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Collation of Hydroxychloroquine Virological Clearance, Effectiveness, Safety in Covid-19 Patients with Control Group (Conventional Therapy) – a Systematic Review and Meta-Analysis

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Abstract

Objectives: Destitute of an effective treatment, several potential repurposed drugs have been tried in COVID-19. Despite unavailability of anecdotal evidence, several guidelines granted both Chloroquine (CQ) and Hydroxychloroquine (HCQ) in treatment. Clinical studies relating to those in COVID-19 disease has reported conflicting results. We sought to systematically evaluate the clinical effects of CQ and HCQ.

Methods: Extensive search was done using multiple databases to 22 October 2020. Proper hand searching of cross-references of original articles, pre-prints was also performed to find additional relevant articles. We summarized the effect of CQ or HCQ on viral clearance, occurrence of ADR, mortality outcomes.

Results: Out of 12 studies included in the systematic review, a total of 2,834 patients enrolled, 1326 patients received HCQ along with standard of care and 1508 patients received conventional standard of care.

The meta-analysis of 5 studies that reported rate of virological clearance or PCR negativity (n=312) found no benefit in HCQ arm. {OR, 1.863; 95% CI, 1.024 to 3.389; p=0.041} with a moderate heterogeneity (I^2 =70.3%, P=0.009). meta-analysis of 5 studies (n=1710) that reported about ADR outcomes found that, there exist an increased risk of ADRs in HCQ arm. {OR, 2.648; 95% CI, 2.068 to 7.717; p=0.000}, with no heterogeneity (I^2 = 0%, P=0.417). 6 studies (n=4,341) showed a significant increase in mortality in HCQ arm when compared with control arm {OR, 1.182; 95% CI, 0.981 to 1.425; p=0.079}, with substantial heterogeneity (I^2 = 82.0%, P=0.000).

Conclusions: The systematic review and meta-analysis revealed a reduced antiviral efficacy in reducing mortality, ADR occurrence and has a decreased virological clearance in patients with COVID-19.

Keywords

COVID-19; HCQ; CQ; Virological clearance; ADR; Mortality

Background

The World Health Organization (WHO) declared COVID-19 (caused by Severe acute respiratory syndrome corona virus 2: SARS-CoV-2) as a global pandemic on 11 March 2020. In the absence of an effective treatment, several potential repurposed drugs have been tried in COVID-19. Mean while two drugs: Chloroquine (CQ) and Hydroxychloroquine (HCQ) took focus of attention, since initial studies showed that both CQ and HCQ inhibits SARS-CoV-2 effectively *in vitro* [1-3]. Vero-E6 cell lines, infected with SARS-CoV-2 were inhibited by low-micro molar concentration of CQ with high selectivity index. Mechanism of action of CQ and derivatives *in vitro* may be increasing endosomal pH, altering glycosylation of ACE-2 (angiotensin-converting enzyme 2) receptors [4], immunomodulation [1], enhanced regulatory T-cell activity [5].

A Chinese commentary on the basis of 15 human trials, profess that CQ Phosphate is superior to the control group in inhibiting exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course in more than 100 patients [6].

Despite the unavailability of anecdotal evidence, several guidelines granted both CQ and HCQ to be used in Covid-19 treatment [7]. A study conducted by Yao et al, it was found that HCQ (EC50 = 0.72 μM) is more potent than CQ *in vitro* and using physiologically based pharmacokinetic model, this concentration can be attained by a loading dose of HCQ 400 mg BD on the first day, followed by 200 mg BD for 4 days for SARS-CoV-2 [3]. Also, ICMR (Indian Council of Medical research recommended the potential use of CQ and HCQ prophylatically in people who are in close contact, mainly in health workers [8]. On March 30, 2020 FDA issued an Emergency Use Authorization (EUA) in order to use both CQ and HCQ in the treatment of COVID-19. FDA issued EUA for the second time in the history. Formerly it was given for an investigational neuraminidase inhibitor, Peramivir during 2009-2010 to treat severely ill patients with H1N1 influenza [9].

Studies which aim to evaluate the HCQ use in Covid-19 have many pitfalls like small sample size, heterogeneity, inconsistent reports, early cessation of trials etc. Hence it is obligatory to systematically review and critically appraise the available literatures, which might help policy makers, clinicians to stick onto a decision [10].

Objectives

To evaluate the safety, efficacy and virological clearance of Hydroxychloroquine in Covid-19 patients when compared to those patients receiving conventional therapy.

Methods

This study was carried out in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [11].

Criteria for considering relevant studies for the review were as follows:

1. **Type of study**

Inclusion Criteria: We included randomised/ non-randomised controlled trials, observational studies, case reports, case series, all studies conducted with Hydroxychloroquine in patients with Covid-19 that was compared to control arm.

Exclusion Criteria: We excluded experimental *in vitro* studies, editorials & expert opinions, case series without control group, review articles, articles with unavailable full text and non – English articles.

2. **Type of participants**

- Human subjects with confirmed Covid-19 by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).
- Individuals with all ages and sexes.

3. **Intervention**: Hydroxychloroquine (HQ)

4. **Control Group**: Conventional therapy

5. **Outcome of Interest**:

    - Virological Clearance
    - Mortality
    - Safety outcome in terms of adverse events with HCQ

6. Search Strategy

An extensive search was carried out using search engines like PubMed, Google search, NHS evidence data base up to October 22, 2020. The key term searched were “Hydroxychloroquine on Covid-19”. Proper hand searching of cross- references of original articles, pre-prints was also performed to find out additional relevant articles (Figure 1).

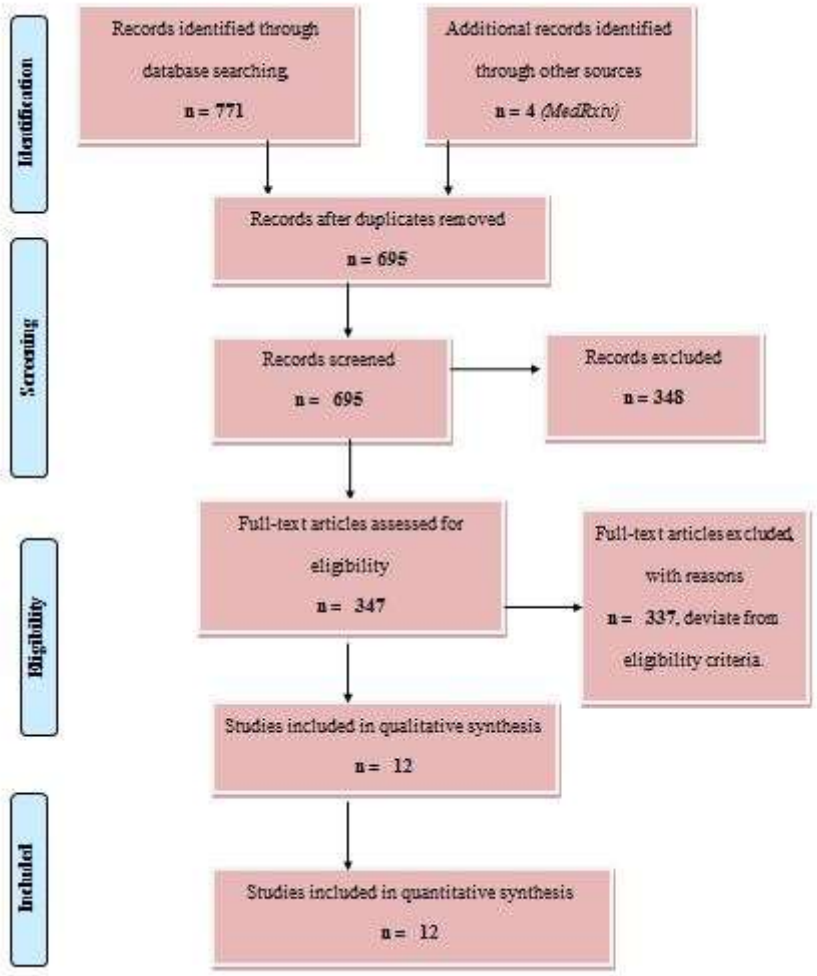

Figure 1: PRISMA flow of study selection process.

Results

Out of 12 studies included in the systematic review, a total of 2,834 patients enrolled. Of which 1326 patients received HCQ along with standard of care and 1508 patients received conventional standard of care. Non-HCQ arm was considered as Control arm (Table 1).

STUDY	TYPE	COUNTRY	CASE, CONTROL	INTERVENTION	OUTCOME
Gautret[12] et al	nRCT	France	Case=20 (6 patients received HCQ+ AZ) Control=16	600mg/day x 10 days	Virological cure on day 3.
Jun[13]et al	RCT	China	Case=15 Control=15	400mg/day x 5 days	No significant difference in viral cure between 2 groups on day 7.
Chen[14]et al	RCT	China	Case=31 Control=31	400mg/day x 5 days	Faster clinical recovery & improvement of pneumonia in CT chest.
Bo Yu[15] et al	Retrospective Cohort	China	Case=48 Control=520	HCQ 200 mg BD x 7-10 days	Mortality 18.8% (n=9) in HCQ group and 45.8% (n=238) in control group.
Geleris[16] et al	Prospective Cohort	US	Case=811 Control=565	HCQ 600 mg on day 1 followed by 400 mg for 4 days	No benefit (Respiratory failure requiring intubation in 31% in HCQ group and 14.8% in control group).
Magagnoli[17] et al	Retrospective cohort	US	Case=210 (of which n=113 received HCQ+AZ) Control=158	NR	No benefit. Risk of death was higher in HCQ arm.
Mahévas [18] et al	Retrospective Cohort	France	Case=84 Control=97	HCQ 600mg/day in first 48 hrs of hospitalisation	No benefit. 27.4% in HCQ and 24.1% in non HCQ group respectively, developed ARDS within 7 days, mortality

					on day 7, ICU care.
Barbosa[19]et al	qRCT	USA	Case=32 Control=31	HCQ 800mg/day on day1-2 followed by 200-400mg/day on day3-4.	Need of respiratory support and intubation on day5.
Tang[20]et al	RCT	China	Case=75 Control=75	HCQ 1200mg/day x 3 days, then 800mg/day x 2 weeks	No benefit. But on post-hoc analysis, there was reduction in CRP & symptoms in HCQ arm, adverse events.
Jihad[21] et al	Retrospective Cohort	UAE	Case=23 Control=11	HCQ 400mg BD on day 1, followed by 400mg OD for 10 days.	Benefit on virological clearance.
Singh[22]et al	Retrospective Cohort	USA	Case=910 Control=910	HCQ dosage regimen is not mentioned. However, 799 received azithromycin.	In 30 days, no much variation in mortality and need for mechanical ventilation when both arm was compared.
Rosenberg[23]et al	Retrospective Cohort	USA		HCQ 200mg-400mg OD or BD	Hospital Mortality, cardiac arrest, abnormal ECG findings.
: nRCT: Non-randomized controlled trial, RCT: Randomized controlled trial, HCQ: Hydroxychloroquine, AZ: Azithromycin, NR: Not reported, qRCT: ARDS: Acute Respiratory Distress Syndrome					

Table 1: Main characteristics of studies included in systematic review.

Outcomes

Virological clearance

Out of 12 studies reviewed, 5 studies (1 Non-randomized controlled trial, 3 randomized controlled trials, 1 retrospective cohort study) had a virological clearance with HCQ. Total number of patients enrolled is 312 (Gautret [12] et al: 36, Jun [13] et al: 30, Chen [14] et al: 62, Tang [20] et al: 150, Jihad et al: 34) (Table 2).

Author	Primary & Secondary Outcome	Results
Gautret[12] et al	Virological clearance, PCR negativity at day 6.	Yes, PCR negativity was higher in HCQ arm. i.e.: 2/16 in control arm and 14/20 in HCQ arm.
Jun[13]et al	PCR negativity of nasopharyngeal for Covid-19 at day 7 after randomisation.	Duration from hospitalisation to PCR negative was similar in HCQ arm and control arm. Radiological progression in CT chest was less (33.3%) than in Control arm (46.7%)
Chen[14]et al	Clinical & pulmonary recovery.	CT chest improved on day 6 in HCQ group 25/31 (80.6%) compared with the control group 17/31 (54.8%). Compared with the control arm, the body temperature recovery time was shortened significantly with HCQ. But did not specifically reported RT-PCR negativity.
Tang[20]et al	Primary endpoint was PCR negativity at day 28. Secondary outcome was clinical symptom improvement, disappearance of respiratory symptoms, normalisation of CRP, TNF-∝, lymphocyte count.	Negative conversion difference was not much between HCQ and Control group. A marked reduction in CRP in HCQ arm than Control arm. Rapid recovery of Lymphopenia in HCQ arm. Post-hoc analysis showed marked improvement in HCQ arm.
Jihad[21] et al	A reduction in time from confirmed positive nasopharyngeal swab to turn negative, RT-PCR assay (Virological Clearance).	47.8% (14/23) patients from HCQ arm and 90.9% (10/11) patients from Control arm tested negative on day 14.

Table 2: Virological clearance of SARS-CoV-2 in COVID-19 patients.

Safety Outcomes

Certain studies had reported occurrence of adverse events with HCQ. Seen adverse events include: nausea, vomiting, variations in LFT, diarrhoea, rashes, head ache, blurred vision and ECG abnormalities (Table 3).

Author	Adverse Event In HCQ Arm
Gautret[12] et al	Despite of PCR negativity, one among the HCQ arm died. One patient from HCQ arm ceased the therapy due to nausea and vomiting.
Jun[13]et al	4 patients (4/15, 26.7%) from HCQ arm had experienced transient diarrhoea and abnormal LFT.
Chen[14]et al	1 patient experienced head ache and 1 patient had incidence of rashes. 4/62 patients progressed to severe Covid-19, all patients are from HCQ arm.
Tang[20]et al	Higher incidence of adverse events was noted in HCQ arm (30%) whereas in control group it is 8.8%. The most common adverse event was diarrhoea in HCQ arm compared to control arm. Also one patient among HCQ arm had experienced blurred vision.
Rosenberg[23]	Higher incidence was on HCQ arm. A greater proportion of patients received HCQ + AZ experienced cardiac arrest (15.5%) and abnormal ECG findings (27.1%), whereas in HCQ alone is 13.7% and 27.3% respectively. In those with no HCQ and AZ, 6.8% and 14.0% respectively.

Table 3: Studies those reported occurrence of ADR in the HCQ Arm.

Normalisation of body temperature

2 studies, had reported outcomes on time to temperature normalization (Table 4).

Study	HCQ Arm	Control Arm
Jun[13]et al	0-3 days	0-2 days
Chen[14]et al	2.2±0.4 days	3.2±1.3 days

Table 4: Normalisation of body temperature.

Cough period

Among these, a study by Chen [14] et al had reported about the outcome on duration of cough. Here, the number of cough days was markedly lesser in HCQ arm than in Control arm (Table 5).

Study	HCQ ARM	CONTROL ARM
Chen[14]et al	2.0±0.2 days	3.1±1.5 days

Table 5: Studies which reported cough periods as outcome.

Discussion

The meta-analysis of 5 studies that reported rate of virological clearance or PCR negativity (n=312) found no benefit in HCQ arm, when compared to the control arm, i.e. did not observe any statistical difference between treatment and control group {OR, 1.863; 95% CI, 1.024 to 3.389; p=0.041} with a moderate heterogeneity (I^2 =70.3%, P=0.009) (Figure 2).

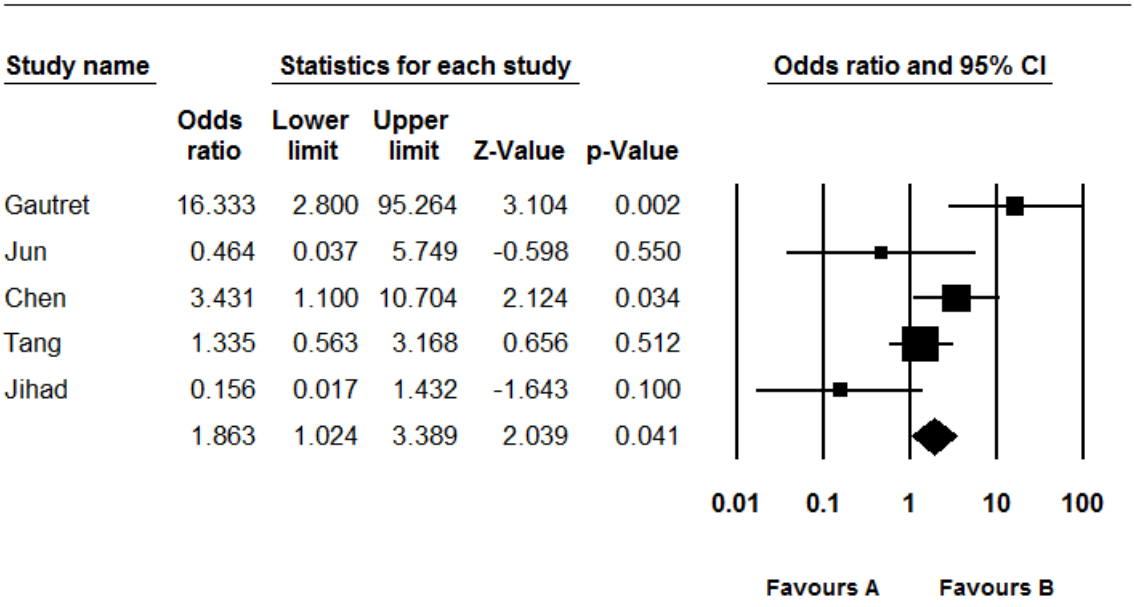

Figure 2: Meta-analysis of Virological clearance of 5 studies (A = HCQ ; B = Control).

Nevertheless, meta-analysis of 5 studies (n=1710) that reported about ADR outcomes found that, there

exist an increased risk of ADRs in HCQ arm when compared {OR, 2.648; 95% CI, 2.068 to 7.717; p=0.000}, with no heterogeneity (I^2 = 0%, P=0.417) (Figure 3).

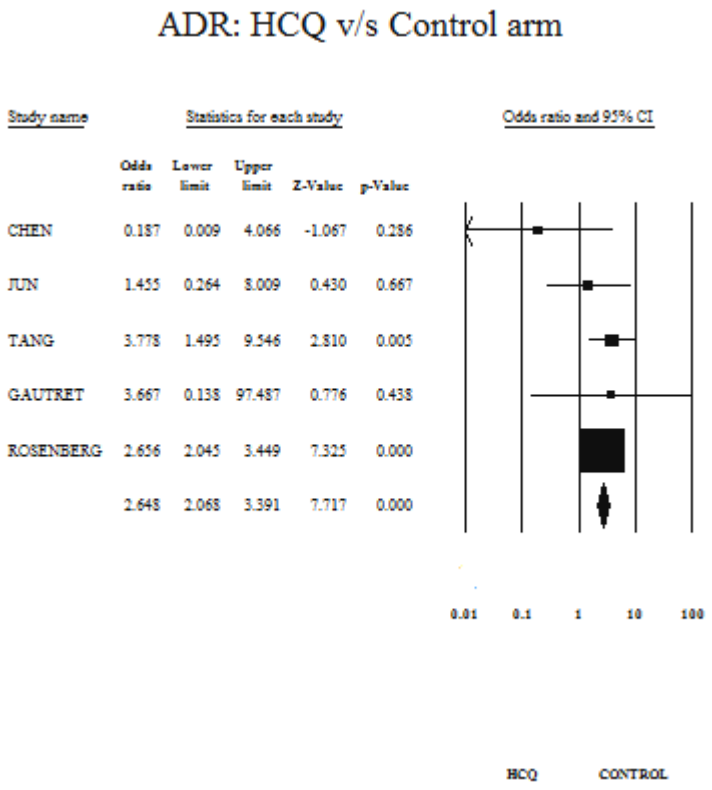

Figure 3: Meta-analysis of occurrence of ADR of 5 studies.

However meta-analysis of 6 studies (n=4,341) showed a significant increase in mortality in HCQ arm when compared with control arm {OR, 1.182; 95% CI, 0.981 to 1.425; p=0.079}, with substantial heterogeneity (I^2 = 82.0%, P=0.000) (Figure 4).

Our systematic review and meta-analysis included 12 studies, with a total of 2,834 patients, HCQ_n = 1326 & Std_n = 1508. Non-HCQ arm was considered as Control arm. Meta-analysis of 5 studies did not exhibit a benefit on virological clearance. Moreover meta-analysis on other outcomes of interest like ADR occurrence, mortality was more on HCQ arm when compared to non-HCQ arm or conventional therapy.

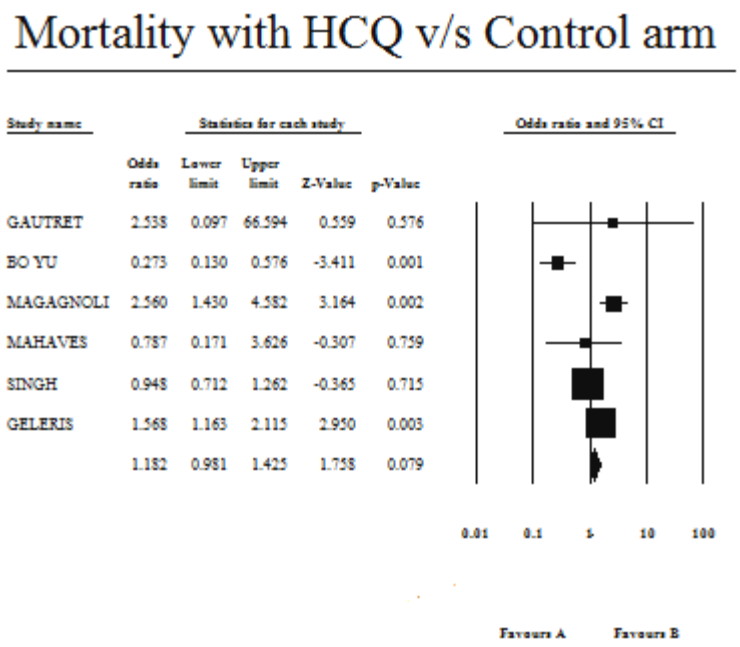

Figure 4: Mortality with HCQ v/s Control arm in Covid 19: A meta-analysis (n=4,341) (A = HCQ ; B = Control).

However our findings of lack of virological clearance efficacy, increased mortality, occurrence of ADR was consistent with various previously published articles which dealt with other viral diseases. CQ was ineffective in preventing and reducing influenza viral load in ferret models [24]. Also CQ did not prevent this infection (influenza) in a double- blinded placebo controlled human trial [25]. In a study, CQ shown to enhance Chikungunya viral load in various animal models [26].

Decreased efficacy of CQ/HCQ in COVID-19 can be of following reasons:

1. Most of the *in vitro* studies do pre-treatment protocols; here the cells are treated with the drug prior infecting with the tested virus. Whereas, in *in vitro* that compared pre treatment and post infection treatment shown CQ/HCQ have decreased antiviral efficacy if added after the infection. This may suggest that chronic prophylactic use of CQ/HCQ may be effective to prevent acquiring SARS-CoV-2 infection [27].
2. Two studies that did pharmacokinetics study revealed that the mean HCQ level was 0.46 µg/mL, in those treated with 600 mg/day which is lower than lowest effective *in vitro* concentration of 0.72 µM [12]. A study by Balevic et al [28] showed that average pdc of HCQ was below the lowest antiviral concentration for SARS-CoV-2 of 0.48 µg/mL in most studies [28].

Conclusion

This systematic review and meta-analysis revealed that HCQ has a reduced antiviral efficacy in reducing mortality, ADR occurrence and has a decreased virological clearance in patients with COVID-19. The drug should be used in patients with at most caution until there is positive results from RCTs with larger patient population.

References

1. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. (2020) Remdesivir and Chloroquine effectively inhibit the recently emerged novel corona virus (2019-nCoV) in vitro. Cell Res. 30(3):269-71.
2. Liu J, Cao R, Xu M, Wang X, Zhang H, et al. (2020) Hydroxychloroquine, a less toxic derivative of Chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 6:16.
3. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P. In vitro antiviral activity and projection of optimized dosing design of Hydroxychloroquine for the treatment of severe acute re (2020) spiratory syndrome corona virus 2 (SARS-CoV-2) Clin Infect Dis. 71(15):732-39.
4. Prajapat M, Sarma P, Shekhar N, Avti P, Sinha S, et al. (2020) Drug targets for corona virus: asystematic review. Indian J Pharmacol. 52(1): 56-65.
5. Thomé R, Moraes AS, Bombeiro AL, Santos Farias AD, Francelin C, et al. (2013) Chloroquine treatment enhances regulatory t cells and reduces the severity of experimental autoimmune encephalomyelitis. PLoS One. 8(6):e65913.
6. Gao J, Tian Z, Yang X. (2020) Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 14:72-73.
7. Singh AK, Singh A, Saikh A, Singh R, Misra A. (2020) Chloroquine and Hydroxychloroquine in the treatment of COVID-19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr. 14(3):241-46.
8. https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf
9. Singh AK, Singh A, Saikh A, Singh R, Misra A. (2020) Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis. Diabetes Metab Syndr. 14(4):589-96.
10. Elavarasi A, Prasad M, Seth T, Sahoo RK, Madan K, et al. (2020) Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis. J Gen Intern Med. 35(11):3308–3314
11. Shamseer L, Moher D, Clarke M. Ghersi D, Liberati A, et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 350:g7647.
12. Gautret P, Lagier J-C, Parola P. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 56(1):105949.
13. Jun C, Danping L, Li L, Liu P, Xu Q, et al. (2020) A pilot study of Hydroxychloroquine in treatment of patients with common corona virus disease-19 (COVID-19). J Zhejiang Univ Med Sci. 49(1):0-0.
14. Chen, J Hu, Z Zhang. (2020) Efficacy of Hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Version 2. medRxiv. p:20040758.
15. Yu B, Wang D W, Li C. (2020) Hydroxychloroquine application is associated with a decreased mortality in critically ill patients with COVID-19. MedRxiv (2020).
16. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, et al. (2020) Observational Study of Hydroxychloroquine in Hospitalised Patients with Covid-19. N Engl J Med. 382:2411-2418.
17. J Magagnoli, S Narendran, F Pereira, T Cummings, HW Hardin, et al. (2020) Outcomes of Hydroxychloroquine usage in United States veterans hospitalized with Covid-19.
18. Mahévas M, Tran VT, Roumier M, Chabet A, Paule R, et al. (2020) Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ. 369:m1844.
19. https://bibliovid.org/clinical-outcomes-of-hydroxychloroquine-in-hospitalized-patients-with-covid-19-a-302

20. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. BMJ. 369:m1849.
21. Jihad Mallat, Hamed F, Balkis M, Mohamed MA, Mooty M, et al. (2020) Hydroxychloroquine is associated with slower viral clearance in clinical COVID-19 patients with mild to moderate disease: A retrospective study. MedRxiv.
22. Singh S, Khan A, Chowdhry M, Chatterjee A. Outcomes of Hydroxychloroquine Treatment Among Hospitalised COVID-19 Patients in the United States- Real-World Evidence From a Federated Electronic Medical Record Network. MedRxiv. 2020 May 19.
23. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, et al. (2020) Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA.
24. Vigerust DJ, McCullers JA. (2007) Chloroquine is effective against influenza A virus in vitro but not in vivo. Influenza Other Respir Viruses. 1(5-6):189-92.
25. Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, et al. Chloroquine for influenza prevention: (2011) a randomised, double-blind, placebo controlled trial. Lancet Infect Dis. 11(9):677-83.
26. Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Labadie K, et al.. (2018) Paradoxical Effect of Chloroquine Treatment in Enhancing Chikungunya Virus Infection. Viruses. 10(5):268.
27. Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. (2020) Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. Autoimmun Rev. 19(7):102566.
28. Balevic SJ, Hornik CP, Green TP, Clowse MEB, Gonzalez D, et al. (2020) Hydroxychloroquine in Patients with Rheumatic Disease Complicated by COVID-19: Clarifying Target Exposures and the Need for Clinical Trials. J Rheumatol. jrheum.200493.