REVIEW

Hydroxychloroquine for treatment of nonsevere COVID-19 patients: Systematic review and meta-analysis of controlled clinical trials

Hozaifa Khalil Elsawah PharmD, MSc[1] 🅘 | Mohamed Ahmed Elsokary PharmD[1] 🅘 | Mahmoud Gamal Elrazzaz PharmD[2] | Ahmed Hanei Elshafie MSc[3] 🅘

[1]Department of Biostatistics, High Institute of Public Health, Alexandria University, Alexandria, Egypt

[2]IQVIA for the Human Data Science, The Fifth Settlement, Cairo, Egypt

[3]Department of Neuropsychiatry, Shebin Elkom Teaching Hospital, Shebin Elkom, Egypt

Correspondence
Hozaifa Khalil Elsawah, Alexandria University, Alexandria 21561, Egypt.
Email: Hiph.hozaifa@alexu.edu.eg and Hozaifa2005@gmail.com

Present address
Hozaifa Khalil Elsawah, Menia Elkamh, Sharkia 44756, Egypt.

Abstract

Being a pandemic and having a high global case fatality rate directed us to assess the evidence strength of hydroxychloroquine efficacy in treating coronavirus disease-2019 (COVID-19) arising from clinical trials and to update the practice with the most reliable clinical evidence.

A comprehensive search was started in June up to 18 July, 2020 in many databases, including PubMed, Embase, and others. Of 432 studies found, only six studies fulfilled the inclusion criteria, which includes: clinical trials, age more than 12 years with nonsevere COVID-19, polymerase chain reaction-confirmed COVID-19, hydroxychloroquine is the intervention beyond the usual care. Data extraction and bias risk assessment were done by two independent authors. Both fixed-effect and random-effect models were utilized for pooling data using risk difference as a summary measure. The primary outcomes are clinical and radiological COVID-19 progression, severe acute respiratory syndrome coronavirus-2 clearance in the pharyngeal swab, and mortality. The secondary outcomes are the adverse effects of hydroxychloroquine.

Among 609 COVID-19 confirmed patients obtained from pooling six studies, 294 patients received hydroxychloroquine and 315 patients served as a control. Hydroxychloroquine significantly prevents early radiological progression relative to control with risk difference and 95% confidence interval of −0.2 (−0.36 to −0.03). On the other hand, hydroxychloroquine did not prevent clinical COVID-19 progression, reduce 5-day mortality, or enhance viral clearance on days 5, 6, and 7. Moreover, many adverse effects were reported with hydroxychloroquine therapy. Failure of hydroxychloroquine to show viral clearance or clinical benefits with additional adverse effects outweigh its protective effect from radiological progression in nonsevere COVID-19 patients. Benefit-risk balance should determine the hydroxychloroquine use in COVID-19.

KEYWORDS

COVID-19, hydroxychloroquine, mortality, Progression, viral clearance

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), also known as severe respiratory syndrome coronavirus-2 (SARS CoV-2),[1] was first recognized in Wuhan city in China in December 2019.[2] Shortly after, it was declared a pandemic by World Health Organization (WHO).[3] Coronaviruses belong to the family of Coronaviridae, which are enveloped viruses with a single-strand RNA.[4] Before discovering COVID-19, two important coronaviruses were discovered a few years ago; severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome.[5] To date, the global case fatality rate of hospitalized patients with COVID-19 infection is estimated to be 6.5%.[6] In Italy, the estimated case fatality rate is 7.2%,[7] which is higher than that reported in China (2.3%).[8]

The pathogenesis of COVID-19 was explained by cytokine storm,[9] reduction in ACE2 expression,[10] and activation of complement pathways-induced microvascular injury and thrombosis.[11]

Despite lack of strong evidence, some agents are proposed to improve clinical outcomes of COVID-19 based on their mechanisms of action, in vitro activity against SARS CoV-2, low-quality observational studies, or small interventional studies. These agents include hydroxychloroquine (HCQ), chloroquine, lopinavir/ritonavir, ivermectin, favipiravir, tocilizumab, colchicine, interferons, macrolides, and so forth.[12] Also remdesivir is a promising broad spectrum anti-coronavirus agent.[13] On 1 May, 2020, the Food Drug Administration issued an emergency use authorization for remdesivir to be used in severe COVID-19 patients.[14] The emergency use authorization was also issued for HCQ in March and revoked in June 2020 due to safety and efficacy concerns.[15]

HCQ is a weak base 4-aminoquinoline, developed in 1946 as an antimalarial agent, which is a safer derivative than chloroquine.[16] The antiviral activity of HCQ against viral diseases such as human immunodeficiency virus and SARS was studied many years ago.[17] It also showed in vitro activity against SARS CoV-2 by inhibiting viral entry through targeting early endosomes and endolysosomes.[18] Moreover, HCQ could modulate the immune response and reduce proinflammatory cytokines,[19] which are important inducers of acute respiratory distress syndrome.[20] Few retrospective observational studies reported some benefits in treating COVID-19 patients, where HCQ decreased mortality and IL-6 level,[21] decreased case fatality rate,[22] and improved patient survival.[23] On the other hand, other observational studies reported no benefits and more frequent side effects while using HCQ.[24-26] The same controversies are found in the randomized clinical trials (RCT) that investigated HCQ efficacy in COVID-19. In addition, HCQ is one of the most widely used agents for treating COVID-19 infection despite insufficient supporting evidence. A few numbers of meta-analyses investigating this subject were conducted. However, they were criticized for some flaws addressed and discussed afterward.

Therefore, there is an urgency to conduct a systematic review and meta-analysis including all available clinical trials that meet the pre-specified inclusion criteria. The objectives are to summarize the efficacy of HCQ use in COVID-19 relative to control based on available clinical trials indicated by all possible improvements of the disease and to pool all short-term possible side effects related to HCQ therapy in COVID-19 patients.

2 | METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement were followed to improve reporting the present systematic review.[27]

2.1 | Protocol and registration

The protocol was registered in the International Prospective Reregister of Systematic Review with registration number CRD42020195886 in June 2020.

2.2 | Eligibility criteria

The inclusion criteria for the eligible studies for systematic review and meta-analysis include: clinical trials either randomized or not. COVID-19 patients more than 12 years. Infected with SARS CoV-2 and had a polymerase chain reaction (PCR) confirmation test; the test should be based on nasopharyngeal or oropharyngeal swab. Nonsevere infection (mild and moderate) based on clinical assessment by each study. The treatment arm is HCQ ± usual treatment that was given according to each hospital and was not proven to be anti-COVID-19. Control group is only on the usual treatment. Outcomes: any clinical outcomes or drug-related side effects during the follow-up period.

2.3 | Information sources

The following databases were used for studies identification: PubMed, Embase, Cochrane, Google Scholar, ClinicalTrial.gov, ProQuest, Science direct, Chinese Clinical Trial Registry (ChiCTR), and medRxiv. The search started in June and continued through July 2020 to track all new studies.

2.4 | Search strategy

The advanced search was used in different databases with limitation to clinical trials and fields of title and abstract without other limitations. The synonyms applied in search terms were SARS or COVID and HCQ or plaquenil. Three researchers independently underwent comprehensive searching and identified certain studies after removing duplicated ones.

2.5 | Study selection

According to the PRISMA flow diagram (Figure 1),[28] the selection of eligible studies for meta-analysis from identified ones was conducted by two researchers through three steps; abstracts screening for relevant studies, full-text articles assessment for eligibility, and effect

measures assessment for quantitative synthesis. Disagreements were resolved by discussion among the authors.

2.6 | Data collection process

"Data collection form for intervention reviews: RCTs and non-RCTs" developed by Cochrane was used for data extraction.[29] Numbers were extracted directly from text and tables and indirectly from graphs using Getdata graph digitizer version 2.26.0.20.[30] Data extraction was done by three independent authors.

2.7 | Variables definition

There are three types of variables; (a) independent variable is HCQ therapy; (b) dependent variables include viral clearance in the pharyngeal swab, clinical progression (increase in the baseline severity), radiological progression, adverse effects, and mortality; (c) confounders include usual treatment that varied among studies, age, sex, disease onset, and different HCQ doses.

2.8 | Risk of bias in the included studies and across the studies

The Cochrane Risk of Bias Tools to assess the bias risk were followed.[31] It includes six domains: selection bias, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. The Consolidated Standards of Reporting Trials were also utilized.[32] The risk of bias was

assessed by three authors and a final consensus was done. Publication bias could not be assessed because of the low number of the included studies. Sensitivity analysis was performed after removing the low-quality studies.

2.9 | Synthesis of the quantitative results

The principal summary measures were risk difference (RD) for the outcomes, odds ratio (OR) for gender, and mean difference (MD) for age with 95% confidence interval (CI) to compare between HCQ arm and control arm using RevMan version 5.4. Statistical heterogeneity was tested using the Q statistic and quantified with I^2 value. Each of fixed-effect and random-effect models was used to pool the effect sizes according to the heterogeneity of each outcome.[33] Mantel Hazel method and inverse variance method were used for dichotomous data and continuous data, respectively. All time point meta-analysis was used to summarize the result of viral clearance at each available time point.

3 | RESULTS

3.1 | Study selection

PRISMA flow diagram in Figure 1 shows that 432 studies were identified after the removal of duplications, 391 studies were removed after screening titles and abstracts based on their relevance, and 35 studies were removed after assessment of full article for eligibility based on the inclusion criteria. The remaining six studies

No. of records identified through database searching
713 studies

No. of records after duplicates removed
432 studies

No. of records screened
432 studies

No. of records excluded
391 studies

No. of full-text articles assessed for eligibility
41 studies

No. of full text records excluded
35 studies

No. of studies included in qualitative synthesis
6 studies

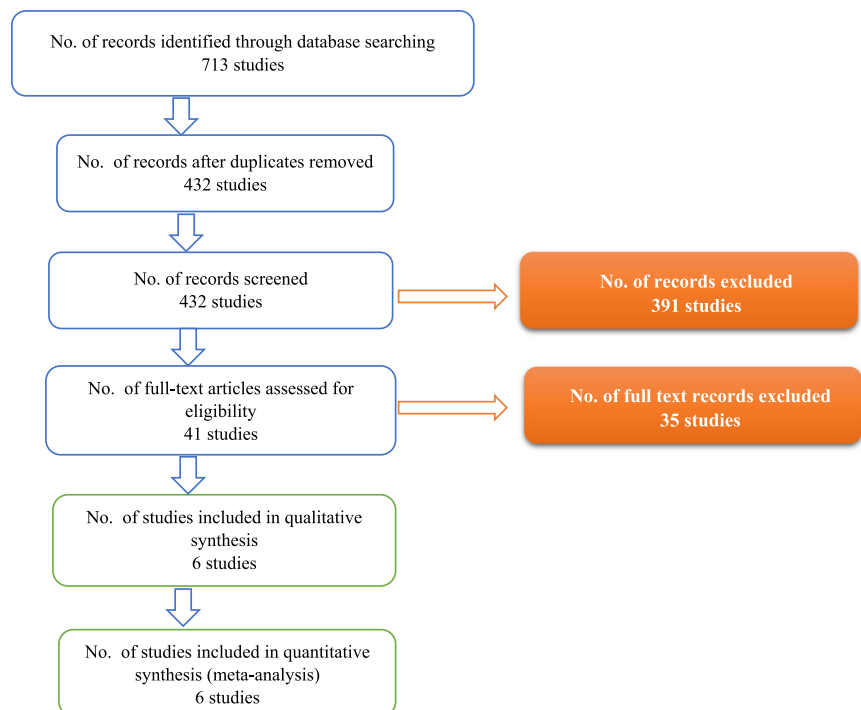No. of studies included in quantitative synthesis (meta-analysis)
6 studies

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the included studies in the qualitative and quantitative synthesis

were included in the systematic review and meta-analysis. Some studies were excluded because of their retrospective design,[34] did not recruit PCR-confirmed cases,[35,36] or recruited less than 12-year-old patients.[36]

3.2 | Study characteristics

The population of the included studies had nonsevere COVID-19 except two severe patients in Tang et al's[37] study. The disease severity definition slightly varied by the studies. It was based on the Chinese guidelines in three studies,[37-40] based on WHO clinical progression scale[41] in Mitjà et al's study,[42] required ICU admission in Gautret et al's[43] study, or who was mechanically ventilated/had comorbid conditions in Barbosa et al's study.[44] The disease onset before HCQ treatment varied from 1 and 4 days in three studies[42-44] to 16 days in another study.[37]

HCQ regimens varied among the studies; only three studies used loading doses of 800 and 1200 mg/d.[37,42,44] Maintenance daily doses of 200, 400, 600, 800 mg were also used according to each study (Table 1).

Usual treatment was given to all patients according to needs and varied widely among the studies. It included supportive care, symptomatic treatment, steroids, antibiotics, and antivirals[37-39,42,43] (Table 1). The two groups were comparable in all mentioned baseline factors in each included study.

3.3 | Risk of bias within studies

The risk of bias is summarized in Figure 2. The study design of Barbosa et al[44] was included as it emulated clinical trial design and the recall bias was unlikely. It was obtained as an under-reviewing article from the New England journal of medicine in June 2020 and considered a low-quality study. The study of Tang et al[37] did not show attrition, at least during the first weeks of the follow-up, but randomization was violated by moving some patients between the groups and changing in baseline factors. Two of the six included studies are of low quality after all authors' agreement, which are Barbosa et al[44] and Gautret et al.[45] The study of Chen et al[39] has been registered in the Chinese Clinical Trial Registry since February 2020 with the unique identifier of ChiCTR2000029559. It has been cited more than 238 times, although it has not been published yet.

3.4 | Synthesis of results

Among 609 COVID-19 confirmed patients obtained from pooling six studies, 294 patients received HQC and 315 patients served as a control (results of the individual studies are summarized in Table 1). The pooled age was significantly higher in the HCQ-treated group compared to control with MD of 2.13 and 95% CI of (0.42-3.85). The pooled gender did not differ between the groups, where the OR of males in the HQC-treated group relative to control was 0.81 (0.58-1.13).

3.4.1 | Efficacy

Viral clearance in pharyngeal swab at three time points pooled from three studies[37,38,43] using all time point meta-analysis and fixed-effect model had a nonsignificant RD of 0.04 (−0.1 to 0.18), 0.06 (−0.08 to 0.2), −0.12 (−0.26 to 0.02) on days 5, 6, 7, respectively. Heterogeneity was significant on days 5 and 6 (χ^2 = 10.16, P = .001, I^2 = 90%; χ^2 = 17.37, P < .0001, I^2 = 94%, respectively). The RD on days 5 and 6 using the random-effect model was 0.19 (−0.33 to 0.7) and 0.25 (−0.38 to 0.88), respectively (Figure 3). Early computed tomography (CT)-based radiological progression (within 5-7 days) pooled from two studies[38,39] using the fixed-effect model had a significant RD of −0.2 (−0.36 to −0.03) which favored HCQ. Heterogeneity was not significant (χ^2 = 0.23, P = .63) (Figure 4). Early clinical progression (within 5-7 days) was not statistically significant between the two groups. RD pooled from four studies[38,39,43,44] using fixed-effect model was 0.06 (−0.03 to 0.15), while in random-effect model it was 0.07 (−0.10 to 0.24). Heterogeneity was significant (χ^2 = 12.6, P = .006, I^2 = 76%). It was identified as a rate of intubation in Barbosa et al's[44] study and the rate of ICU admissions in Gautret et al's[43] study (Figure 4). Clinical progression within 28 days was not statistically significant between the two groups. RD pooled from two studies[37,42] using the fixed-effect model was −0.00 (−0.04 to 0.04). Heterogeneity was not significant (χ^2 = 0.96, P = .33). It was identified as a rate of hospitalization in Mitjà et al's[42] study and a progression from mild to moderate or severe in Tang et al's[37] study (Figure 4). Five-day mortality was not statistically significant between the two groups. RD pooled from four studies[37,42-44] using the fixed-effect model was 0.01 (−0.01 to 0.03). Heterogeneity was not significant (χ^2 = 2.47, P = .48) (Figure 4). Twenty-eight days mortality was not statistically significant between the two groups. RD pooled from two studies[37,42] using the fixed-effect model was 0.00 (−0.01 to 0.01). Heterogeneity was not significant (χ^2 = 0.00, P = 1) (Figure 4).

3.4.2 | Safety

Gastrointestinal adverse effects pooled from three studies[37,38,42] using the fixed-effect model had a significant RD of 0.59 (0.55 to 0.64) which favored control, while using the random-effect model gave a nonsignificant RD of 0.36 (−0.21 to 0.64). Heterogeneity was significant (χ^2 = 264, P < .001). The three studies with different follow-up periods; 7 and 28 days were combined based on that the gastrointestinal side effects of HCQ are more likely to occur early and with high doses.[46] The gastrointestinal adverse effects included nausea, vomiting, diarrhea, abdominal bloating and discomfort, and decreased appetite (Figure 5). Dermatological adverse effects pooled from three studies[37,39,42] using the fixed-effect model had a significant RD of 0.05 (0.02 to 0.08) which favored control. Heterogeneity was not significant (χ^2 = 3.99, P = .14). They included skin rash and flush. (Figure 5). Cardiac adverse effects over a 28-day follow-up period pooled from two studies[37,42] using fixed-effect model had a nonsignificant RD of 0.01 (−0.01 to 0.03), while in the

TABLE 1 Characteristics of the included studies

Study ID	Mean age ± SD (male %)	HCQ arm (follow-up)	Usual treatment that was given to all patients as required	Outcomes (combinable and not combinable)	Events HCQ (control)
Chen et al[38]	HCQ: 50.5 ± 3.8 (60%) Control: 46.7 ± 3.6 (80%)	400 mg/d for 5 d (7 d)	O_2 therapy, interferon-alpha, lopinavir/ritonavir, antibiotics, and supportive treatment	Viral clearance HCQ side effects Clinical progression Radiological progression	13/15 (14/15) 4/15 (3/15) 1/15 (0/15) 5/15 (7/15)
Barbosa et al[44]	HCQ: 59.76 ± 18.92 (46.9%) Control: 64.00 ± 15.92 (71%)	400 mg LD BID for 1-2 d then 200-400 mg/d for a total 5 d (7 d)	O_2 therapy	Rate of intubation Change in Respiratory Support level: mean ± SD Change in lymphocyte count Mortality	7/17 (2/21) 0.76 ± 0.83 (0.24 ± 0.7) 0.8 ± 0.46 (1 ± 0.49) 2/17 (1/21)
Gautret et al[43]	HCQ: 51.2 ± 18.7 (45%) Control: 37.3 ± 24.0 (37.5%)	200 mg TID for 10 d (14 d)	Symptomatic treatment and antibiotics	Viral clearance Clinical progression Mortality	14/20 (2/16) 3/26[a] (0/16) 1/26[a] (0/16)
Tang et al[37]	HCQ: 48.0 ± 14.1 (56%) Control: 44.1 ± 15 (53%)	1200 mg/d LD for 3 d, then 800 mg daily for 2-3 wk (4 wk)	Some antiviral agents, antibiotics, and corticosteroids	Viral clearance Disease progression Mortality All adverse effects	60/70 (65/80) 1/70 (0/80) 0/70 (0/80) 21/70 (7/80)
Chen et al[39]	HCQ: 44.1 ± 16.1 (45.2%) Control: 45.2 ± 14.7 (48.3%)	400 mg/d for 5 d (5 d)	O_2 therapy, antiviral agents, antibacterial agents, and immunoglobulin, ±corticosteroids	Clinical progression Radiological progression Radiological improvement Fever: days ± SD Cough: days ± SD Adverse effects	0/31 (4/31) 2/31 (9/31) 25/31 (17/31) 2.2 ± 0.4 (3.2 ± 1.3) 2 ± 0.2 (3.1 ± 1.5) 2/31 (0/31)
Mitjà et al[42]	HCQ: 41.6 ± 12.4 (27.9%) Control: 41.7 ± 12.6 (34.4%)	800 mg/d LD for 1 day, then 400 mg daily for 6 d (28 d)	Usual care	Viral load reduction ($\log_{10}$ copies/mL): mean ± SE (day 3) Viral load reduction ($\log_{10}$ copies/mL): mean ± SE (day 7) Hospitalization Adverse effects (absolute)	-1.41 ± 0.15 (-1.41 ± 0.14) -3.44 ± 0.19 (-3.37 ± 0.18) 8/136 (11/154) 282 (23)

Abbreviations: BID, twice daily; HCQ, hydroxychloroquine; LD, loading dose; O_2, oxygen; SD, standard deviation; SE, standard error; TID, trice daily.

[a]Denominator is the initial sample size in HCQ arm.

FIGURE 2 Risk of bias assessment of the included six studies; "+" in the green circles: low risk; "−" in the red circles: high risk; "?" in the yellow circles: unknown

random-effect model it was 0.02 (−0.05 to 0.09). Heterogeneity was significant ($\chi^2 = 6.35$, $P = .01$). They included sinus bradycardia, hypertension, and orthostatic hypotension. There were no arrhythmias detected among the studies (Figure 5). CNS adverse effects pooled from three studies[37,39,42] using the fixed-effect model had a significant RD of 0.23 (0.18 to 0.28) which favored control, while in the random-effect model, it was not significant 0.13 (−0.20 to 0.46). Heterogeneity was significant ($\chi^2 = 158$, $P < .0001$). They included blurred vision, headache, drowsiness, and metallic test (Figure 5).

3.5 | Sensitivity analysis

After excluding the two low-quality studies,[44,45] the same analyses on the applicable outcomes were performed. No difference was observed between the two analyses on the progression, mortality, and viral clearance.

4 | DISCUSSION

HCQ therapy in COVID 19 is still a matter of debate among healthcare providers.[47] It was introduced early in the pandemic based on early studies.[48] Meanwhile, numerous observational and interventional studies raised concerns about the safety of the drug
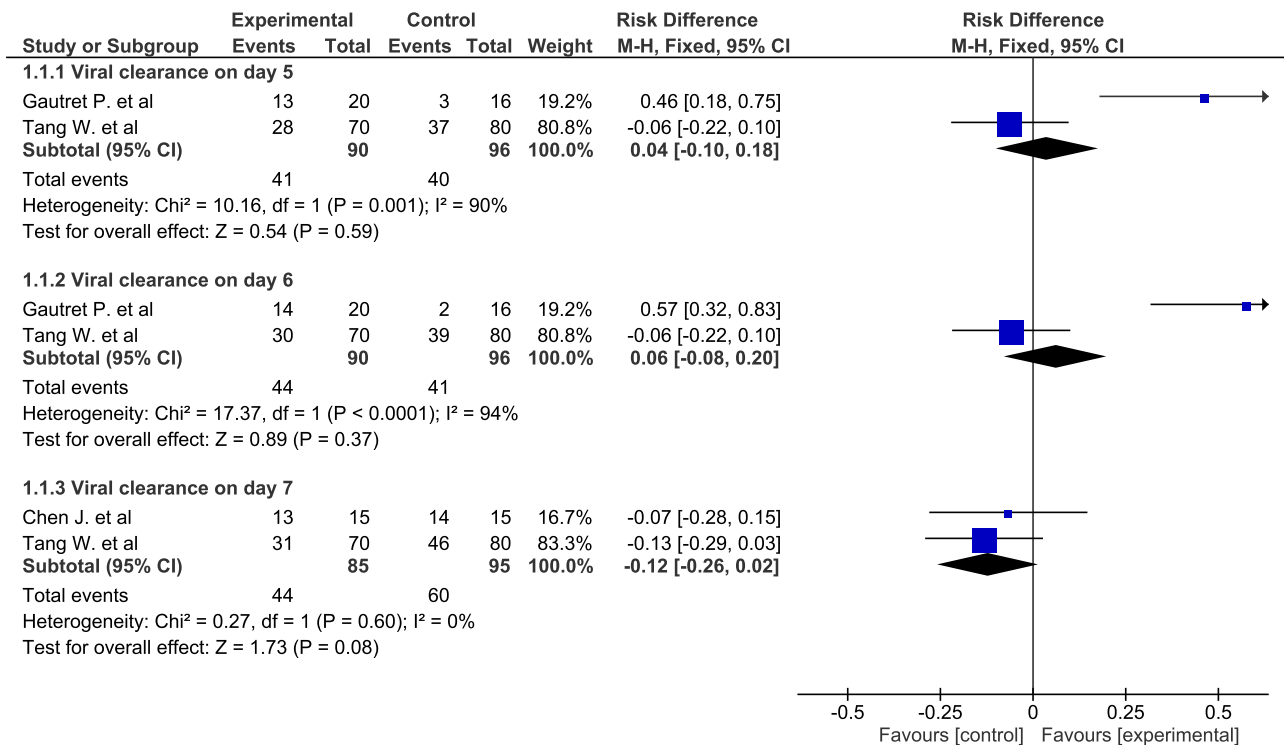

FIGURE 3 Forest plot of viral clearance at three time points using the fixed-effect model and risk difference with 95% confidence interval

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
1.11.1 Early radiological progression							
Chen J. et al	5	15	7	15	32.6%	-0.13 [-0.48, 0.21]	
Chen Z. et al	2	31	9	31	67.4%	-0.23 [-0.41, -0.04]	
Subtotal (95% CI)		**46**		**46**	**100.0%**	**-0.20 [-0.36, -0.03]**	
Total events	7		16				
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%							
Test for overall effect: Z = 2.30 (P = 0.02)							
1.11.2 Early clinical progression							
Barbosa J. et al	7	17	2	21	22.2%	0.32 [0.05, 0.58]	
Chen J. et al	1	15	0	15	17.7%	0.07 [-0.10, 0.23]	
Chen Z. et al	0	31	4	31	36.6%	-0.13 [-0.26, -0.00]	
Gautret P. et al	3	26	0	16	23.4%	0.12 [-0.03, 0.27]	
Subtotal (95% CI)		**89**		**83**	**100.0%**	**0.06 [-0.03, 0.15]**	
Total events	11		6				
Heterogeneity: Chi² = 12.59, df = 3 (P = 0.006); I² = 76%							
Test for overall effect: Z = 1.34 (P = 0.18)							
1.11.3 Clinical progression over 28 days							
Mitjà O. et al	8	136	11	154	65.9%	-0.01 [-0.07, 0.04]	
Tang W. et al	1	70	0	80	34.1%	0.01 [-0.02, 0.05]	
Subtotal (95% CI)		**206**		**234**	**100.0%**	**-0.00 [-0.04, 0.04]**	
Total events	9		11				
Heterogeneity: Chi² = 0.96, df = 1 (P = 0.33); I² = 0%							
Test for overall effect: Z = 0.17 (P = 0.86)							
1.11.4 5-days mortality							
Barbosa J. et al	2	17	1	21	7.3%	0.07 [-0.11, 0.25]	
Gautret P. et al	1	26	0	16	7.6%	0.04 [-0.08, 0.16]	
Mitjà O. et al	0	136	0	157	56.3%	0.00 [-0.01, 0.01]	
Tang W. et al	0	70	0	80	28.8%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)		**249**		**274**	**100.0%**	**0.01 [-0.01, 0.03]**	
Total events	3		1				
Heterogeneity: Chi² = 2.47, df = 3 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.82 (P = 0.41)							
1.11.5 28-days mortality							
Mitjà O. et al	0	169	0	184	70.2%	0.00 [-0.01, 0.01]	
Tang W. et al	0	70	0	80	29.8%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)		**239**		**264**	**100.0%**	**0.00 [-0.01, 0.01]**	
Total events	0		0				
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%							
Test for overall effect: Z = 0.00 (P = 1.00)							

-0.2 -0.1   0   0.1   0.2
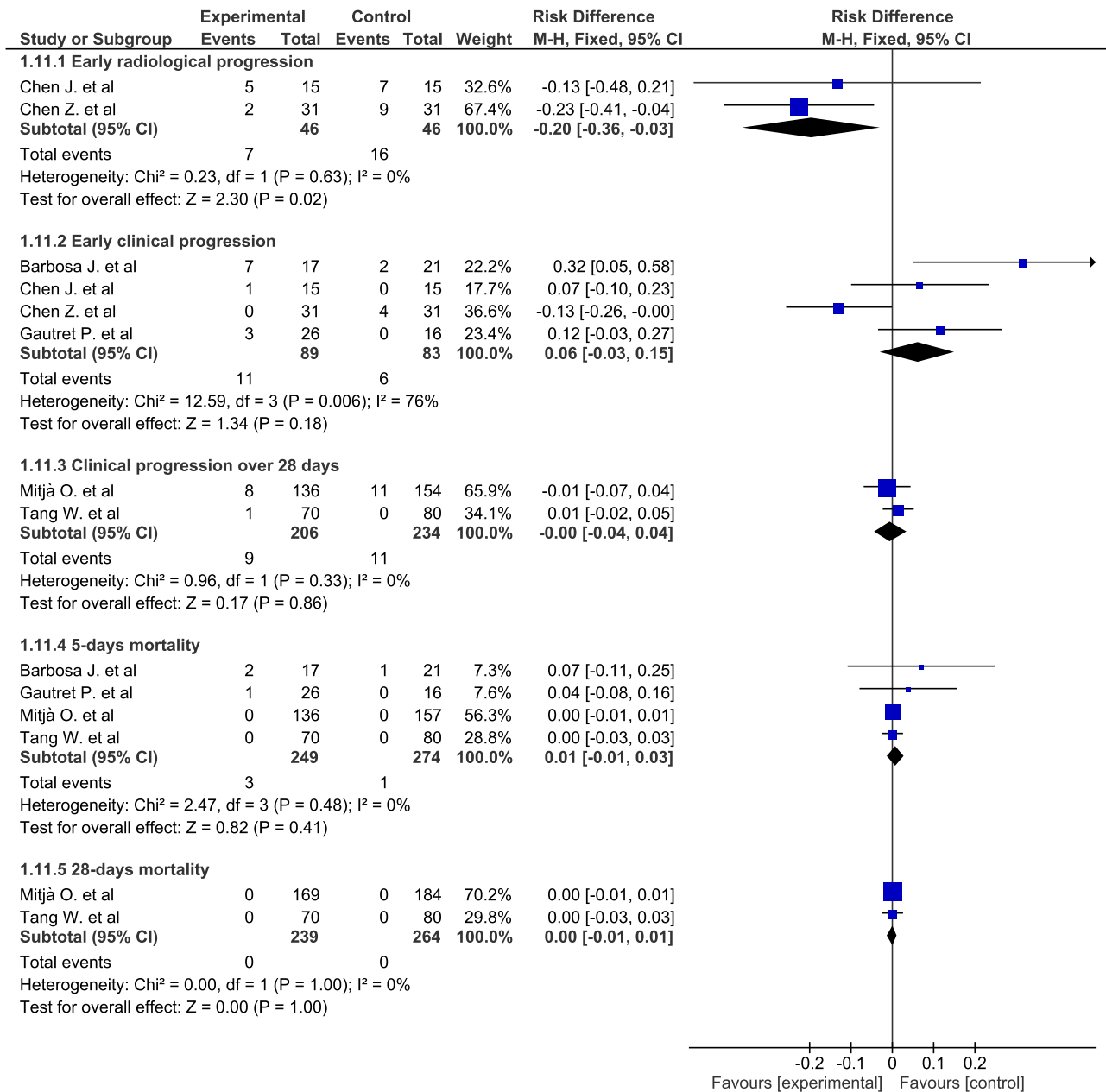Favours [experimental]   Favours [control]

FIGURE 4 Forest plot of radiological and clinical progression and mortality using the fixed-effect model and risk difference with 95% confidence interval

and even prematurely terminated due to serious cardiac side effects.[24,49-51]

Sensitive indicators for a possible efficacy of anti-COVID-19 drugs should rely on the improvement in the disease clinical course and modification in possible causes of the related mortality. Radiological abnormalities of the lung could be a good measure of drug efficacy. Lung abnormalities on chest CT in patients with COVID-19 changed gradually from ground-glass opacities on the first days to an increase in the crazy-paving pattern after 1 week, then became consolidated on day 10 and started to resolve after 2 weeks of the disease course.[52] The ability of a drug to prevent disease progression from mild/moderate to severe has been targeted as a reliable efficacy measure.[53]

Accordingly, it could inhibit the pathophysiological pathways of the virus. The disease severity was defined by WHO as $SpO_2 < 94\%$ on room air, including those who require any form of supplemental oxygen.[54] Viral clearance is of clinical importance as it correlated with the clinical and biochemical outcomes,[55] but may underestimate the immunomodulators effect including HCQ.[12,56] On the other hand, low rates of mortality were reported among nonsevere COVID-19, large number is required to get enough power to show a significant difference.[57] Mortality may not be a sensitive indicator among those with nonsevere COVID-19.

The present meta-analysis targeted nonsevere COVID-19 patients to assess the efficacy and safety of HCQ based on the available evidence.
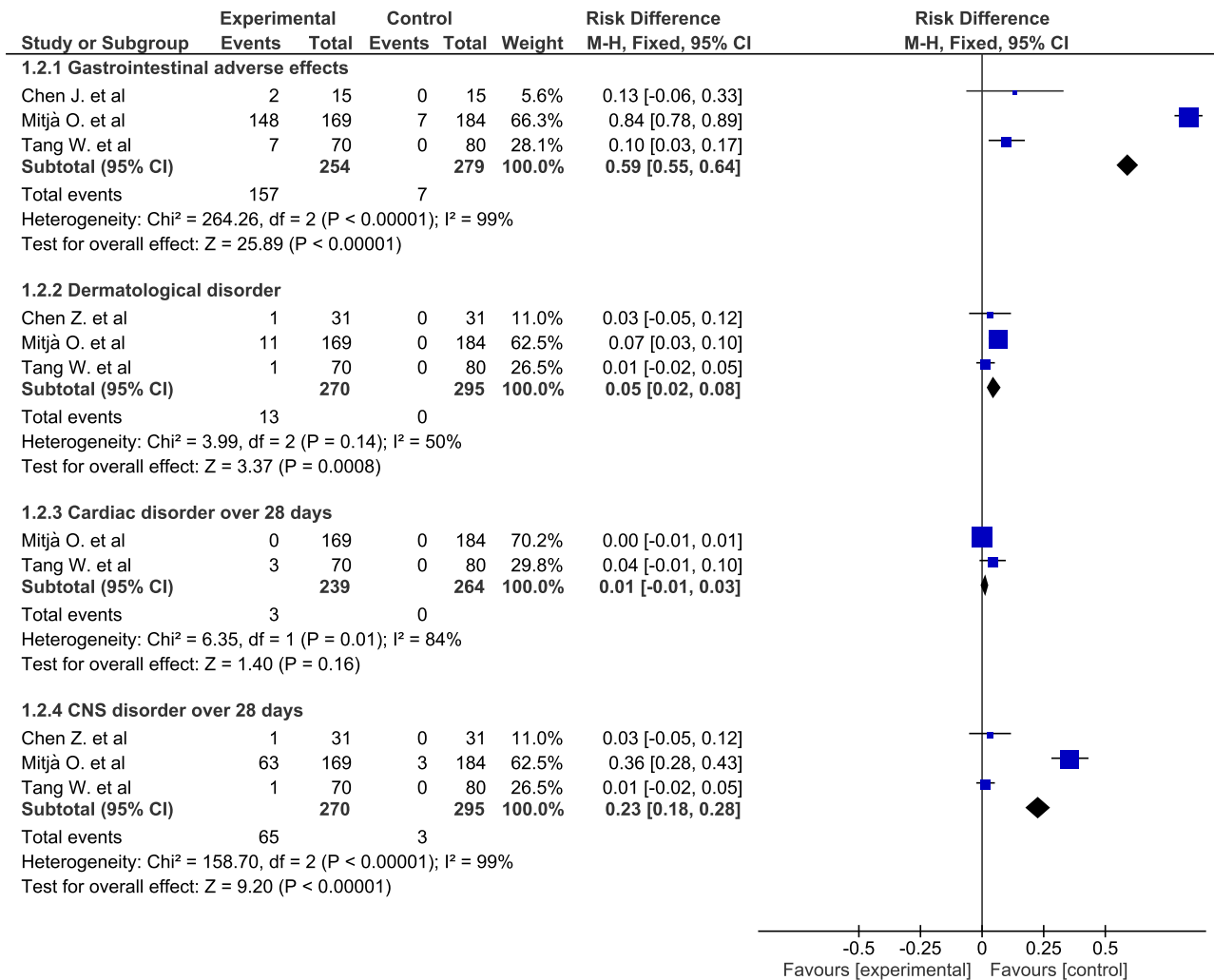
| Study or Subgroup | Experimental | | Control | | | Risk Difference | Risk Difference |
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.2.1 Gastrointestinal adverse effects							
Chen J. et al	2	15	0	15	5.6%	0.13 [-0.06, 0.33]	
Mitjà O. et al	148	169	7	184	66.3%	0.84 [0.78, 0.89]	
Tang W. et al	7	70	0	80	28.1%	0.10 [0.03, 0.17]	
Subtotal (95% CI)		254		279	100.0%	**0.59 [0.55, 0.64]**	
Total events	157		7				

Heterogeneity: Chi² = 264.26, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 25.89 (P < 0.00001)

1.2.2 Dermatological disorder							
Chen Z. et al	1	31	0	31	11.0%	0.03 [-0.05, 0.12]	
Mitjà O. et al	11	169	0	184	62.5%	0.07 [0.03, 0.10]	
Tang W. et al	1	70	0	80	26.5%	0.01 [-0.02, 0.05]	
Subtotal (95% CI)		270		295	100.0%	**0.05 [0.02, 0.08]**	
Total events	13		0				

Heterogeneity: Chi² = 3.99, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 3.37 (P = 0.0008)

1.2.3 Cardiac disorder over 28 days							
Mitjà O. et al	0	169	0	184	70.2%	0.00 [-0.01, 0.01]	
Tang W. et al	3	70	0	80	29.8%	0.04 [-0.01, 0.10]	
Subtotal (95% CI)		239		264	100.0%	**0.01 [-0.01, 0.03]**	
Total events	3		0				

Heterogeneity: Chi² = 6.35, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 1.40 (P = 0.16)

1.2.4 CNS disorder over 28 days							
Chen Z. et al	1	31	0	31	11.0%	0.03 [-0.05, 0.12]	
Mitjà O. et al	63	169	3	184	62.5%	0.36 [0.28, 0.43]	
Tang W. et al	1	70	0	80	26.5%	0.01 [-0.02, 0.05]	
Subtotal (95% CI)		270		295	100.0%	**0.23 [0.18, 0.28]**	
Total events	65		3				

Heterogeneity: Chi² = 158.70, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 9.20 (P < 0.00001)

-0.5 -0.25 0 0.25 0.5
Favours [experimental] Favours [control]

FIGURE 5 Forest plot of adverse effects of hydroxychloroquine among patients with coronavirus disease-2019 using the fixed-effect model and risk difference with 95% confidence interval

In addition, the minimal age of the inclusion criteria was expanded to 12 years to add more studies. HCQ was used in the RECOVERY trial for infants more than 6 months without concerns,[58] but it could not be included in this review as it also had no PCR-based confirmation test.

The present study offers moderate-quality evidence built on five clinical trials and one quasi-trial. The meta-analysis investigated five measurable objective outcomes, two of them showed statistical significance; chest CT progression and incidence of some adverse drug effects. However, clinical progression, viral clearance at three time points, and 5-day mortality did not differ between the two groups. All time points meta-analysis to summarize the effect size on 5, 6, and 7 days was performed to get more accurate results.[59]

The chest CT-based disease assessment was performed on days 0 and 6 to evaluate the disease progression.[39] It depended on pneumonia absorption on CT and weather it was absorbed by more or less 50%, it also depended on pneumonia absorption on CT.[38]

The clinical progression definition was consistent in three studies[37-39] which included increasing in the disease severity from nonsevere to severe, while in the other three studies, it was the requirement for mechanical ventilation,[44] ICU admission,[43] or hospitalization.[42]

The authors faced a significant heterogeneity in viral clearance on days 5 and 6, where the study of Gautret et al's[45] had a different effect size direction to the other two studies. Low quality of the study might be the cause. Heterogeneity was also found in a disease progression as a result of the deference in the definition of clinical progression among the included studies. Heterogeneity was obvious among the studies in the occurrence of adverse effects. The study of Mitjà et al[42] reported more gastrointestinal, dermatological, and neurological adverse effects than Tang et al's[37] during the 28-day follow-up period, although it used lower HCQ dose for shorter treatment course.

The heterogeneity in the disease severity assessment among the included studies was addressed in this meta-analysis. Common severity assessment tools were found in four studies; one of them[42] followed WHO Clinical Progression Scale which defined severe cases as at least hospitalized patients and received oxygen by noninvasive ventilation or high flow, while the other three[37-39] followed the Chinese Center for

Disease Control and Prevention guidelines that defined severe cases as having dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≥ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours. The other two studies[43,44] lacked a well-defined disease severity definition.

Adverse effects of HCQ are common; it includes gastrointestinal, cutaneous, central nervous system, ocular, cardiological, and hematological adverse effects.[60] A significant dermatological, gastrointestinal, and neurological adverse effects with HCQ therapy were pooled by the fixed-effect model in the present meta-analysis. However, the random-effect model gave a very wide nonsignificant 95% CI because of the heterogeneity. The reported side effects did not result in a significant withdrawal or attrition bias. On the other hand, no cardiac arrythmias were reported along the 28 days in the studies and the other cardiac adverse effects were not significant.

A meta-analysis first done by Sarma et al[61] consisted of three studies of the present meta-analysis reported the same significant effect size of the radiological progression in the present meta-analysis. On the other hand, the author combined days 5 and 6 viral clearance, mortality/progression, and all possible side effects in three variables that gave inconsistent results with us. In addition, wrong denominators for viral clearance and death/worsening were observed in effect size pooling.[61] The second meta-analysis conducted by Singh et al[62] summarized mortality and viral clearance with HCQ use from seven comparative studies either clinical trial or observational studies. It found a significant pooled mortality associated with HCQ use. It is criticized for combining 6-, 7-, 28-day viral clearance from three studies in one effect size.[37,38,43] The third preprint meta-analysis conducted by Shamshirian et al[63] included 18 comparative studies for quantitative synthesis. The study found a higher mortality rate, adverse drug effects, and more radiological improvement associated with HCQ. The fourth preprint meta-analysis by Amani et al[64] tried to investigate only among controlled trials but suffered from fallacies such as failure of combinability between CT progression and CT improvement, wrong denominators in extracting data for viral clearance and clinical progression from Tang et al,[37] and invalid combinability between different time-based outcomes.

Large RCT with sufficient power is required with a longer follow-up period, it should report more sensitive outcomes stratified by the disease severity and based on the proposed mechanisms of action of HCQ to improve the clinical course of COVID-19.

5 | LIMITATIONS

A lot of limitations faced the investigators due to conflicts between the included trials, high level of heterogeneity which is present among some studies methodologies and outcomes such as COVID-19 severity definitions and the background treatment. The low number of studies with relatively small sample size and low quality is also another challenge.

6 | CONCLUSION

There are no tangible beneficial effects of adding HCQ to the treatment of patients suffering from nonsevere PCR-confirmed COVID-19 infection. Reducing the chest CT progression by HCQ was neither sufficient to reduce the early mortality nor promote the early clinical progression more than the usual therapy used. Its use was accompanied with a significant incidence of adverse effects without any effect on viral clearance.

AUTHOR CONTRIBUTIONS
HKE was responsible for studies search, data extraction, data analysis, and final revision of the manuscript. MAE helped in studies searching and data extraction and was responsible for manuscript writing. MGE helped in data searching, data extraction, and manuscript writing. AHE was responsible for the final revision of the manuscript and the work.

ORCID
Hozaifa Khalil Elsawah http://orcid.org/0000-0003-2965-9944
Mohamed Ahmed Elsokary https://orcid.org/0000-0002-9832-5086
Ahmed Hanei Elshafie https://orcid.org/0000-0002-2901-2158

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