REVIEW

Hydroxychloroquine in the treatment of coronavirus disease 2019: Rapid updated systematic review and meta-analysis

Tejpal Gupta[1] 🄳 | Prafulla Thakkar[2] | Babusha Kalra[1] | Sadhana Kannan[3]

[1]Department of Radiation Oncology, Clinical Research Centre, Advanced Centre for Treatment Research & Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Kharghar, Navi Mumbai, India

[2]Division of Internal Medicine, Clinical Research Centre, Advanced Centre for Treatment Research & Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Kharghar, Navi Mumbai, India

[3]Clinical Research Secretariat, Clinical Research Centre, Advanced Centre for Treatment Research & Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Kharghar, Navi Mumbai, India

Correspondence
Tejpal Gupta, Department of Radiation Oncology, Clinical Research Centre, Advanced Centre for Treatment Research & Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Kharghar 410210, Navi Mumbai, India.
Email: tejpalgupta@rediffmail.com

Summary

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 continues to grow and spread throughout the world since being declared a pandemic. Despite extensive scientific research globally including repurposing of several existing drugs, there is no effective or proven therapy for this enigmatic disease which is still largely managed empirically This systematic review evaluated the role of hydroxychloroquine (HCQ) in the treatment of COVID-19 infection and was conducted using Cochrane methodology for systematic reviews of interventional studies including risk of bias assessment and grading of the quality of evidence. Only prospective clinical trials randomly assigning COVID-19 patients to HCQ plus standard of care therapy (test arm) versus placebo/standard of care (control arm) were included. Data were pooled using the random-effects model and expressed as risk ratio (RR) with 95% confidence interval (CI). A total of 10,492 patients from 19 randomised controlled trials were included. The use of HCQ was not associated with higher rates of clinical improvement (RR = 1.00, 95% CI: 0.96–1.03, $p = 0.79$) or reduction in all-cause mortality by Day14 (RR = 1.07, 95% CI: 0.97–1.19, $p = 0.19$) or Day28 (RR = 1.08, 95% CI: 0.99–1.19, $p = 0.09$) compared to placebo/standard of care. There was no significant difference in serious adverse events between the two arms (RR = 1.01, 95% CI: 0.85–1.19, $p = 0.95$). There is low-to-moderate certainty evidence that HCQ therapy is generally safe but does not reduce mortality or enhance recovery in patients with COVID-19 infection.

KEYWORDS
coronavirus, hydroxychloroquine, toxicity

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to grow and spread throughout the world since being declared a pandemic[1,2] by the World Health Organization (WHO) in March 2020 with over 180 million confirmed cases and nearly 4 million deaths by the time of this report. Although lungs remain the primary target organ of SARS-CoV-2, the disease can affect multiple organ systems and elicit highly variable inflammatory response in the host with

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resultant heterogeneous clinical spectrum.[3,4] Despite extensive scientific research globally including repurposing of several existing drugs, there is no effective or proven therapy for this enigmatic disease which is still largely managed empirically.[4,5] A plethora of medical and pharmacological therapies including antivirals, antibiotics, anti-malarials, anti-parasitic agents, non-steroidal anti-inflammatory drugs, corticosteroids and immunomodulators are currently being investigated in over a thousand randomised controlled trials (RCTs) across the world with an aim to generate high-quality evidence to inform and guide clinical practice during the ongoing pandemic.[6-11] Various anti-viral drug groups such as fusion inhibitors (umifenovir), protease inhibitors (lopinavir/ritonavir), neuraminidase inhibitors (oseltamivir) and nucleotide reverse transcriptase inhibitors (remdesivir and favipiravir) have been tested in multiple prospective studies since the outbreak of the pandemic.[12,13] Only about 9 months ago, remdesivir became the first drug to receive United States Food and Drug Administration (US-FDA) approval for treatment of hospitalised COVID-19 patients.[14] Hydroxychloroquine (HCQ), a less toxic derivative of chloroquine (CQ) is a widely used anti-parasitic agent for malaria and immunomodulatory drug for rheumatologic diseases. In the lab, HCQ has demonstrated impressive activity against COVID-19 by blocking the entry of SARS-CoV-2 into cells by inhibiting glycosylation of cell-surface receptors, interfering with proteolytic processing and increasing endosomal pH to limit endosome-mediated viral entry and late-stage viral replication.[15,16] In addition, HCQ reduces the production of several pro-inflammatory cytokines potentially involved in the development and progression to acute respiratory distress syndrome in patients with COVID-19 infection. Based on promising in vitro activity and favourable clinical experience in observational studies[17,18] during early phase of the pandemic, HCQ received emergency use authorisation (EUA) from US-FDA in March 2020, which was revoked later due to concerns regarding cardiac toxicity.[19,20]

Over a year and half into the pandemic, several RCTs have investigated and reported on the safety and efficacy of HCQ as a prophylactic and therapeutic agent in COVID-19 infection. Multiple systematic reviews and meta-analyses of HCQ treatment in COVID-19 have also been reported with conflicting and contradictory results. A meta-review[21] of systematic reviews and updated meta-analysis concluded that treatment with HCQ and CQ with or without azithromycin did not reduce mortality in COVID-19 infection but was associated with a higher risk of adverse events. However, despite the lack of clear evidence of efficacy and presence of valid concerns regarding safety, HCQ continues to be used widely in the management of COVID-19 infection.

2 | AIMS

The aim of this rapid, updated, structured systematic review and direct comparison meta-analysis was to evaluate the safety and efficacy of HCQ in the treatment of COVID-19 for generating high-quality evidence to inform and guide therapeutic decision-making.

3 | METHODS

This systematic review was conducted using Cochrane methodology for systematic reviews of interventional studies[22] and reported in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] Data analysis included risk of bias assessment using Cochrane Risk of Bias tool[24] and grading of the quality of evidence and strength of recommendation based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[25]

3.1 | Literature search strategy

The priority sources of relevant studies for this rapid systematic review included PubMed (https://pubmed.ncbi.nlm.nih.gov) with its curated version LitCOVID and medRxiv (https://www.medrxiv.org). In addition, the National Library of Medicine database of clinical studies (https://clinicaltrials.gov), WHO International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/), Cochrane living registry of COVID-19 studies (http://covid-19.cochrane.org) and Living mapping and living systematic review of Covid-19 studies (http://covid-nma.com) were also queried. A systematic search of the medical literature (online supplementary file S1) without any language restrictions was conducted on 25 September 2020 and later updated periodically till 28 February 2021 in accordance with international guidelines for living systematic reviews.[26]

3.2 | Study eligibility

Only prospective clinical trials randomly assigning patients with suspected and/or proven COVID-19 infection to HCQ plus standard of care therapy (test arm) versus placebo/standard of care (control arm) were included in this review. Given the lack of globally accepted standard of care therapy, this could be variable across trials but had to be similar in both arms within individual studies and not contain CQ or HCQ therapy in the control arm. Trials comparing CQ versus placebo/standard of care were not considered eligible. Multi-arm trials were eligible, if they directly compared HCQ versus placebo/standard of care therapy, with only the relevant arms being pooled in the meta-analysis. Trials allowing co-enrolment of patients across multiple studies were also eligible provided the concurrent medical therapy was similar in each of the randomised arms. Trials randomly comparing different schedules (dose and/or duration) of HCQ were not included in this review. Quasi-randomised trials, propensity matched analyses, non-randomised comparative studies or observational studies were also excluded. Trials comparing HCQ against complementary and alternative medicines, traditional Chinese medicine, nutraceuticals, phytoceuticals and herbal formulations were considered ineligible. Preventive trials using HCQ for pre- or post-exposure prophylaxis were also not considered under the purview of this review.

3.3 | Outcome measures

The primary outcome of interest was clinical benefit as measured on the WHO or similar ordinal scale and all-cause mortality. Clinical improvement was defined as reaching a score of 1 or 2 on the ordinal scale (becoming asymptomatic and/or getting discharged). Relevant endpoints included clinical improvement rate (CIR) on specified days (defined as proportion of patients with clinical improvement by Day7, Day14, Day28 of randomisation) and time-to-clinical improvement (TTCI). Death due to any cause within 14 days or 28 days of randomisation was defined as the event of interest for early (Day14) or late (Day28) mortality, respectively. Secondary endpoints included viral negativity rate on specified days (defined as proportion of patients with viral negativity on D7, D14 of randomisation) and time to viral clearance based on a negative COVID-19 reverse transcriptase polymerase chain reaction test. Safety outcomes included comparison serious adverse events (grade 3 or worse toxicity) between the two arms.

3.4 | Data extraction and analyses

Two reviewers (Babusha Kalra and Prafulla Thakkar) independently read each pre-print, publication, protocol or any other available study report and extracted relevant data from individual studies. Discrepancy was resolved by consensus through interpretation by a third reviewer (Tejpal Gupta). Extracted data included study characteristics (first author and journal), number of participants randomised, patient characteristics (severity of clinical presentation), intervention details (class and type of treatment) and outcome measures. For all dichotomous outcomes (mortality, CIR, viral negativity rate and adverse event rate), the number of events of interest and the number of participants in each study arm were extracted per outcome. Data were pooled using the random-effects model and expressed as risk ratio (RR) with 95% confidence interval (CI). For continuous outcomes (TTCI and time to viral clearance), mean/median values with their dispersion as reported in individual studies were extracted and expressed as difference in median time (in days) with 95% CI. Any p-value <0.05 was considered as statistically significant. Sensitivity analysis, subgroup analysis and publication bias were also assessed as appropriate. All analyses were done using Review Manager (RevMan) version 5.3 and GRADE profiler (GRADEpro) version 3.6.1 (The Nordic Cochrane Centre, Cochrane Collaboration, 2008), Stata 14.0 (StataCorp LP) and R Studio. No funding was involved in the study and its protocol is registered with the International Platform of Registered Systematic Reviews and Meta-analysis Protocols (INPLASY202090092).

4 | RESULTS

The flow diagram of study selection and inclusion in the meta-analysis as per the PRISMA guidelines is depicted in Figure 1. Detailed PRISMA checklist is also provided as an online supplementary file S2. Systematic search of PubMed/LitCOVID identified 1517 records with an additional 344 records being retrieved through supplementary search of other sources. After removing duplicates (159 records) and excluding irrelevant/inappropriate records (n = 1596) through rigorous screening all titles/abstracts, a total of 106 full-text articles (including pre-prints) were assessed for eligibility, of which 19 RCTs[27–45] were finally included and pooled in this systematic review and meta-analysis.

4.1 | Description of included studies

Patient characteristics, treatment details and relevant outcomes of all the 19 RCTs randomly assigning COVID-19 patients to HCQ plus standard of care versus placebo/standard of care therapy are briefly summarised in online supplementary files S3 and S4, respectively. Most of the included studies were open-label trials (excepting few which were placebo-controlled) conducted between January 2020 and September 2020 in almost all parts of the world ensuring good geo-ethnic representation. Most trials enrolled only hospitalised patients (excepting two which were done in outpatient setting) with varying degree of disease severity. Primary endpoints in the included RCTs were variable, but they included measures of both efficacy and safety. The dose and duration of HCQ therapy was somewhat variable across different studies based on prevalent local/national guidelines. The standard of care though different in various trials was in keeping with institutional protocols and national guidelines dictated by the best available evidence at the time and comprised of antivirals (oseltamivir, lopinavir/ritonavir and remdesivir), broad-spectrum antibiotics (azithromycin and doxycycline), immunomodulators (steroids, tocilizumab and anakinra), traditional herbal medicines and supportive care (oxygen inhalation and ventilatory support) as appropriate.

4.2 | Data synthesis and meta-analyses

There was modest methodologic heterogeneity across the 19 included studies prompting the use of random-effects model for statistical pooling of data.

Clinical efficacy: There were no significant differences in rates of clinical improvement (Figure 2) between HCQ (test arm) versus placebo/standard of care therapy (control arm) in terms of either overall CIR (RR = 1.00, 95% CI: 0.96–1.03, p = 0.79) or CIR on Day7 (RR = 0.98, 95% CI: 0.85–1.11, p = 0.71), D14 (RR = 0.99, 95% CI: 0.96–1.03, p = 0.58) and Day28 (RR = 1.01, 95% CI: 0.96–1.07, p = 0.62), respectively. Similarly, there was no significant difference in TTCI between the two arms (Figure 3) with a median difference of 0.41 days (95%CI: −0.12 to +0.95 days) in favour of HCQ treatment. The use of HCQ was not associated with reduction in all-cause mortality (Figure 4). There was no significant difference in early (D14) mortality (RR = 1.07, 95% CI: 0.97–1.19, p = 0.19) or late (D28) mortality (RR = 1.08, 95% CI: 0.99–1.19, p = 0.09) between HCQ and placebo/standard of care therapy.

Virologic clearance: Viral negativity rates were also similar between the two arms, both overall (RR = 1.00, 95% CI: 0.92–1.09, $p = 0.93$) and on Day7 (RR = 1.06, 95% CI: 0.87–1.28, $p = 0.56$) and Day14 (RR = 0.96, 95% CI: 0.89–1.04, $p = 0.34$), respectively (online supplementary file S5). The use of HCQ was not associated with significantly faster viral clearance with a median difference of 1.38 days (95% CI: −0.52 to +3.28 days) favouring the HCQ arm (online supplementary file S6).

Safety analysis: Reassuringly, HCQ therapy was generally safe with no significant increase in the rates of serious adverse events (grade 3 or worse toxicity) compared to placebo/standard of care therapy (RR = 1.01, 95% CI: 0.85–1.19, $p = 0.95$) (Figure 5).

Sensitivity analysis: Sensitivity analysis showed that no single trial was driving the results of the analysis (online supplementary file S7).

Publication bias: There was mild asymmetry in the funnel plot suggesting the presence of publication bias (online supplementary file S8).

Subgroup analysis: Subgroup analysis for all-cause mortality by severity of disease, dose of HCQ, trial setting, sample size and study design could not identify any significant difference in the overall results, inferences and conclusions of the meta-analysis (data not shown).

Strength of recommendation: All 19 included RCTs[27–45] were of moderate to good quality with low risk of bias for most domains for the relevant outcomes of interest. However, there was high risk of performance and detection bias due to open-label nature of most studies without any placebo-controls and lack of blinding of patients and/or physicians. Based on the present analysis, there is low to moderate certainty evidence that HCQ is not associated with significant clinical benefit or harm in patients with COVID-19 infection (Table 1).

5 | DISCUSSION

The outbreak of COVID-19 pandemic prompted the scientific and medical community not only to develop new and/or novel medical therapies but also to explore the possibility of repurposing existing drugs with promising anti-viral activity against SARS-CoV-2.[2,5] A widely used anti-malarial and anti-rheumatic drug CQ and its less
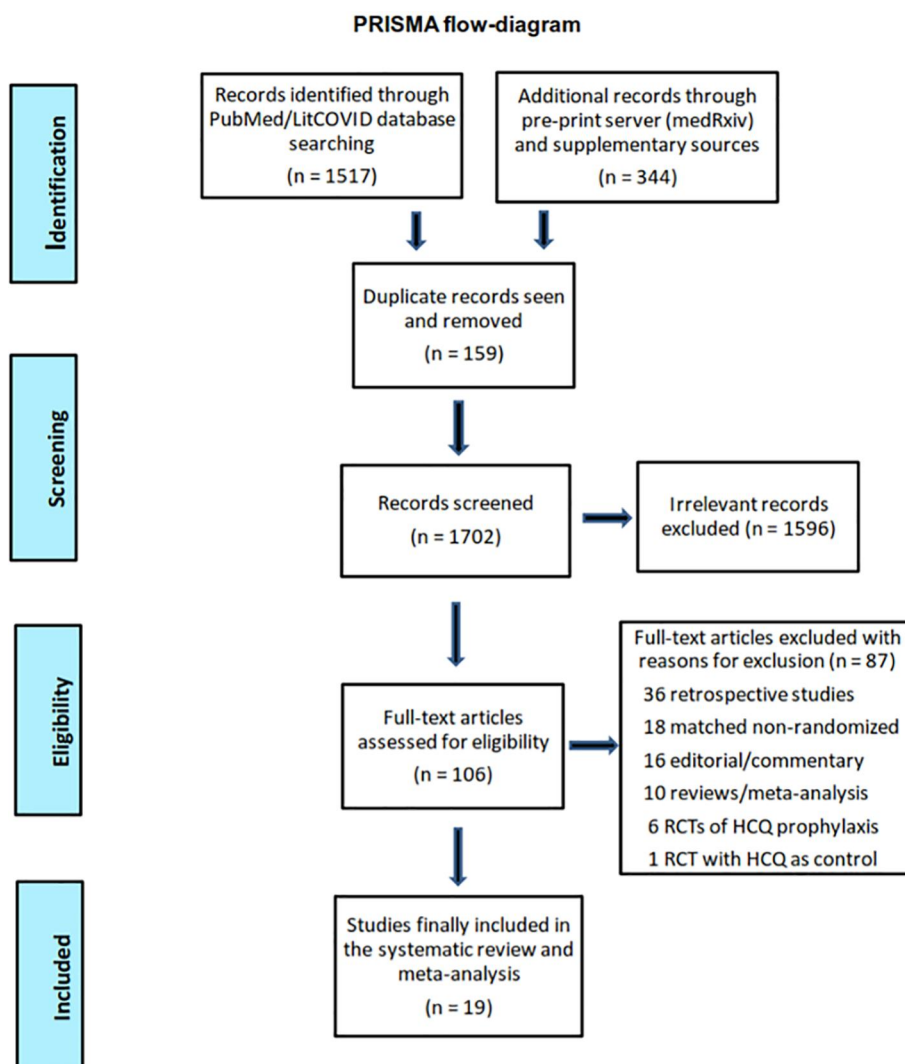

PRISMA flow-diagram

FIGURE 1 Flow diagram of study selection and inclusion in the meta-analysis as per Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines
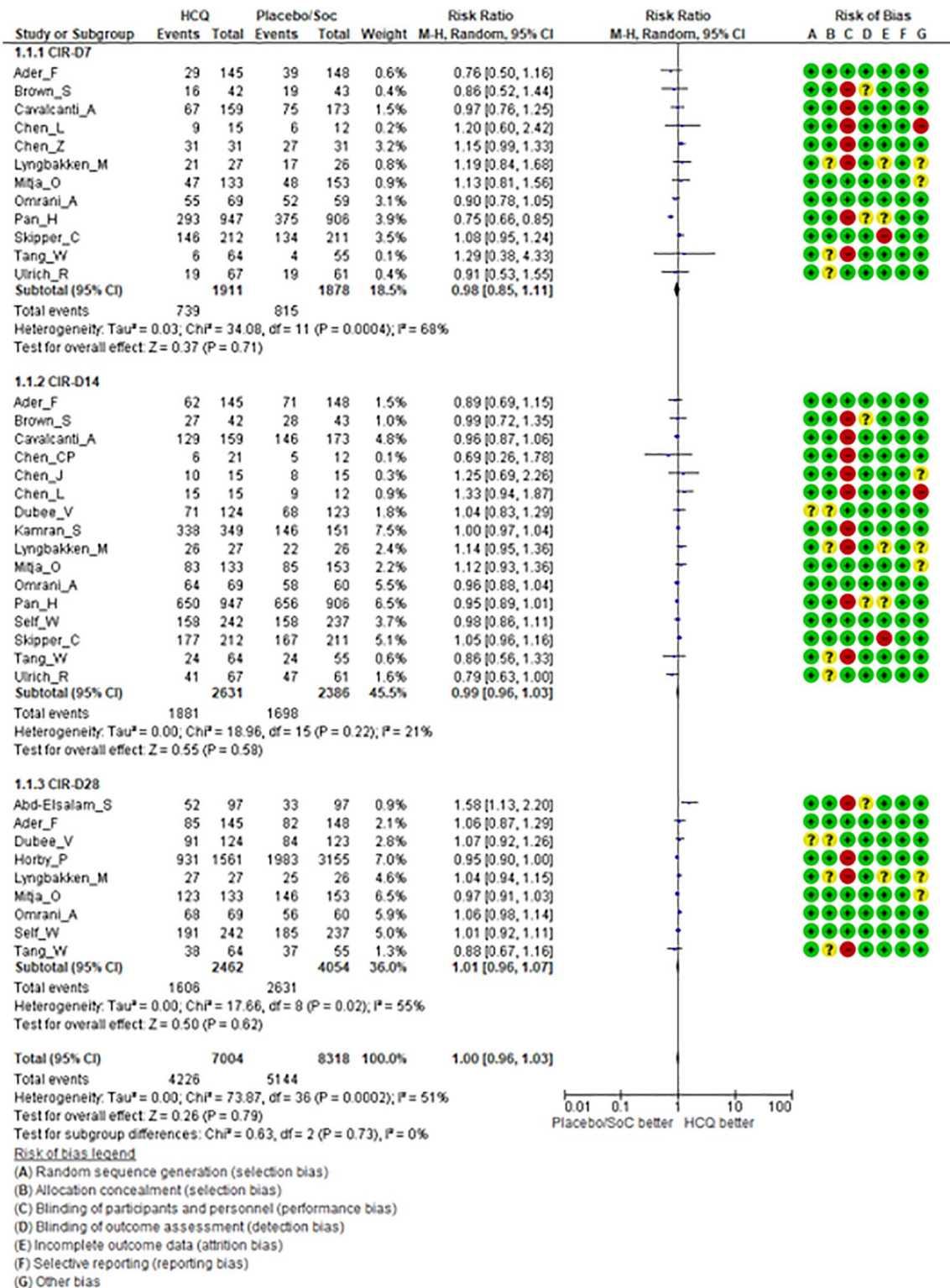
Study or Subgroup	HCQ Events	HCQ Total	Placebo/Soc Events	Placebo/Soc Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 CIR-D7						
Ader_F	29	145	39	148	0.6%	0.76 [0.50, 1.16]
Brown_S	16	42	19	43	0.4%	0.86 [0.52, 1.44]
Cavalcanti_A	67	159	75	173	1.5%	0.97 [0.76, 1.25]
Chen_L	9	15	6	12	0.2%	1.20 [0.60, 2.42]
Chen_Z	31	31	27	31	3.2%	1.15 [0.99, 1.33]
Lyngbakken_M	21	27	17	26	0.8%	1.19 [0.84, 1.68]
Mitja_O	47	133	48	153	0.9%	1.13 [0.81, 1.56]
Omrani_A	55	69	52	59	3.1%	0.90 [0.78, 1.05]
Pan_H	293	947	375	906	3.9%	0.75 [0.66, 0.85]
Skipper_C	146	212	134	211	3.5%	1.08 [0.95, 1.24]
Tang_W	6	64	4	55	0.1%	1.29 [0.38, 4.33]
Ulrich_R	19	67	19	61	0.4%	0.91 [0.53, 1.55]
Subtotal (95% CI)		1911		1878	18.5%	0.98 [0.85, 1.11]
Total events	739		815			

Heterogeneity: Tau² = 0.03; Chi² = 34.08, df = 11 (P = 0.0004); I² = 68%
Test for overall effect: Z = 0.37 (P = 0.71)

Study or Subgroup	HCQ Events	HCQ Total	Placebo/Soc Events	Placebo/Soc Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 CIR-D14						
Ader_F	62	145	71	148	1.5%	0.89 [0.69, 1.15]
Brown_S	27	42	28	43	1.0%	0.99 [0.72, 1.35]
Cavalcanti_A	129	159	146	173	4.8%	0.96 [0.87, 1.06]
Chen_CP	6	21	5	12	0.1%	0.69 [0.26, 1.78]
Chen_J	10	15	8	15	0.3%	1.25 [0.69, 2.26]
Chen_L	15	15	9	12	0.9%	1.33 [0.94, 1.87]
Dubee_V	71	124	68	123	1.8%	1.04 [0.83, 1.29]
Kamran_S	338	349	146	151	7.5%	1.00 [0.97, 1.04]
Lyngbakken_M	26	27	22	26	2.4%	1.14 [0.95, 1.36]
Mitja_O	83	133	85	153	2.2%	1.12 [0.93, 1.36]
Omrani_A	64	69	58	60	5.5%	0.96 [0.88, 1.04]
Pan_H	650	947	656	906	6.5%	0.95 [0.89, 1.01]
Self_W	158	242	158	237	3.7%	0.98 [0.86, 1.11]
Skipper_C	177	212	167	211	5.1%	1.05 [0.96, 1.16]
Tang_W	24	64	24	55	0.6%	0.86 [0.56, 1.33]
Ulrich_R	41	67	47	61	1.6%	0.79 [0.63, 1.00]
Subtotal (95% CI)		2631		2386	45.5%	0.99 [0.96, 1.03]
Total events	1881		1698			

Heterogeneity: Tau² = 0.00; Chi² = 18.96, df = 15 (P = 0.22); I² = 21%
Test for overall effect: Z = 0.55 (P = 0.58)

Study or Subgroup	HCQ Events	HCQ Total	Placebo/Soc Events	Placebo/Soc Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.3 CIR-D28						
Abd-Elsalam_S	52	97	33	97	0.9%	1.58 [1.13, 2.20]
Ader_F	85	145	82	148	2.1%	1.06 [0.87, 1.29]
Dubee_V	91	124	84	123	2.8%	1.07 [0.92, 1.26]
Horby_P	931	1561	1983	3155	7.0%	0.95 [0.90, 1.00]
Lyngbakken_M	27	27	25	26	4.6%	1.04 [0.94, 1.15]
Mitja_O	123	133	146	153	6.5%	0.97 [0.91, 1.03]
Omrani_A	68	69	56	60	5.9%	1.06 [0.98, 1.14]
Self_W	191	242	185	237	5.0%	1.01 [0.92, 1.11]
Tang_W	38	64	37	55	1.3%	0.88 [0.67, 1.16]
Subtotal (95% CI)		2462		4054	36.0%	1.01 [0.96, 1.07]
Total events	1606		2631			

Heterogeneity: Tau² = 0.00; Chi² = 17.66, df = 8 (P = 0.02); I² = 55%
Test for overall effect: Z = 0.50 (P = 0.62)

Total (95% CI)		7004		8318	100.0%	1.00 [0.96, 1.03]
Total events	4226		5144			

Heterogeneity: Tau² = 0.00; Chi² = 73.87, df = 36 (P = 0.0002); I² = 51%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%

0.01 0.1 1 10 100
Placebo/SoC better HCQ better

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

FIGURE 2 Forest plots including risk of bias in individual studies comparing hydroxychloroquine versus placebo/standard of care therapy for clinical improvement rate (CIR) on specified days from randomisation (Day7, Day14, and Day28)

toxic congener HCQ were among the first such repurposed agents that showed remarkable in vitro activity against COVID-19 in the lab[15,16] and combined with promising results in early observational studies[17,18] received EUA in March 2020 by the US-FDA to facilitate widespread adoption during the ongoing pandemic. A large-scale multinational registry analysis reported a significant increase in risk of mortality with CQ/HCQ treatment in COVID-19 infection related to cardiotoxicity which was subsequently

Difference (in days) of median time to clinical improvement

Study	Difference [95% CI]
Abd−Elsalam_S	0.09 [-0.60, 0.78]
Ader_F	-2.00 [-5.58, 1.58]
Cavalcanti_A	-1.00 [-2.88, 0.88]
Chen_J	0.00 [-0.71, 0.71]
Chen_L	1.50 [-4.73, 7.73]
Chen_Z	1.00 [0.52, 1.48]
Lyngbakken_M	0.00 [-7.96, 7.96]
Mitja_O	2.00 [-1.06, 5.06]
Self_W	1.00 [-1.08, 3.08]
Tang_W	2.00 [-0.65, 4.65]
Ulrich_J	0.48 [-2.00, 2.96]
RE Model	0.41 [-0.12, 0.95]

-10 -5 0 5 10

Placebo/SoC better   **HCQ better**
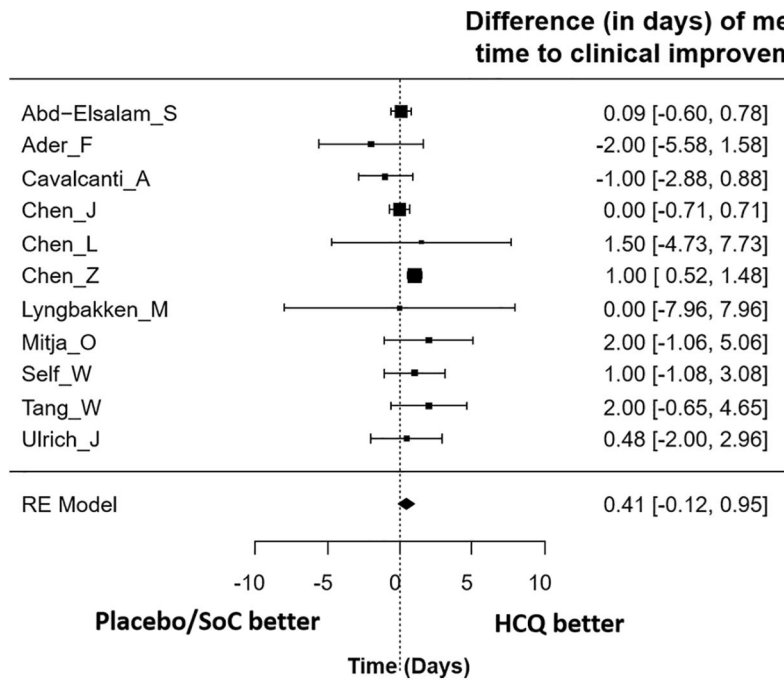
Time (Days)

FIGURE 3 Median difference (in days) in time-to-clinical improvement (TTCI) between hydroxychloroquine versus placebo/standard of care therapy in coronavirus disease 2019 (COVID-19)

Study or Subgroup	HCQ Events	HCQ Total	Placebo/Soc Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
1.4.1 D14							
Ader_F	7	145	11	148	0.6%	0.65 [0.26, 1.63]	+ + + + + + +
Brown_S	4	42	1	43	0.1%	4.10 [0.48, 35.14]	+ + − ? + + +
Cavalcanti_A	5	159	5	173	0.3%	1.09 [0.32, 3.69]	+ + − + + + +
Chen_CP	0	21	0	12		Not estimable	+ + − + + + +
Dubee_V	6	124	6	123	0.4%	0.99 [0.33, 2.99]	? ? + + + + +
Horby_P	335	1561	629	3155	34.6%	1.08 [0.96, 1.21]	+ + − + + + +
Lyngbakken_M	1	26	1	25	0.1%	0.96 [0.06, 14.55]	+ ? − + ? + ?
Mitja_O	0	133	0	153		Not estimable	+ + + + + + ?
Pan_H	79	947	69	906	5.0%	1.10 [0.80, 1.49]	+ + − ? ? + +
Self_W	18	242	14	237	1.1%	1.26 [0.64, 2.47]	+ + + + + + +
Skipper_C	1	212	1	211	0.1%	1.00 [0.06, 15.81]	+ + + + − + +
Tang_W	0	75	0	75		Not estimable	+ ? − + + + +
Ulrich_R	3	67	5	61	0.2%	0.55 [0.14, 2.19]	+ ? + + + + +
Subtotal (95% CI)		3754		5322	42.4%	1.07 [0.97, 1.19]	
Total events	459		742				

Heterogeneity: Tau² = 0.00; Chi² = 3.81, df = 9 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

1.4.2 D 28							
Abd-Elsalam_S	6	97	5	97	0.4%	1.20 [0.38, 3.80]	+ + − ? + + +
Ader_F	11	145	12	148	0.8%	0.94 [0.43, 2.05]	+ + − + + + +
Brown_S	6	42	1	43	0.1%	6.14 [0.77, 48.87]	+ + − ? + + +
Cavalcanti_A	7	159	6	173	0.4%	1.27 [0.44, 3.70]	+ + − + + + +
Chen_L	0	18	0	12		Not estimable	+ + − + + + −
Dubee_V	6	124	11	123	0.5%	0.54 [0.21, 1.42]	? ? + + + + +
Horby_P	421	1561	790	3155	46.6%	1.08 [0.97, 1.19]	+ + − + + + +
Lyngbakken_M	1	26	1	25	0.1%	0.96 [0.06, 14.55]	+ ? − + ? + ?
Mitja_O	0	133	0	153		Not estimable	+ + + + + + ?
Omrani_A	0	152	0	152		Not estimable	+ + + + + + +
Pan_H	104	947	84	906	6.5%	1.18 [0.90, 1.56]	+ + − ? ? + +
Self_W	25	242	25	237	1.7%	0.98 [0.58, 1.65]	+ + + + + + +
Tang_W	0	75	0	75		Not estimable	+ ? − + + + +
Ulrich_R	7	67	6	61	0.4%	1.06 [0.38, 2.99]	+ ? + + + + +
Subtotal (95% CI)		3788		5360	57.6%	1.08 [0.99, 1.19]	
Total events	594		941				

Heterogeneity: Tau² = 0.00; Chi² = 5.51, df = 9 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)

Total (95% CI)		7542		10682	100.0%	1.08 [1.01, 1.16]	
Total events	1053		1683				

Heterogeneity: Tau² = 0.00; Chi² = 9.33, df = 19 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%

0.02 0.1 1 10 50
HCQ better   Placebo/SoC better

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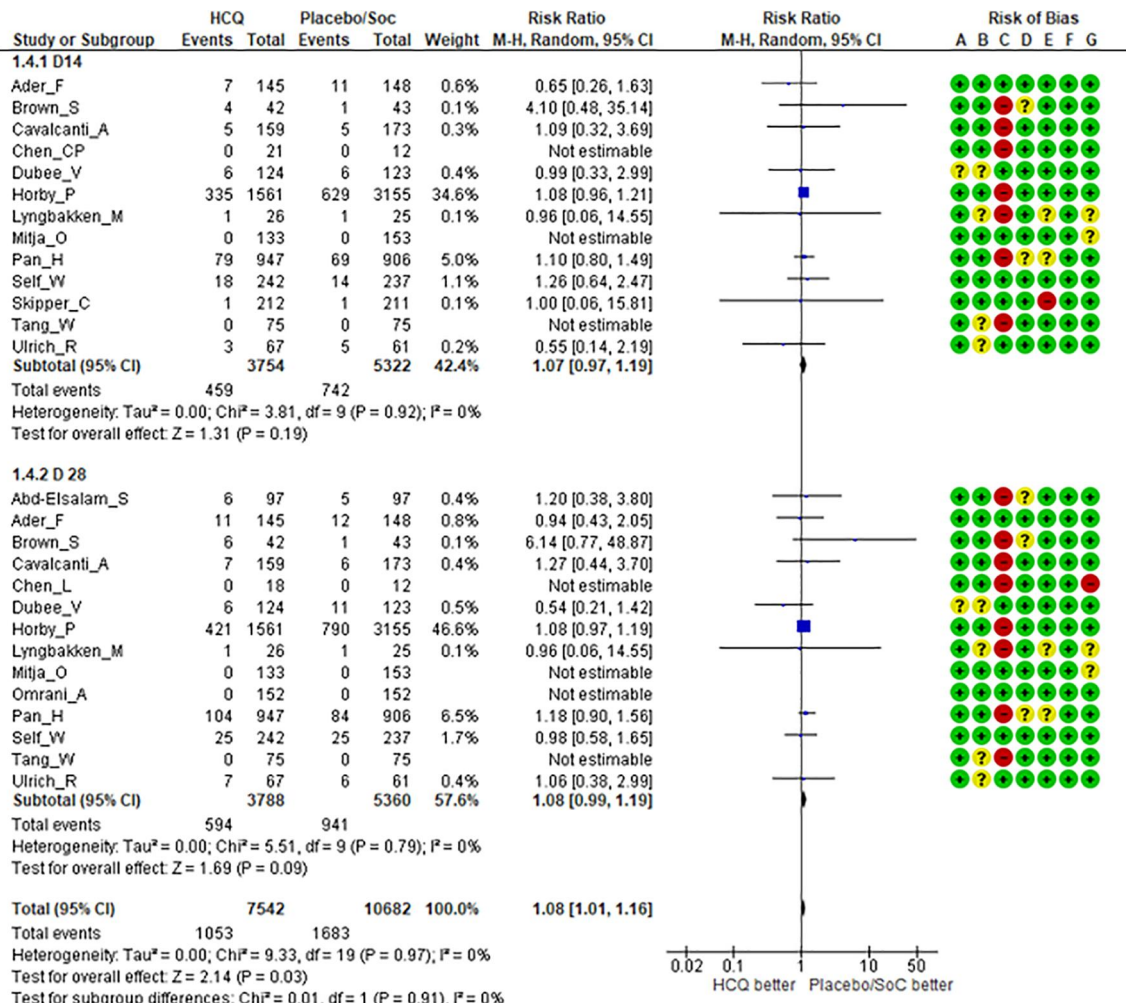(G) Other bias

FIGURE 4 Forest plots including risk of bias in individual studies comparing hydroxychloroquine versus placebo/standard of care therapy for early (Day14) and late (Day28) all-cause mortality in coronavirus disease 2019 (COVID-19)
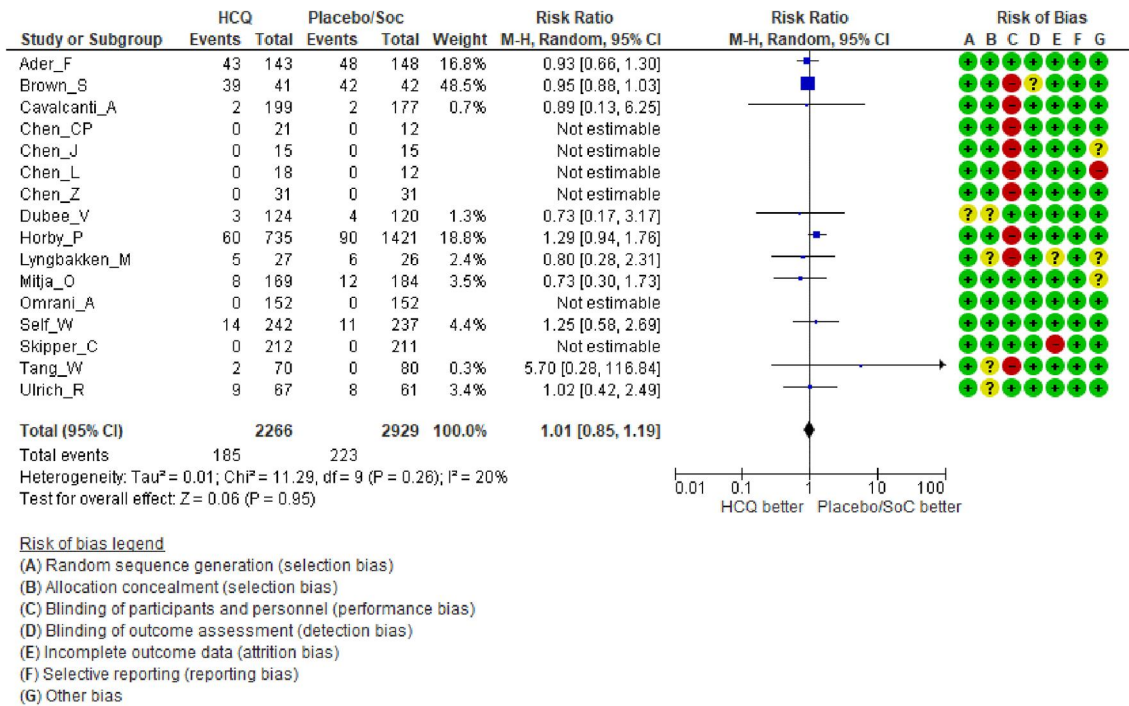
Study or Subgroup	HCQ Events	Total	Placebo/Soc Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ader_F	43	143	48	148	16.8%	0.93 [0.66, 1.30]
Brown_S	39	41	42	42	48.5%	0.95 [0.88, 1.03]
Cavalcanti_A	2	199	2	177	0.7%	0.89 [0.13, 6.25]
Chen_CP	0	21	0	12		Not estimable
Chen_J	0	15	0	15		Not estimable
Chen_L	0	18	0	12		Not estimable
Chen_Z	0	31	0	31		Not estimable
Dubee_V	3	124	4	120	1.3%	0.73 [0.17, 3.17]
Horby_P	60	735	90	1421	18.8%	1.29 [0.94, 1.76]
Lyngbakken_M	5	27	6	26	2.4%	0.80 [0.28, 2.31]
Mitja_O	8	169	12	184	3.5%	0.73 [0.30, 1.73]
Omrani_A	0	152	0	152		Not estimable
Self_W	14	242	11	237	4.4%	1.25 [0.58, 2.69]
Skipper_C	0	212	0	211		Not estimable
Tang_W	2	70	0	80	0.3%	5.70 [0.28, 116.84]
Ulrich_R	9	67	8	61	3.4%	1.02 [0.42, 2.49]
Total (95% CI)		**2266**		**2929**	**100.0%**	**1.01 [0.85, 1.19]**
Total events	185		223			

Heterogeneity: Tau² = 0.01; Chi² = 11.29, df = 9 (P = 0.26); I² = 20%
Test for overall effect: Z = 0.06 (P = 0.95)

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

FIGURE 5 Forest plots including risk of bias in individual studies comparing hydroxychloroquine versus placebo/standard of care therapy for serious adverse events in COVID-19

retracted due to concerns regarding authenticity and integrity of data.[46] The FDA authorisation for HCQ was later revoked in June 2020 based on emerging data on the lack of efficacy and valid concerns regarding cardiac safety.[19,20]

Early evidence for the efficacy of HCQ in COVID-19 was initially reported by Gautret et al. in a small, prospective cohort, open-label, non-randomised study.[17] Subsequently, multiple large retrospective cohorts[47–49] have found the use of HCQ to be associated with significantly decreased risk of prolonged hospitalisation, need for intensive care or death and shorter duration of viral shedding with marginally increased risk of cardiac events compared to other regimens. This apparent clinical benefit of HCQ in observational studies, however, did not stand the scrutiny and rigour of randomised trials. The most robust data demonstrating lack of effectiveness of HCQ in COVID-19 come from the largest two RCTs, RECOVERY and Solidarity both of which failed to demonstrate any significant clinical benefit and terminated accrual to the HCQ arm on the first interim analysis. Critics argue that both of the RCTs (RECOVERY and Solidarity) initiated treatment with HCQ quite late in the course of the disease (median of 9 days from symptom onset), whereas HCQ appears to be consistently effective[50] if provided much earlier (within 48 h of symptom onset) on outpatient basis and is generally safe when used responsibly. A rapid meta-analysis[51] involving 10,012 patients in 26 ongoing, completed or discontinued RCTs reported a significant increase in all-cause mortality with HCQ in patients with COVID-19 infection with an odds ratio (OR) of 1.11 (95% CI: 1.02–1.20, $p = 0.02$) compared to placebo/standard of care therapy. More recently, a Cochrane review[52] concluded that treatment with HCQ

for COVID-19 makes little or no difference to death due to any cause (RR = 1.09, 95% CI: 0.99–1.19, 8208 patients in nine trials, high-certainty evidence). On the contrary, HCQ probably results in nearly threefold increase in the risk of adverse events (RR = 2.90, 95% CI: 1.49–5.64, 1394 patients in six trials, moderate-certainty evidence), although the risk of serious adverse events is not significantly increased (RR = 0.82, 95% CI: 0.37–1.79, 1004 patients in six trials, low-certainty evidence). A systematic review of the effects of CQ/HCQ on non-SARS-CoV2 viral infections[53] also does not support the use of these agents in COVID-19 due to lack of efficacy and potential for harm.

Increasing concerns regarding cardiac safety of CQ/HCQ prompted a global review of pharmacovigilance database to identify the prevalence, severity and type of cardiotoxicity. The French Pharmacovigilance network database[54] evaluating postmarketing adverse cardiac adverse drug reactions associated with HCQ reported a significant increase in repolarisation, ventricular rhythm disorders and sinus bradycardia in patients exposed to off-label, empirical HCQ in COVID-19 compared to its usage in approved indications (lupus and rheumatoid arthritis) in the pre-COVID era. Similar conclusions were drawn by a large-scale disproportionality analysis of the FDA Adverse Events Reporting System database[55] which demonstrated that HCQ was associated with higher reporting of ventricular hypertrophy, diastolic dysfunction, pericarditis, cardiomyopathy, atrio-ventricular block, torsades de pointes and QT prolongation, the last two of which are most relevant to COVID regimens (higher doses over short periods) and represent the most common HCQ-associated cardiac adverse events.

TABLE 1 Summary of findings for the safety and efficacy of hydroxychloroquine compared to controls (placebo/standard of care therapy) in COVID-19 infection including the quality of evidence with grade of recommendation

HCQ for COVID 19

Outcome of interest	No of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with HCQ (95% CI)
Clinical improvement rate	14,443 (18)	⊕⊕⊝⊝ LOW[a,b] due to risk of bias, imprecision	RR 1.00 (0.96–1.03)	Study population	
				629 per 1000	0 fewer per 1000 (from 25 fewer to 19 more)
				Moderate	
				660 per 1000	0 fewer per 1000 (from 26 fewer to 20 more)
All-cause mortality	17,638 (15)	⊕⊕⊝⊝ LOW[a,c] due to risk of bias, imprecision	RR 1.08 (1.01–1.16)	Study population	
				160 per 1000	13 more per 1000 (from 0 more to 26 more)
				Moderate	
				40 per 1000	3 more per 1000 (from 0 more to 7 more)
Viral negativity rate	2425 (7)	⊕⊕⊕⊝ MODERATE[a] due to risk of bias	RR 1.01 (0.92–1.12)	Study population	
				435 per 1000	4 more per 1000 (from 35 fewer to 52 more)
				Moderate	
				396 per 1000	4 more per 1000 (from 32 fewer to 48 more)
Serious adverse events	4904 (15)	⊕⊝⊝⊝ VERY LOW[a,d,e] due to risk of bias, inconsistency, imprecision	RR 1.03 (0.76–1.4)	Study population	
				63 per 1000	2 fewer per 1000 (from 15 fewer to 25 more)
				Moderate	
				11 per 1000	0 fewer per 1000 (from 3 fewer to 4 more)

Note: The basis for the assumed risk (the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Abbreviations: CI, confidence interval; HCQ, hydroxychloroquine; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; RR, risk ratio.

[a]Most studies were open labelled without placebo control or blinding.

[b]A significant number of studies straddle the line of unity with RR increase or decrease by >25%.

[c]All studies straddle the line of unity with RR increase or decrease by >25%.

[d]The direction of effect is opposite to one another in individual studies.

[e]All studies straddle the line of unity with RR increase or decrease by >25%.

The conflicting comparative evidence between big data and the real world[56] on the effectiveness of HCQ in COVID-19 has led to divided opinion within the medical community. Big data observational studies are associated with conflicts of interest, lack details on HCQ dosage and duration, and have shown the absence of efficacy. On the other hand, real-world data from clinical studies have reported favourable clinical and virological outcomes with HCQ including trend towards reduction in mortality.[56] A comparison of the mortality estimates from COVID-19 between developing countries (manly from Asia and Far East) that adopted CQ/HCQ early versus those that expressed concerns regarding its usage (developed countries mainly in Europe and America) shows a striking inverse relationship between widespread CQ/HCQ usage and deaths per million population, which warrants more in-depth analysis.[57] The current systematic review and meta-analysis (including both RE-COVERY and Solidarity) thus provides the largest (over 10,000 randomised patients) and most updated contemporary evidence regarding the safety and efficacy of HCQ in the treatment of COVID-19 infection. The addition of HCQ to current standard of care therapy is not associated with statistically significant or clinically meaningful benefit (reduction in mortality or improvements in clinical recovery and/or virological clearance). Reassuringly, HCQ is neither associated with serious harm compared to placebo/standard of care therapy allaying fears regarding its safety.

An analysis of the WHO-ICTRP database[58] in April 2020 had identified a total of 51 registered RCTs evaluating CQ or HCQ, either

alone or in combination against other treatments in COVID-19. The median (inter-quartile range) sample size was 262 (100–520) patients with 34 (67%) trials proposing clinical outcome, 12 (24%) trials a surrogate outcome and 5 (10%) trials a combination of clinical and surrogate outcome as primary endpoints. Twenty-four (47%) RCTs did not describe plans to assess safety outcomes, prompting the conclusion that RCTs investigating CQ/HCQ during the early stages of the COVID-19 pandemic included heterogeneous and insufficient approaches to measure efficacy/effectiveness and safety relevant to patients and clinical practice. Since the early days of the pandemic, over a thousand studies have been launched to test repurposed medicines and newer drugs as potential therapeutics for COVID-19. Current global clinical research activity in COVID-19 appears fragmented with research agenda being driven by anecdote and hype rather than informativeness and societal value. Substantial heterogeneity of study design and diversity of outcome measures has rendered meaningful comparisons difficult. Despite the availability of several large multi-arm trials, evidence on comparative effectiveness of potential therapeutic alternatives has not been forthcoming. Determining the comparative effectiveness of drugs requires selection of appropriate treatments to be tested in large clinical trials, streamlining trial design, analysis and reporting and timely sharing of individual participant data with greater collaboration and coordination among trialists, meta-analysts, guideline developers and other stakeholders to facilitate producing trustworthy comparative evidence and guidance.[59,60]

5.1 | Strengths and limitations

Despite being the largest data set derived only from RCTs and pooled using modern meta-analytic methods, certain caveats and limitations remain. Large majority of studies including the two largest trials (RECOVERY and Solidarity) were open-label without any placebo-controls with significant potential for performance and detection bias. The standard of care therapy (control arm) as well as dose and duration of HCQ therapy (test arm) was variable across studies further confounding the analyses and inferences. Finally, unpublished data from completed or prematurely terminated trials were not available for pooling in the meta-analysis. However, given the number of randomised patients included in the analysis, it is highly unlikely that any further updated pooled analysis would substantially enhance the certainty of evidence or improve the strength of recommendation.

6 | CONCLUSIONS

There is low to moderate certainty evidence that HCQ therapy is generally safe but does not reduce mortality or enhance clinical/virological recovery compared to placebo/standard of care therapy in patients with COVID-19 infection.

CONFLICTS OF INTEREST
None of the authors have any conflicts of interest to declare.

ETHICAL STATEMENT
Not applicable.

AUTHOR CONTRIBUTIONS
Tejpal Gupta: Conceptualization, Methodology, Analysis, and Writing - original draft; Prafulla Thakkar: Data curation and Writing - review & editing; Babusha Kalra: Data curation and Writing - review & editing; Sadhana Kannan: Methodology, Literature search strategy, and Statistical analysis.

ORCID
Tejpal Gupta https://orcid.org/0000-0001-8256-9206

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.