Supplementary Information

Supplementary Document S1. Search Strategy

PubMed Search

A. Search 1 HCQ

1. HCQ OR Hydroxychloroquine OR + chloroquine OR CQ

B.Search COVID-19

2. COVID19 OR Coronavirus OR novel coronavirus OR SARS-CoV-2 OR COVID OR COVID-19

C.Combine 2 AND 3

C.Apply filters

-January 2020 – May 30 2020

- Systematic reviews, reviews, meta-analysis, clinical trial, randomized controlled trials and trials

Search: **HCQ OR Hydroxychloroquine OR chloroquine OR CQ** Filters: **Clinical Study, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Reviews, in the last 1 year**

"HCQ"[All Fields] OR "hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields] OR "chloroquin"[All Fields] OR "chloroquine"[MeSH Terms] OR "chloroquine"[All Fields] OR "chloroquine s"[All Fields] OR "chloroquines"[All Fields] OR "crit q"[Journal] OR "cost qual"[Journal] OR "cost qual q j"[Journal] OR "commun q"[Journal] OR "caribb q"[Journal] OR "camb q healthc ethics"[Journal] OR "cq"[All Fields]

Translations

Hydroxychloroquine: "hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields]

chloroquine: "chloroquin"[All Fields] OR "chloroquine"[MeSH Terms] OR "chloroquine"[All Fields] OR "chloroquine's"[All Fields] OR "chloroquines"[All Fields]

CQ: "Crit Q"[Journal:__jid101653381] OR "Cost Qual"[Journal:__jid101126987] OR "Cost Qual Q J"[Journal:__jid9602863] OR "Commun Q"[Journal:__jid101580483] OR

"Caribb Q"[Journal:__jid101553695] OR "Camb Q Healthc Ethics"[Journal:__jid9208482] OR "cq"[All Fields]

Search: **COVID19 OR Coronavirus OR novel coronavirus OR SARS-CoV-2 OR COVID OR COVID-19** Filters: **Clinical Study, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Reviews, in the last 1 year**

((((((("covid 19"[Supplementary Concept] OR "covid 19"[All Fields]) OR "covid19"[All Fields]) OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields])) OR ((("novel"[All Fields] OR "novel s"[All Fields]) OR "novels"[All Fields]) AND (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields]))) OR (("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "sars cov 2"[All Fields])) OR "COVID"[All Fields]) OR (((((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication])))

Translations

COVID19: "COVID-19"[Supplementary Concept] OR "COVID-19"[All Fields] OR "covid19"[All Fields]

Coronavirus: "coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]

novel: "novel"[All Fields] OR "novel's"[All Fields] OR "novels"[All Fields]

coronavirus: "coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]

SARS-CoV-2: "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]

COVID-19: "COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR

"SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))

Scopus

TITLE-ABS-KEY(1. HCQ OR Hydroxychloroquine OR chloroquine OR CQ) AND (COVID19 OR Coronavirus OR novel coronavirus OR SARS-CoV-2 OR COVID OR COVID-19) AND (REVIEW OR SYSTEMATIC REVIEW OR META-ANALYSIS OR METAANALYSIS OR METAANALYSES OR RCT OR CLINICAL STUDY OR RANDOMIZED CONTROLLED TRIAL OR CLINICAL TRIAL) AND (LIMIT-TO (PUBYEAR,2020))

CINAHL

(HCQ OR Hydroxychloroquine OR chloroquine OR CQ) AND (COVID19 OR Coronavirus OR novel coronavirus OR SARS-CoV-2 OR COVID OR COVID-19) AND (REVIEW OR SYSTEMATIC REVIEW OR META-ANALYSIS OR METAANALYSIS OR METAANALYSES OR RCT OR CLINICAL STUDY OR RANDOMIZED CONTROLLED TRIAL OR CLINICAL TRIAL) AND (LIMIT-TO (PUBYEAR,2020))

Supplementary Table S2. Characteristics of excluded reviews

Study and year	Date of publications	Title	Objective	Design	Reason of exclusion
Cortegiani et al., 2020	10-March-2020	A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19	To summarize the evidence regarding chloroquine for the treatment of COVID-19.	Systematic review (SR)	Did not include completed clinical studies on COVID-19
Zhu et al., 2020	17-March-2020	Systematic Review of the Registered Clinical Trials of Coronavirus	To analyze the characteristics and existing problems of the registered clinical trials	Systematic review (SR)	Did not include completed clinical studies on COVID-19
Singh et al., 2020	22-March-2020	Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without	The efficacy of chloroquine and hydroxychloroquine, in the	Narrative review	Did not include completed

		diabetes: A systematic search and a narrative review with a special reference to India and other developing countries	treatment of participants with COVID19		clinical studies on COVID-19 Narrative review
Kapoor et al., 2020	30-March-2020	Role of Chloroquine and Hydroxychloroquine in the Treatment of COVID-19 Infection- A Systematic Literature Review	To summarize the available evidence regarding the role of chloroquine in treating coronavirus infection.	Systematic review (SR)	Did not include completed clinical studies on COVID-19
Gbinigie et al., 2020	7-April-2020	Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review	To establish the current evidence for the effectiveness of CQ and HCQ in treating COVID-19 infection	Narrative review	Narrative review Did not include completed clinical studies on COVID-19
Pastick et al, 2020	13-April-2020	Review: Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19)	A review of all the available evidence of safety and efficacy of HCQ & CQ	Narrative review	Narrative review
Shukla et al., 2020	28-April-2020	Chloroquine and hydroxychloroquine in the context of COVID-19	To present the available in vitro and clinical data for the role of chloroquine/ hydroxychloroquine in COVID-19 and attempts to put them into perspective, especially in relation to the different risks/benefits particular to each patient who may require treatment.	Narrative review	Narrative review
Hashem et al., 2020	29-April-2020	Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review	To comprehensively review previous studies which used CQ or HCQ as an antiviral treatment.	Narrative review	Narrative review
Patil et al., 2020	11-May-2020	A systematic review on use of aminoquinoline for the therapeutic management of COVID-19: Efficacy, safety and clinical trials	Provides a systematic review of mechanism of action, efficacy, and safety of chloroquine and hydroxychloroquine which are being used as therapeutic measure to cure COVID-19 infection.	Systematic review (SR)	Did not include completed clinical studies on COVID-19

Supplementary Table S3. Quality Assessment for Included Reviews

		Methodological Quality Assessment of the included studies Systematic Reviews - AMSTAR Items											
		1	2	3	4	5	6	7	8	9	10	11	Rating
Takla 2020		1	1	1	1	1	1	1	1	0	0	1	9
Yang 2020		1	1	1	1	0	1	1	1	1	1	1	10
Jankelson 2020		1	1	1	1	0	1	0	0	0	0	0	5
Shamshirian		1	0	1	1	1	1	1	1	1	1	1	10
Sarma 2020		1	1	1	1	0	0	1	1	1	1	1	9
Singh 2020		1	1	1	1	1	1	1	1	1	1	1	11
Suranagi 2020		1	1	1	1	0	1	1	1	0	0	0	7
Das 2020		1	0	1	1	1	1	1	1	0	0	1	9
Chowdhury 2020		1	1	1	1	1	1	1	1	0	0	1	9
Chacko 2020		1	1	1	1	1	1	1	1	1	0	1	10
Hernandez 2020		1	1	1	1	1	1	1	1	0	0	0	8
Rodrigo 2020		1	1	1	1	0	0	1	1	0	0	1	7
Wang 2020		1	1	0	1	1	1	0	0	0	0	1	6

Supplementary Table S4: Characteristics of Excluded Primary Studies

Study and date of publication	Country	Reviews	Reason for exclusion
Bessière et al., (1-May-2020)	France	8	Observational studies
Borba et al., (24-April-2020)	Brazil	6, 8, 11, 12	Comparison between two different doses of CQ (not SOC)
Carlucci et al., (8-May-2020)	USA	9	Observational study
Chorin et al., (1-May-2020)	USA and Italy	8	Observational study
Chorin et al., (3-April-2020)	USA	2, 4, 8, 9, 11, 12,	Observational study
Gao et al., (16-March-2020)	China	7, 13	No data presented
Gautret et al., (11-April-2020)	France	1, 2, 3, 4, 8, 9, 10, 12, 13	Observational study
Geleris et al., (7-May-2020)	USA	4, 7, 8, 9, 10, 11	Observational study
Huang et al., (4-May-2020)	China	8	Observational study
Ip et al., (25-May-2020)	USA	11	Observational study
Jiang et al., (12-July-2020)??	China	13	No full text - abstract only
Kim et al., (18-May-2020)	South Korea	9, 11	Observational study
Lee et al., (8-May-2020)	South Korea	9	Observational study
Magnagnoli et al., (23-April-2020)	USA	3, 4, 5, 7, 8, 9, 10, 11,	Observational study
Mallat et al., (2-May-2020)	UAE	7, 8, 9, 11	Observational study
Mehra et al., (22-May-2020)	USA	9, 11	Observational study which was retracted
Membrillo et al., (9-May-2020)	Spain	8, 9	Observational study
Mercuro et al., (1-May-2020)	USA	8, 10, 11	Observational study
Million et al., (5-May-2020)	France	1, 3, 9, 10, 11, 12, 13	Observational study
Molina et al., (17-April-2020)	France	1, 3, 4, 8, 9, 10, 12, 13	No control group
Okour et al., (13-May-2020)	USA	9	Duplicate data
Perinel et al., (7-April-2020)	France	12	Observational study
Ramireddy et al., (25-April-2020)	USA	8, 9, 10, 11	Case series
Raoult et al., (11-April-2020)	France	8	Case series
Regina et al., (12-May-2020)	Switzerland	9	Observational study

Rosenberg et al., (11-May-2020)	USA	7, 9, 11	Observational study
Saleh et al., (29-April-2020)	USA	8, 9, 11	Observational study
Singh et al., (19-May-2020)	USA	9, 11	Observational study
Van den Broek et al., (29-April-2020)	Netherlands	8	Observational study
Yu et al., (1-May-2020)	China	7, 8	Observational study
Yu et al., (15-May-2020)	China	11	Observational study
Esper et al.,	Brazil	None	COVID not confirmed by PCR
Barbosa et al, (15-April-2020)	Brazil	None	1. Design not clear 2. Both groups of participants received HCQ
Mahevas et al, (14-April-2020)	France	None	Observational study
Skipper et al, (16-July-2020)	Canada	None	Covid-19 not confirmed with PCR
Cavalcanti et al, 23-July-2020)	Brazil	None	Some participants had suspected Covid-19 not confirmed by PCR

Supplementary Table S5. Assessment of risk of bias in included experimental studies

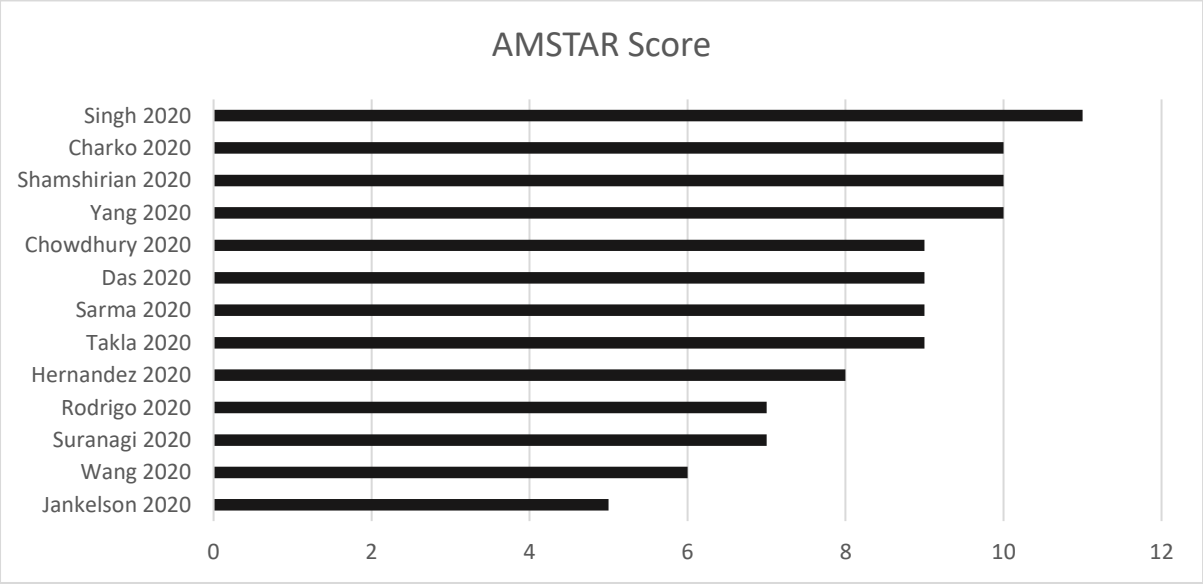
Safeguard item	S1	S2	S3	S4	S5	S6	S7	S8
	Chen Jun et al. 2020	Chen Z et al. 2020	Gautret et al. 2020	Tang et al. 2020	Huang et al 2020	Horby et al. 2020	Oriol et al. 2020	Chen P.C. et al 2020
1. Data collected after the start of the study was not used to exclude participants or to select them into the analysis	1	1	1	1	1	1	1	1

2. Participants in all comparison groups were from the same population and timeframe	1	1	0	1	1	1	1	1
3. Inclusion/ exclusion criteria specified and applied equally to all groups prior to group assignment	1	1	0	1	1	1	1	1
4. Any attrition (or exclusions after entry) is less than 20% of total participant numbers	1	1	0	1	1	1	1	1
5. Missing data is less than 20%	1	1	1	1	1	1	1	1
6. Analysis accounted for missing data	1	1	0	1	1	1	1	1
7. Treatment deviations or non-compliance/ non-adherence were less than 20%	1	1	1	1	1	1	1	1
8. Analysis accounted for treatment deviations/ withdrawals	1	1	0	1	1	1	1	1
9. Procedures for data collection of covariates were reliable and the same for all participants	1	1	0	1	1	1	1	1
10. Outcome was objectively defined	1	1	1	1	1	1	1	1
11. Analyst was blinded	0	1	0	1	1	1	0	0
12. Outcome assessor(s) were blinded	0	1	0	0	0	0	1	0
13. Participants were blinded	0	1	0	0	0	0	0	0
14. Caregivers were blinded	0	1	0	0	0	1	0	0
15. Exposures/ interventions were objectively defined	1	1	1	1	1	1	1	1
16. Care was delivered equally to all participants	1	1	0	1	1	1	1	1
17. Cointerventions that could impact the outcome were comparable between groups or avoided	1	1	0	1	1	1	1	1
18. Control and active interventions/ exposures are sufficiently distinct	1	1	1	1	1	1	1	1
19. Exposure/intervention definition consistently applied to all participants	1	1	1	1	1	1	1	1
20. Outcome definition consistently applied to all participants	1	1	1	1	1	1	1	1
21. The time period between exposure and outcome is similar across patients and between groups or the analyses adjust for different lengths of follow-up of patients	1	1	1	1	1	1	1	1
22. Design features in place that account for confounding	1	1	0	1	1	1	1	1
23. Analytic strategies in place for key confounders	0	0	0	1	0.5	1	0	1
24. Key baseline characteristics / prognostic indicators for the study were comparable across groups	1	1	0	1	0.5	1	1	1
25. Allocation procedure was adequately concealed	1	0	0	0	0	1	1	0

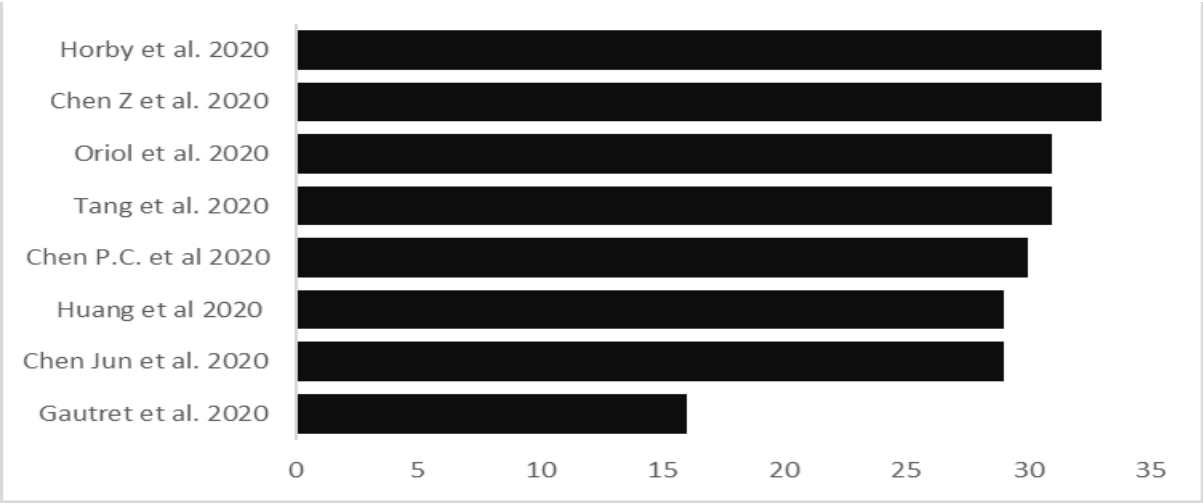
26. Conflict of interests were declared and absent	0	1	1	1	1	1	1	1
27. Participants were randomly allocated to groups with adequate randomisation process	1	1	0	1	0.5	1	1	1
28. Analytic method was justified by study design	1	1	0	1	0.5	1	1	1
29. Computation errors or contradictions were absent	1	1	1	1	1	1	1	1
30. There was no data dredging or selective reporting of the outcome	1	1	1	1	1	1	1	1
31. All subjects were selected prior to intervention/exposure and evaluated prospectively	1	1	0	1	1	1	1	1
32. Carry-over or refractory effects were avoided or considered in the design of the study or were not relevant	1	1	1	1	1	1	1	1
33. The intervention/ exposure period was long enough to have influenced the study outcome	1	1	1	1	1	1	1	1
34. Dose of intervention/ exposure was sufficient to influence the outcome	1	1	1	1	1	1	1	1
35. Length of follow-up was not too long or too short in relation to the outcome assessment	1	1	1	1	1	1	1	1
Summary count of safeguard items	29	33	16	31	29	33	31	30

Supplementary Fig. 1: Quality Assessment

A: AMSTAR Assessment for Included Reviews



B: MASTER for experimental studies



Supplementary Table S6. Outcomes of Included reviews

Author, date & design	Drug	Mortality	ICU, intubation	Virological Cure	Disease worsening	Adverse events
Shamshirian (28 May 2020) SRMA	HCQ	No significant difference in mortality (RR: 1.13, 95%CI 0.71 - 1.80)	Intubation - no significant differences HCQ - OR: 2.11, 95% CI, 0.31-14.03, I^2 =75.6%)	HCQ - No effectiveness (RR: 0.96, 95% CI, 0.76-1.22), (RD: 0.00, 95% CI, - 0.18-0.18)	No considerable disease exacerbation difference HCQ (RR: 0.59, 95% CI, 0.04-7.79)	Higher risk of events HCQ (OR: 4.01, 95% CI, 1.17-13.84
	HCQ+AZI	Higher mortality in HCQ+AZI (RR 2.46, 95% CI 1.4-4.3)	-	HCQ +AZI - No significant difference with control (RR 2.15, 95%CI 0.31 - 14.77)		
Chacko (20 May 2020) SRMA	HCQ	No significant difference in mortality (OR: 1.41, 95% CI: 0.76 – 2.62)	-	No significant different between the HCQ and control groups (OR: 1.13, CI: 0.26–5.01; p = 0.87)	No difference in clinical worsening (OR 1.1, 95% CI: 0.6–2.02).	Higher risk of adverse events in HCQ arm (OR: 4.1, CI: 1.42 – 11.88; p = 0.009)
Yang (14 May 2020) SRMA	HCQ+AZI	Increased mortality in HCQ +/- AZI (OR 2.5 (95% CI 1.4 - 4.5)	-	No difference between HCQ alone vs. control (OR = 1.74 95% CI 0.51 - 5.91)	No significant difference between HCQ alone versus Control (OR = 1.37, 95% CI 0.09 - 21.97)	
	HCQ	HCQ alone was associated with increased mortality (OR 2.98 (95%CI 1.6 – 5.7)	-	No difference between HCQ with or without AZI vs control (OR = 1.95, 95% CI 0.19 - 19.73)	No difference between HCQ+AZI versus Control (OR = 1.00, 95% CI 0.27 – 3.75)	
Singh (7 May 2020) SRMA	HCQ	Higher mortality in HCQ arm (RR, 2.17; 95% 1.32 to 3.57)	No difference in transfer to the ICU (20.2 vs 22.1%; RR 0.91, 0.47–1.80)	No benefit with HCQ (RR, 1.05; 95% CI, 0.79 to 1.38; p=0.74)	Improvement in pneumonia with HCQ (80.6 vs 54.8%, p=0.048), chest CT with HCQ (61.3 vs 16.1%)	1 study reported no adverse events. 1 reported no cardiac toxicity although it did not report how they assessed this. 7 other studies reported moderate to large increases in occurrence of adverse events

Sarma (13 April 2020) SRMA	HCQ	No difference in death or clinical worsening between treatment and control group (OR, 1.37, 95% CI, 0.09-21.97)	-	No difference in virological cure 2.37; 95% CI, [0.13-44.53]	2 studies found shorter time for body temperature normalization and the number of cough days. 3 studies reported no difference in clinical worsening OR, 1.37 (95% CI, 0.09-21.97).	Reported adverse events but No significant difference on all studies (OR, 2.19; 95% CI, [0.59-8.18])
	HCQ+AZI		-	Higher virological cure in 1 study while others reported moderate effect of the combination	-	Reported adverse events and QTc prolongation. 1 study found no signs of cardiac toxicity
Wang (1 June 2020) SR	HCQ-AZI	One study had no deaths, second study had lower mortality in HCQ-AZ group, but was statistically non-significant.	Marginally lower percentage in HCQ were transferred to ICU but differences were not significant	-	HCQ improved pneumonia: 80.6% vs 54.8%; (1 study), CQ reduced exacerbation of pneumonia, improved lung imaging, promoted virological clearance, and shortened disease course. Poor clinical outcome significantly associated with greater severity (OR 10.05) in one study.	More adverse events in HCQ and CQ than control like QTc interval prolongation. 2 studies reported no serious adverse events
Takla (30 May 2020) SR	CQ/HCQ	60% of studies reported no difference on mortality, 30% reported higher mortality in the HCQ group, 10% reported reduced mortality in HCQ group	No difference in need for mechanical ventilation, and transfer to an intensive care unit	67% of studies showed significant higher viral clearance, 33% no difference	-	A higher probability of adverse events in 82% of the studies
Das (28 May 2020) SR	HCQ	Reported no significant effect of HCQ on death	Reported no significant effect of HCQ on intubation	5 studies (1269 participants) reported good virological and clinical outcomes in the HCQ arm 5 studies (808 participants) showed negative or equivocal results	Reported “good virological and clinical outcomes in the HCQ arm”	4 studies (1207 participants) reported HCQ as safe with mild adverse events. 2 studies (101 participants) reported QT prolongation associated with HCQ treatment 5 studies (859 participants) reported HCQ associated with serious adverse events

Hernandez (27 May 2020) SR	HCQ CQ	1 study reported no deaths, 2 studies found decreases in mortality, 2 found no change in mortality, 4 found moderate to large increases in mortality	2 studies reported CQ/HCQ had increased need for ICU admission, intubation and/ mechanical ventilation. 3 studies reported no effect of CQ/HCQ on ICU, intubation or need for mechanical ventilation	2 studies reported moderate to large increases in virologic clearance for the CQ/HCQ arm. 3 studies found no difference or effect. 1 study found large decreases of virologic clearance in the CQ/HCQ arm	1 study reported increased progression of the disease (progressing to need respiratory support), 1 study reported fewer participants in HCQ had disease progression and others had 1.0- and 1.1-day reduction in fever and cough. 3 studies found no effect.	6 studies reported modest to large increase in adverse events and QTc prolongation in HCQ alone and HCQ+AZI group. 1 study reported both in adverse events and 1 study reported no difference and insufficient evidence of risk of adverse events
Rodrigo (16 May 2020) SR	CQ HCQ	Mortality higher in higher dose of CQ arm (15% vs 39%, p=0.03)	-	No statistically significant difference by day 14 of illness (10/10 in CQ group vs. 11/12 in Lopinavir). The other study terminated early	-	-
				3 studies reported no statistical difference in clearance of viremia 1 study reported statistical significance (70% in HCQ group vs. 12.5% in placebo group, p=0.001)	-	-
Suranagi (13 May 2020) SR	HCQ	HCQ increased risk of death	1 study reported intubations, but No significant effect of HCQ on risk of either mechanical ventilation or intubation	3 studies reported HCQ reduced viral load and effect reinforced by Azithromycin. 1 study reported no effect on viral clearance	HCQ reduced duration of illness and improved pneumonia and pulmonary image changes	-
Chowdhury (28 April 2020) SR	CQ HCQ	-	-	Better virological clearance in in the CQ/HCQ arm than control (standard care/Lopinavir/ritonavir arm).	Improved pneumonia per chest CT and reduced progression to severe illness. 2 studies reported no significant different in alleviating or increasing severity of disease	Adverse effects CQ arm but not in Lopinavir/ritonavir arm, (n= 1 study), HCQ arm (Adverse events: 30% vs 8.8 %). 1 study found some minor adverse events in HCQ arm. 1 study sound no significant difference on adverse events between groups.
Jankelson (31 May 2020) SR	CQ/HCQ	-	-	-	-	QTc prolongation in 40 participants Ventricular arrythmia reported in 2 participants, first degree AV

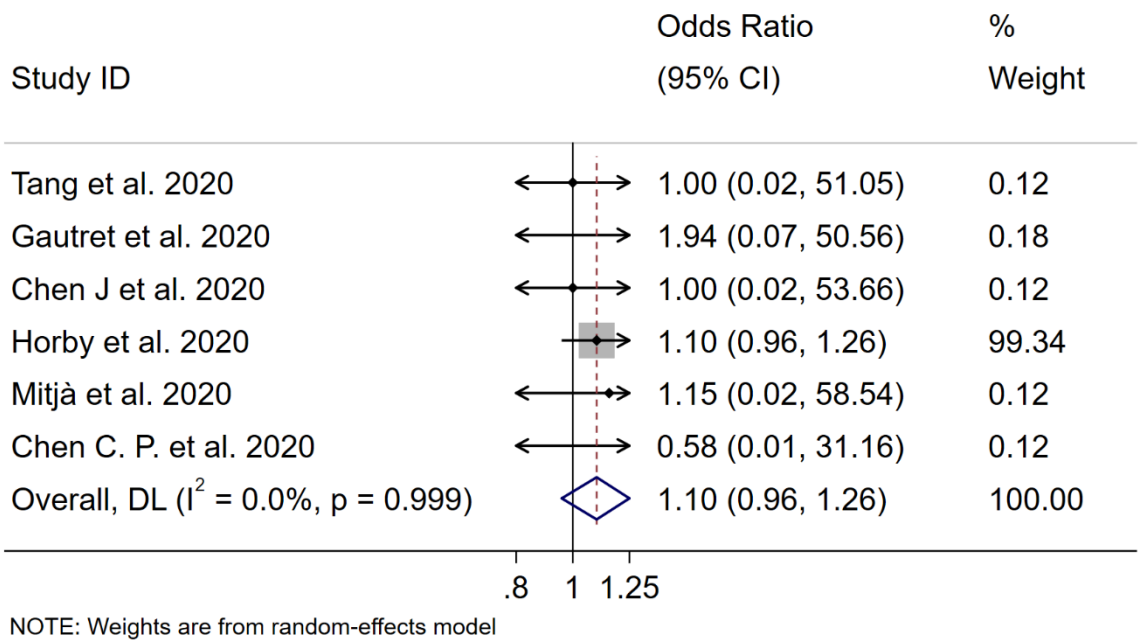
						block developed in 1 and LBBB in another patient

Supplementary Table S7. Limitations and conclusions from reviews

Author name & date	Review Conclusion	Limitations of the review
Shamshirian (28 May 2020)	No clinical benefits regarding HCQ treatment with/without azithromycin for COVID-19 participants	Few included studies (6 studies) with small sample sizes in the meta-analysis
Chacko (20 May 2020)	Meta-analysis does not support the treatment of COVID-19 infection with HCQ	Small studies, small sample sizes, different outcome measurements and endpoints measured at different intervals
Yang (14 May 2020)	HCQ with or without AZI are beneficial for treatment of COVID-19 participants, but may also have higher mortality	Few included studies with small sample sizes.
Singh (7 May 2020)	While no benefit on viral clearance demonstrated by HCQ, a significant 2-fold increase in mortality with the HCQ warrants its use, if at all, with extreme caution.	Small number of participants overall, combining the results of RCT with other non-randomized studies.
Sarma (13 April 2020)	Treatment with HCQ may result in reducing radiological progression with comparable safety	Few studies, small sample sizes, and several studies without controls
Wang (1 June 2020)	No solid evidence supporting the efficacy and safety of HCQ and CQ as a treatment for COVID-19 with or without azithromycin	Search not comprehensive, only searched 2 English databases, few studies with small sample sizes
Jankelson (31 May 2020)	Compelling evidence that CQ & HCQ induce significant QTc prolongation and can be potential risk factors of arrythmia.	Small number of studies, small sample sizes. Efficacy outcomes not part of scope of review
Takla (30 May 2020)	Relative to standard in-hospital management of symptoms, the use of CQ and HCQ to treat hospitalised COVID-19 has likely been unsafe	Data synthesize by describing percentage of studies with outcome not optimal
Das (28 May 2020)	Inconclusive evidence of HCQ efficacy and safety	Lack of data from well-designed RCTs
Hernandez (27 May 2020)	Insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19.	There were few controlled studies, and control for confounding was inadequate in observational studies.
Rodrigo (16 May 2020)	Role of CQ & HCQ in covid19 is yet unclear and needs to be assessed by well-designed double-blind clinical trails	Small number of studies that were not similar hence a meta-analysis was not performed
Suranagi (13 May 2020)	Current evidence stands inadequate to support the use of hydroxychloroquine in pharmacotherapy of COVID-19	Small studies with weak study designs
Chowdhury (28 April 2020)	No enough data to support the routine use of either HCQ or CQ for treatment of COVID19	Narrative review. Indiscriminate inclusion criteria

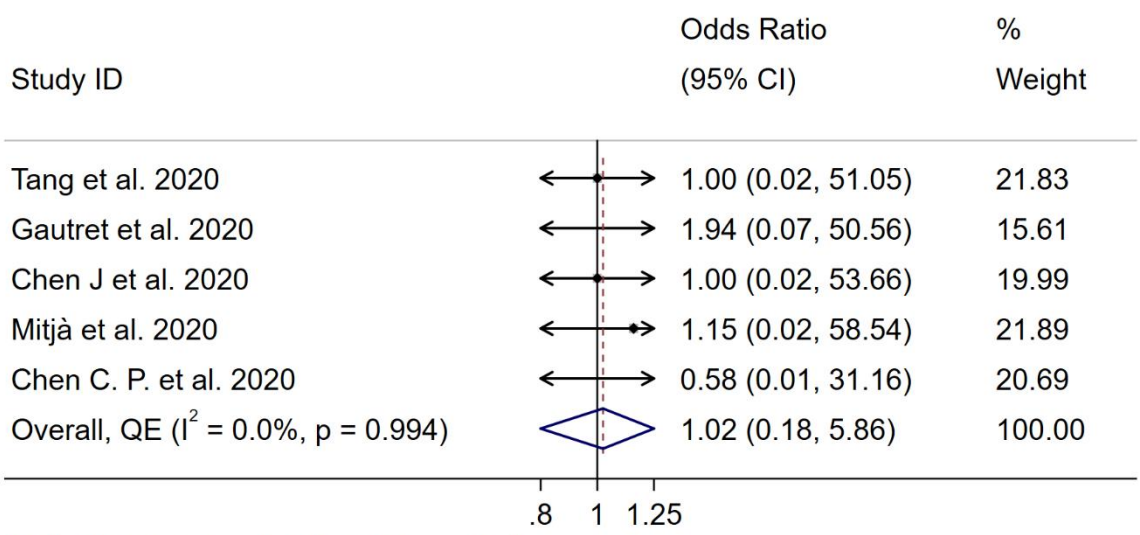
Random Effects Models

Mortality – random effects model

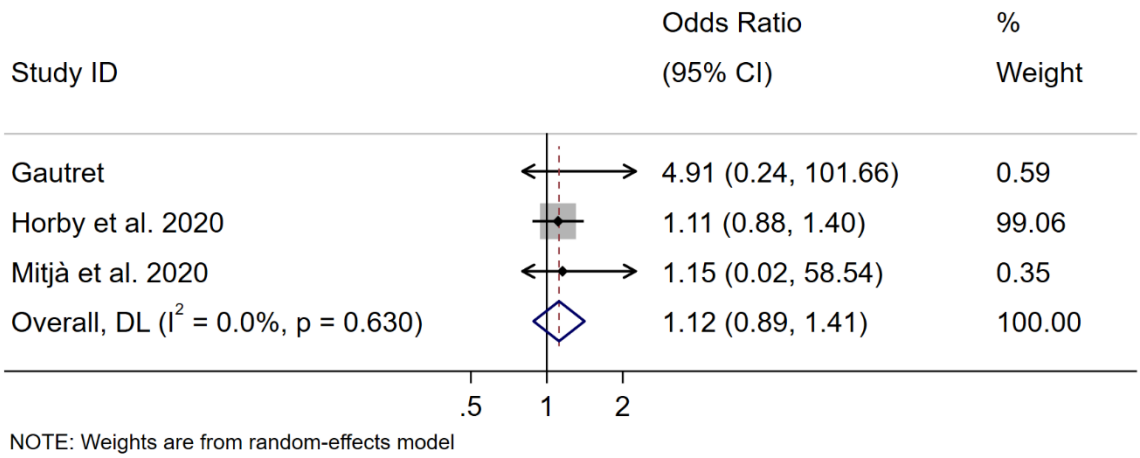


NOTE: Weights are from random-effects model

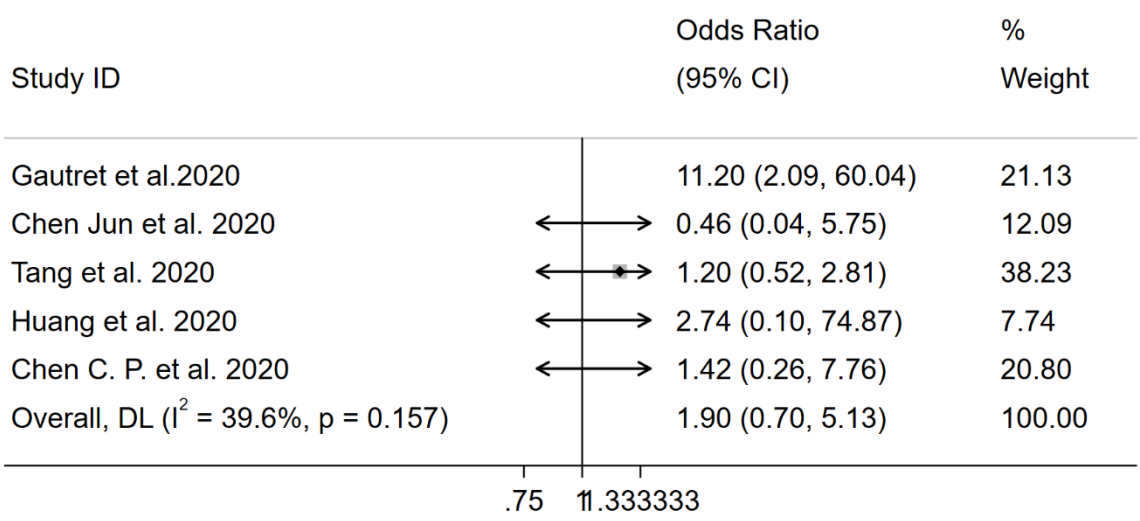
Mortality – excluding Horby et al. (2020)



ICU – random effects model

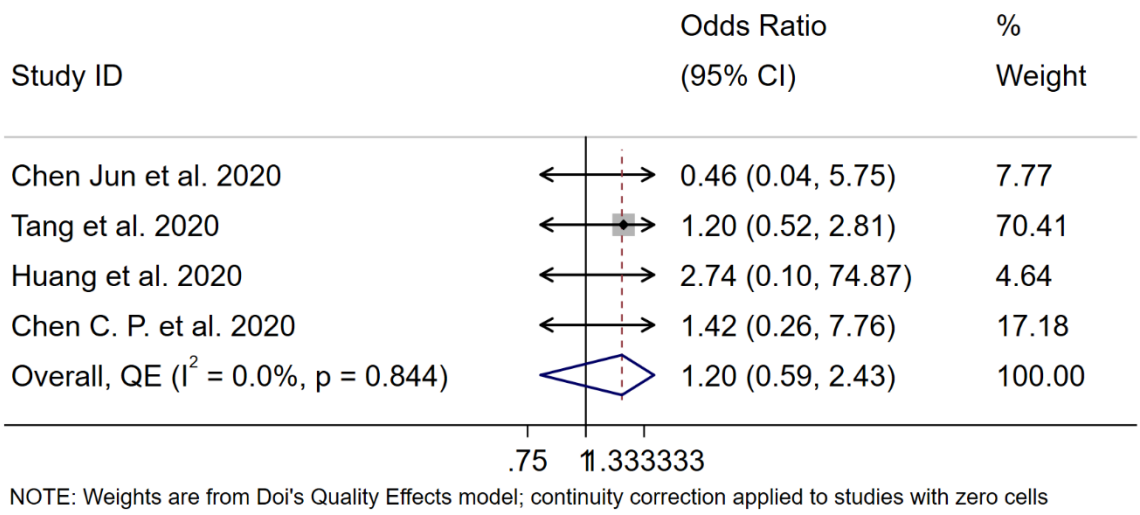


Virological cure – random effects



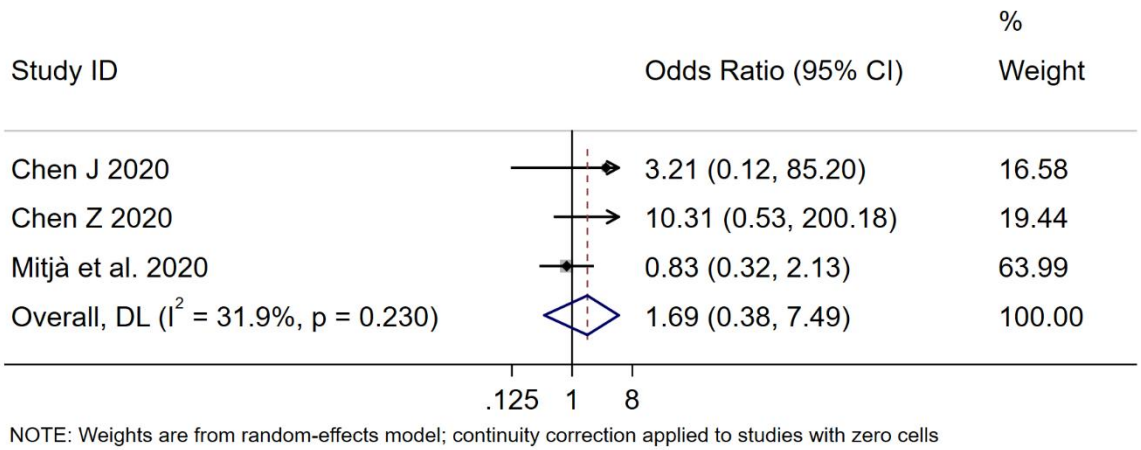
NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

Virological cure – without Gautret

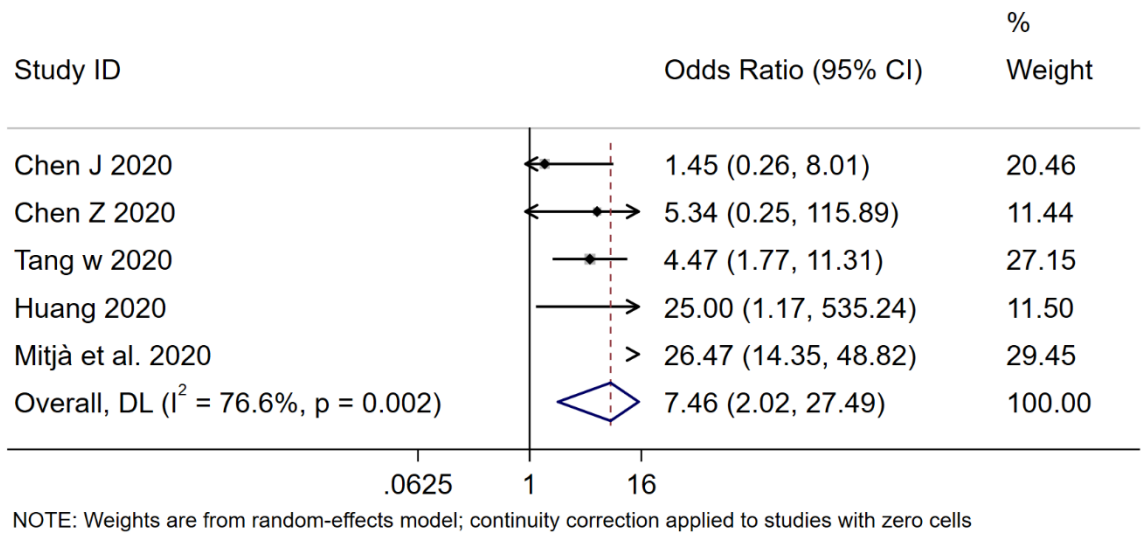


NOTE: Weights are from Doi's Quality Effects model; continuity correction applied to studies with zero cells

Disease worsening - random effects model

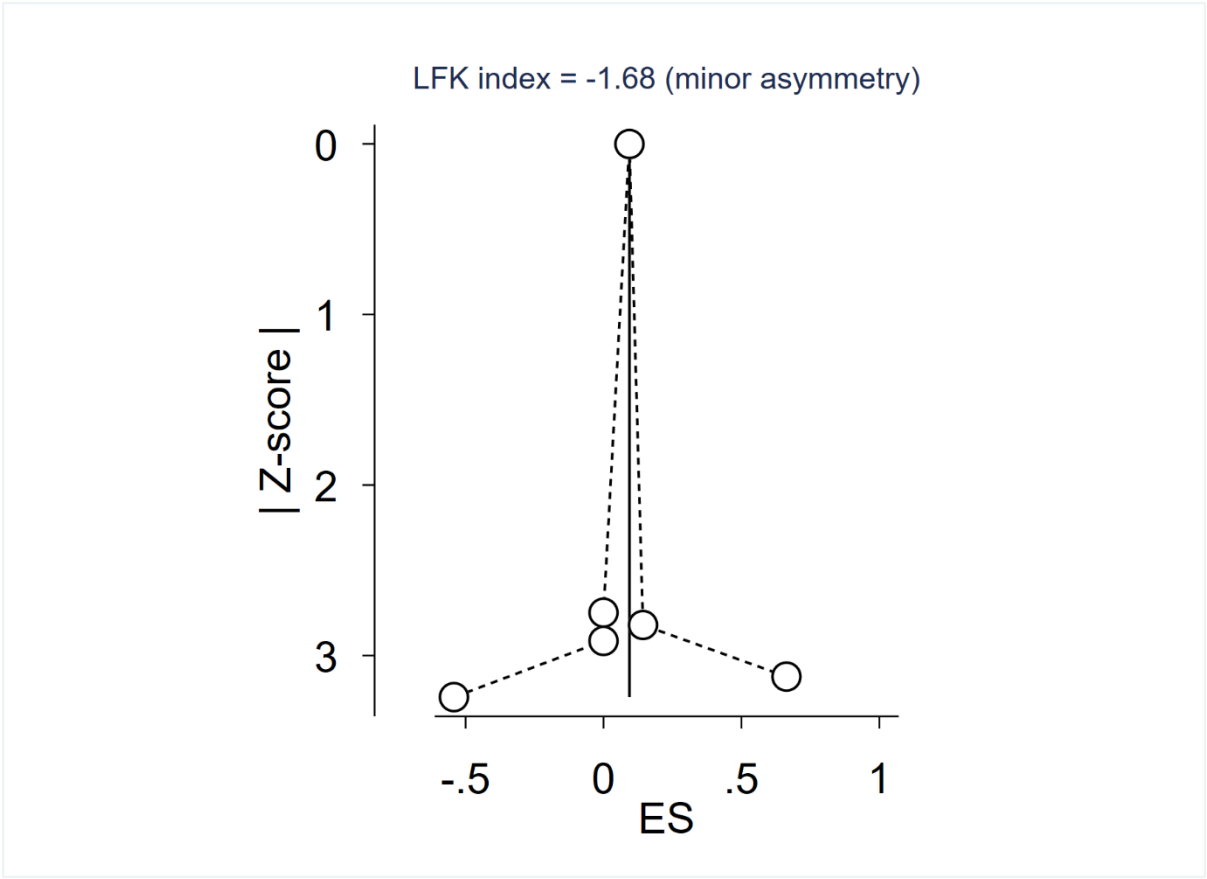


Adverse events – random effects

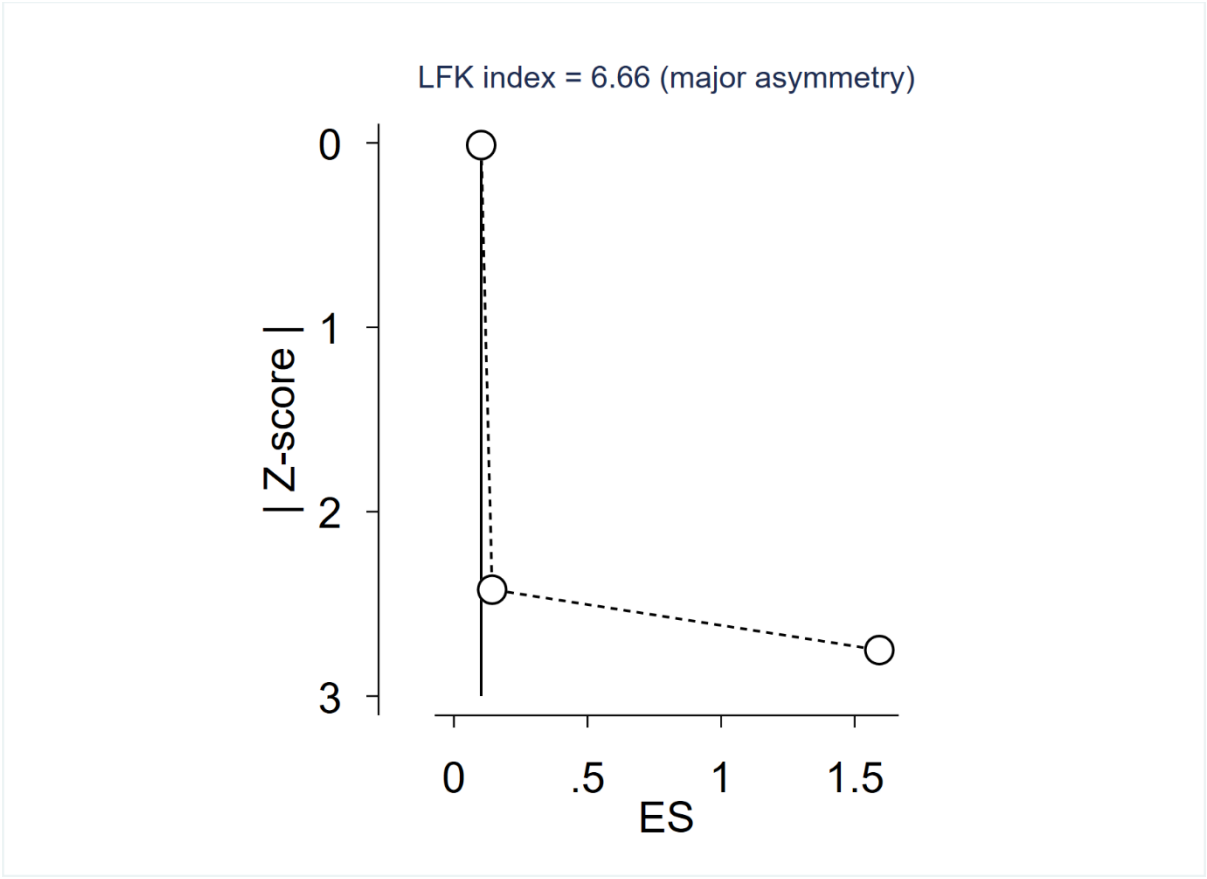


Supplementary Fig. 3: Doi Plots and LFK Index

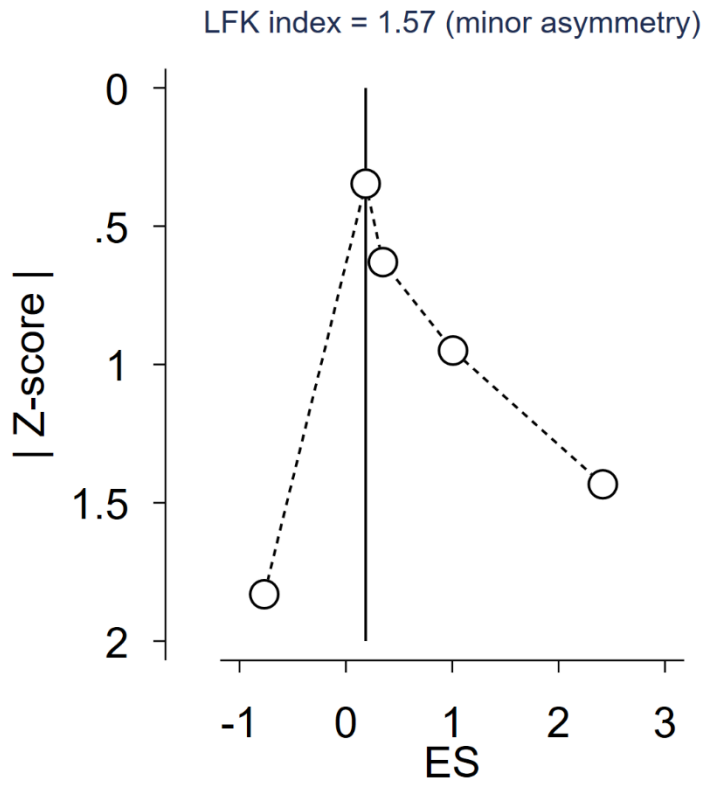
3A: Mortality



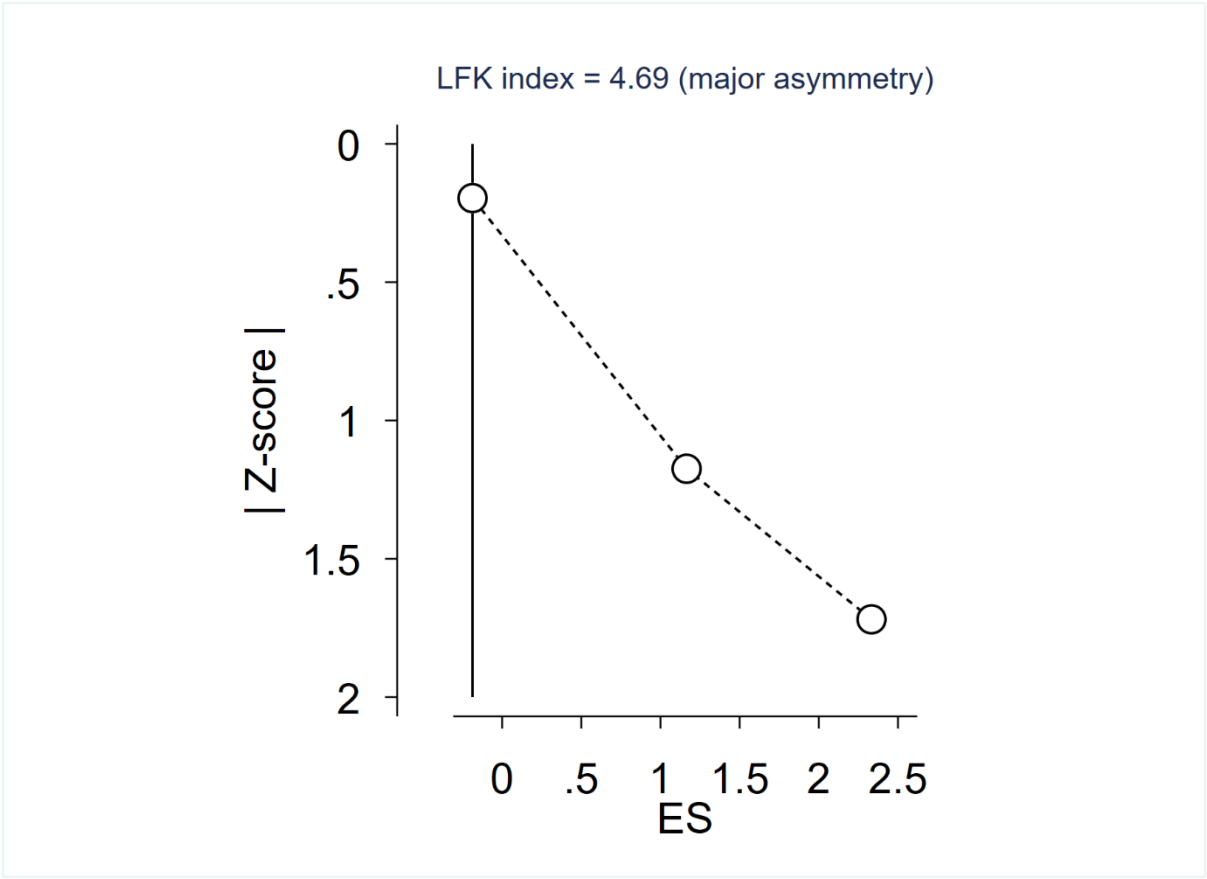
3B: ICU Admission



3C: Virological cure



3D: Disease Exacerbation



3E: Adverse events