Efficacy and Safety of Immunomodulators in Patients with COVID-19: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials

Thundon Ngamprasertchai*, MD, **Rattagan Kajeekul****, MD, Chaisith Sivakorn*, MD, Narisa Ruenroegnboon***,Pharm.D., Viravarn Luvira*, MD, PhD, Tanaya Siripoon*, MD, Nantasit Luangasanatip, PhD****

* Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Thundon Ngamprasertchai Email: thundon.ngm@mahidol.ac.th, Chaisith Sivakorn Email: chaisith.siv@mahidol.edu, Viravarn Luvira Email: viravarn.luv@mahidol.ac.th, Tanaya Siripoon Email: tanaya.sir@mahidol.ac.th

**Email: rattagan_k@yahoo.com, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand

***Email: polladew@gmail.com, Department of Pharmaceutics (Clinical Pharmacy), Faculty of Pharmacy, Slipakorn University, Nakhon Pathom, Thailand

****Email: nantasit_l@yahoo.com, Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Corresponding Author

Rattagan Kajeekul, MD

Infectious Disease Physician

Department of Medicine, Maharat Nakhon Ratchasima Hospital

49 Changphuak Rd, Tambon Nai Mueang Nakhon Ratchasima District,

Nakhon Ratchasima 30000, Thailand

Phone No: +66(0) 85-088-7736

Email: rattagan_k@yahoo.com

Table of Contents

1. Search strategies

1.1 MEDLINE

((((((((((corticoid*) OR (glucocorticoid*)) OR (steroid*)) OR (corticosteroid*)) OR (cortison*)) OR (prednison*)) OR (prednisolon*)) OR (dexamethason*)) OR ((methylprednisolone) OR (methylpredni*))) OR ((((((siltuximab) OR (sylvant)) OR (CNTO- 328)) OR ((sarilumab) OR (kevzara))) OR (((((tocilizumab) OR (R-1569)) OR (actemra)) OR (atlizumab)) OR (RoActemra))) AND (((Anti-IL-6 receptor monoclonal antibod*) OR (IL-6 blockade)) OR (IL-6 receptor antagonist)))) OR ((((Janus kinase inhibitor) OR (JAK-inhibitor)) OR (Janas kinase antagonists)) AND (((Baricitinib) OR (olumiant)) OR (LY3009104)))) AND ((((((((((covid 19[MeSH Terms]) OR (covid-19[MeSH Terms])) OR (covid19)) OR (covid 19)) OR (covid-19)) OR (Severe acute respiratory syndrome coronavirus 2)) OR (SARS-CoV-2)) OR (2019 novel coronavirus)) OR (coronavirus disease 2019)) OR (COVID2019))

1.2 Scopus

Table S1. PICO searching: Scopus database

Search	Domain	Query	Results
Population			
#1	Covid-19	TITLE-ABS-KEY (covid19)	
#2		TITLE-ABS-KEY (covid-19)	
#3		TITLE-ABS-KEY (Severe acute respiratory syndrome coronavirus 2)	
#4		TITLE-ABS-KEY (2019-nCoV)	
#5		TITLE-ABS-KEY (SARS-CoV-2)	
#6		TITLE-ABS-KEY (2019 novel coronavirus)	
#7		TITLE-ABS-KEY (coronavirus disease 2019)	
#8		**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7**	
Intervention			
#9	Corticosteroid	TITLE-ABS-KEY (glucocorticoid*)	
#10		TITLE-ABS-KEY (steroid*)	
#11		TITLE-ABS-KEY (corticosteroid*)	
#12		TITLE-ABS-KEY (cortison*)	
#13		TITLE-ABS-KEY (prednison*)	
#14		TITLE-ABS-KEY (prednisolon*)	
#15		TITLE-ABS-KEY (dexamethason*)	
#16		#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	
#17	Methylprednisolone	TITLE-ABS-KEY (methylprednisolone)	
#18		TITLE-ABS-KEY (methylpredni*)	
#19		#17 OR #18	
Search	**Domain**	**Query**	**Results**

#20	Interleukin inhibitor	TITLE-ABS-KEY (tocilizumab)	
#21		TITLE-ABS-KEY (atlizumab)	
#22		TITLE-ABS-KEY (R-1569)	
#23		TITLE-ABS-KEY (Actemra)	
#24		TITLE-ABS-KEY (RoActemra)	
#25		#20 OR #21 OR #22 OR #23 OR #24	
#26		TITLE-ABS-KEY (sarilumab)	
#27		TITLE-ABS-KEY (kevzara)	
#28		#26 OR #27	
#29		TITLE-ABS-KEY (siltuximab)	
#30		TITLE-ABS-KEY (sylvant)	
#31		TITLE-ABS-KEY (CNTO- 328)	
#32		#29 OR #30 OR #31	
#33		TITLE-ABS-KEY (Anti-IL-6 receptor monoclonal antibod*)	
#34		TITLE-ABS-KEY (IL-6 blockade)	
#35		TITLE-ABS-KEY (IL-6 receptor antagonist)	
#36		#33 OR #34 OR #35	
#37		TITLE-ABS-KEY (IL-1 blockade)	
#38	JAK inhibitors	TITLE-ABS-KEY (Baricitinib)	
#39		TITLE-ABS-KEY (olumiant)	
#40		TITLE-ABS-KEY (LY3009104)	
#41		#38 OR #39 OR #40	
#42		TITLE-ABS-KEY (Janus kinase inhibitor)	
#43		TITLE-ABS-KEY (JAK-inhibitor)	

#44		TITLE-ABS-KEY (Janus kinase antagonists)	
#45		#42 OR #43 OR #44	
#46		#41 AND #45	
#47	**All intervention**	**#16 OR #19 OR #25 OR #28 OR #32 OR #36 OR #46**	
Population AND intervention			
#48		**#8 AND #47**	

Table S2. Age group of participants in included studies.

No.	Study	Mean (SD) or median (range)			
		Intervention 1	**Intervention 2**	**Control**	**Total**
1	P. Horby (RECOVERY)	66.9 (15.4)	NA	65.8 (15.8)	-
2	H. Jamaati	54 (37-63), survivor 63 (55.5-72.5), Non-survivor	NA	61.5 (54-62), survivor 67 (48-73), non-survivor	-
3	B.M. Tomazini (CoDEX)	60.1 (15.8)	NA	62.7 (13.1)	-
4	J. Vilar (Dexa-COVID19 network)	NA	NA	NA	NA
5	D.C. Angus (REMAP-CAP)	60.4 (11.6)	59.5 (12.7)	59.9 (14.6)	-
6	P.F. Dequin (CAPE COVID)	63.1 (51.5-70.8)	NA	66.3 (53.5-72.7)	-
7	M.W Petersen (COVID STEROID)	59 (52-74)	NA	62 (55-71)	61 (53-73)
8	L. Corral-Gudino (Glucocovid)	73 (11)	NA	66 (12)	70 (12)
9	M. Edalatifard	55.8 (16.35)	NA	61.7 (16.62)	58.5 (16.60)
10	C.M.P. Jeronimo (Metacovid)	54 (15)	NA	57 (15)	55 (15)
11	X. Tang	57 (49-67)	NA	55 (38-65)	56 (39–66)
12	P.W. Horby (RECOVERY)	63.3 (13.7)	NA	63.9 (13.6)	-
13	O. Hermine (CORINUMO-TOCI)	64.0 (57.1-74.3)	NA	63.3 (57.1-72.3)	-
14	O. Rosas (COVACTA)	60.9 (14.6)	NA	60.6 (13.7)	-

No.	Study	Mean (SD) or median (range)			
		Intervention 1	**Intervention 2**	**Control**	**Total**
15	C. Salama (EMPACTA)	56.0 (14.3)	NA	55.6 (14.4)	55.9 (14.4)
16	C. Salvarani (RCT-TCZ-COVID-19)	61.5 (51.5-73.5)	NA	60.0 (54.0-69.0)	60.0 (53.0-72.0)
17	A.S. Soin (CONVINTOC)	56 (47-63)	NA	54 (43-63)	-
18	J.H. Stone (BACC Bay)	61.6 (46.4-69.7)	NA	56.5 (44.7-67.8)	59.8 (45.3–69.4)
19	V.C. Veiga	57.4 (15.7)	NA	57.5 (13.5)	-
20	F.X. Lescure	58.0 (48.0-67.0) (Sarilumab 400 mg)	58.0 (51.0-67.0) (Sarilumab 200 mg)	60.0 (53.0-69.5)	59.0 (50.0–68.0)
21	X. Mariette CORIMONO-19 (ANA-1)	67.0 (55.5-74.3)	NA	64.9 (59.5-78.3)	-
22	Y. Cao	63 (51-65)	NA	64 (59-71)	63 (58-68)
23	A.C. Kalil	55.0 (15.4)	NA	55.8 (16.0)	55.4 (15.7)
24	P.O. Guimaraes (STOP-COIVD)	55 (14)	NA	57 (14)	56 (14)
25	H. Zhao	70 (45-89) (favipiravir)	71 (48-77) (tocilizumab)	75 (34-81) (tocilizumab+favipiravir)	-
26	A.C. Gordon (REMAP-CAP)	61.5 (12.5) (tocilizumab)	63.4 (13.4) (Sarilumab)	61.1 (12.8)	61.4 (12.7)
27	Rashad	64 (55-72)	60.5 (49.5-66.5)	NA	-
28	K. Ranjbar	56.2 (17.5)	NA	61.3 (17.3)	-

2. Transitivity assessment subgroup by severity

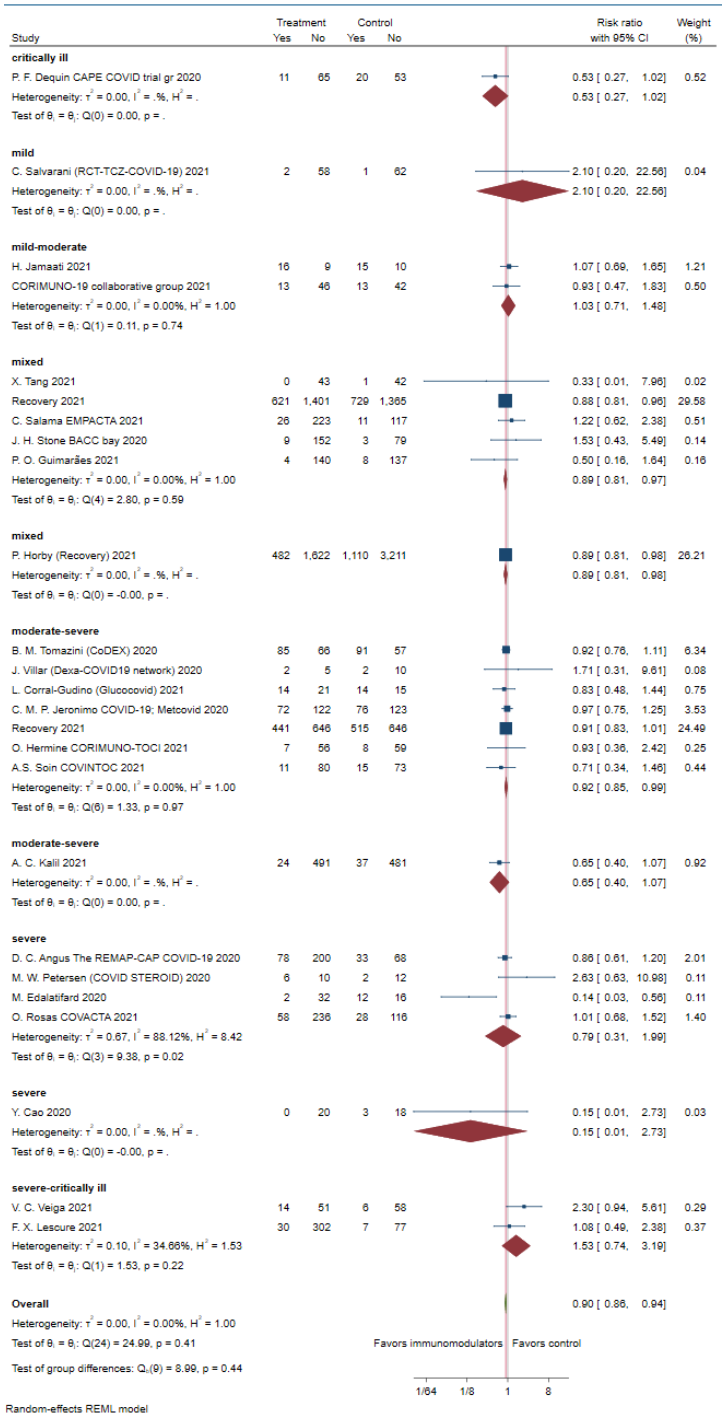


Figure S1. Transitivity assessment on mortality rate (I^2=0%)

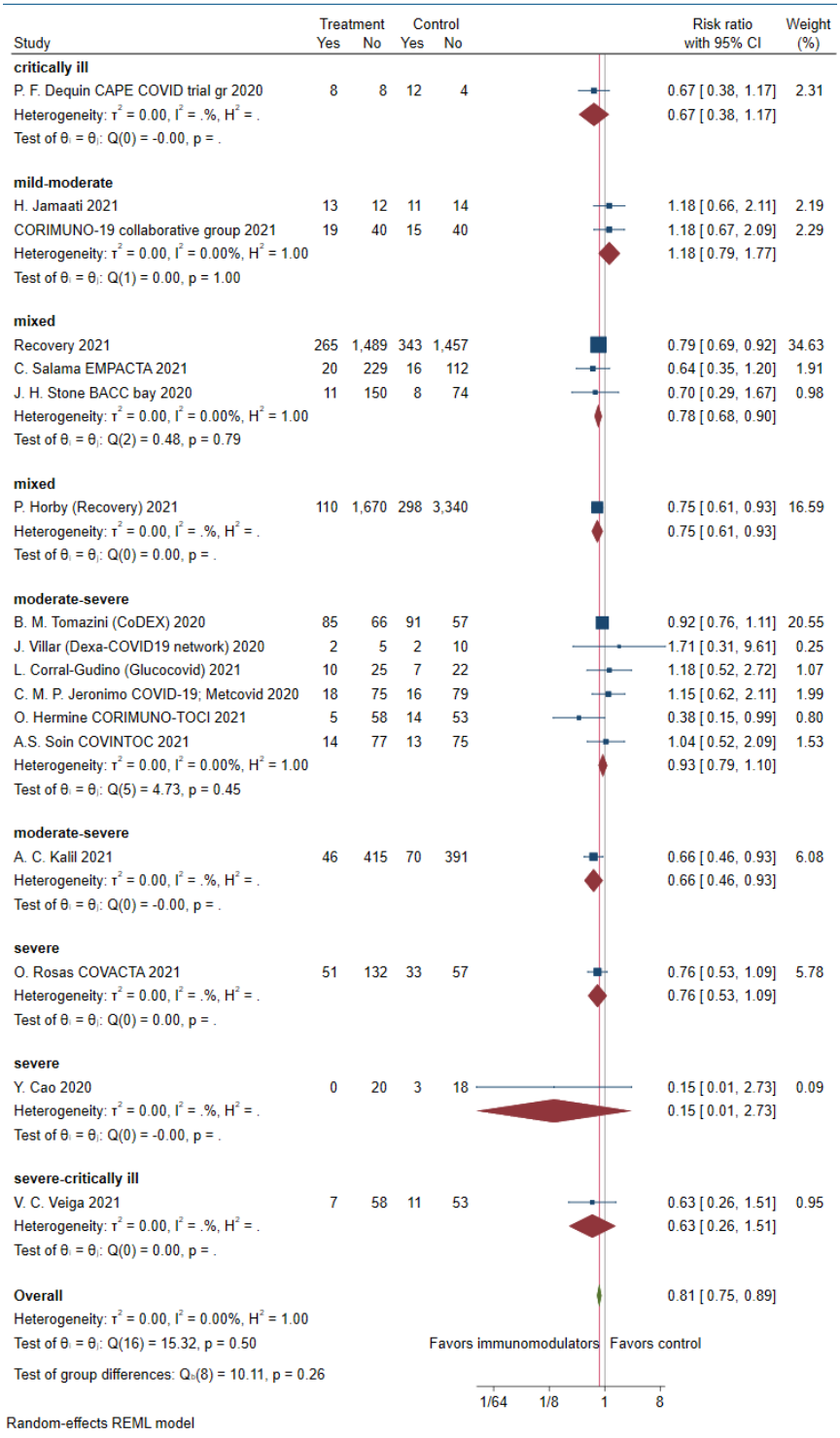


Figure S2. Transitivity assessment on incidence of IMV (I^2=0%)

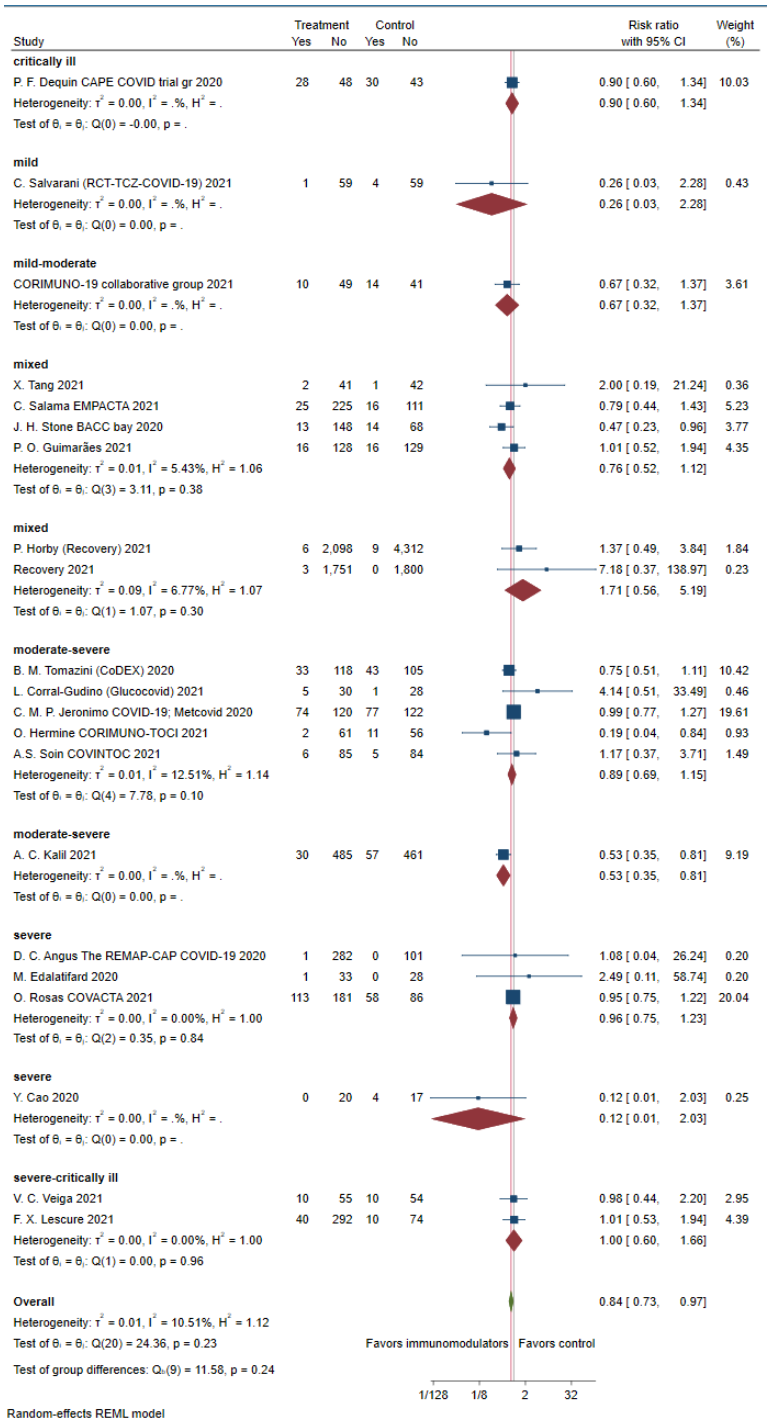
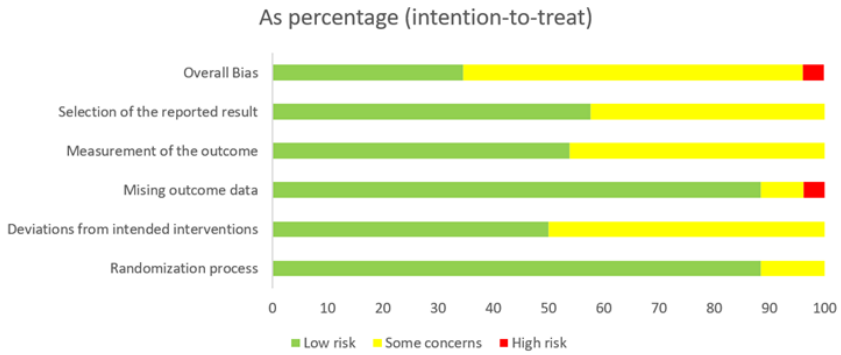


Figure S3. Transitivity assessment on incidence of superimposed infection (I^2=10.51%)

3. Risk of bias assessment



	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Assignment to intervention (the 'intention-to-treat' effect)						
Total number of study = 26						
Low risk	88.5	50	88.5	53.8	57.7	34.6
Some concerns	11.5	50	7.7	46.2	42.3	61.5
High risk	0	0	3.8	0	0	3.8

Unique ID	study ref	year	D1	D2	D3	D4	D5	Overall
1	P. Horby (Recovery)	2021	+	+	+	!	+	!
2	H. Jamaati	2021	!	!	+	!	!	!
3	B. M. Tomazini (CoDEX)	2020	+	!	+	!	!	!
4	J. Villar (Dexa-COVID19 network)	2020	+	+	+	+	+	+
5	D. C. Angus The REMAP-CAP COVID-19	2020	+	!	+	!	!	!
6	P. F. Dequin CAPE COVID trial gr	2020	+	+	+	+	!	!
7	M. W. Petersen (COVID STEROID)	2020	+	+	+	+	+	+
8	L. Corral-Gudino (Glucocovid)	2021	+	+	+	+	+	+
9	M. Edalatifard	2021	!	!	+	!	!	!
10	C. M. P. Jeronimo COVID-19; Metcovid	2020	+	!	-	+	!	-
11	X. Tang	2021	!	!	+	+	+	!
12	Recovery	2021	+	+	+	+	+	+
13	O. Hermine CORIMUNO-TOCI	2021	+	!	+	!	+	!
14	O. Rosas COVACTA	2021	+	+	+	+	+	+
15	C. Salama EMPACTA	2021	+	!	+	+	+	+
16	C. Salvarani (RCT-TCZ-COVID-19)	2021	+	!	+	!	!	!
17	A.S. Soin COVINTOC	2021	+	!	+	!	+	!
18	J. H. Stone BACC bay	2020	+	+	+	+	+	+
19	V. C. Veiga	2021	+	!	+	!	+	!
20	F. X. Lescure	2021	+	+	+	+	!	!
21	CORIMUNO-19 collaborative group	2021	+	+	+	!	!	!
22	Y. Cao	2020	+	!	!	!	!	!
23	A. C. Kalil	2021	+	+	+	+	+	+
24	P. O. Guimarães	2021	+	+	+	+	+	+
25	A.C. Gordon REMAP-CAP	2021	+	!	+	!	+	!
26	K. Ranjbar	2021	+	+	!	+	!	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure S4. Cochrane Risk of Bias 2.0 Tool of included randomized controlled trials

Description risk of bias

For detail of rating criteria, see published article (Sterne JAC et al., BMJ. 2019). C. M. P. Jeronimo et al. had high RoB in missing outcome data; Y. Cao et al. had some concerns of bias in deviations from the intended interventions, missing outcome data, measurement of outcome and selection of the reported result. H. Jamaati et al. and M. Edalatifard et al. had some concerns of bias in randomisation process, deviations from the intended interventions, measurement of the outcome and selected of the reported results.

4. Direct meta-analysis immunomodulators vs placebo

a. corticosteroids

4.1.1 mortality rate outcome

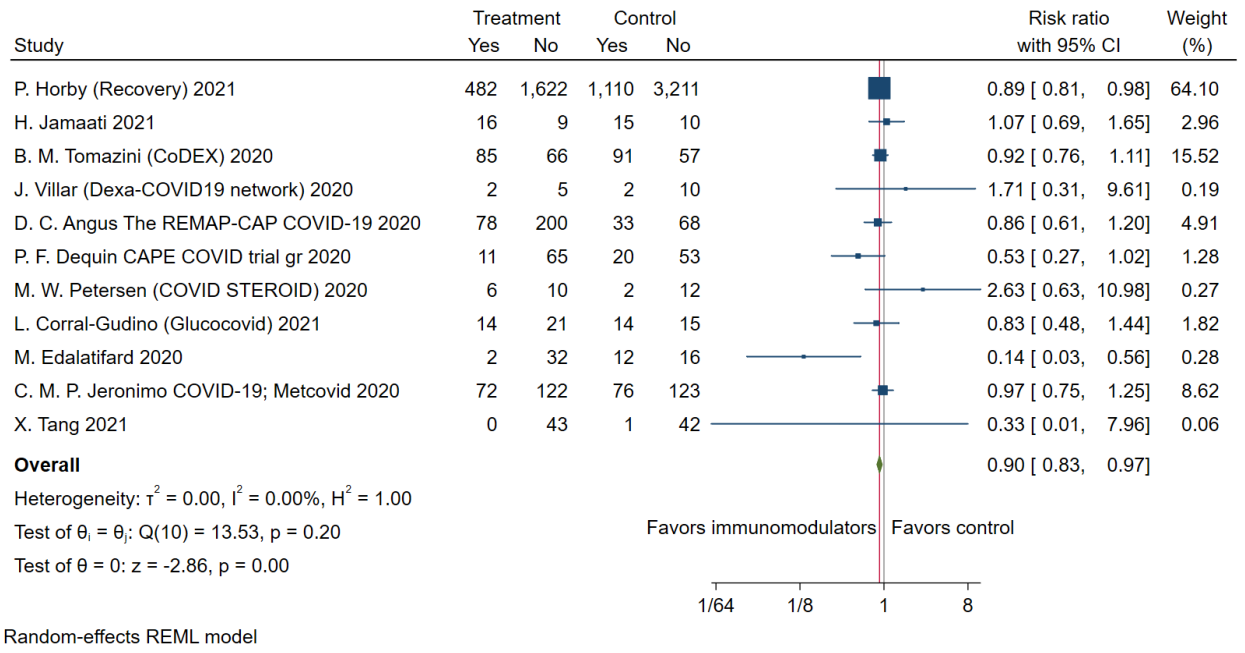


Figure S5: Forest plot the effect of corticosteroid on mortality rate in direct meta-analysis

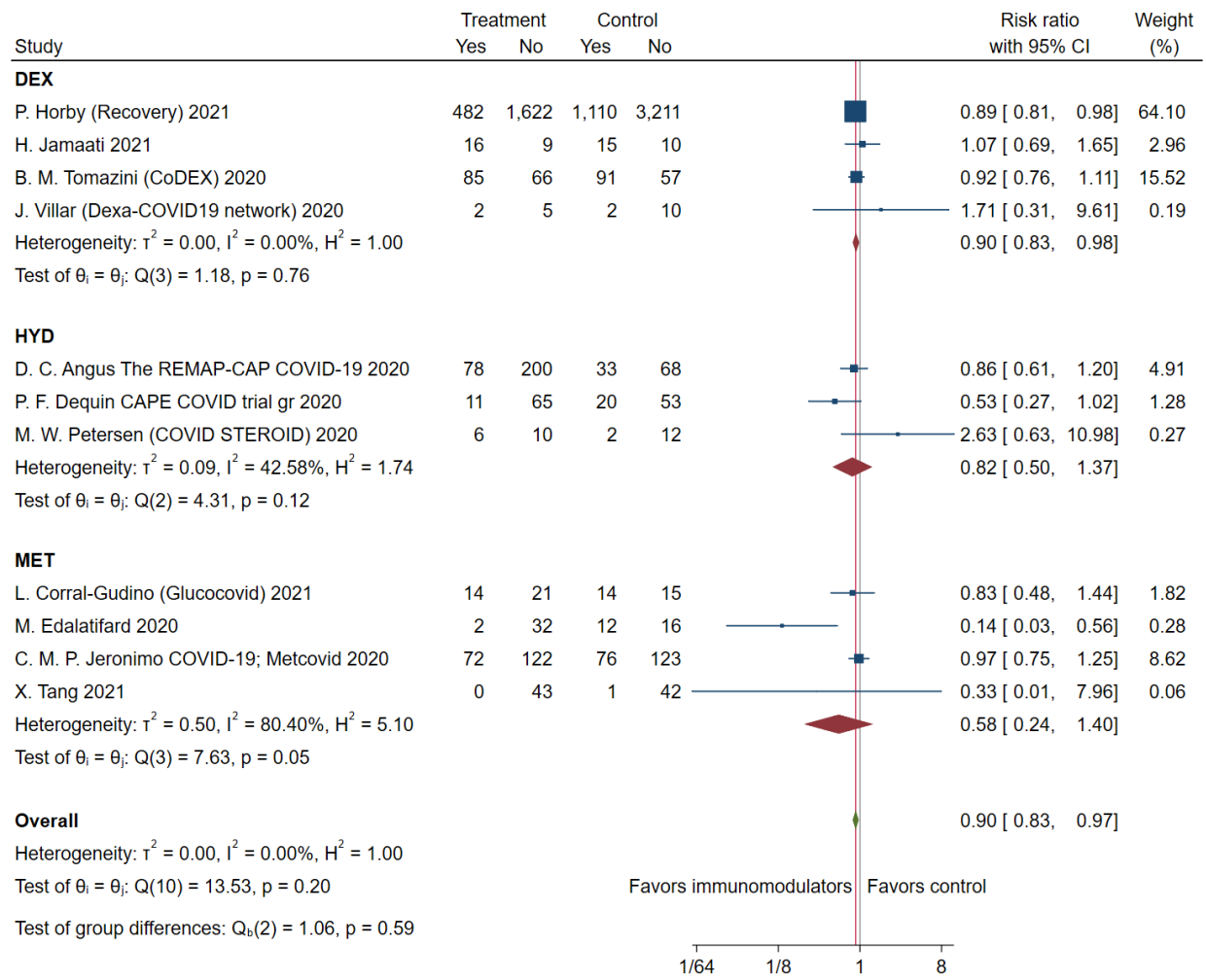


Figure S6: Forest plot the effect of corticosteroid on mortality rate in direct meta-analysis subgroup by types of corticosteroid

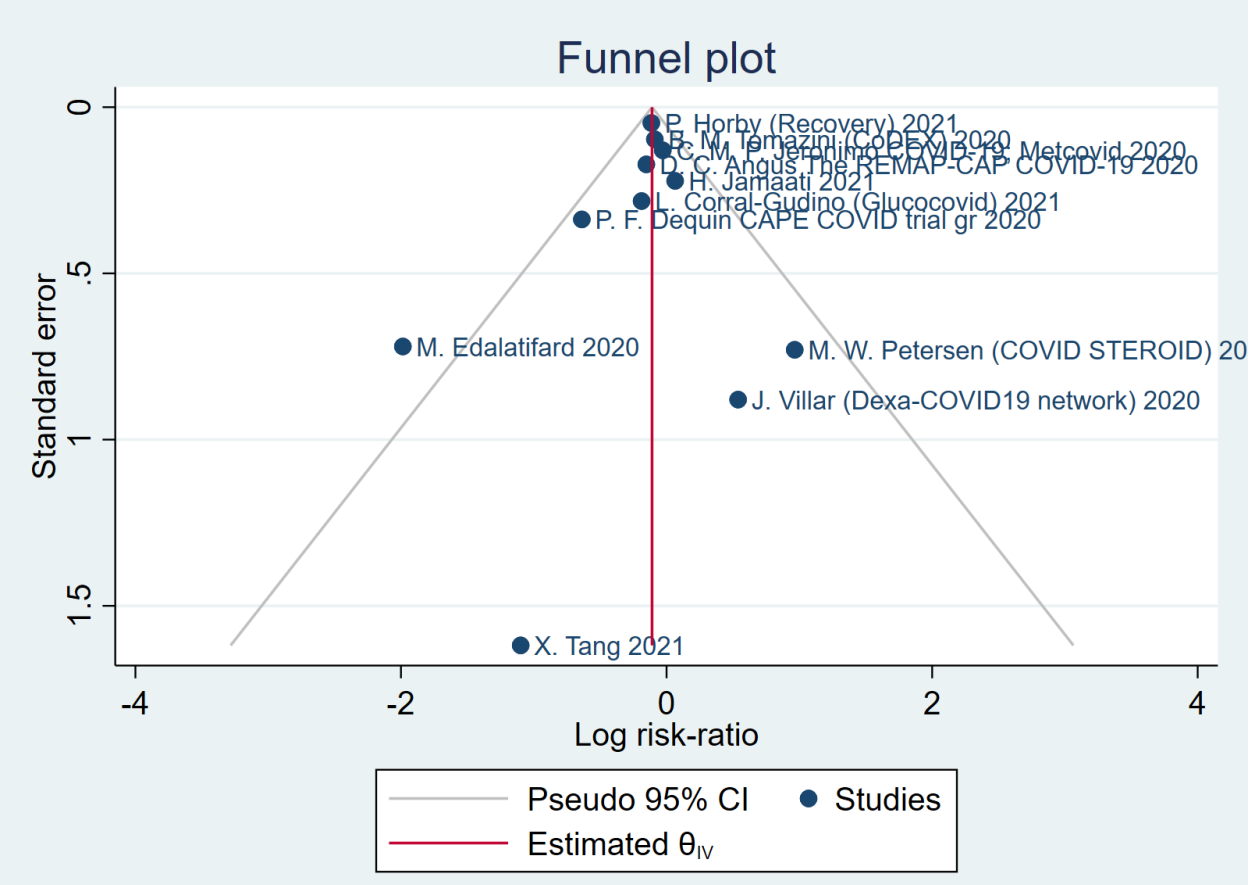


Figure S7: funnel plots the effect of corticosteroid on mortality rate
(egger's test; p=0.504)

4.1.2 incidence of IMV outcome

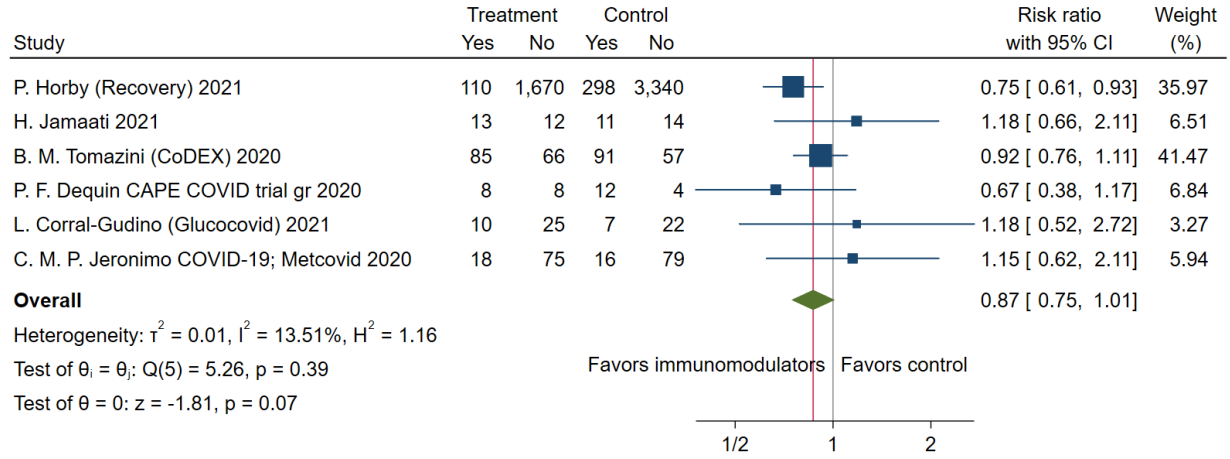


Figure S8: Forest plot the effect of corticosteroid on incidence of IMV in direct meta-analysis

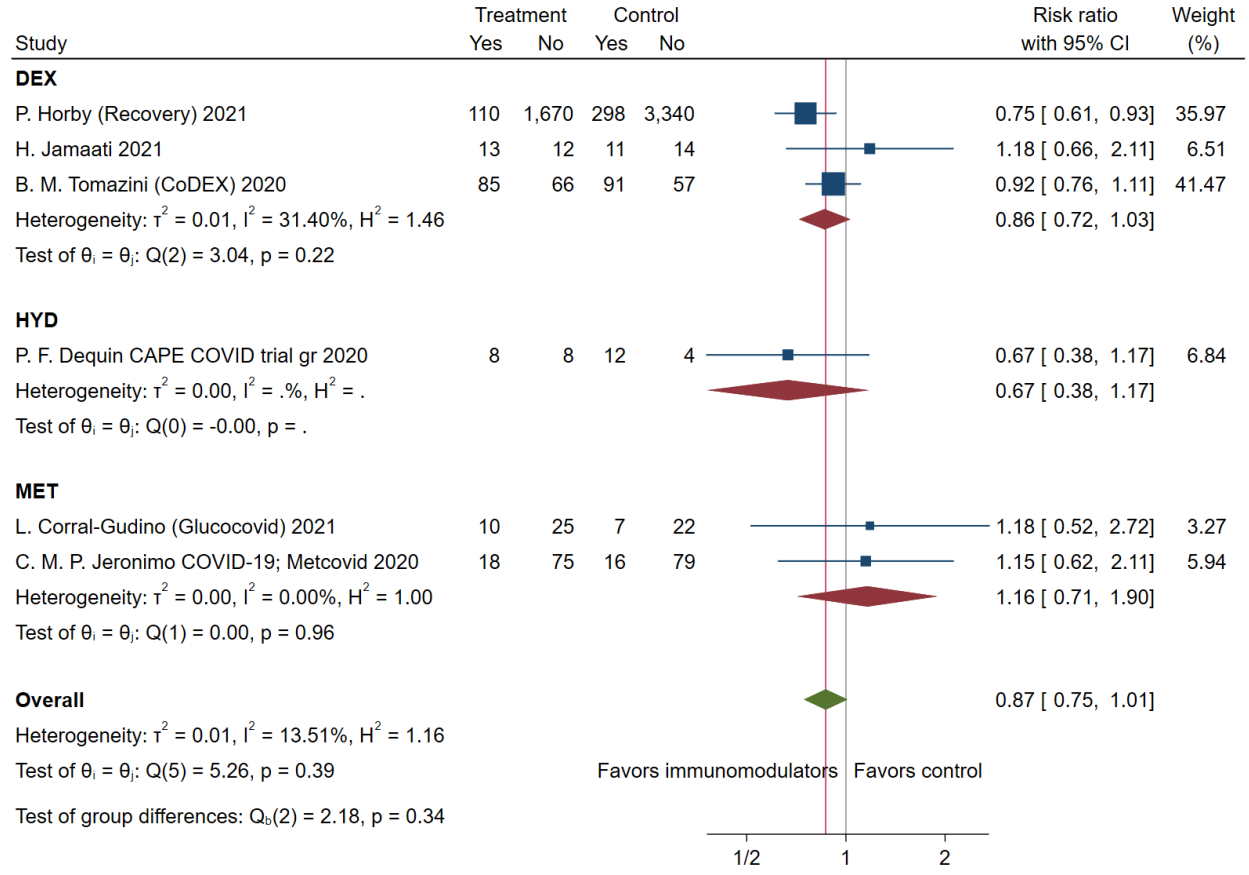


Figure S9: Forest plot the effect of corticosteroid on incidence of IMV in direct meta-analysis subgroup by types of corticosteroid

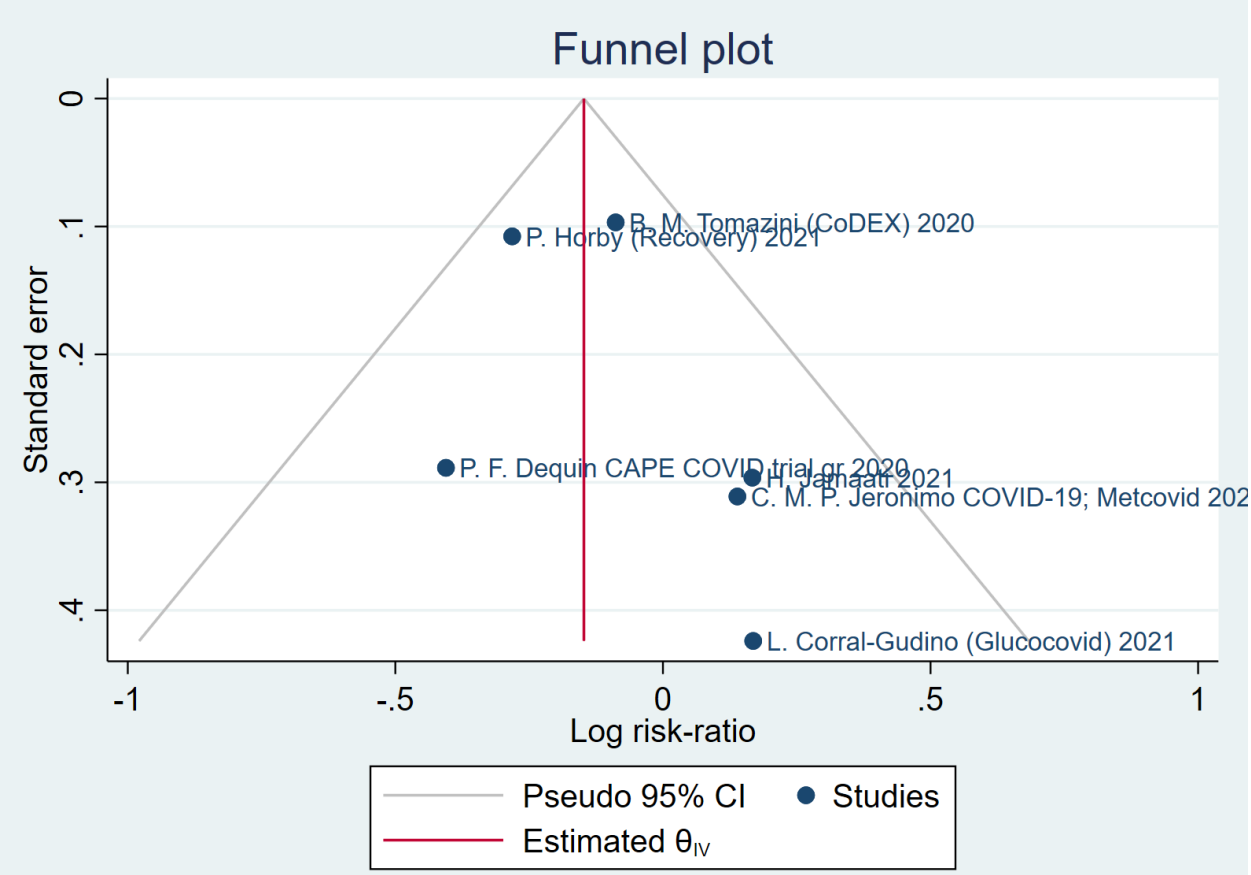


Figure S10: funnel plots the effect of corticosteroid on incidence of IMV (egger's test; p=0.345)

4.1.3 superimposed infection

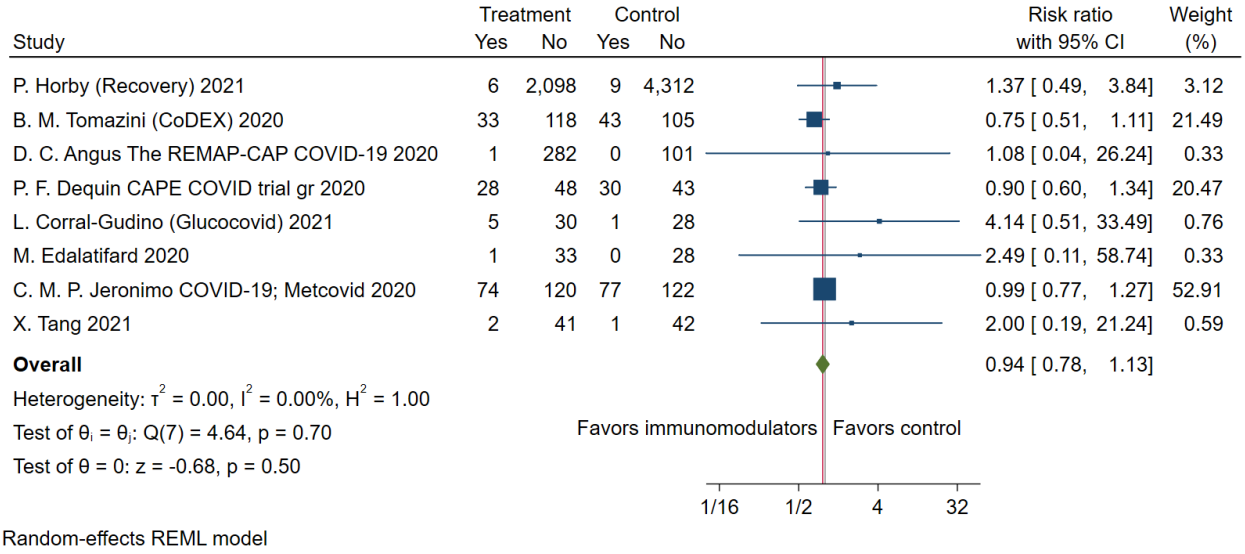


Figure S11: Forest plot the effect of corticosteroid on superimposed infection in direct meta-analysis

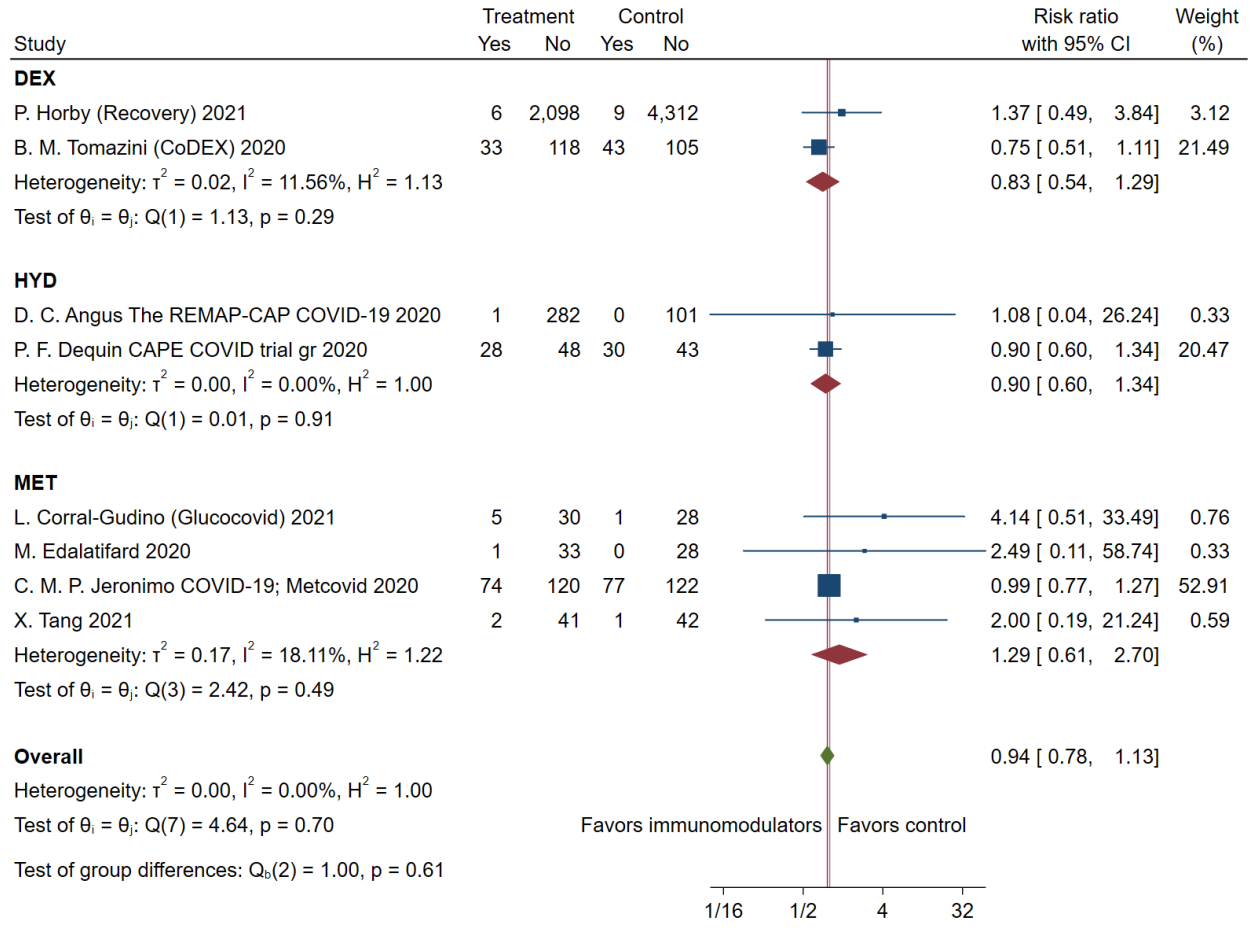


Figure S12: Forest plot the effect of corticosteroid on superimposed infection in direct meta-analysis subgroup by types of corticosteroid

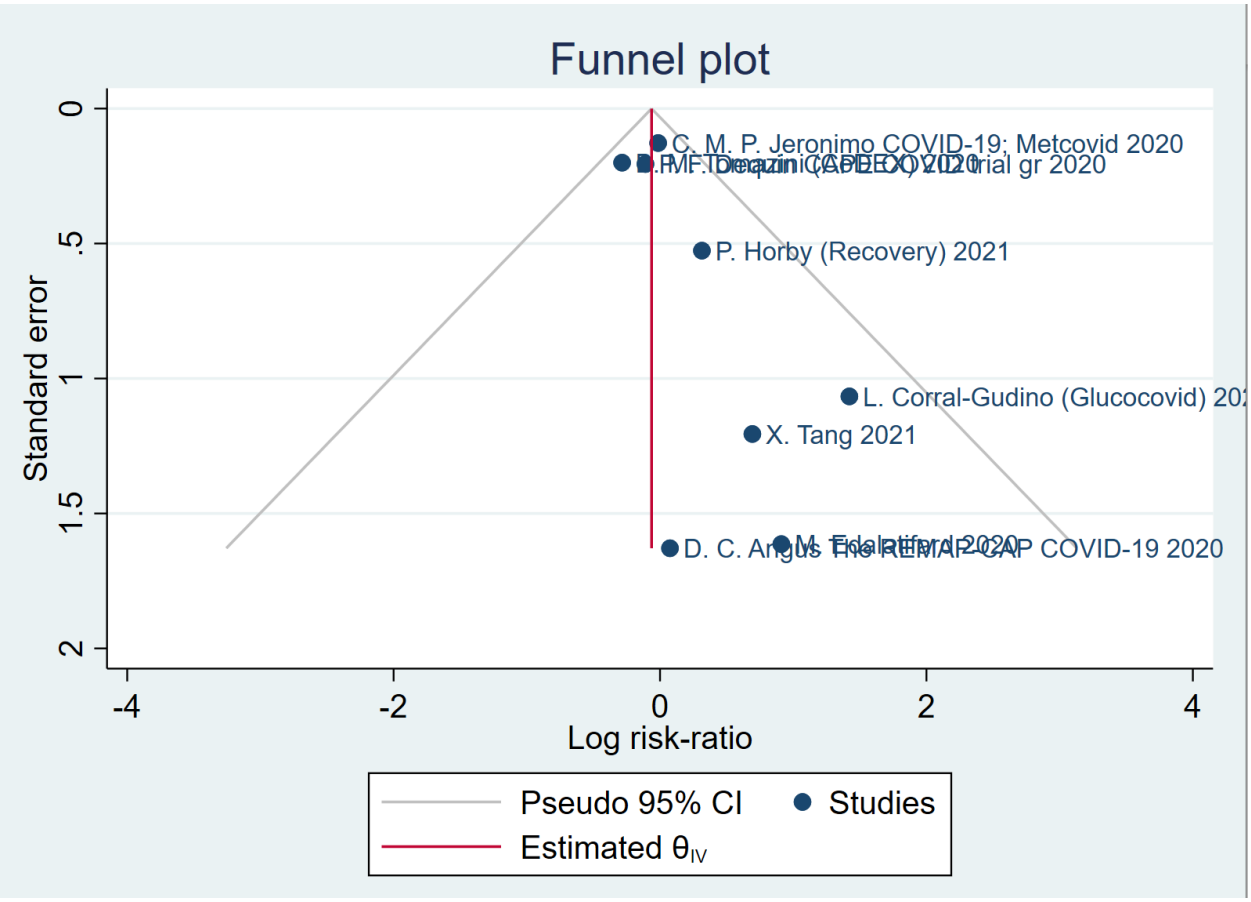


Figure S13: funnel plots the effect of corticosteroid on superimposed infection (egger's test; p=0.191)

b. Interleukin (IL) antagonists

i. mortality rate outcome

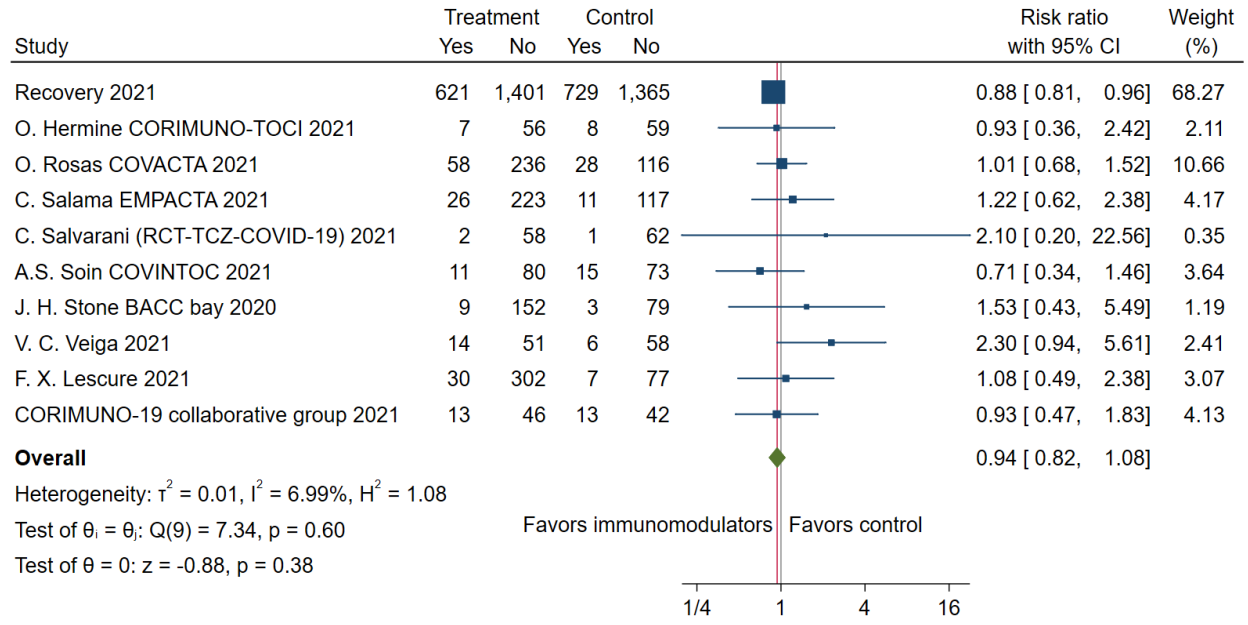


Figure S14: Forest plot the effect of IL antagonist on mortality rate in direct meta-analysis

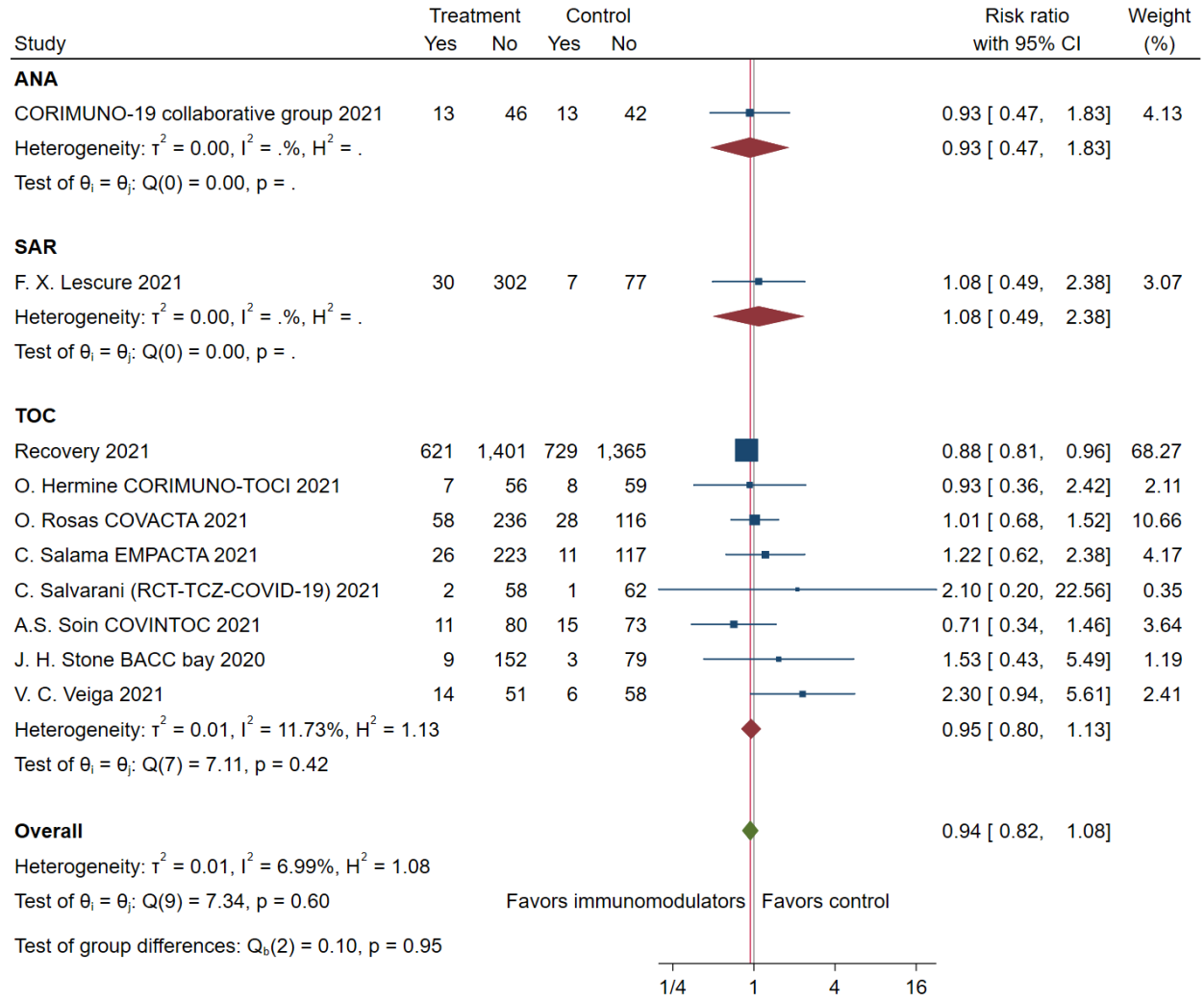


Figure S15: Forest plot the effect of IL antagonist on mortality rate in direct meta-analysis subgroup by types of IL antagonist

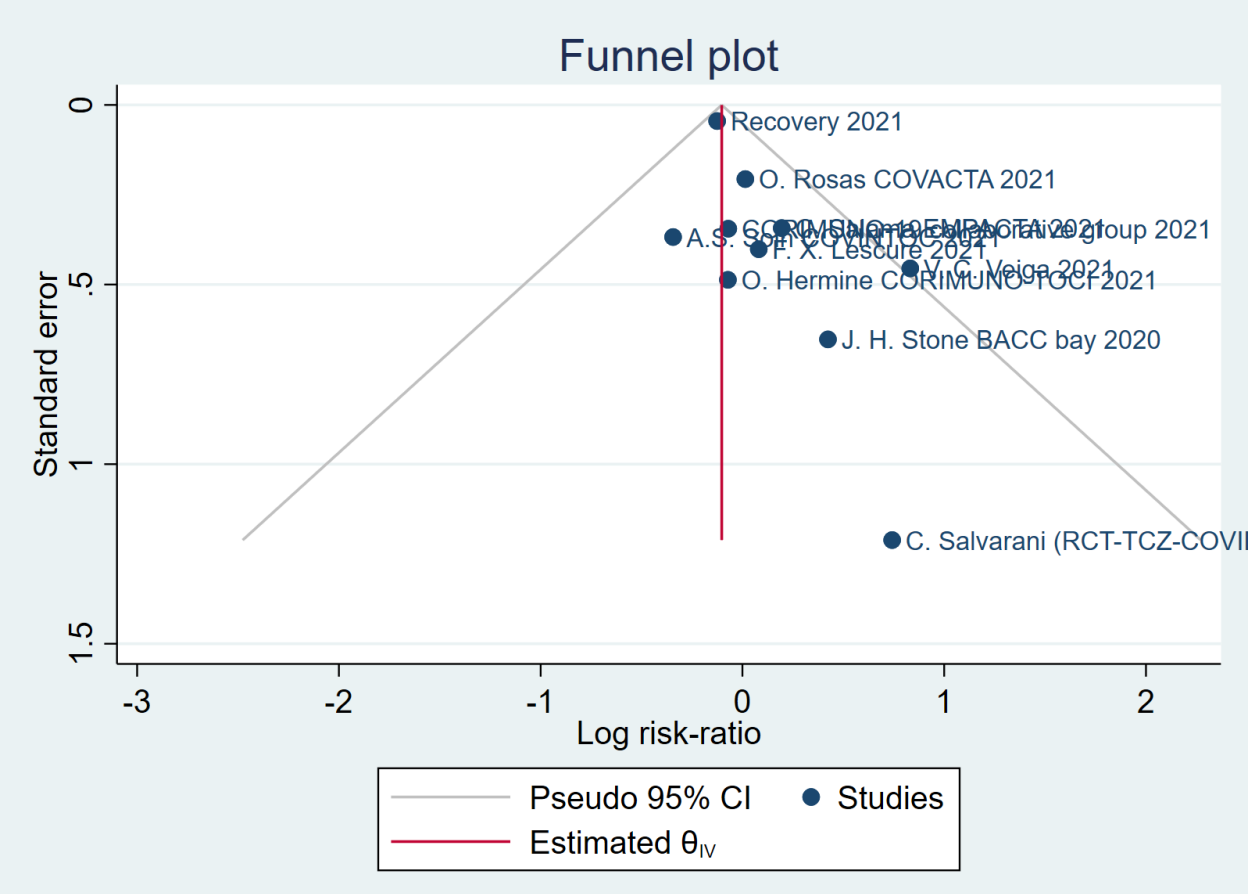
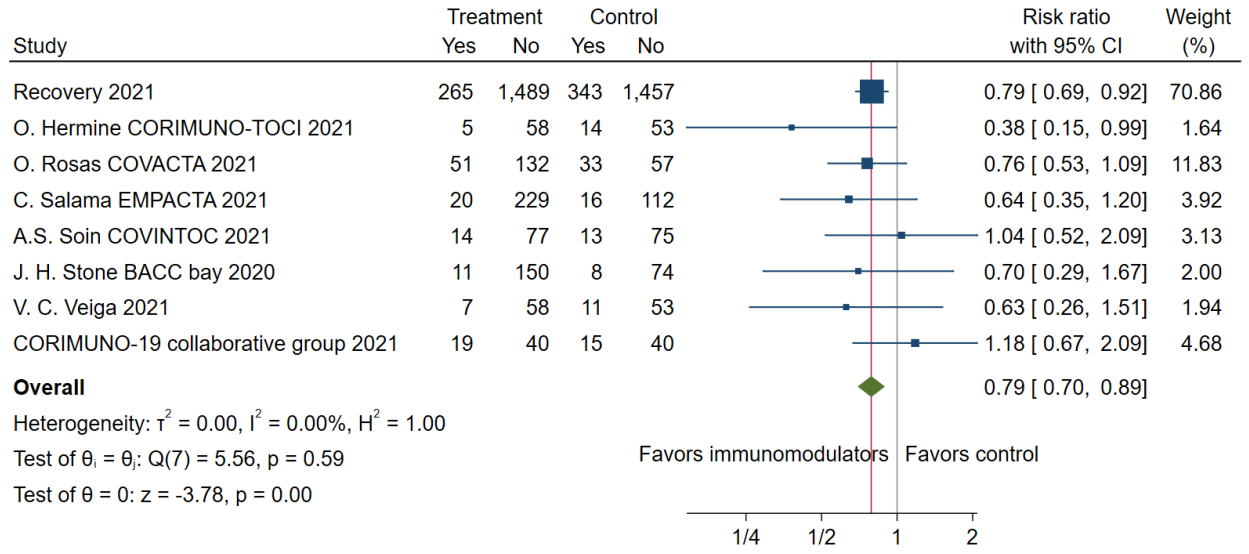


Figure S16: funnel plots the effect of IL antagonists on mortality rate
(egger's test; p=0.08)

4.2.2 incidence of IMV



Random-effects REML model

Figure S17: Forest plot the effect of IL antagonist on incidence of IMV in direct meta-analysis

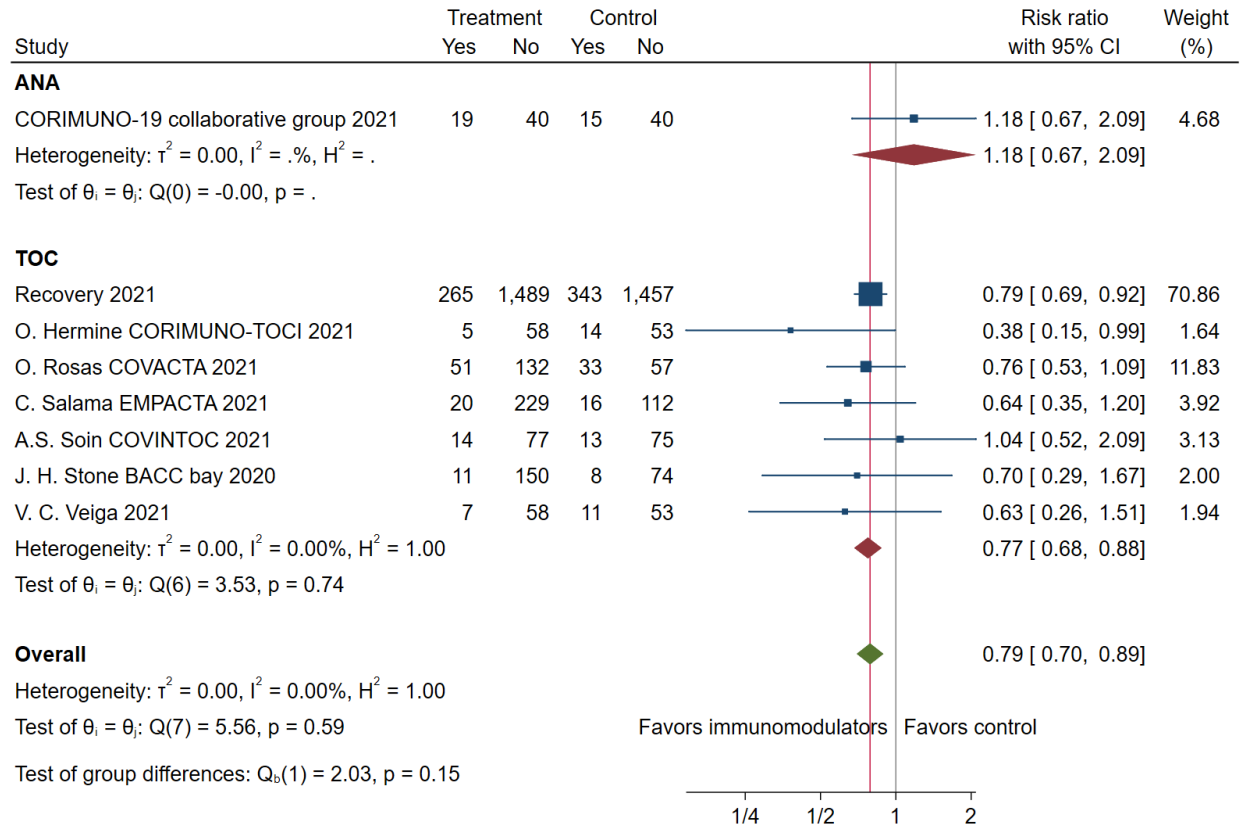


Figure S18: Forest plot the effect of IL antagonist on incidence of IMV in direct meta-analysis subgroup by types of IL antagonist

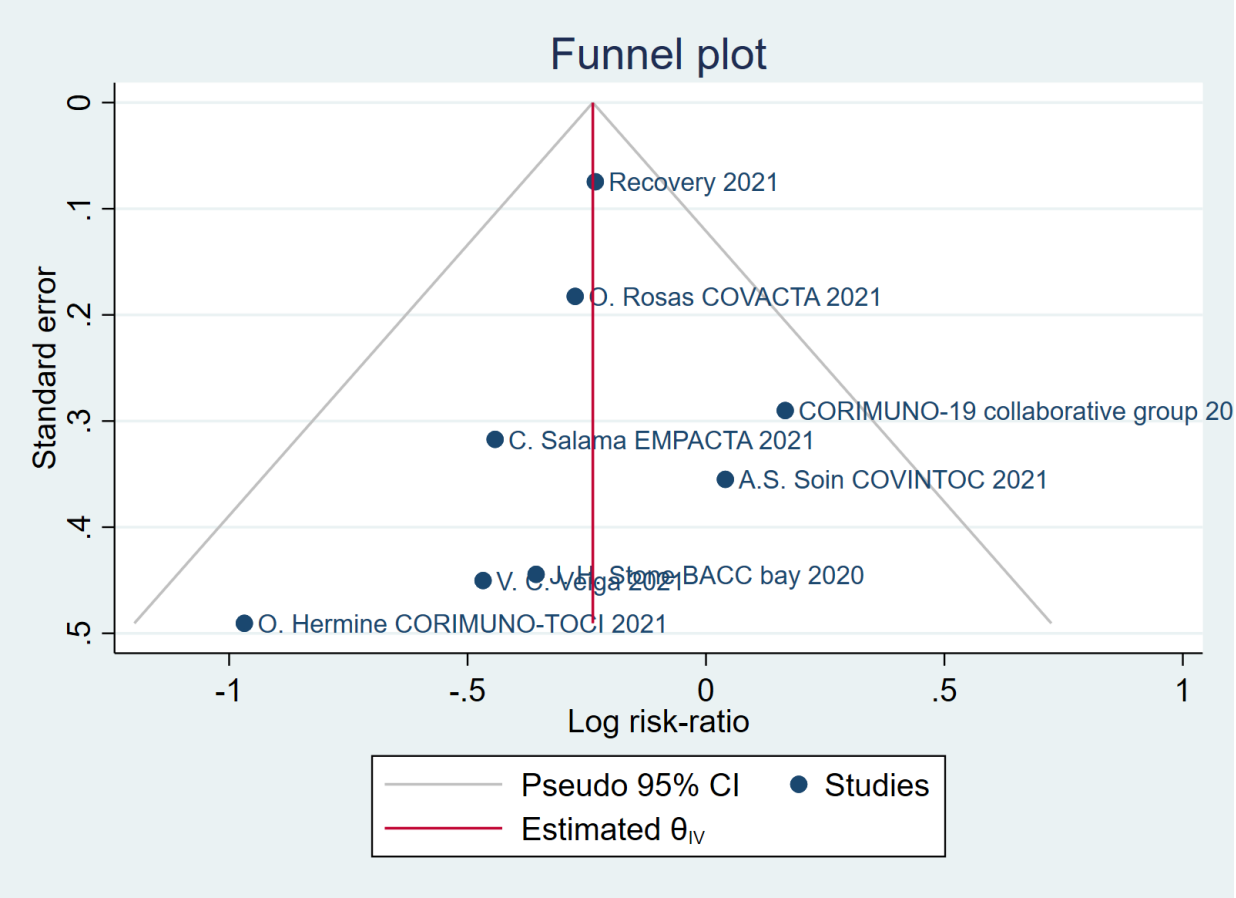


Figure S19: funnel plots the effect of IL antagonists on incidence of IMV
(egger's test; p=0.626)

4.2.3 superimposed infection

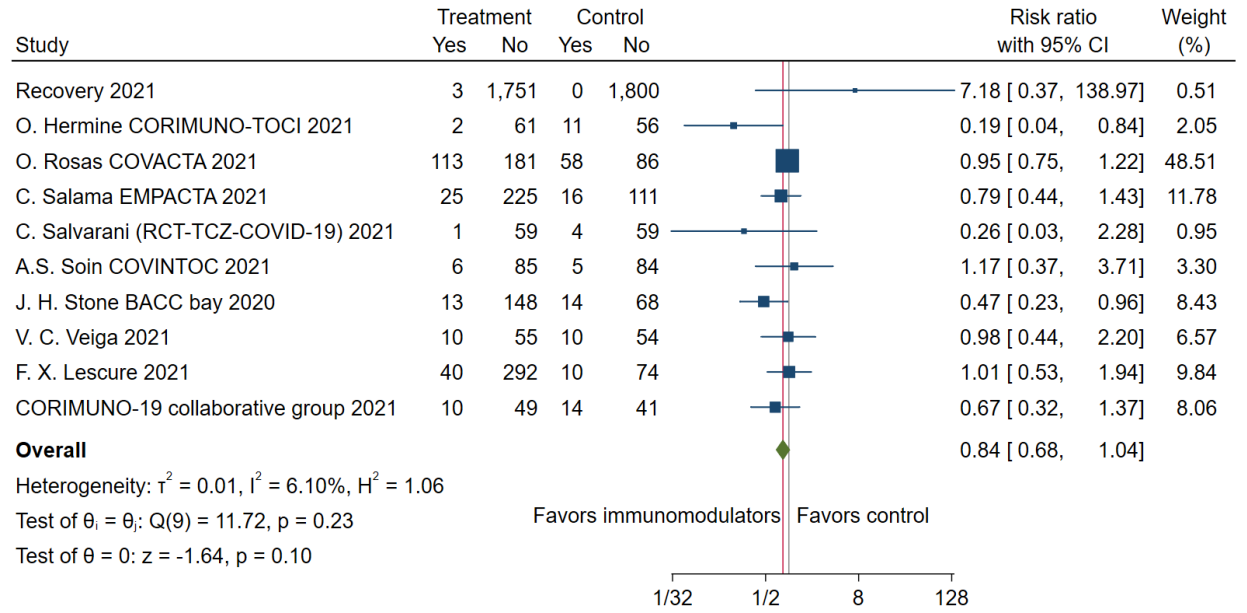


Figure S20: Forest plot the effect of IL antagonist on superimposed infection in direct meta-analysis

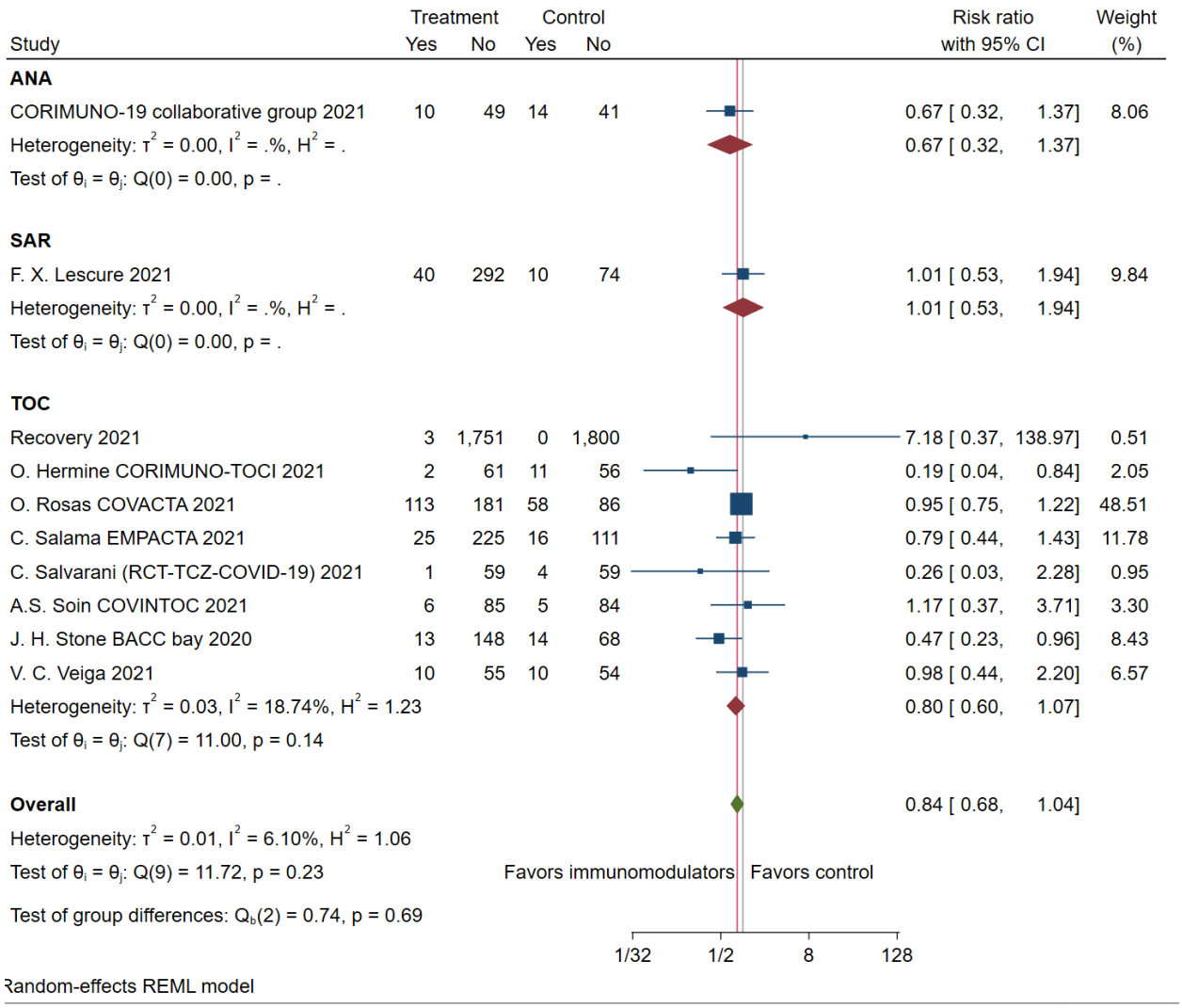


Figure S21: Forest plot the effect of IL antagonist on superimposed infection in direct meta-analysis subgroup by types of IL antagonist

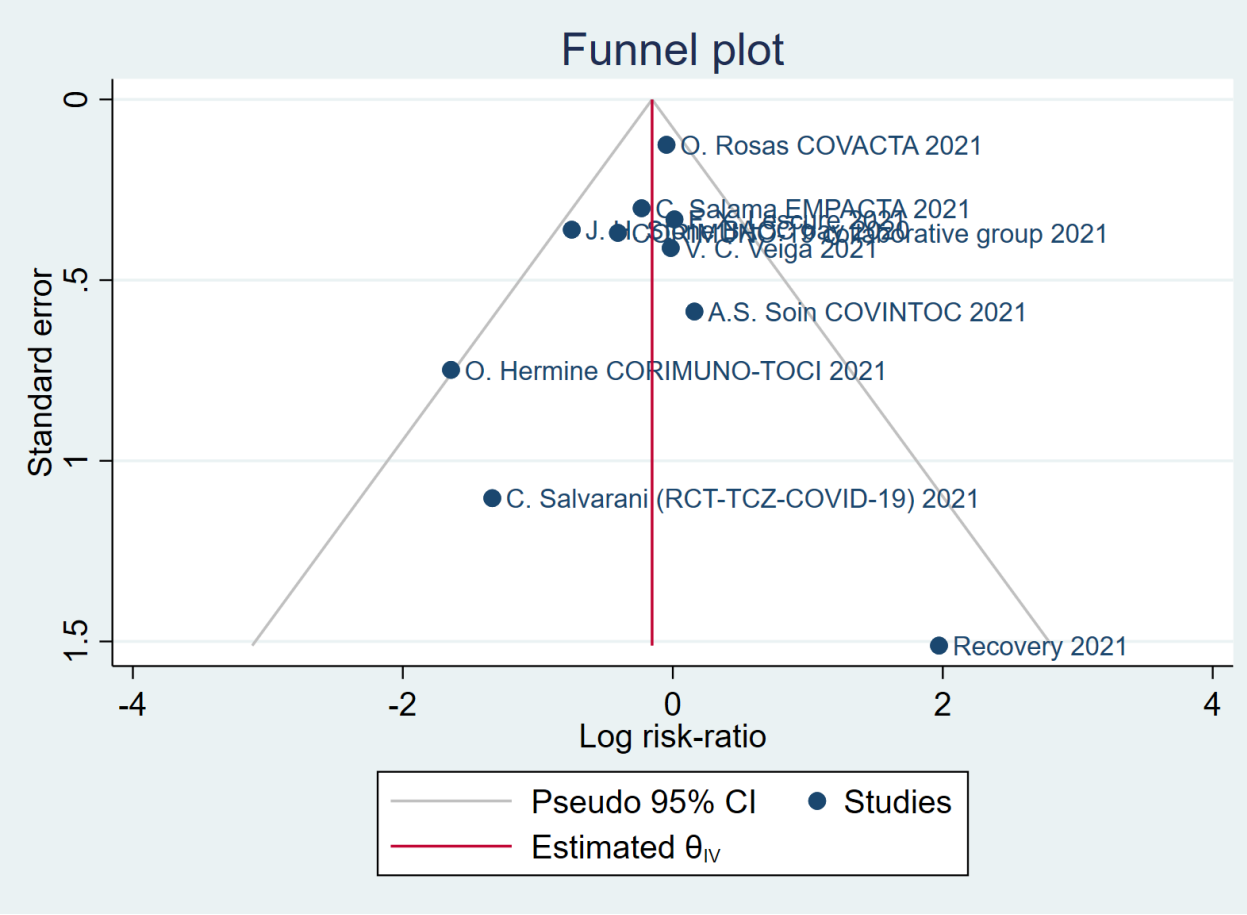


Figure S22: funnel plots the effect of IL antagonists on superimposed infection (egger's test; p=0.276)

c. JAK inhibitors

4.3.1 mortality rate

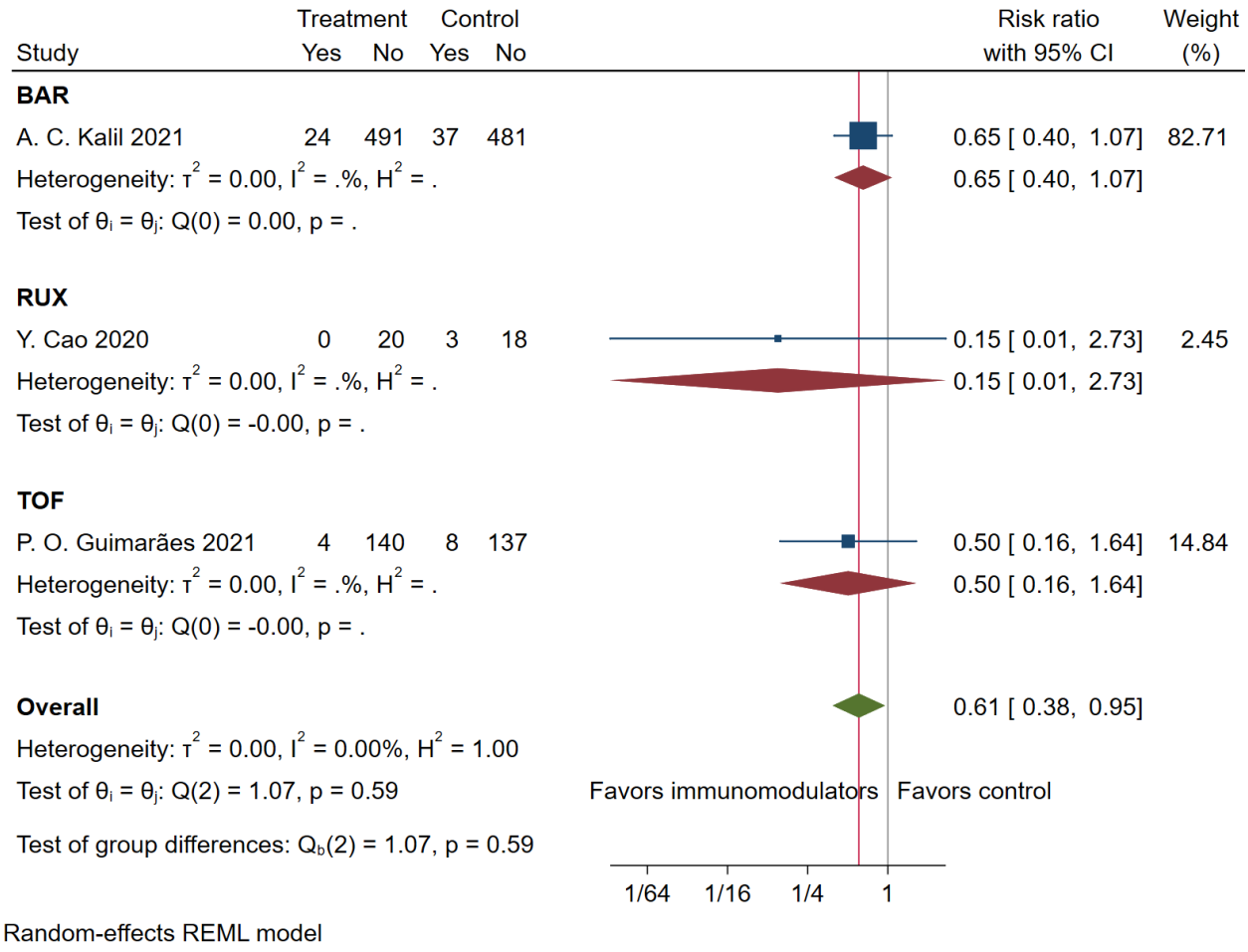


Figure S23: Forest plot the effect of JAK inhibitors on mortality rate in direct meta-analysis

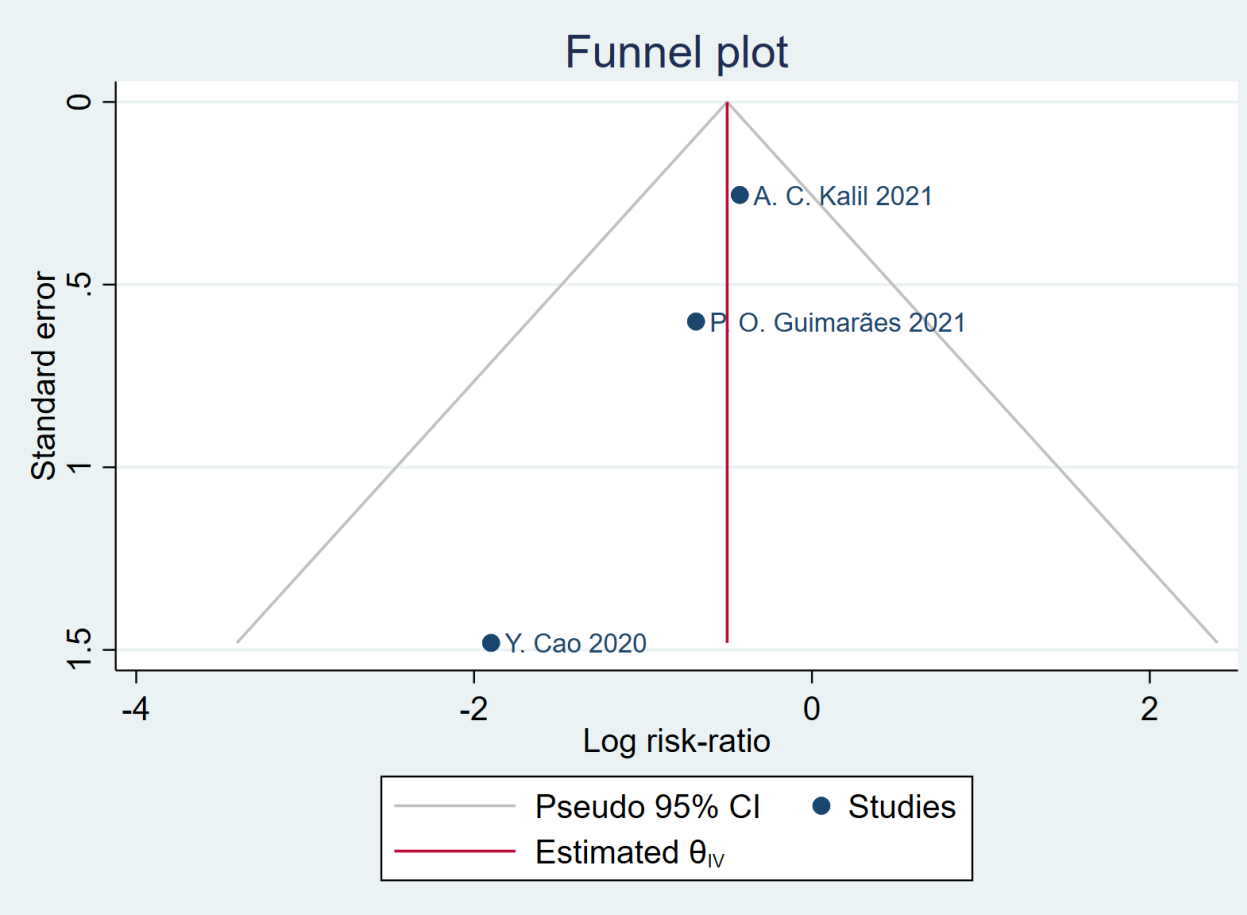


Figure S24: funnel plots the effect of JAK inhibitors on mortality rate
(egger's test; p=0.311)

4.3.2 incidence of IMV (not performed due to insufficient for poolings)

4.3.3 superimposed infection

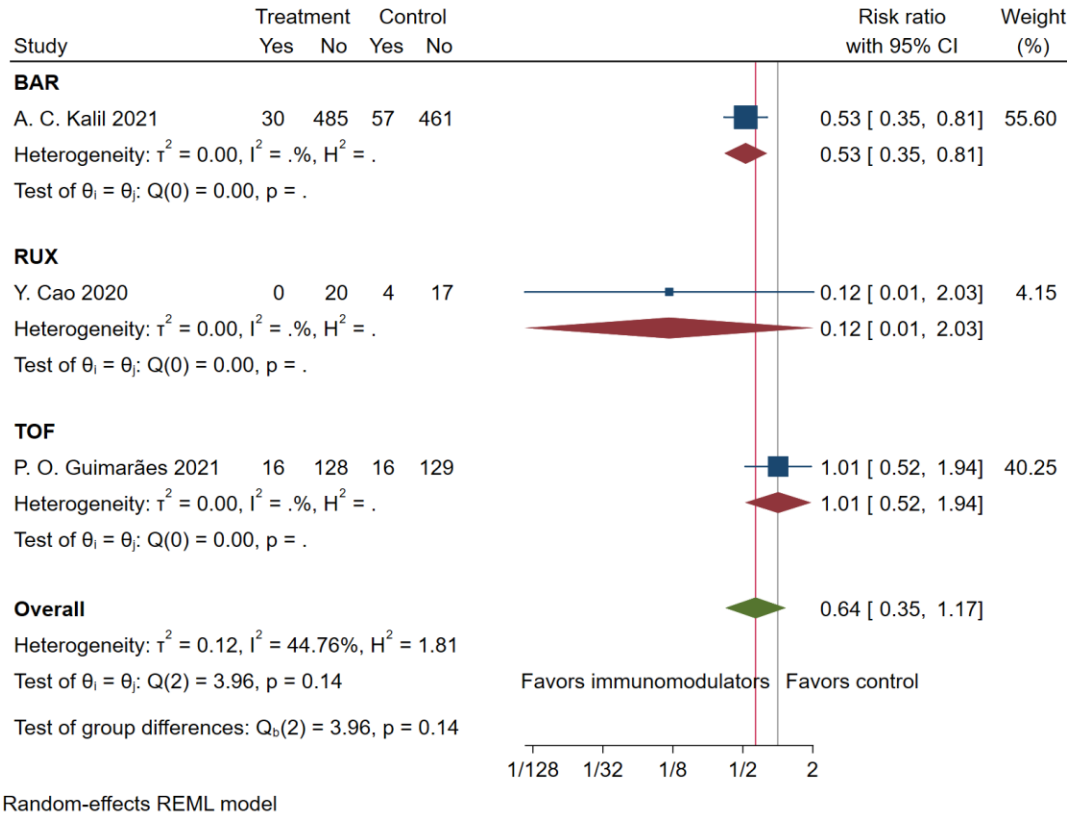


Figure S25: Forest plot the effect of JAK inhibitors on superimposed infection in direct meta-analysis

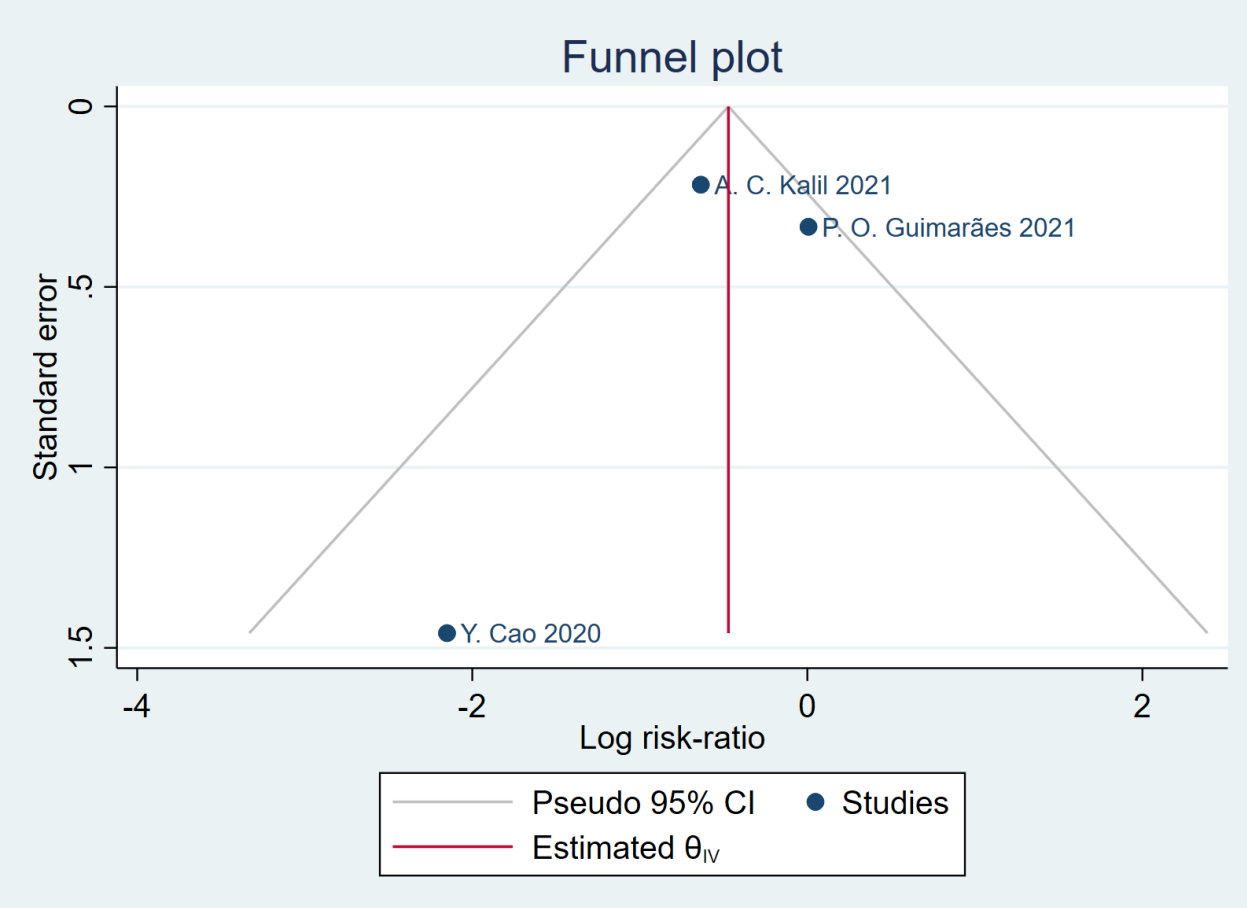


Figure S26: funnel plots the effect of JAK inhibitors on superimposed infection (egger's test; p=0.337)

5. Network map of eligible comparison for efficacy and adverse events

Network meta-analysis of eligible comparisons for mortality rate, incidence of mechanical ventilation and superimposed infection following immunomodulators for COVID-19 treatment. The Figure plots the network of direct comparisons (black bold lines) and indirect comparison (dashed line); (A) mortality rate, (B) incidence of mechanical ventilation and (C) superimposed infection. The width of the lines is proportional to the number of trials comparing every pair of treatment. Size of every circle is proportional to the number of randomly assigned participants (sample size).

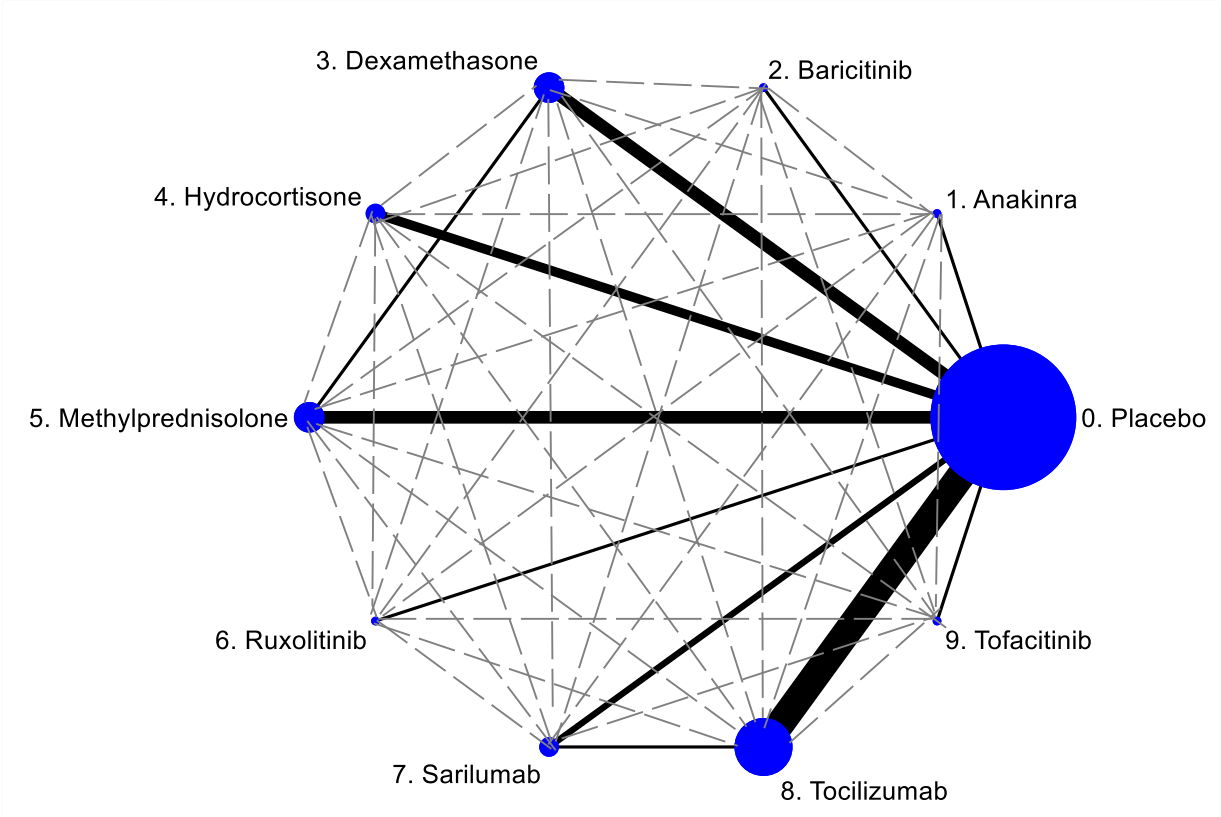


Figure S27A: Network meta-analysis of eligible comparison for mortality rate

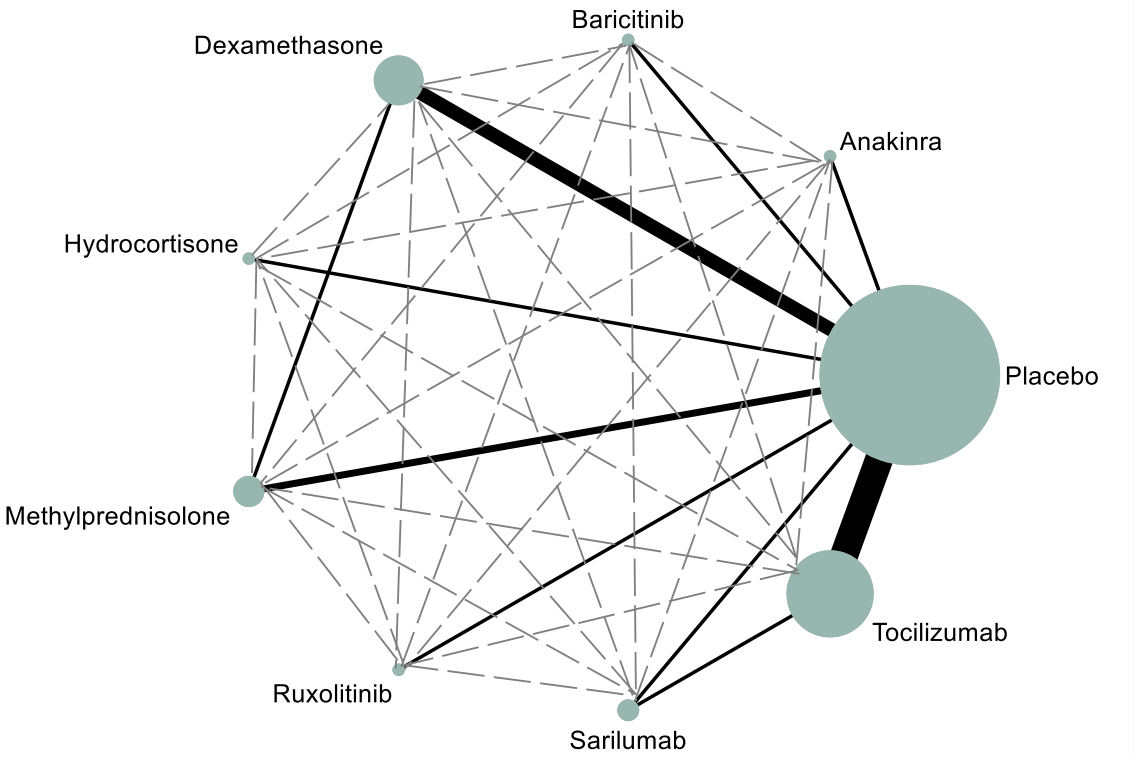


Figure S27B: Network meta-analysis of eligible comparison for incidence of invasive mechanical ventilation

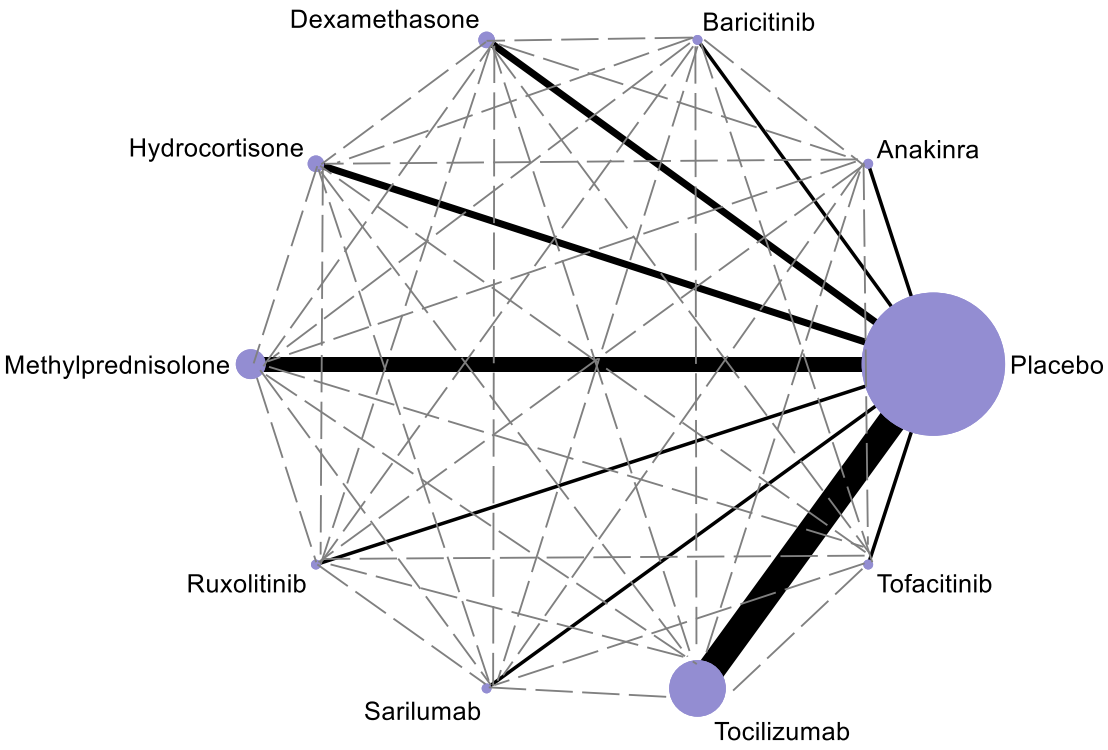


Figure S27C: Network meta-analysis of eligible comparison for superimposed infection

6. Network meta-analysis outcome

Table S3: Network meta-analysis of efficacy on mortality rate and superimposed infection

ANA	1.21 (0.54-2.73)	1.05 (0.53-2.08)	1.02 (0.52-2.02)	1.14 (0.55-2.38)	1.10 (0.54-2.24)	1.43 (0.62-3.31)	6.23 (0.32-122.60)	1.85 (0.48-7.20)	0.93 (0.47-1.83)
0.0868 (-0.0951, 0.2681)	**SAR**	0.87 (0.55-1.38)	0.85 (0.53-1.35)	0.94 (0.55-1.62)	0.91 (0.55-1.51)	1.18 (0.60-2.32)	5.16 (0.27-97.29)	1.53 (0.43-5.42)	0.77 (0.49-1.22)
0.0601 (-0.1006, 0.2208)	-0.0263 (-0.1235, 0.0708)	**TOC**	0.97 (0.87-1.09)	1.08 (0.80-1.47)	1.05 (0.83-1.32)	1.36 (0.82-2.25)	5.91 (0.32-107.80)	1.76 (0.54-5.72)	**0.88 (0.82-0.96)***
0.0742 (-0.0898, 0.2382)	0.0123 (-0.0902, 0.1148)	-0.0140 (-0.0666, 0.0384)	**DEX**	1.11 (0.82-1.51)	1.08 (0.85-1.35)	1.39 (0.84-2.31)	6.08 (0.33-110.87)	1.81 (0.55-5.89)	**0.91 (0.84-0.99)***
0.0817 (-0.0827, 0.2462)	0.0048 (-0.0984, 0.1079)	-0.0216 (-0.0789, 0.0357)	0.0075 (-0.0584, 0.0735)	**HYD**	0.97 (0.67-1.40)	1.25 (0.70-2.24)	5.47 (0.30-101.04)	1.62 (0.48-5.47)	0.82 (0.61-1.10)
0.1137 (-0.0518, 0.2792)	-0.0272 (-0.1322, 0.0777)	-0.0536 (-0.1164, 0.0092)	0.0396 (-0.0313, 0.1104)	0.0320 (-0.0393, 0.1034)	**MET**	1.30 (0.75-2.23)	5.65 (0.31-103.73)	1.68 (0.51-5.56)	0.85 (0.68-1.05)
0.0327 (-0.1343, 0.2009)	-0.0037 (-0.0037, 0.1135)	0.0268 (-0.0406, 0.0943)	0.0409 (-0.0341, 0.1159)	-0.0491 (-0.1580, 0.0598)	**0.0805 (0.0022, -0.1587)***	**BAR**	4.36 (0.23-82.86)	1.30 (0.36-4.66)	0.65 (0.40-1.07)
-0.0957 (-0.3399, 0.1485)	0.1821 (-0.0257, 0.3901)	0.1558 (-0.0341, 0.3457)	-0.1699 (-0.3625, 0.0228)	-0.1774 (-0.3705, 0.0156)	**-0.2094 (-0.4034, -0.0153)***	-0.1289 (-0.3247,0.0668)	**RUX**	0.30 (0.01-6.81)	0.15 (0.01-2.73)
0.0858 (-0.0936, 0.2653)	-0.0007 (-0.1263, 0.1250)	0.0257 (-0.0673, 0.1187)	0.0116 (-0.0869, 0.1102)	0.0041 (-0.0952, 0.1034)	-0.0279 (-0.1290, 0.0732)	0.0526 (-0.0519,0.1570)	0.1815 (-0.0245, 0.3875)	**TOF**	0.50 (0.16-1.64)
-0.0850 (-0.2422, 0.0721)	0.0014 (-0.0896, 0.0925)	-0.0249 (-0.0588, 0.0089)	-0.0108 (-0.0579, 0.03617	-0.0033 (-0.05176, 0.04512)	0.0287 (-0.0235,0.0804)	-0.0518 (-0.1101, 0.0066)	-0.1807 (-0.3676, 0.0062)	0.0007 (-0.0858, 0.0874)	**SOC**

*statistical significance are in bold and underscored, NA = Not available values, RR=Risk Ratio, RD=Risk Difference

mortality rate (RR with 95%CI) superimposed infection (RD with 95%CI) treatment

Drug are reported in order of types of immunomodulators; interleukin antagonist, corticosteroid and JAK inhibitors. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For mortality rate, RRs less than 1 favor the row-defining treatment. For superimposed infection, RDs below 0 favor the column-defining treatment. To obtain RDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. To obtain RRs for comparisons in the opposite direction, reciprocals should be taken.

Table S4: Network meta-analysis of efficacy on IMV and superimposed infection

ANA	3.14 (1.23-8.00)	1.51 (0.84-2.69)	1.34 (0.75-2.41)	1.77 (0.79-3.95)	1.39 (0.69-2.81)	1.80 (0.92-3.50)	7.89 (0.41-151.86)	NA	1.18 (0.67-2.09)
0.0868 (-0.0951, 0.2681)	**SAR**	2.09 (0.99-4.39)	**0.43 (0.20-0.91)***	0.56 (0.22-1.43)	0.44 (0.19-1.03)	0.57 (0.25-1.30)	0.40 (0.02-7.97)	NA	**0.38 (0.18-0.79)***
0.0601 (-0.1006, 0.2208)	-0.0263 (-0.1235, 0.0708)	**TOC**	1.12 (0.94-1.34)	0.85 (0.48-1.51)	1.08 (0.71-1.66)	0.84 (0.58-1.21)	0.19 (0.01-3.48)	NA	**0.78 (0.70-0.87)***
0.0742 (-0.0898,0.2382)	0.0123 (-0.0902, 0.1148)	-0.0140 (-0.0666, 0.0384)	**DEX**	0.76 (0.42-1.35)	0.96 (0.63-1.47)	0.75 (0.51-1.08)	0.17 (0.01-3.11)	NA	0.88 (0.77-1.01)
0.0817 (-0.0827, 0.2462)	0.0048 (-0.0984, 0.1079)	-0.0216 (-0.0789, 0.0357)	0.0075 (-0.0584, 0.0735)	**HYD**	0.79 (0.39-1.58)	0.99 (0.51-1.92)	0.22 (0.01-4.32)	NA	0.67 (0.38-1.17)
0.1137 (-0.0518, 0.2792)	-0.0272 (-0.1322, 0.0777)	-0.0536 (-0.1164, 0.0092)	0.0396 (-0.0313, 0.1104)	0.0320 (-0.0393, 0.1034)	**MET**	0.77 (0.45-1.33)	0.18 (0.01-3.31)	NA	0.85 (0.56-1.28)
0.0327 (-0.1343, 0.2009)	-0.0037 (-0.0037, 0.1135)	0.0268 (-0.0406, 0.0943)	0.0409 (-0.0341, 0.1159)	-0.0491 (-0.1580, 0.0598)	**0.0805 (0.0022,0.1587)***	**BAR**	0.23 (0.01-4.24)	NA	**0.66 (0.46-0.93)***
-0.0957 (-0.3399, 0.1485)	0.1821 (-0.0257, 0.3901)	0.1558 (-0.0341, 0.3457)	-0.1699 (-0.3625, 0.0228)	-0.1774 (-0.3705, 0.0156)	**-0.2094 (-0.4034, -0.0153)***	-0.1289 (-0.3247,0.0668)	**RUX**	NA	0.15 (0.01-2.73)
0.0858 (-0.0936, 0.2653)	-0.0007 (-0.1263, 0.1250)	0.0257 (-0.0673,0.1187)	0.0116 (-0.0869, 0.1102)	0.0041 (-0.0952,0.1034)	-0.0279 (-0.1290, 0.0732)	0.0526 (-0.0519,0.1570)	0.1815 (-0.0245, 0.3875)	**TOF**	0.50 (0.16-1.64)
-0.0850 (-0.2422, 0.0721)	0.0014 (-0.0896, 0.0925)	-0.0249 (-0.0588, 0.0089)	-0.0108 (-0.0579, 0.03617	-0.0033 (-0.05176, 0.04512)	0.0287 (-0.0235,0.0804)	-0.0518 (-0.1101, 0.0066)	-0.1807 (-0.3676, 0.0062)	0.0007 (-0.0858, 0.0874)	**SOC**

Incidence of IMV (RR with 95%CI) superimposed infection (RD with 95%CI) treatment

*statistical significance are in bold and underscored, NA = Not available value, RR=Risk Ratio, RD=Risk Difference

Drug are reported in order of types of immunomodulators; interleukin antagonist, corticosteroid and JAK inhibitors. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For incidence of IMV, RRs less than 1 favor the row-defining treatment. For superimposed infection, RDs below 0 favor the column-defining treatment. To obtain RDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. To obtain RRs for comparisons in the opposite direction, reciprocals should be taken.

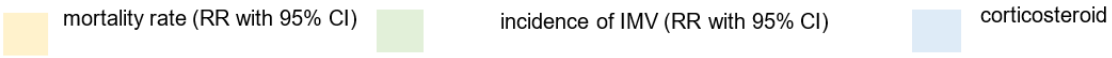
Table S5: The relative treatment effect of corticosteroid in mortality rate and incidence of invasive mechanical ventilation (IMV)

SOC	**0.91 (0.84-0.99)** (*p*-value=0.024)	0.82 (0.61-1.10)	0.85 (0.68-1.05)
0.93 (0.66-1.31)	**DEX**	0.90 (0.66-1.22)	0.93 (0.74-1.17)
0.67 (0.34-1.29)	0.72 (0.34-1.51)	**HYD**	1.03 (0.72-1.49)
0.69 (0.36-1.31)	0.74 (0.40-1.37)	1.03 (0.41-2.59)	**MET**

*statistical significance is in bold and underscored

DEX=dexamethasone. HYD=hydrocortisone. MET=methylprednisolone. SOC=standard of care.

RR=Risk Ratio



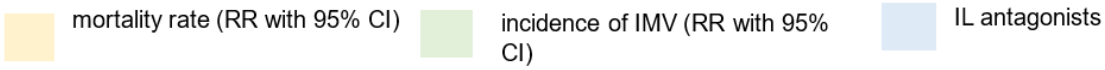
Drugs are reported in alphabetical order. Comparisons between treatments should be read from right to left and the estimate RR is in the cell in common between the column-defining treatment and the row-defining treatment. For mortality rate, RRs less than 1 favor the column-defining treatment. For incidence of mechanical ventilation, RRs less than 1 favor the row-defining treatment. To compare in the opposite direction, reciprocals should be taken.

Table S6: The relative treatment effect of interleukin (IL) antagonists in mortality rate and incidence of invasive mechanical ventilation (IMV)

SOC	0.93 (0.47-1.83)	0.77 (0.49-1.22)	**0.88 (0.82,0.96)** (*p*-value=0.002)
1.18 (0.67-2.09)	**ANA**	0.83 (0.37-1.87)	0.95 (0.48-1.87)
0.38 (0.18-0.79) (*p*-value=0.010)	**0.32 (0.12,0.81)** (*p*-value<0.001)	**SAR**	1.15 (0.73-1.81)
0.78 (0.70-0.87) (*p*-value<0.001)	0.66 (0.37-1.18)	2.09 (0.99-4.39)	**TOC**

*statistical significance is in bold and underscored

ANA=anakira. SAR=sarilumab. TOC=tocilizumab. SOC=standard of care. RR=Risk Ratio



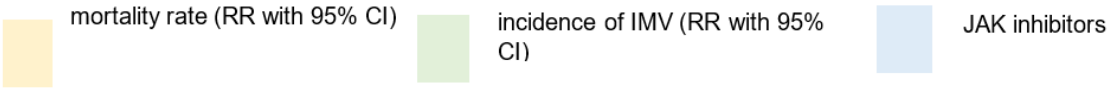
Drugs are reported in alphabetical order. Comparisons between treatments should be read from right to left and the estimate RR is in the cell in common between the column-defining treatment and the row-defining treatment. For mortality rate, RRs less than 1 favor the column-defining treatment. For incidence of mechanical ventilation, RRs less than 1 favor the row-defining treatment. To compare in the opposite direction, reciprocals should be taken.

Table S7: The relative treatment effect of JAK inhibitors in in mortality rate and incidence of invasive mechanical ventilation

SOC	0.65 (0.16-2.60)	**0.15 (0.02-0.97)** (*p*-value 0.046)	NA
0.66 (0.26-1.68)	**BAR**	0.23 (0.04-1.23)	0.77 (0.19-3.07)
0.15 (0.01-1.59)	0.23 (0.02-2.61)	**RUX**	3.36 (0.52-21.74)
NA	NA	NA	**TOF**

*

statistical significance are in bold and underscored, NA=Not available values
BAR=baricitinib. RUX=ruxolitinib. TOF=tofacitinib. SOC=standard of care. RR=Risk Ratio



Drugs are reported in alphabetical order. Comparisons between treatments should be read from right to left and the estimate RR is in the cell in common between the column-defining treatment and the row-defining treatment. For mortality rate, RRs less than 1 favor the column-defining treatment. For incidence of mechanical ventilation, RRs less than 1 favor the row-defining treatment. To compare in the opposite direction, reciprocals should be taken.

Table S8: Results of treatment ranking from network meta-analysis of mortality rate, incidence of IMV and superimposed infection

Rank	Mortality rate		Incidence of IMV		Superimposed infection	
	Treatment	SUCRA	Treatment	SUCRA	Treatment	SUCRA
1	RUX	82.7	SAR	89.2	RUX	13.1
2	TOF	76.9	RUX	83.9	BAR	16.2
3	BAR	74.4	BAR	64.2	ANA	33.0
4	SAR	53.6	HYD	62.1	TOC	45.7
5	HYD	52	TOC	51.5	HYD	55.2
6	MET	45.3	MET	38.6	DEX	55.9
7	TOC	39.1	DEX	35	TOF	65.6
8	ANA	34.1	SOC	14.9	SAR	67.3
9	DEX	30.9	ANA	10.5	SOC	71.8
10	SOC	11.0	TOF	NA	MET	76.2

ANA=anakira. SAR=sarilumab. TOC=tocilizumab. DEX=dexamethasone. HYD=hydrocortisone. MET=methylprednisolone. BAR=baricitinib. RUX=ruxolitinib. TOF=tofacitinib. SOC=standard of care.

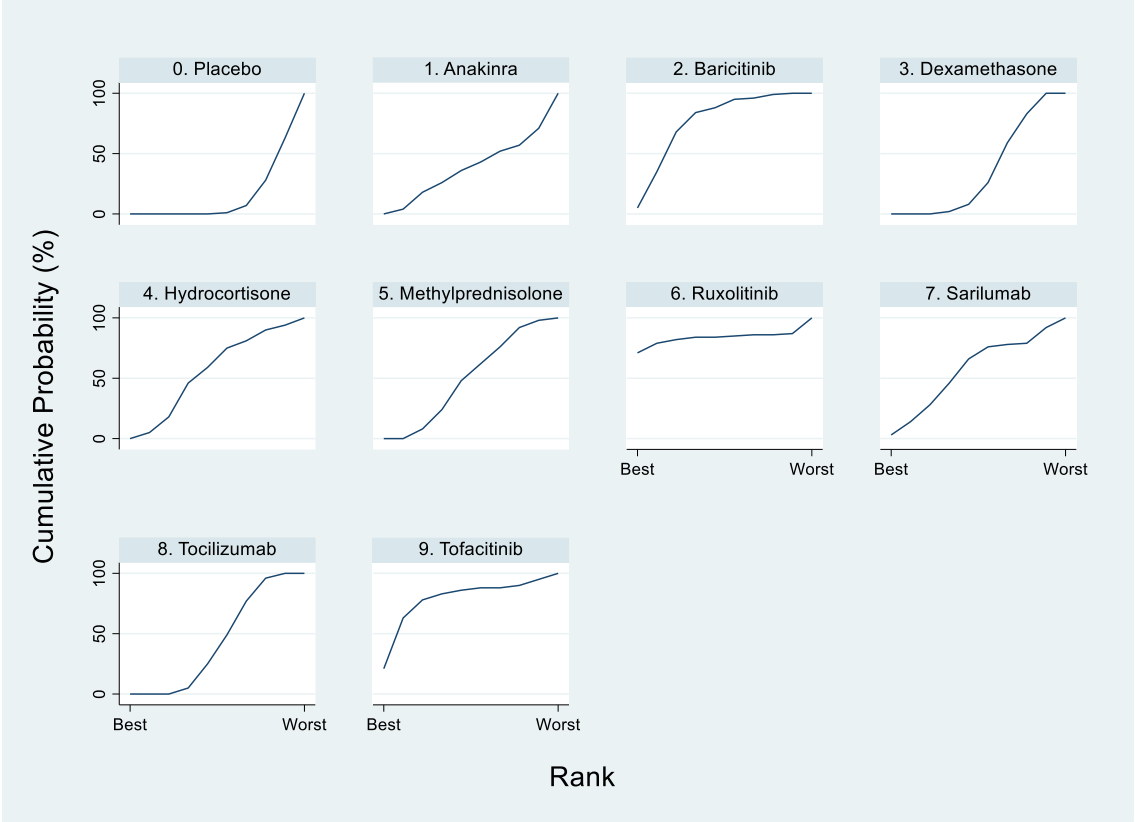


Figure S28: Cumulative Probability (%) of the best treatment in mortality rate with immunomodulators

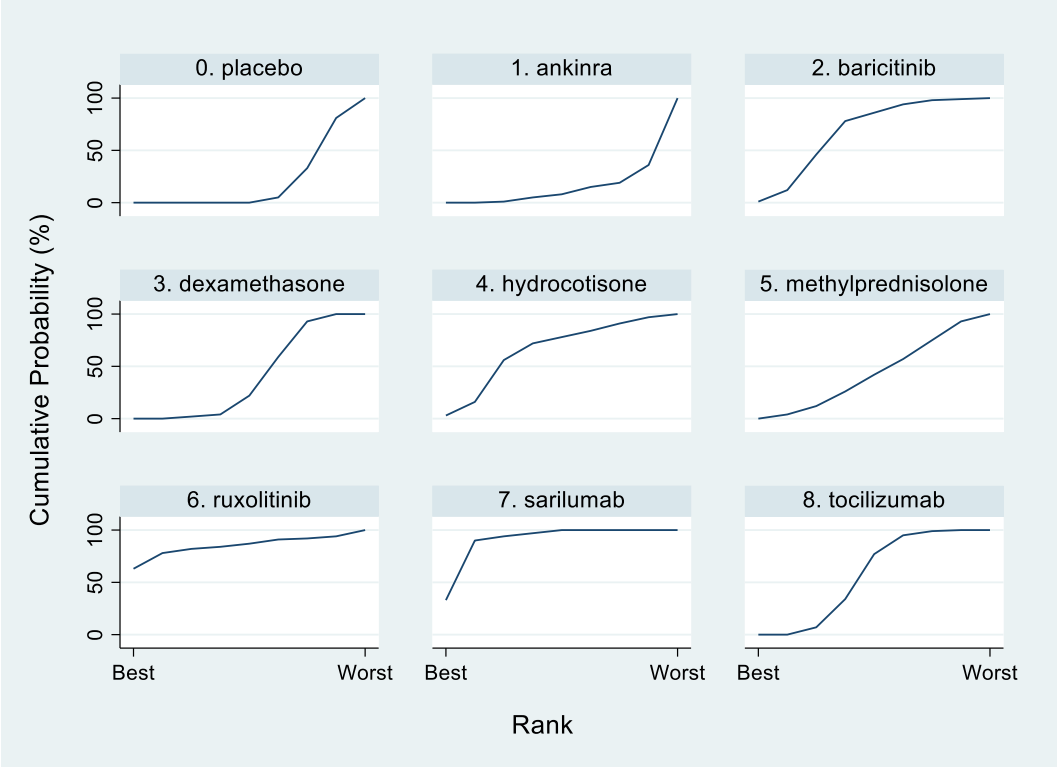


Figure S29: Cumulative Probability (%) of the best treatment in incidence of IMV with immunomodulators

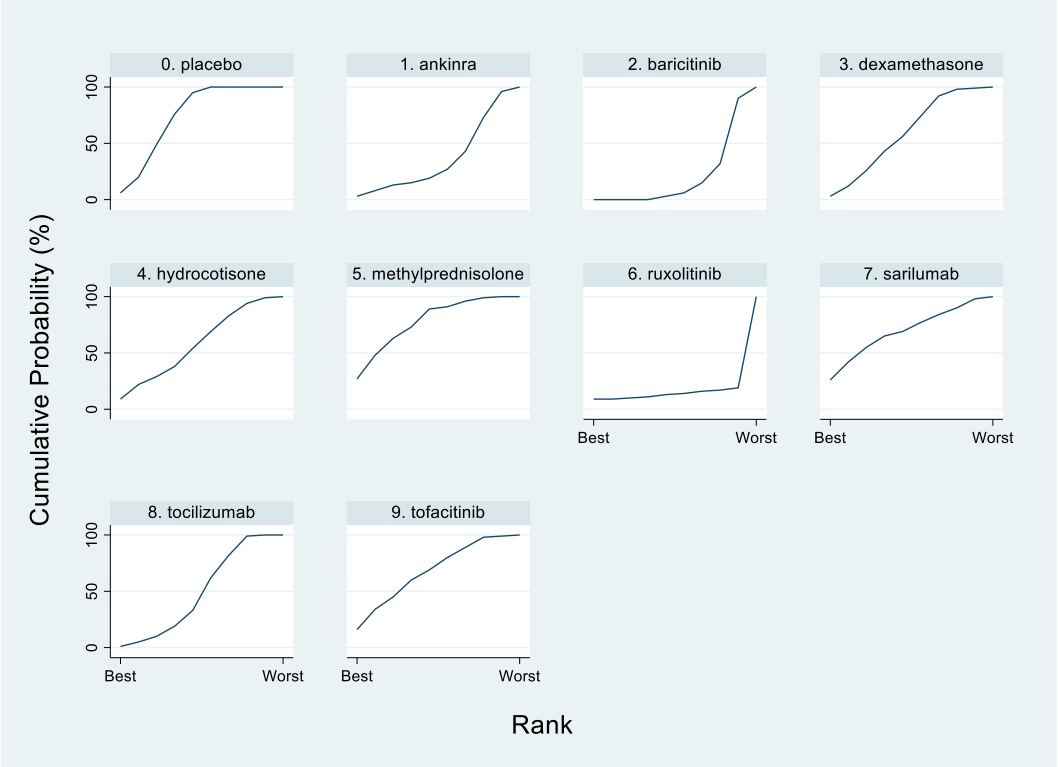


Figure S30: Cumulative Probability (%) of the best treatment in superimposed infection with immunomodulators

7. Evaluation of consistency

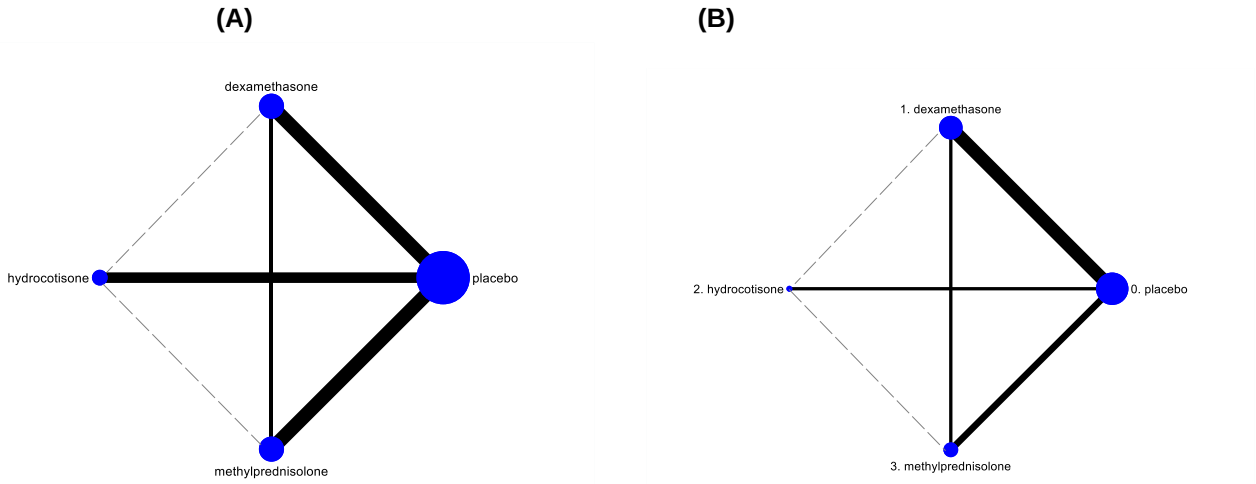


Figure S31: Network map of subgroup analysis in mortality rate and incidence of IMV among corticosteroid; mortality rate (A) Inconsistency testing: Chi-square = 2.76, *p*-value 0.096, incidence of IMV (B) Inconsistency testing: Chi-square = 3.17, *p*-value 0.075

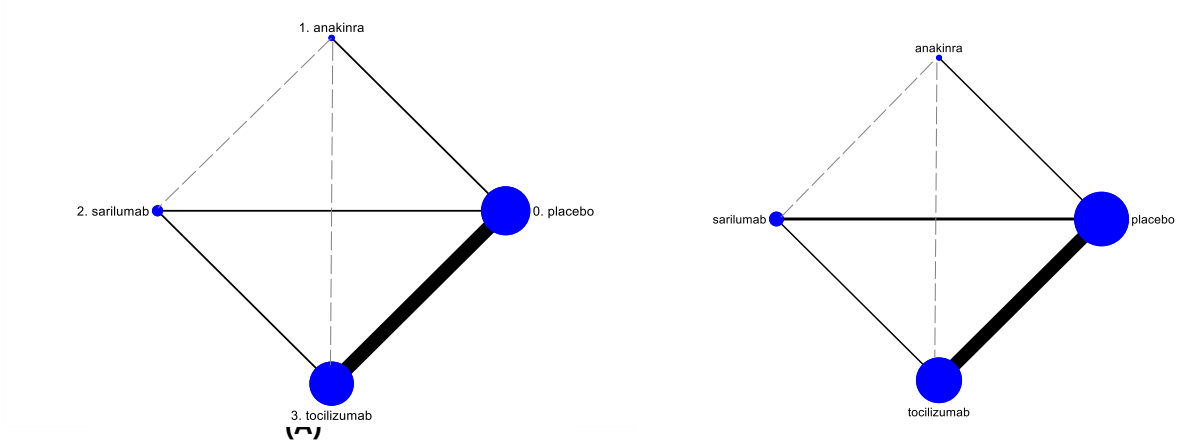
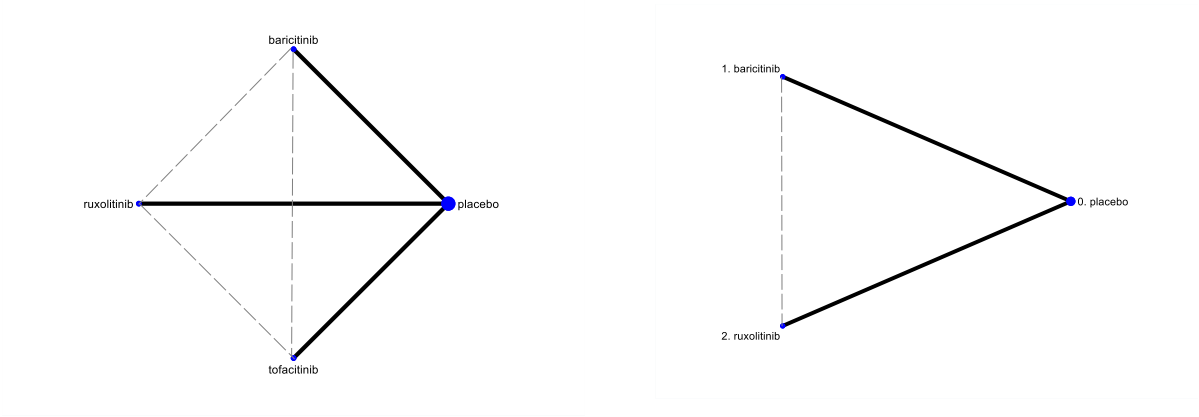
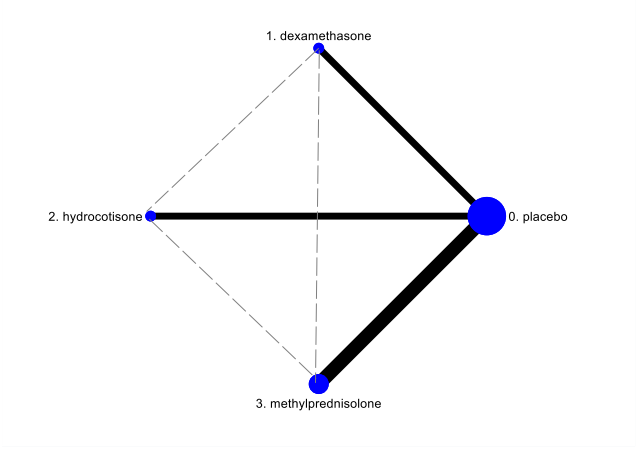


Figure S32: Network map of subgroup analysis in mortality rate and incidence of IMV among IL antagonists; mortality rate (A) Inconsistency testing: Chi-square =1.88, *p*-value 0.391, incidence of IMV (B) Inconsistency testing: Chi-square = 0.18, *p*-value 0.674

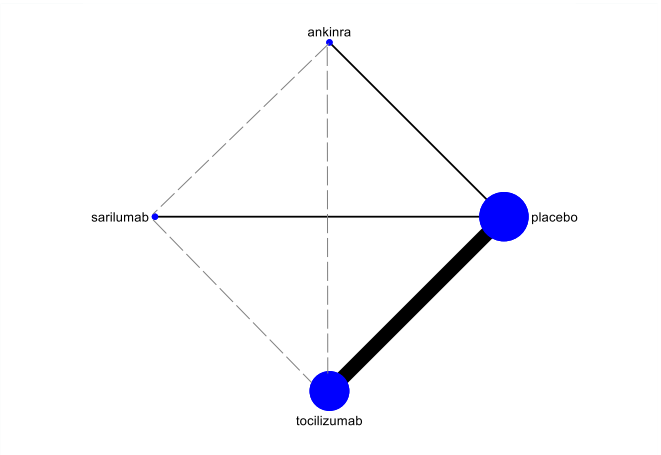


(A) **(B)**

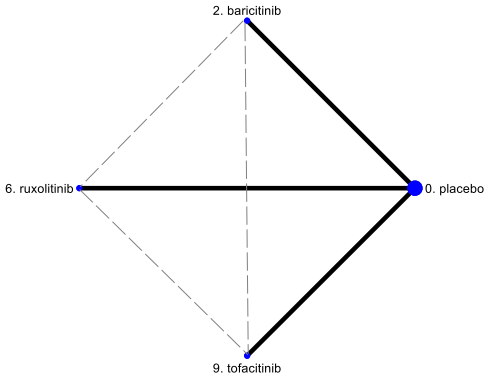
Figure S33: Network map of subgroup analysis in mortality rate and incidence of IMV among JAK inhibitors; mortality rate (A) Inconsistency testing: Chi-square =NA, incidence of IMV (B) Inconsistency testing: Chi-square =2.49, *p*-value 0.115



(A)



(B)



(C)

Figure S34: Network map of superimposed infection; corticosteroids (A) Inconsistency testing: Chi-square=0.05, *p*-value=0.825; IL antagonist (B) Inconsistency testing: Chi-square=1.45, *p*-value=0.228; JAK inhibitors (C) Inconsistency testing: Chi-square=0.00, *p*-value=0.997

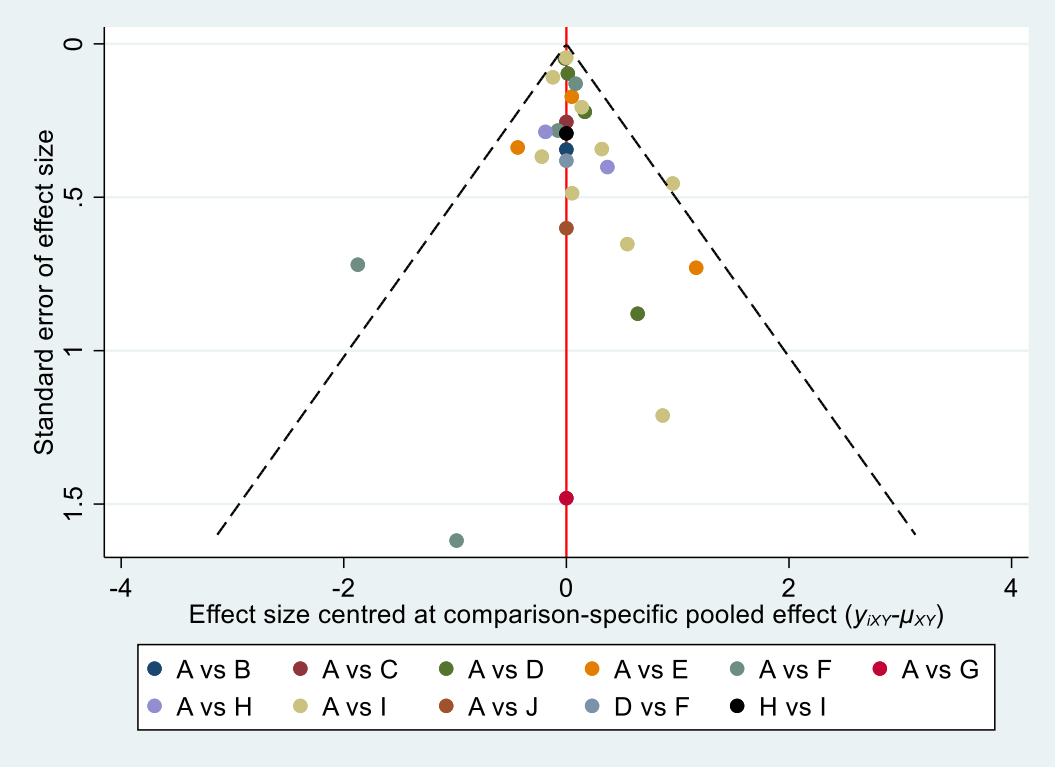


Figure S35: Comparison adjusted funnel plots of mortality rate
A="Placebo", B = "Anakinra", C= "Baricitinib", D= "Dexamethasone", E= "Hydrocortisone"
F= "Methylprednisolone", G= "Ruxolitinib", H= "Sarilumab, I= "Tocilizumab", J="Tofacitinib"

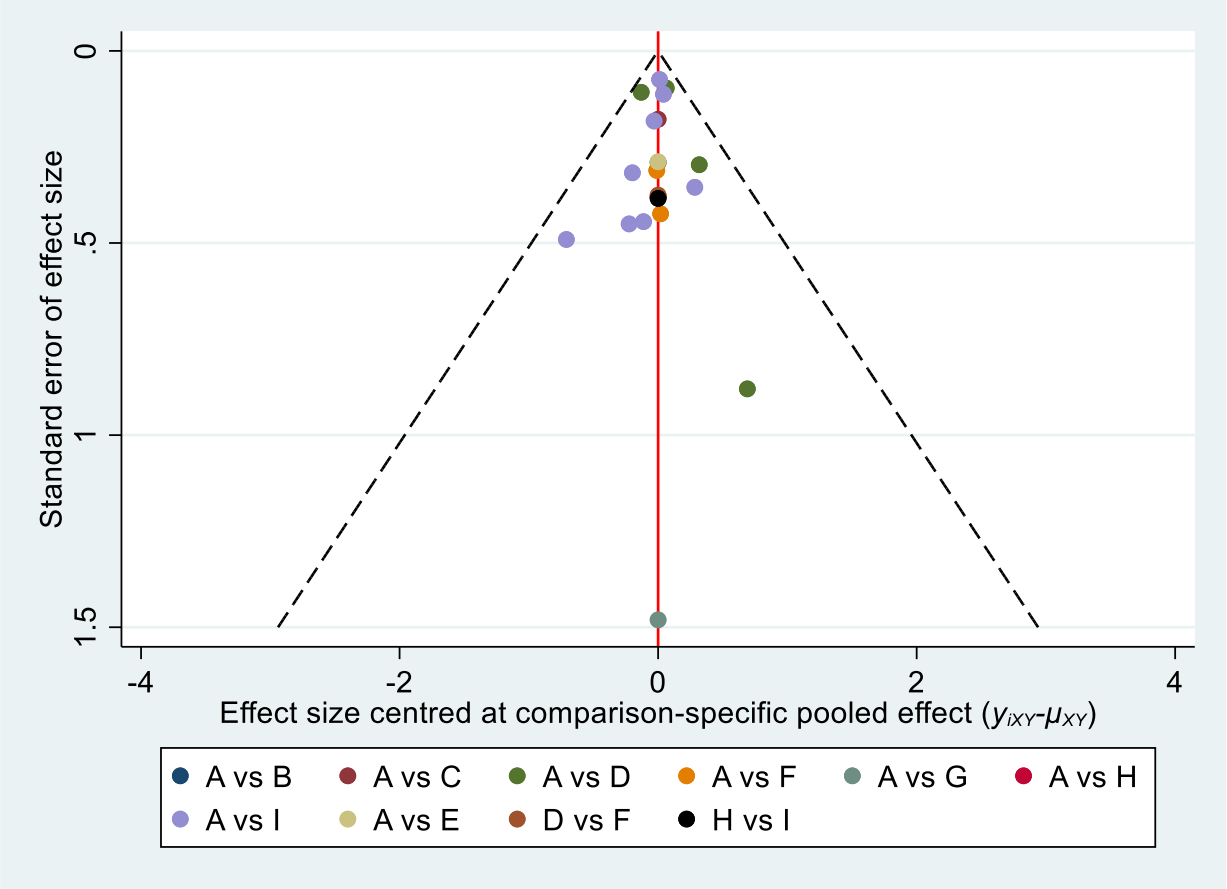


Figure S36: Comparison adjusted funnel plots of incidence of IMV
A = "Placebo" B = "Anakinra" C= "Baricitinib" D= "Dexamethasone" E= "Hydrocortisone"
F= "Methylprednisolone" G= "Ruxolitinib" H= "Sarilumab" I= "Tocilizumab" J="Tofacitinib"

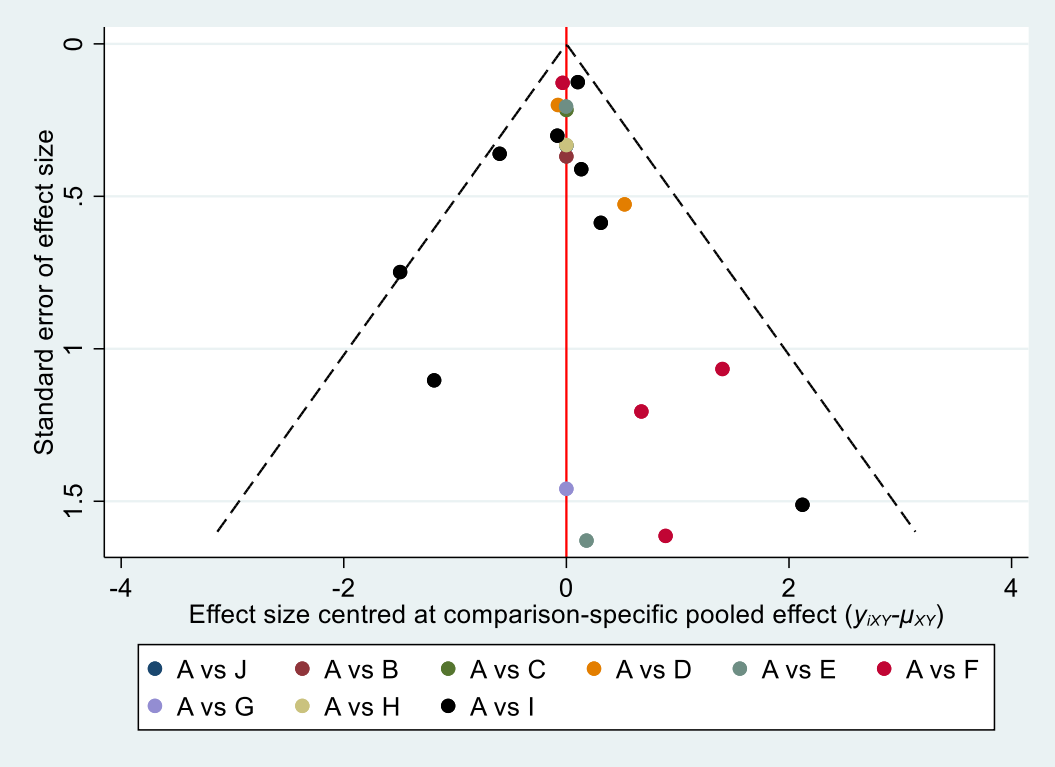


Figure S37: Comparison adjusted funnel plots of superimposed infection
A = "Placebo" B = "Anakinra" C= "Baricitinib" D= "Dexamethasone" E= "Hydrocortisone"
F= "Methylprednisolone" G= "Ruxolitinib" H= "Sarilumab" I= "Tocilizumab" J="Tofacitinib"