2':ab,ti OR coronavirus:ab,ti
5	#3 OR #4
6	'vaccines'/exp
7	vaccin*:ab,ti OR prevent*:ab,ti OR 'prophylaxis':ab,ti OR 'prophylactic':ab,ti
8	#6 OR #7
9	'drug therapy'/exp
10	pharmacotherap*:ab,ti OR treat*:ab,ti OR therap*:ab,ti OR management:ab,ti
11	#9 OR #10
12	(drug:ab,ti OR pharmacologic*:ab,ti OR antiviral:ab,ti OR 'anti-viral':ab,ti) AND (treat*:ab,ti OR therap*:ab,ti OR agent*:ab,ti)
13	#8 OR #11 OR #12
14	#5 AND #13
15	#5 AND #13 AND ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)
16	#5 AND #13 NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)
17	(animal:ab,ti OR rat:ab,ti OR mouse:ab,ti OR guinea*:ab,ti OR ferret:ab,ti OR monkey:ab,ti OR hamster:ab,ti OR pig:ab,ti OR rabbit:ab,ti OR chimpanzee:ab,ti OR rodent:ab,ti OR mammal*:ab,ti OR ape:ab,ti) AND (model*:ab,ti OR study:ab,ti)
18	animal*:ab,ti OR rodent*:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR ferret*:ab,ti OR guinea*:ab,ti OR rabbit*:ab,ti OR monkey*:ab,ti OR hamster*:ab,ti OR pig:ab,ti OR pigs:ab,ti OR chimpanze*:ab,ti OR mammal*:ab,ti OR ape:ab,ti OR apes:ab,ti
19	#17 OR #18
20	#16 NOT #19
21	#20 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim) AND [animals]/lim
22	#20 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim)
23	#20 NOT #22

24	#20 NOT #22 AND [2019-2020]/py
25	#20 NOT #22 AND [2019-2020]/py AND [english]/lim

Cochrane Library search string

Search number	Search
#1	MeSH descriptor: [Coronavirus] explode all trees
#2	COVID*
#3	#1 OR #2
#4	("covid 19" OR "covid19" OR "corona virus" OR "Novel Corona Virus" OR "corona virus disease" OR "Coronavirus disease" OR "Coronavirus disease 2019" OR nCOV OR COVID19 OR "SARS coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR 2019nCoV OR nCoV2019 OR "severe acute respiratory syndrome coronavirus 2" OR SARSCoV19 OR "HCoV19" OR "WNCoV" OR "coronavirus SARSCoV2" OR Coronavirus):ti,ab,kw
#5	#3 OR #4
#6	MeSH descriptor: [Vaccines] explode all trees
#7	vaccin* OR prevent* OR "prophylaxis" OR "prophylactic"
#8	#6 OR #7
#9	MeSH descriptor: [Drug Therapy] explode all trees
#10	pharmacotherap* OR treat* OR therap* OR management
#11	#9 OR #10
#12	((drug OR pharmacologic* OR antiviral OR anti-viral) AND (treat* OR therap* OR agent*)):ti,ab,kw
#13	#8 OR #11 OR #12
#14	#5 AND #13
#15	((animal OR rat OR mouse OR guinea* OR ferret OR monkey OR hamster OR pig OR rabbit OR chimpanzee OR rodent OR mammal* OR ape) AND (model* OR study)):ti,ab,kw
#16	(animal* OR rodent* OR rat OR rats OR mouse OR mice OR ferret* OR guinea* OR rabbit* OR monkey* OR hamster* OR pig OR pigs OR chimpanze* OR mammal* OR ape OR apes):ti,ab,kw
#17	#15 OR #16
#18	#14 NOT #17 with Cochrane Library publication date Between Oct 2019 and Dec 2020

PubMed Central search string

Search number	Query
#1	Search ("covid 19"[Title/Abstract] OR "covid 19"[Title/Abstract] OR "corona"[Title/Abstract] OR "coronae"[Title/Abstract] OR "coronas"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "Novel Corona Virus"[Title/Abstract] OR "corona virus disease"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "Coronavirus disease"[Title/Abstract] OR "Coronavirus disease 2019"[Title/Abstract] OR "nCOV"[Title/Abstract] OR "n-COV"[Title/Abstract])
#2	Search Vaccines[MeSH]
#3	Search (vaccin*[Title/Abstract] OR prevent*[Title/Abstract] OR "prophylaxis"[Title/Abstract] OR "prophylactic"[Title/Abstract])
#4	Search (#2 OR #3)
#5	Search Drug therapy[MeSH]
#6	Search (pharmacotherap*[Title/Abstract] OR treat*[Title/Abstract] OR therap*[Title/Abstract] OR management[Title/Abstract])
#7	Search (#5 OR #6)
#8	Search ((drug[Title/Abstract] OR pharmacologic*[Title/Abstract] OR antiviral[Title/Abstract] OR anti-viral[Title/Abstract]) AND (treat*[Title/Abstract] OR therap*[Title/Abstract] OR agent*[Title/Abstract]))
#9	Search (#4 OR #7 OR #8)
#10	Search (#1 AND #9)
#11	Search ((animal OR rat OR mouse OR guinea* OR ferret OR monkey OR hamster OR pig OR rabbit OR chimpanzee OR rodent OR mammal* OR ape) AND (model* OR study))
#12	Search (animal* OR rodent* OR rat OR rats OR mouse OR mice OR ferret* OR guinea* OR rabbit* OR monkey* OR hamster* OR pig OR pigs OR chimpanze* OR mammal* OR ape OR apes)
#13	Search (#11 OR #12)
#14	Search (#10 NOT #13)
#15	Search (case* AND (report* OR stud* OR histor* OR observation* OR series))
#16	Search (#14 NOT #15)
#17	Search (#14 NOT #15) Filters: Publication date from 2020/07/01 to 2020/10/05

Supplementary Table 1. Details of interventions and categorisation

Disease stage	Interventions
Early infection/early pulmonary phase	**Antivirals:** non-specific (interferons); broad-spectrum (favipiravir, ribavirin, sofosbuvir + daclatasvir, triazavirin); antiretrovirals (lopinavir/ritonavir, remdesivir, darunavir/cobicistat, azvudine); antiviral combinations (lopinavir/ritonavir + interferons); other (leflunomide)[a]
	Anti-malarial drugs: hydroxychloroquine and derivatives
	Mucolytic drugs: bromhexine
Late pulmonary phase/host inflammatory response phase/repair phase	**Anti-inflammatory drugs:** non-specific (dexamethasone, hydrocortisone, methylprednisolone); other (febuxostat, colchicine)
	Kinase inhibitors: ruxolitinib
	CRAC channel inhibitors: auxora
	Anticoagulants: enoxaparin
	Immunomodulatory therapies: convalescent plasma, hyperimmune plasma
	Repair therapies: N-acetylcysteine, rhG-CSF

[a]Leflunomide is an immunosuppressant that may also exhibit antiviral activity.

CRAC: calcium release-activated calcium; rhG-CSF: recombinant human granulocyte colony-stimulating factor.

Supplementary Table 2. Characteristics of studies in articles not included in the qualitative synthesis

Study	Study design	No. of participants	Country	Mean age, years	Male, %	Patients + disease state	Intervention(s) (mode of administration)	Comparator (mode of administration)	Reason for exclusion
Zhu, FC *et al.* [1]	Non-randomised, open label phase I dose escalation trial	108	China	Low-dose, 37.2; middle-dose, 36.3; high-dose, 35.5	51.0	Healthy adults, no previous SARS-CoV-2 infection	Non-replicating adenovirus type-5 (Ad5) vectored COVID-19 vaccine, intramuscular injection	None	No outcomes of interest reported
Zhu, FC *et al.* [2]	Randomised, double-blind, placebo-controlled phase II trial	508	China	39.7	50.0	Healthy adults, no previous SARS-CoV-2 infection	Non-replicating adenovirus type-5 (Ad5) vectored COVID-19 vaccine, intramuscular injection	Placebo (containing only vaccine excipients), intramuscular injection	No outcomes of interest reported
Humeniuk, R *et al.* [3]	Randomised, blinded, placebo-controlled (single- and multiple-dose) phase I trials	Single dose: 96 Multiple dose: 24	US	Single dose: 44.0 Multiple dose: 44.0	Single dose: 58.3 Multiple dose: 58.3	Healthy adults	Remdesivir (IV)	Placebo (IV)	No outcomes of interest reported
Cai, Q *et al.* [4]	Non-randomised open-label trial; phase not reported	80	China	Median, 47.0	43.8	Moderate disease; hospitalised	Favipiravir (oral). In addition, all participants received IFN-α1b (aerosol inhalation)	Lopinavir/ritonavir (oral). In addition, all participants received IFN-α1b (aerosol inhalation)	No outcomes of interest reported
Gautret, P *et al.* [5]	Non-randomised open-label phase III trial	36	France	45.1	41.7	Unspecified disease severity; hospitalised	Hydroxychloroquine with/without azithromycin (oral)	Standard care	No outcomes of interest reported
Antorini, S *et al.* [6]	Non-randomised, single-arm, open-label trial	35	Italy	Median, 63.0	74.3	Severe disease; hospitalised	Remdesivir (IV). Patients could continue their existing treatments, apart from lopinavir/ritonavir which was required to be discontinued	None	Randomised trial data available for interventions reported
Erkurt, MA *et al.* [7]	Non-randomised,	26	Turkey	67.4	69.2	Severe disease; patients in ICU	Convalescent plasma therapy (IV)	None	Randomised trial data available for

	single-arm trial								interventions reported
Abolghasemi, H *et al.* [8]	Non-randomised, open-label trial	189	Iran	Plasma, 54.4; control, 56.8	Plasma, 58.3; control, 50.0	Unspecified disease severity; hospitalised patients	Convalescent plasma therapy (IV) in addition to standard care (including lopinavir/ritonavir, hydroxychloroquine and an anti-inflammatory agent)	Standard care	Randomised trial data available for interventions reported
Liu, X *et al.* [9]	Randomised, open label phase IV trial	31	China	56.0	67.7	Non-severe to critical COVID-19; hospitalised	Dipyridamole (oral) in addition to standard care	Standard care	Unclear reporting of the study design, including blinding
Leng, Z *et al.* [10]	Randomised, open label (pilot) phase I/II trial	10	China	59.4	40.0	Mild, moderate and severe disease; hospitalised	MSC treatment (IV)	Placebo (IV)	Very low patient number (N=10) Unclear reporting with most outcomes data reported for one critically severe patient
Abella, BS *et al.* [11]	Randomised, double-blind, placebo-controlled phase II study	132	US	Median, 33;	31.0	Mostly healthy/asymptomatic healthcare workers in hospital settings	Hydroxychloroquine (oral)	Placebo (oral)	No outcomes of interest reported
Anderson, EJ *et al.* [12]	Non-randomised, open label, phase I trial	40	US	68.7	48.0	Healthy older patients (≥56 years)	mRNA-1273 (IM injection)	None	No outcomes of interest reported
Bradfute, SB *et al.* [13]	Single-arm, open label phase II trial	12	US	Median, 52	66.7	SARS-CoV-2 infected patients with respiratory symptoms and in need of supplemental oxygen; hospitalised	Convalescent plasma therapy (IV)	None	No outcomes of interest reported
Keech, C *et al.* [14]	Randomised, blinded, placebo-controlled phase I/II trial	131 Vaccine + adjuvant: 83 Vaccine without adjuvant: 25 Placebo: 23	Australia	30.8	50.4	Healthy adults (18–59 years), no previous SARS-CoV-2 infection	NVX-CoV2373 nanoparticle vaccine (IM injection)	Placebo	No outcomes of interest reported
Logunov, DY *et al.* [15]	Non-randomised, open label phase I/II trial	76	Russia	Gam-COVID-Vac – rAd26-S, 27.8; rAd5-s, 25.3; rAd26-S+rAd5-S,	Gam-COVID-Vac – rAd26-S, 100; rAd5-S, 100; rAd26-S+rAd5-S,	Healthy adults (18–60 years), no previous SARS-CoV-2 infection	rAd26-S and rAd5-S (IM injection)	None	No outcomes of interest reported

				26.4 Gam-COVID-Vac-Lyo – rAd26-S, 31.4; rAd5-S, 27.0; rAd26-s+rAd5-S, 26.7	70 Gam-COVID-Vac-Lyo – rAd26-S, 56; rAd5-S, 22; rAd26-s+rAd5-S, 70				
Xia, S *et al.* [16]	Randomised, double-blind, placebo-controlled, phase I/II trial	Phase I: 96 Phase II: 224	China	Phase I, 41.2; Phase II, 43.5 Overall: 42.8	Phase I, 39.6; Phase II, 36.6 Overall: 37.5	Healthy adults (18–59 years), no previous SARS-CoV-2 infection	Inactivated whole-virus COVID-19 vaccine (IM injection)	Placebo (only used in phase II study)	No outcomes of interest reported
Zheng, F *et al.* [17]	Randomised, open label, parallel-group phase IV trial	89	China	Novaferon, 46.5; lopinavir/ritonavir + novaferon, 50.0; Lopinavir/ritonavir, 37.0	Novaferon, 56.7, lopinavir/ritonavir + novaferon, 43.3; Lopinavir/ritonavir, 41.4	Hospitalised adult patients with moderate-to-severe SARS-CoV-2 infection	Novaferon (aerosolized inhalation) Novaferon aerosolized inhalation + lopinavir/ritonavir (oral)	Lopinavir/ritonavir (oral)	No outcomes of interest reported
Fu, W [18]	Non-randomised, open label pilot trial; phase not specified	33	China	Median, 50	57.6	Hospitalised patients with moderate SARS-CoV-2 infection	IFN-κ + TFF2 (aerosol inhalation)	Standard care	Non-randomised study

COVID-19: Coronavirus disease 2019; ICU: intensive care unit; IFN, interferon; IM, intramuscular; IV: intravenous; mRNA: messenger RNA; MSC, mesenchymal stem cells; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TFF2: trefoil factor 2.

Supplementary Table 3. Characteristics of studies in articles included in the qualitative synthesis

Study	Study design	No. of participants	Country	Mean age, years	Male, %	Patients + disease state	Intervention(s) (mode of administration)	Comparator (mode of administration)
Antivirals								
Hung IF *et al.* [19]	Randomised, open label phase II/IIb study	127	Hong Kong	Median, 52.0	54.0	Unspecified disease severity; hospitalised	Lopinavir/ritonavir (NG tube) + RBV (inhaled) + IFN beta-1b (SC)	Lopinavir/ritonavir (NG tube)
Goldman, J *et al.* [20]	Randomised, open label phase III study	397	Multinational	Median, 5-day group: 61.0 10-day group: 62.0	5-day group: 60.0 10-day group: 68.0	Severe disease, evidence of pneumonia; hospitalised	Remdesivir (IV) in addition to supportive therapy	No comparator (study compared 5 or 10 days of remdesivir treatment)
Beigel, JH *et al.* [21]	Randomised, double-blind, placebo-controlled phase III study	1062	Multinational	58.9	64.4	Severe disease; hospitalised	Remdesivir (IV) in addition to supportive care (including other treatments for COVID-19)	Placebo in addition to supportive care (including other treatments for COVID-19)
Wang, Y *et al.* [22]	Randomised, double-blind, placebo-controlled phase III study	236	China	Median, 65.0	Remdesivir: 56.0 Placebo: 65.0	Severe COVID-19 pneumonia; hospitalised	Remdesivir (IV)	Placebo
Chen, J *et al.* [23]	Randomised, parallel assignment, open label phase III study	30	China	47.2	60.0	Mild COVID-19 pneumonia; hospitalised	Darunavir (oral) + cobicistat (oral) + interferon alpha 2b (inhaled) in addition to standard care	Interferon alpha 2b (inhaled) in addition to standard care
Li, Y *et al.* [9]	Randomised, partially blinded phase IV study	86	China	49.4	46.5	Mild/moderate disease; hospitalised	Lopinavir/ritonavir (oral) or arbidol (oral) in addition to standard care	Standard care
Cao, B *et al.* [24]	Randomised, open label study; phase not reported	199	China	Median, 58.0	60.3	Severe disease; hospitalised	Lopinavir/ritonavir (oral) in addition to standard care	Standard care
Huang, Y-Q *et al.* [25]	Randomised, open label study; phase not reported	101	China	42.5	46.0	Mild to moderate disease; hospitalised	RBV (initial dose IV and then oral) + lopinavir/ritonavir (oral) + IFN-a (inhaled)	RBV (IV) + IFN-a (inhaled) Lopinavir/ritonavir (oral) + IFN-a (inhaled)
Spinner, CD	Randomised,	596	USA	Median: 5-day	5-day	Moderate disease;	Remdesivir (IV)	Standard care

et al. [26]	open label phase III study			remdesivir, 58; 10-day remdesivir, 56; standard care, 57	remdesivir, 60; 10-day remdesivir, 61; standard care, 63	hospitalised		
Shih, WJ *et al.*[a] [27]	Randomised, double-blind, placebo-controlled phase III study	231 patients included in re-analysis of data from Wang, Y *et al.* [22]	China	NR	NR	Severe Covid-19 pneumonia; hospitalised	Remdesivir (IV)	Placebo
Abbaspour Kasgari, H *et al.* [28]	Randomised, open label phase III study	48	Iran	Median: sofosbuvir/ daclatasvir, 45; control, 60	Sofosbuvir/ daclatasvir, 46; control, 29	Moderate disease; hospitalised	Sofosbuvir + daclatasvir + ribavirin (oral)	Standard care
Davoudi-Monfared, E *et al.* [29]	Randomised, open label phase III study	81	Iran	IFN-β, 56.0; control, 59.5	54.3	Severe disease; hospitalised	Interferon β-1a (SC injections) in addition to standard care	Standard care
Sadeghi, A *et al.* [30]	Randomised, open label phase III study	66	Iran	Median, 58	52	Moderate/severe disease; hospitalised	Sofosbuvir + daclatasvir (oral) in addition to standard care	Standard care
Wu, X *et al.* [31]	Randomised, double-blind phase III study	52	China	Median, 58	50	Unspecified disease severity; hospitalised	Triazavirin (oral) in addition to standard care	Placebo in addition to standard care
Wang, M *et al.* [32]	Randomised, open label phase III study	48	China	Median: combination group, 56.0; control group, 55.5	Combination group, 54.2; control group, 37.5	Mild to severe disease; hospitalised	Leflunomide (oral) plus nebulized IFN alpha-2a	Nebulized IFN alpha-2a (inhalation)
Doi, Y *et al.* [33]	Randomised, open label study	88	Japan	Median, 50.0	61.4	Asymptomatic or mild disease; hospitalised	Favipiravir (oral)	No comparator
Rahmani, H *et al.* [34]	Randomised, open label study	66	Iran	Median, 60	59.1	Severe disease; hospitalised	IFN β-1b (SC injections) in addition to standard care	Standard care: lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine (oral)
Fu, W *et al.* [35]	Randomised, open label study	80	China	35.3	63.8	Moderate disease; hospitalised	IFN-k and TFF2 (aerosol inhalation) in addition to standard care	Standard care
Ren, Z *et al.* [36]	Randomised, open label study	20	China	Median, 52	60	Mild disease; hospitalised	Azvudine (oral) plus symptomatic treatment	Standard antiviral treatment plus symptomatic treatment
Antimalarial drugs								
Borba, M *et al. [37]*	Randomised, parallel assignment, double-blind phase II/IIb study	81	Brazil	51.1	75.3	Severe disease; hospitalised	Chloroquine diphosphate (oral/NG tube) in addition to standard care	No comparator
Boulware,	Randomised,	821	US/Canada	Median, 40.0	48.4	Asymptomatic adults with	Hydroxychloroquine (oral)	Placebo

DR *et al.* [38]	double-blind, placebo-controlled phase III study					occupational/household exposure to COVID-19		
Skipper, C *et al.* [39]	Randomised, double-blind, placebo-controlled phase III study	491	North America	Median, 40.0	44.0	Mild COVID-19; non-hospitalised	Hydroxychloroquine (oral)	Placebo
Mitja, O *et al.* [40]	Randomised, open label phase III study	293	Spain	41.6	31.4	Mild COVID-19; outpatients	Hydroxychloroquine (oral)	Standard care
Cavalcanti *et al.* [41]	Randomised, open label phase III study	665	Brazil	50.3	58.3	Mild-to-moderate COVID-19; hospitalised	Hydroxychloroquine (oral) in addition to standard care Hydroxychloroquine (oral) + azithromycin (oral) in addition to standard care	Standard care
Tang, W *et al.* [42]	Randomised, open label phase IV study	150	China	46.1	54.7	Mild, moderate and severe disease; hospitalised	Hydroxychloroquine (oral) in addition to standard care	Standard care
Abd-Elsalem, S *et al.* [43]	Randomised, open label, phase III study	194	Egypt	40.7	58.8	Mild, moderate and severe disease; hospitalised	Hydroxychloroquine (oral) in addition to standard care	Standard care
Furtado, RHM *et al.* [44]	Randomised, open label phase III study	447	Brazil	Median, 59.8	66	Severe disease; hospitalised	Azithromycin + hydroxychloroquine (oral) in addition to standard care	Hydroxychloroquine in addition to standard care
Mucolytic drugs								
Li, T *et al.* [45]	Randomised, open label study; phase not reported	18	China	Median, 52	77.8	Mild or moderate disease; hospitalised	Bromhexine hydrochloride (oral) in addition to standard care	Standard care
Ansarin, K *et al.* [46]	Randomised, open label phase III study	78	Iran	Treatment group, 58.4; standard group, 61.1	54.4	Unspecified disease severity; hospitalised	Bromhexine hydrochloride (oral) in addition to standard care	Standard care
Anti-inflammatory drugs								
Horby, P *et al.* [47]	Randomised, open label phase III study	6425	UK	66.1	64.0	Unspecified disease severity; hospitalised	Dexamethasone (IV and oral) in addition to standard care	Standard care
Deftereos SG *et al.* [48]	Randomised, open label phase II/IIb study	105	Greece	Median, 64.0	58.1	Unspecified disease severity; hospitalised	Colchicine (oral) in addition to standard care	Standard care
Davoodi, L *et al.* [49]	Randomised, double-blind phase III study	54	Iran	57.7	59.3	Mild to moderate COVID-19; outpatients	Febuxostat (oral) in addition to supportive care (acetaminophen 325	Hydroxychloroquine in addition to supportive care (acetaminophen

							mg, as needed, for controlling fever)	325 mg, as needed, for controlling fever)
Edalatifard, M *et al.* [50]	Randomised, single blind phase II study	62	Iran	58.5	62.9	Severe disease; hospitalised	Methylprednisolone (IV) in addition to standard care	Standard care
Dequin, PF *et al.* [51]	Randomised, double blind phase III study	149	France	62.2	69.8	Severe disease; hospitalised	Hydrocortisone (IV) (adjunctive treatments were also permitted)	Placebo (adjunctive treatments were also permitted)
Jeronimo, CMP *et al.* [52]	Randomised, double-blind phase IIb study	416	Brazil	55	64.6	Severe disease; hospitalised	Methylprednisolone (IV) in addition to standard care	Placebo in addition to standard care
Angus, DC *et al.* [53]	Randomised, open label phase IV study	403	Multi-national	60	71	Severe disease; hospitalised	Hydrocortisone (IV) (participants could be randomly assigned to other interventions within other therapeutic domains)	Standard care (participants could be randomly assigned to other interventions within other therapeutic domains)
Kinase inhibitors								
Cao, Y *et al.* [54]	Randomised, single-blind, placebo-controlled phase II/IIb study	43	China	63	58.5	Severe disease; hospitalised	Ruxolitinib (oral) in addition to standard care	Placebo in addition to standard care
Calcium release-activated calcium channel inhibitors								
Miller, J *et al.* [55]	Randomised, open label phase II study	30	US	Arm A – Auxora, 59; standard care, 61 Arm B – Auxora, 64; standard care, 36	Arm A – Auxora, 41; SOC, 56 Arm B – Auxora, 33; SOC, 100	Severe disease; hospitalised	Auxora (IV) in addition to standard care	Standard care
Anticoagulants								
Lemos, ACB *et al.* [56]	Randomised, open label phase II study	20	Brazil	Standard prophylactic anticoagulation, 58; therapeutic enoxaparin, 55	Standard prophylactic anticoagulation, 70; therapeutic enoxaparin, 90	Severe disease; hospitalised	Enoxaparin (SC)	Standard anticoagulant thromboprophylaxis
Immunomodulatory therapies								
Li, L *et al.* [57]	Randomised, open label; phase not reported	103	China	Median, 70	58.3	Severe disease; hospitalised	Convalescent plasma (IV) and supportive treatments	Standard care
Perotti, C *et al.* [58]	Single-arm proof of concept study; phase not reported	46	Italy	63.0	61.0	Moderate to severe disease; hospitalised	Hyperimmune plasma (IV)	None
Repair therapies								
Cheng, L *et al.* [59]	Randomised, open label study	200	China	Median, 45	56	Severe disease; hospitalised	rhG-CSF (SC injection) in addition to standard care	Standard care

De Alencar, JCG *et al.* [60]	Randomised, double-blind study	135	Brazil	Median: N-acetylcysteine, 59; placebo, 58	N-acetylcysteine, 67; placebo, 54	Severe disease; hospitalised	N-acetylcysteine (IV) in addition to standard care	Placebo in addition to standard care

[a]: Re-analysis of the clinical trial reported by Wang *et al.,* using different criteria.

COVID-19: Coronavirus disease 2019; IFN, interferon; IV: intravenous; NG: nasogastric; NR: not reported; RBV: ribavirin; rhG-CSF: recombinant human granulocyte colony-stimulating factor; SC: subcutaneous; SOC: standard of care; TFF2: trefoil factor 2.

Supplementary Table 4. Need for ventilation: other outcomes reported in trials included in the qualitative synthesis

Study	Interventions	Median (IQR) duration of respiratory support, days	No. days free from respiratory report, days	Other outcomes
Antivirals				
Davoudi-Monfared, E *et al.* [29]	IFN ß-1a[a] (n=42)	Mean (SD), IMV: 10.8 (5.38)	NR	Extubation rate, % of intubated patients: 53.5
	Standard care (n=39)	Mean (SD), IMV: 7.82 (7.84)	NR	Extubation rate, % of intubated patients: 11.8
	Between-group difference/comparison	*P*=0.47	NR	***P*=0.019***
Rahmani, H *et al.* [34]	IFN β-1b[a] (n=33)	NR	NR	Intubation requirement, % of patients: 6.1
	Standard care (n=33)	NR	NR	Intubation requirement, % of patients: 18.2
	Between-group difference/comparison	NR	NR	*P*=0.12
Abbaspour Kasgari, H *et al.* [28]	Sofosbuvir + daclatasvir + RBV (n=24)	IMV: 0	NR	NR
	Hydroxychloroquine + lopinavir/ritonavir +/- RBV (n=24)	IMV: 2.5 (1.5, 7.0)	NR	NR
	Between-group difference/comparison	NR	NR	NR
Cao, B *et al.* [24]	Lopinavir/ritonavir[a] (n=99)	Oxygen: 12.0 (9.0, 16.0) IMV: 4.0 (3.0, 7.0)	NR	NR
	Standard care (n=100)	Oxygen: 13.0 (6.0, 16.0) IMV: 5.0 (3.0, 9.0)	NR	NR
	Between-group difference/comparison	Difference (95% CI) Oxygen: 0 (−2.0, 2.0) IMV: −1.0 (−4.0, 2.0)	NR	NR
Wang, Y *et al.* [22]	Remdesivir (n=158)	Oxygen: 19 (11, 30) IMV: 7 (4, 16) Ventilation (survivors): 19.0 (5.0, 42.0) Ventilation (non-survivors): 7.0 (2.0, 11.0)	NR	NR
	Placebo (n=78)	Oxygen: 21 (14, 30.5) IMV: 15.5 (6.0, 21.0) Ventilation (survivors): 42.0 (17.0, 46.0) Ventilation (non-survivors): 8.0 (5.0,	NR	NR

		16.0)		
	Between-group difference/comparison	Difference (95% CI) Oxygen: −2.0 (−6.0, 1.0) IMV: −4.0 (−14.0, 2.0) Ventilation (survivors): −12.0 (−41.0, 25.0) Ventilation (non-survivors): −2.5 (−11.0, 3.0)	NR	NR
Beigel, JH *et al.* [21]	Remdesivir[a] (n=541)	Oxygen: 4 (2, 12) Non-invasive ventilation/high-flow oxygen: 3 (1, 10.5) IMV/ECMO: 21.5 (9, 28)	NR	NR
	Placebo (n=521)	Oxygen: 5.5 (1, 15) Non-invasive ventilation/high-flow oxygen: 4 (2, 23.5) IMV/ECMO: 23 (12, 28)	NR	NR
	Between-group difference/comparison,	Difference (95% CI) Oxygen: −1.0 (−7.6, 5.6) Non-invasive ventilation/high-flow oxygen: −1.0 (−4.0, 2.0) IMV: 1.0 (−6.0, 8.0)	NR	NR
Antimalarial drugs				
Calvacanti *et al.* [41]	Hydroxychloroquine + AZ[a] (n=169)	NR	11.1 (4.9)	NR
	Hydroxychloroquine[a] (n=157)	NR	11.2 (4.9)	NR
	Standard care (n=171)	NR	11.1 (4.9)	NR
	Between-group difference/comparison	NR	Effect estimate (95% CI), hydroxychloroquine + AZ *versus* standard care): 0.1 (−7.0, 0.9) Effect estimate (95% CI), hydroxychloroquine *versus* standard care: −0.2 (−1.1, 0.6)	NR
Furtado *et al.* [44]	Hydroxychloroquine + AZ[a] (n=214)	NR	Ventilation-free days: 0 (0, 14)	NR
	Hydroxychloroquine[a] (n=183)	NR	Ventilation-free days: 1 (0, 18)	NR
	Between-group difference/comparison	NR	*P*=0.37	NR

Anti-inflammatory drugs				
Angus, DC *et al.* [53]	Hydrocortisone, fixed dose[b] (n=137)	NR	NR	Respiratory support-free days, adjusted odds ratios: Mean (SD): 1.45 (0.34) Median (95% CI): 1.42 (0.90, 2.24)
	Hydrocortisone, shock-dependent dosing[b] (n=141)	NR	NR	Respiratory support-free days, adjusted odds ratios: Mean (SD): 1.31 (0.30) Median (95% CI): 1.28 (0.81, 2.00)
	Standard care[b] (n=101)	NR	NR	Respiratory support-free days, adjusted odds ratios: Mean: 1 (reference) Median: 1 (reference)
	Between-group difference/comparison	NR	NR	Probability of superiority to no hydrocortisone, %: 94 (fixed dose), 85% (shock-dependent dosing)
Dequin, PF *et al.* [51]	Hydrocortisone (n=76)	NR	NR	Treatment failure on day 21[c], %: 42.1 Endotracheal intubation (patients noninvasively ventilated at inclusion), %: 50 ECMO, %: 2.7
	Placebo (n=73)	NR	NR	Treatment failure on day 21[c], %: 50.7 Endotracheal intubation (patients noninvasively ventilated at inclusion), %: 75 ECMO, %: 2.7
	Between-group difference/comparison	NR	NR	*P (treatment failure)*: 0.29 No comparison for other outcomes
Kinase inhibitors				
Cao, Y *et al.* [54]	Ruxolitinib[a] (n=20)	IMV: 0	NR	NR
	Placebo[a] (n=21)	IMV: 5.0 (2.0, 8.0)	NR	NR
	Between-group difference/comparison	NR	NR	NR

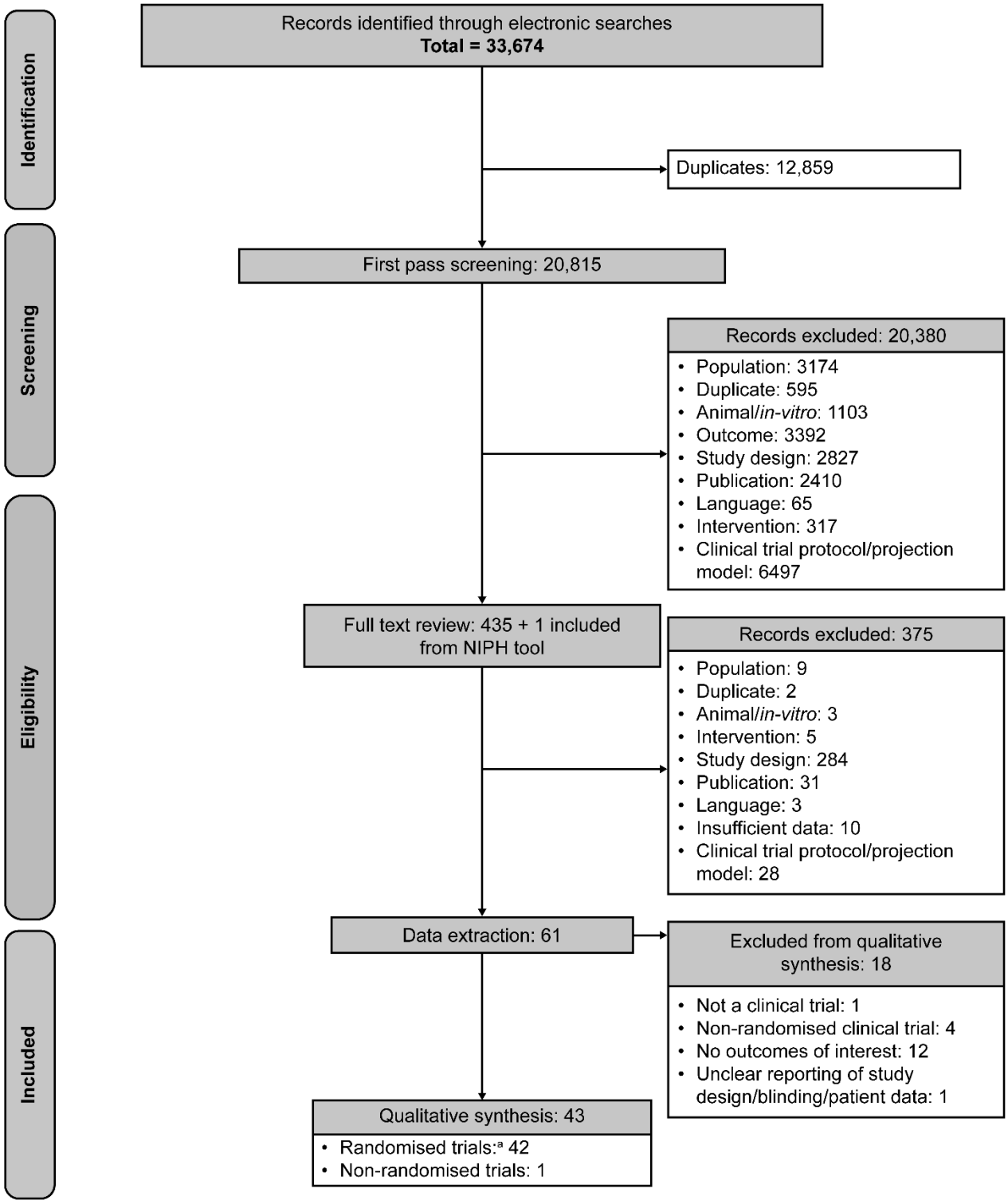
Calcium release-activated calcium channel inhibitors				
Miller, J *et al.* [55]	Auxora[a] (n=17)	NR	NR	Need for IMV or death within 30 days of randomisation: 17.6%
	Standard care (n=9)	NR	NR	Need for IMV or death within 30 days of randomisation: 55.6%
	Between-group difference/comparison	NR	NR	**HR: 0.23 (95% CI: 0.05, 0.96); *P*<0.05***
Anticoagulants				
Lemos, ACB *et al.* [56]	Therapeutic enoxaparin (n=10)	NR	NR	Median (IQR) ventilator-free days: 15 (6, 16)
	LMW or unfractionated heparin (n=10)	NR	NR	Median (IQR) ventilator-free days: 0 (0, 11)
	Between-group difference/comparison	NR	NR	**Median ventilator-free days: *P*=0.028*** **Ratio of successful liberation from mechanical ventilation: HR (95% CI): 4.0 (1.035, 15.053); *P*=0.031***
Repair therapies				
Cheng, L *et al.* [59]	rhG-CSF[a] (n=100)	Oxygen: 10 (9, 12)	NR	NR
	Standard care (n=100)	Oxygen: 10 (8, 13)	NR	NR
	Between-group difference/comparison	Difference (95% CI): 0 (−1, 1)	NR	NR

*: Denotes a statistically significant *P*-value or between-group comparison.

[a]: Treatment administered in addition to standard care, as defined by the investigators in each trial; [b]: Participants could be randomly assigned to other interventions within other therapeutic domains; [c]: Death or persistent dependence of mechanical ventilation or high-flow oxygen therapy.

AZ: azithromycin; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; IFN: interferon; IMV: intensive/invasive mechanical ventilation; IQR: interquartile range: LMW: low molecular weight; NR: not reported; RBV: ribavirin; rhG-CSF: recombinant human granulocyte-colony stimulating factor; SD: standard deviation.

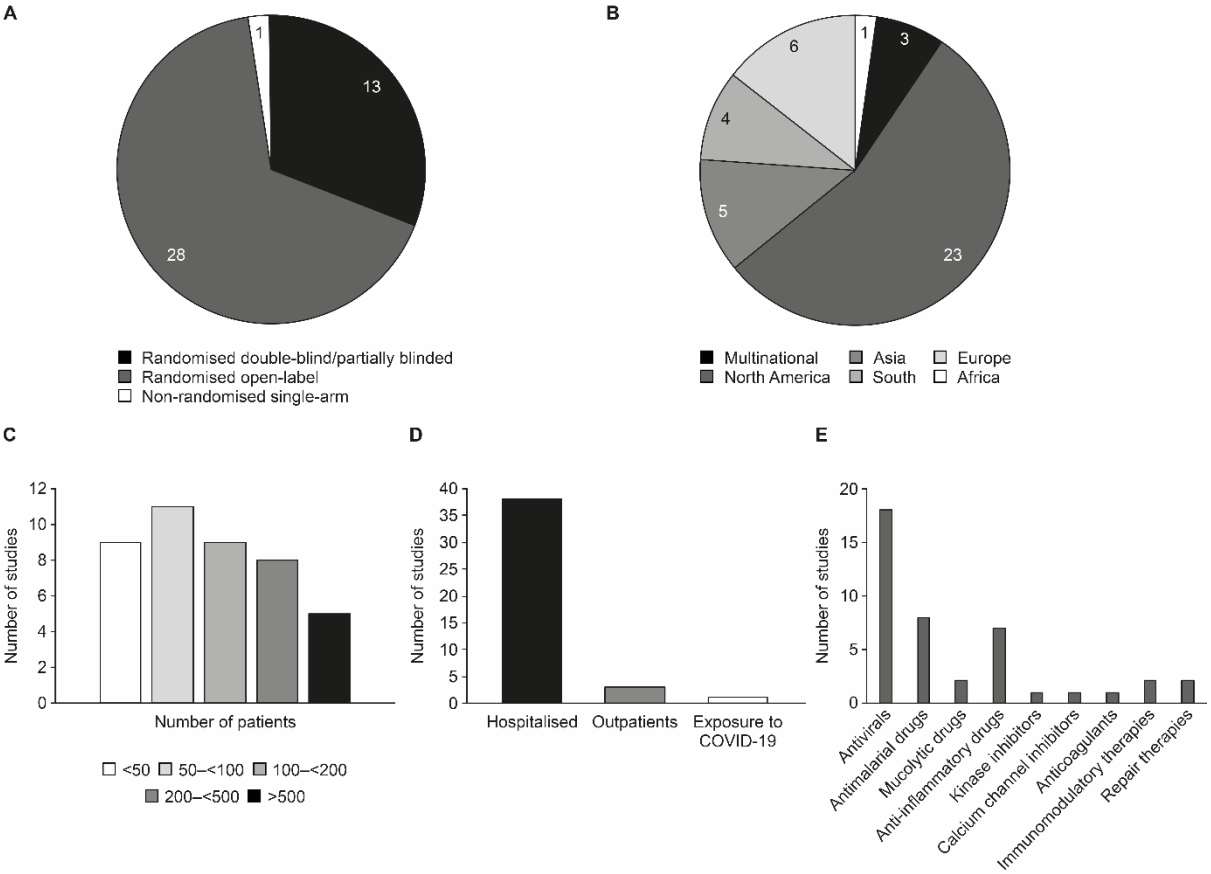
Supplementary Figure 1. PRISMA flow diagram of the SLR



[a]: One study was a re-analysis of data from another included trial (Wang, Y *et al.*).

NIPH: Norwegian Institute of Public Health; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

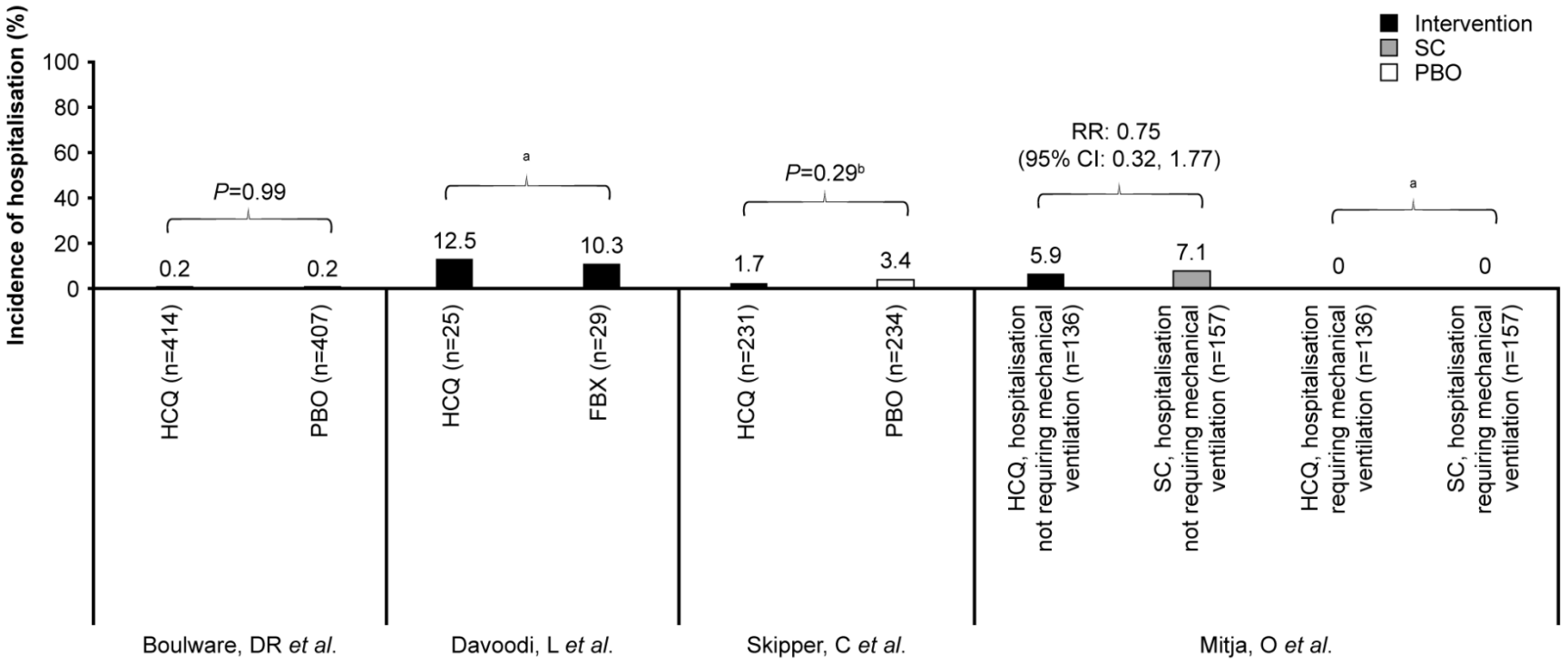
Supplementary Figure 2. Summary of studies included in qualitative synthesis in terms of study design (A), country (B), number of patients (C), hospitalisation status (D) and therapies assessed (E)



Data presented do not include the article by Shih, WJ et al., as this was a re-analysis of data from another included trial (Wang, Y et al.).

COVID-19: Coronavirus disease 2019.

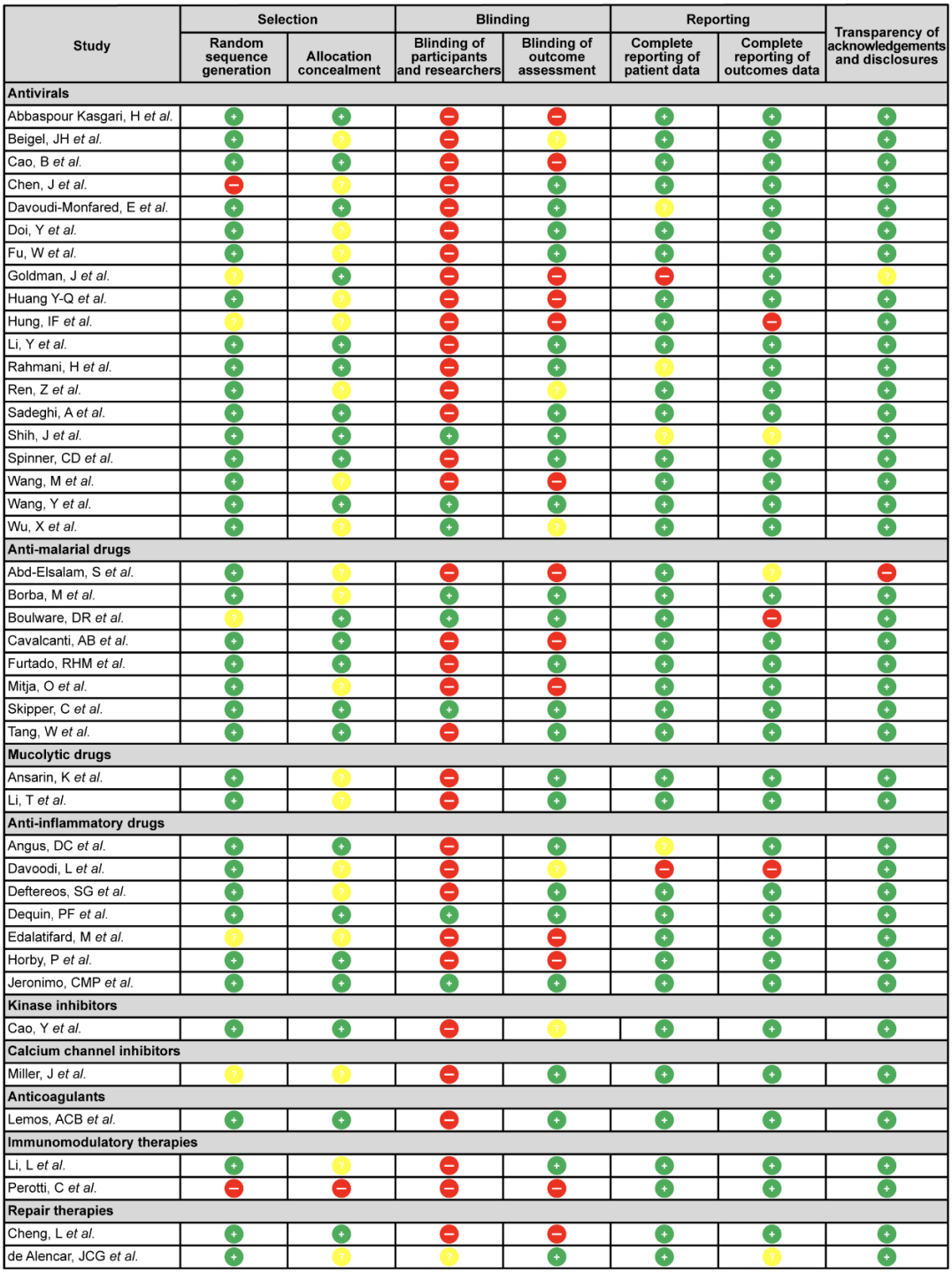
Supplementary Figure 3. Incidence of hospitalisation



Data from trials reporting on non-hospitalised patients. *: Indicates a statistically significant *P*-value; [a]: No between-group comparison; [b]: *P*-value for the incidence of hospitalisation or death.

CI: confidence interval; FBX: febuxostat; HCQ: hydroxychloroquine; PBO: placebo; RR: risk ratio; SC: standard care.

Supplementary Figure 4. Quality assessment of trials included in qualitative synthesis



Red: high risk of bias; yellow: unclear risk of bias; green: low risk of bias.

Note: Shih, J *et al*. is a re-analysis of the study published by Wang, Y *et al*.

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