



Does Adding of Hydroxychloroquine to the Standard Care Provide any Benefit in Reducing the Mortality among COVID-19 Patients?: a Systematic Review

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Abstract

Hydroxychloroquine has been promoted for its use in treatment of COVID-19 patients based on in-vitro evidences. We searched the databases to include randomized and observational studies evaluating the effect of Hydroxychloroquine on mortality in COVID-19 patients. The outcome was summarized as odds ratios (OR) with a 95% confidence interval (CI). We used the inverse-variance method with a random effect model and assessed the heterogeneity using I^2 test. We used ROBINS-I tool to assess methodological quality of the included studies. We performed the meta-analysis using 'Review manager software version 5.3'. We identified 6 observational studies satisfying the selection criteria. In all studies, Hydroxychloroquine was given as add on to the standard care and effect was compared with the standard care alone. A pooled analysis observed 251 deaths in 1331 participants of the Hydroxychloroquine arm and 363 deaths in 1577 participants of the control arm. There was no difference in odds of mortality events amongst Hydroxychloroquine and supportive care arm [1.25 (95% CI: 0.65, 2.38); $I^2 = 80%$]. A similar trend was observed with moderate risk of bias studies [0.95 (95% CI: 0.44, 2.06); $I^2 = 85%$]. The odds of mortality were significantly higher in patients treated with Hydroxychloroquine + Azithromycin than supportive care alone [2.34 (95% CI: 1.63, 3.34); $I^2 = 0%$]. A pooled analysis of recently published studies suggests no additional benefit for reducing mortality in COVID-19 patients when Hydroxychloroquine is given as add-on to the standard care.

Keywords Hydroxychloroquine · Standard care · COVID-19 · Mortality · Meta-analysis · Azithromycin

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the pandemic of Corona Virus Disease 2019 (COVID-19). In severe cases, it results in acute respiratory distress syndrome, multi-organ failure and death (Zhou et al. 2020). Mortality rate varies from 11.0 to 28.3% of hospitalized patients (Zhou et al. 2020; Li et al. 2020). The risk of mortality is significantly higher in patients with old age, diabetes mellitus, and concomitant cardiac disease (Zhou et al. 2020; Huang et al. 2020; Inciardi et al. 2020). There is a need for interventions and effective drugs, which can reduce mortality in COVID-19 patients.

In the absence of specific drugs for COVID-19, Hydroxychloroquine is being promoted and used for its treatment based on the results of several in-vitro studies showing the efficacy of chloroquine and Hydroxychloroquine against influenza A and SARS-CoV-2 (Ooi et al. 2006; Vigerust and McCullers 2007; Yao et al. 2020). Chloroquine is suggested

to prevent viral attachment to host cells, interfere with terminal glycosylation of the cellular receptors, inhibit viral release and to block the production of various cytokines (Ooi et al. 2006; Vigerust and McCullers 2007; Yao et al. 2020; Vincent et al. 2005). Hydroxychloroquine is a hydroxyl analogue of chloroquine that shares a similar pharmacokinetics and efficacy profile with chloroquine. Animal toxicity studies suggested two to three times less toxicity of hydroxychloroquine than chloroquine (McChesney 1983). Hydroxychloroquine had also shown comparatively less retinal toxicity in humans than chloroquine (Finbloom et al. 1985). Hence, Hydroxychloroquine is preferred over chloroquine and is being utilized more than chloroquine. However, the clinical evidences about its efficacy, especially for reducing mortality rates in COVID-19 patients are limited. Now, some literatures for the effect of Hydroxychloroquine in the treatment of COVID-19 have been started publishing. In this systematic review, we aimed to find out early trends of mortality in COVID-19 patients treated with Hydroxychloroquine based on published literature.

Methods

We searched PubMed, Google Scholar, medrxiv.org, biorxiv.org, mediterranean-infection.com/pre-prints-ihu and CNKI. The search terms were: Hydroxychloroquine, supportive care, mortality, COVID-19, coronavirus, and clinical trial. The last search was run on 13th May 2020. There was no language restriction for inclusion of published articles.

Selection Criteria

We focused on the comparative clinical studies (randomized and non-randomized) of Hydroxychloroquine with other treatment modalities, conducted on confirmed COVID-19 patients. We considered studies irrespective dose and duration of Hydroxychloroquine. We considered those studies describing mortality as an outcome or provide sufficient data to extract in Hydroxychloroquine and control arms. We excluded non-comparative, in-vitro and animal studies.

Data Extraction

We extracted following data in a Microsoft Excel sheet, 2016: first author, publication year, country of study site, study design, baseline data in treatment arms (age, gender, severity of disease), Hydroxychloroquine (dosage, duration and route of administration), supportive care, study population characteristics and mortality in treatment arms.

Risk of Bias Assessment of Included Studies

Two investigators assessed the methodological quality of the included studies as per “risk of bias in non-randomized studies - of interventions (ROBINS-I)” tool (Sterne et al. 2016).

Outcomes and Data Synthesis

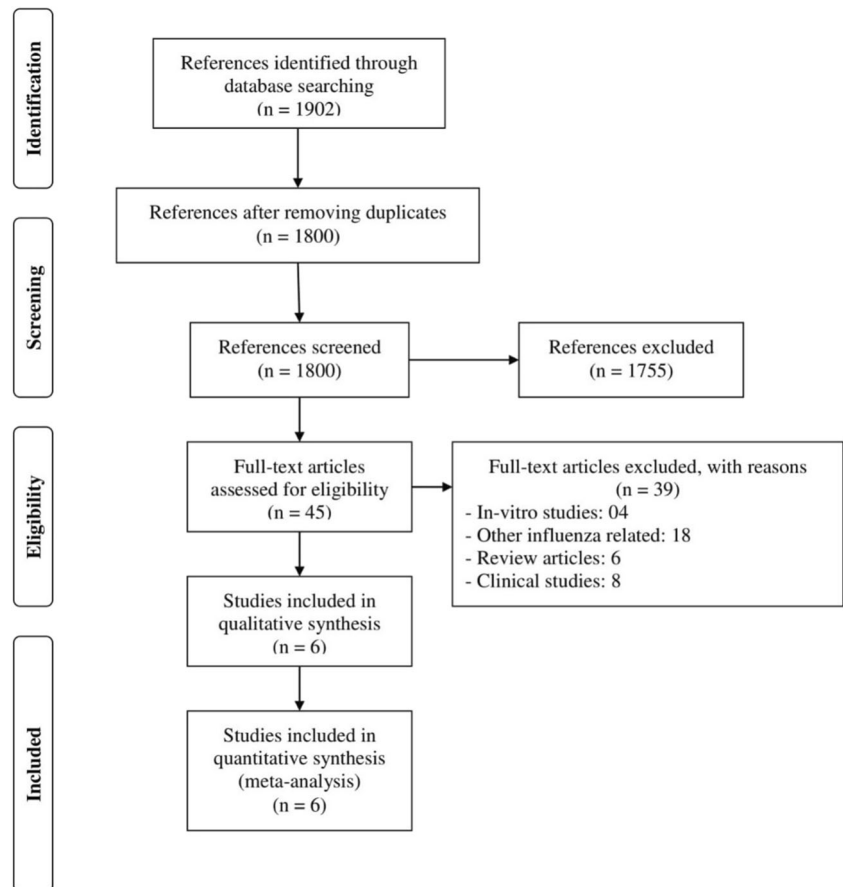
The primary outcome variable was to compare mortality between patients who received Hydroxychloroquine and supportive care at the end of the study period. The secondary outcomes were to compare the mortality between patients who received a) Hydroxychloroquine + Azithromycin and supportive care and b) Hydroxychloroquine + Azithromycin and Hydroxychloroquine alone at the end of the study period. The mortality outcome, a dichotomous variable, was summarized as odds ratio (OR) with 95% CI. The meta-analytic summary was pooled using the inverse-variance method. We used either fixed or random-effect model based on the heterogeneity present. In the absence of substantial heterogeneity, a fixed-effect model was used to estimate the meta-analytic summary. We assessed heterogeneity using I^2 test and publication bias through a ‘funnel plot’. We performed a sensitivity analysis of the primary outcome based on the characteristics of study participants (demographics and severity status of participants) and time point for the evaluation of the mortality outcome. In the case of demographics, the primary outcome was estimated by excluding studies with non-comparable age and/gender population in hydroxychloroquine and supportive care arms. Similarly, studies with different severity status population at baseline were excluded. In case of time-point evaluation, studies were divided based on a minimum follow up duration to observe mortality for each patient. It was possible to categorise studies into two groups: ≤ 14 and > 14 days follow up duration. It was not possible to perform a sensitivity analysis based on the dose and duration of Hydroxychloroquine, and co-morbidities. We also performed sensitivity analysis of the studies showing the moderate risk of bias in ‘overall assessment’ of ROBINS-I tool.

The meta-analysis was conducted through ‘Review manager software version 5.3’.

Results

Out of 1902 search items, we retrieved 14 clinical studies (3 randomized and 11 non-randomized) analyzing the effects of Hydroxychloroquine in COVID-19 patients [Fig. 1]. Ten studies were comparative. Three randomized controlled studies reported zero mortality in Hydroxychloroquine and supportive care arms (Chen et al. 2020a, b; Tang et al. 2020). One observational study compared Zinc as add-on to Hydroxychloroquine and Azithromycin (Carlucci et al.

Fig. 1 Study selection – PRISMA flow diagram



2020). It was possible to extract mortality data of Hydroxychloroquine and control arm in six non-randomized studies (1 prospective, 5 retrospective studies) hence, included in the analysis (Gautret et al. 2020; Geleris et al. 2020; Magagnoli et al. 2020; Mahévas et al. 2020; Rosenberg et al. 2020; Yu et al. 2020).

Table 1 shows the general characteristics of all the included studies like study design, demographics, intervention and severity status details. The findings of risk of bias assessment in individual studies are in Supplementary file (Supplementary Table 1). Four studies were considered of having a moderate risk of bias (Geleris et al. 2020; Mahévas et al. 2020; Rosenberg et al. 2020; Yu et al. 2020) and two were of serious (Gautret et al. 2020; Magagnoli et al. 2020) in the overall assessment.

In Gautret P et al. of 42 patients, 20 patients received Hydroxychloroquine, 6 Hydroxychloroquine + Azithromycin and 16 supportive care treatments. Gautret P et al. excluded 6 patients who received Hydroxychloroquine due to loss to follow up, clinical worsening and death. We considered one death in Hydroxychloroquine arm on day 3 based on the intention to treat principle and included in the study. Gautret P et al. included the patients aged ≥ 18 years and the age of patients in Hydroxychloroquine-treated arm was

higher (51.2 vs. 37.3 years) than the supportive care arm (Gautret et al. 2020).

In the case of Geleris J et al., 811 patients received Hydroxychloroquine and 565 supportive care. Some of the patients had also received sarilumab, remdesivir and Azithromycin as a part of the treatment. It was not possible to exclude patients receiving other interventions in both arms, and patients who did not receive Hydroxychloroquine were considered as a supportive care group. A total of 85.9% of patients received Hydroxychloroquine within 48 h of admission to the emergency department. Participants of Hydroxychloroquine and control arms were comparable for the age group and gender. Hydroxychloroquine-treated patients had a lower ratio of arterial oxygen partial pressure to fractional inspired oxygen (Pao₂:Fio₂) at baseline (median: 233 vs. 360 mmHg) than control arm patients (Geleris et al. 2020).

In the case of Magagnoli J et al. of 368 patients, 97 patients received Hydroxychloroquine, 113 Hydroxychloroquine + Azithromycin and 158 supportive care treatments. Magagnoli J et al. included patients with age ≥ 65 years. All three treatment arms were comparable for age, gender, body mass index, diabetes mellitus, cardiovascular diseases, chronic lung and kidney diseases. However, the proportions of

Table 1 General characteristic of the included studies

Study ID, Location and total number of participants	Design	Age years	Number male/ female	Details of study groups		Follow up duration of mortality	Severity of disease
				Test	Comparator		
Gautret et al. 2020 (France) <i>n</i> = 42	Non-randomized controlled trial	Mean ± SD HCQ/ HCQ + AZT: 51.2 ± 18.7 Control: 37.3 ± 24.0 Total: 45.1 ± 22.0	15/21	HCQ 600 mg/d (200 mg TDS) for 10 days (<i>n</i> = 20) HCQ 600 mg/d + AZT 500 mg on day1 f/b 250 mg/d, the next 4 days (<i>n</i> = 6)	Control (<i>n</i> = 16) Details not specified	14 days	6 asymptomatic (2 in HCQ/ HCQ + AZT) 22 URTI (12 in HCQ/ HCQ + AZT) 8 LRTI (6 in HCQ/ HCQ + AZT) 6 loss to follow up in HCQ group
Geleris et al. 2020 (USA) <i>n</i> = 1376	Retrospective study	Frequency distribution HCQ: < 40 year: 80 40–59 year: 217 60–79 year: 367 ≥ 80 year: 147 No HCQ: < 40 year: 105 40–59 year: 142 60–79 year: 220 ≥ 80 year: 98	781/595	HCQ (<i>n</i> = 811) 600 mg BD on day 1, f/b 400 mg/d for 4 addi- tional days given to moderate to severe pa- tients	No HCQ (<i>n</i> = 565) Details of standard care not specified	≥ 17 days	Pao2:FiO2 ratio at baseline (HCQ median: 233 vs. supportive care 360 mmHg)
Magagnoli et al. 2020 (USA) <i>n</i> = 368	Retrospective study	Median (IQR) HCQ: 70 (60–75) HCQ + AZT 68 (59–74) Control: 69 (59–75)	368/0	HCQ (<i>n</i> = 97) HCQ + AZT (<i>n</i> = 113) (Dose and duration not specified)	No HCQ (<i>n</i> = 158) Details of standard care not specified	Followed up until discharge or death	SpO ₂ ≥ 95 HCQ (62.9%), HCQ + AZT (57.5%), Supportive care (73.4%)
Mahevas et al. 2020 (France) <i>n</i> = 181	Retrospective study	Median (IQR) HCQ: 59 (48–67) No HCQ: 62 (53–68) Control: 60 (52–68)	128/53	HCQ (<i>n</i> = 84) 600 mg/d	No HCQ (<i>n</i> = 97) Details of standard care not specified	7 days	Initial severity was well balanced between the groups. All co morbidities were less frequent in the HCQ group.
Rosenberg et al. 2020 (USA) <i>n</i> = 1438	Retrospective study	Median years HCQ: 65.5 HCQ + AZT: 61.4 AZT: 62.5 Neither drug: 64	858/580	HCQ 200–600 mg OD/BD (<i>n</i> = 271) HCQ + AZT (<i>n</i> = 735) AZT 200–500 mg once/ OD/ BD (<i>n</i> = 211)	Neither drug (<i>n</i> = 221) Details of standard care not specified	≥ 27 days	SpO ₂ > 93 HCQ (70.6%), HCQ + AZT (56.5%), Supportive care (83.3%) ICU admission within 0–1 day: HCQ (8.1%), HCQ + AZT (17.1%), Supportive care (8.5%) Mechanical ventilation within 0–1 day: HCQ (5.9%),

Table 1 (continued)

Study ID, Location and total number of participants	Design	Age years	Number male/ female	Details of study groups		Follow up duration of mortality	Severity of disease
				Test	Comparator		
Yu et al. 2020 (China) <i>n</i> = 568	Retrospective study	Median (IQR) HCQ: 68 (60–75) Control: 68 (57–77)	358/210	HCQ 400 mg/d (200 mg BD) for 7–10 days (<i>n</i> = 48)	No HCQ (<i>n</i> = 520) Details of standard care not specified	Not specified	HCQ + AZT (13.3%), Supportive care (5.2%) Only critically ill patients included Mechanical ventilation (58.3% in HCQ, 61.7% control)

CQ Hydroxychloroquine, AZT Azithromycin, UR77 Upper respiratory tract infection, LRT77 Lower respiratory tract infection, *SD* Standard deviation, *IQR* Interquartile range, *OD* Once daily, *BD* Twice daily, *TDS* Thrice a day

patients with a SpO₂ level ≥ 95 at baseline were significantly lower in patients who received Hydroxychloroquine (62.9%) and Hydroxychloroquine+Azithromycin (57.5%) than supportive care group (73.4%) (Magagnoli et al. 2020).

In the case of Mahévas Met al., 84 received Hydroxychloroquine and 97 control treatment. Seventeen patients in Hydroxychloroquine arm also received Azithromycin and none in the control arm. Patients who did not receive Hydroxychloroquine were considered as a supportive care group. Both groups were comparable for age, gender, time from symptom onset to admission and oxygen saturation at admission. Patients receiving Hydroxychloroquine and supportive care group were differed in the percentage of diabetes mellitus, cardiovascular diseases, chronic lung and kidney diseases (Mahévas et al. 2020).

In the case of Rosenberg E et al., 54 received Hydroxychloroquine, 189 Hydroxychloroquine +Azithromycin, 211Azithromycin alone and 221 patients received neither drug. Patients who received neither drug were considered a supportive care group. Patients who received Azithromycin alone were excluded from the analysis in our systematic review. The median lag period for initiation of Hydroxychloroquine was 1 day(Interquartile range: 1–2). All three treatment arms were comparable for the median age. The study groups differed in the percentage of male population, obese, diabetes mellitus, cardiovascular diseases and chronic lung disease. Patients receiving Hydroxychloroquine and supportive care groups were comparable for the mechanical ventilation and intensive care admission within 0–1 day of admission (Rosenberg et al. 2020).

In Yu B et al., 48 received Hydroxychloroquine and 520 control treatments. The authors did not specify the other treatment modalities in study arms. Patients who did not receive Hydroxychloroquine were considered as a supportive care group. The authors only included critically ill patients. Patients with any of the following categories were considered as critically ill: respiratory failure requiring mechanical ventilation, septic shock or other organ failure requiring ICU admission. However, they have not specified the lag period of the start of treatment arms in the included patients. Hydroxychloroquine and control groups were comparable for the age, gender and severity of disease (Yu et al. 2020).

Hydroxychloroquine Versus Supportive Care

Studies reported a total of 251 deaths in 1331 participants of the hydroxychloroquine arm and 363 in 1577 participants of the control arm. Three reported higher odds of mortality with Hydroxychloroquine than supportive care (Geleris et al. 2020; Magagnoli et al. 2020; Rosenberg et al. 2020). In

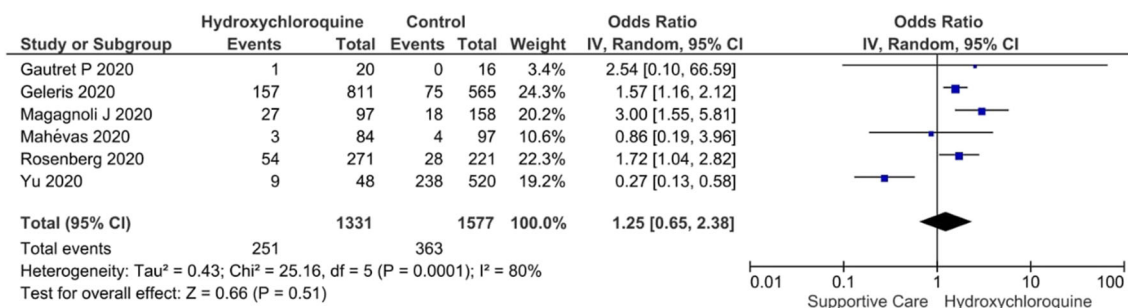


Fig. 2 Meta-analytic summary of mortality data(Hydroxychloroquine versus supportive care) through random effect model

contrast, Yu B et al. observed a significant reduction in mortality in patients receiving Hydroxychloroquine than supportive care (Yu et al. 2020). As shown in Fig. 2, the odds of mortality did not differ between Hydroxychloroquine and control arm [1.25 (95% CI: 0.65, 2.38)]. There was significant heterogeneity (I² = 80%) in this outcome. The funnel plot was asymmetrical on visual inspection [Fig. 3]. Insensitivity analysis, four studies had a comparable study populations concerning age and gender in Hydroxychloroquine and supportive care arm (Geleris et al. 2020; Magagnoli et al. 2020; Mahévas et al. 2020; Yu et al. 2020). Their meta-analytic summary was 1.07 [95% CI: 0.41, 2.79] I² = 88%. Three studies had comparable severity status of the study population at baseline between Hydroxychloroquine and supportive care arm (Mahévas et al. 2020; Yu et al. 2020). Their meta-analytic summary was 0.74 [95% CI: 0.19, 2.86], I² = 88%. Two studies each belonged to a minimum follow up duration of ≤14 (Gautret et al. 2020; Mahévas et al. 2020) and > 14 days (Geleris et al. 2020; Rosenberg et al. 2020). The other two studies did not specify the participant follow up duration. The meta-analytic of ≤14 and > 14 days follow up duration studies were 1.05 (95% CI: 0.26, 4.17), I² = 0% and 1.24 (95% CI: 1.24, 2.08), I² = 0%, respectively. The sensitivity analysis of moderate risk of bias studies suggested no difference in odds

of mortality between hydrxychloroquine and supportive care arm [0.95 [(95% CI: 0.44, 2.06), I² = 85%]].

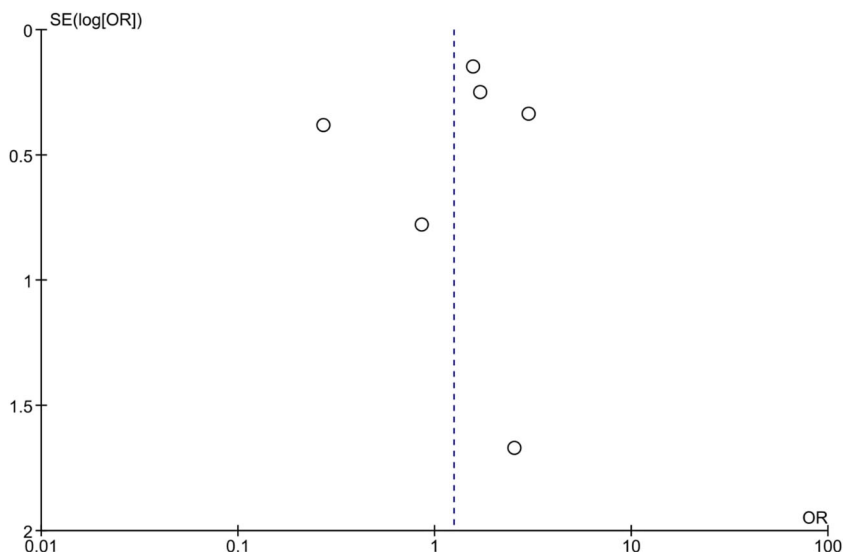
Hydroxychloroquine + Azithromycin Versus Supportive Care

As shown in Fig. 4, three studies reported a total of 214 deaths in 854 participants of the hydroxychloroquine + Azithromycin arm and 46 in 395 participants of the supportive care arm. The odds of mortality were significantly higher in patients receiving hydroxychloroquine + Azithromycin than those who received supportive care [2.34 (95% CI: 1.63, 3.34); I² = 0%].

Hydroxychloroquine + Azithromycin Versus Hydroxychloroquine

As shown in Fig. 5, three studies reported a total of 214 deaths in 854 participants of the Hydroxychloroquine + Azithromycin arm and 81 in 388 participants of the Hydroxychloroquine arm. The odds of mortality did not differ between Hydroxychloroquine + Azithromycin and Hydroxychloroquine arm [1.07 (95% CI: 0.58, 1.98); I² = 67%].

Fig. 3 The funnel plot (Hydroxychloroquine versus supportive care)



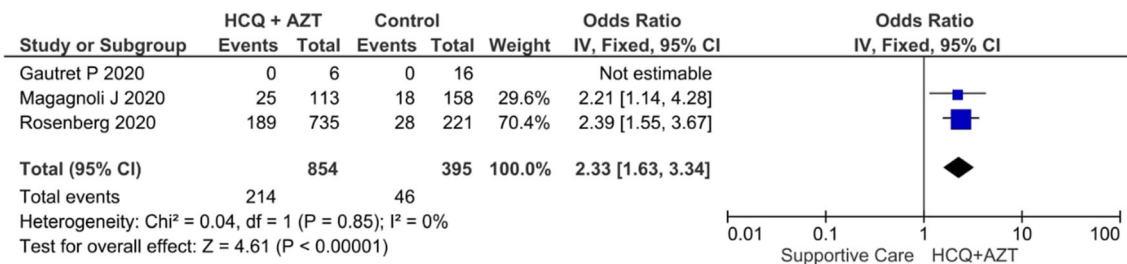


Fig. 4 Meta-analytic summary of mortality data (Hydroxychloroquine+Azithromycin versus supportive care) through fixed effect model

Discussion

The present meta-analytic summary emphasizes a cautious approach in the widespread clinical use of Hydroxychloroquine ± Azithromycin in the absence of clinical evidence of its efficacy in randomized controlled trials. There is tremendous pressure on health care professionals and researchers across the world to curb the effect of SARS-CoV-2. Being highly contagious and associated with higher mortality demand the early identification of effective interventions, including therapeutics and vaccines. It has promoted the widespread use of various treatment modalities based on in-vitro evidences. Hydroxychloroquine is one of such treatment modalities, which is being given priority due to its proven and known safety records of its use in patients of malaria, systematic lupus erythematosus, and rheumatoid arthritis. However, the present meta-analytic summary of six observational studies suggests that the use of Hydroxychloroquine did not reduce mortality in COVID-19 patients. A similar trend was observed with the moderate risk of bias studies. The sensitivity analysis of studies based on demographics, severity status and shorter duration follow up suggest trend of no benefit with the use of Hydroxychloroquine. Studies of longer duration follow-up (>14 days) suggest trends of higher mortality in Hydroxychloroquine arm. It emphasizes the need for active monitoring of mortality data and risk-benefit ratio from ongoing randomized studies of Hydroxychloroquine in COVID-19 patients. The future studies should have longer duration follow up of the mortality data.

There is a possibility of doing more harm than providing the benefits with the use of Hydroxychloroquine especially with the addition of Azithromycin. The risk of mortality was significantly higher in patients who received

Hydroxychloroquine as well as Azithromycin. Three included studies of United State suggest a higher risk of mortality due to Hydroxychloroquine, while one Chinese study suggests its possible benefit. This could be because of different dose, duration and selection of patients in Hydroxychloroquine arm. Included studies used Hydroxychloroquine arbitrarily. They could have varying strategy of its use, or its selection based on discretion of treating physician. However, it represents the outcome of real-world practice with the use of Hydroxychloroquine. This simply cannot be ignored just of the non-randomized nature of the studies especially, when cardiac safety issues raised with its use with Azithromycin in COVID-19 patients. Two recent observational studies reported significant QT interval prolongation with increasing drug exposure (Ramireddy et al. 2020; Chorin et al. 2020). Studies reported one or two out of ten COVID-19 patients treated with Hydroxychloroquine±Azithromycin developed critical QT interval prolongation. The risk of cardiac toxicity is higher with the combination of Hydroxychloroquine and Azithromycin. These patients were at risk of developing tachyarrhythmia (Ramireddy et al. 2020; Chorin et al. 2020). Similarly, Rosenberg E et al. reported overall significantly higher percentage of arrhythmia in patients who treated with hydroxychloroquine+Azithromycin (20.4%) than Hydroxychloroquine alone (16.2%) and supportive care (10.4%) (Ramireddy et al. 2020). A recently, the US FDA has advised the caution against use of Hydroxychloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of cardiac arrhythmias (US FDA 2020).

The clinical evidences of randomized controlled trials are not unidirectional (Chen et al. 2020a, b; Tang et al. 2020). They do not suggest a clear benefit of hydroxychloroquine in COVID-19 patients. They showed no benefits of

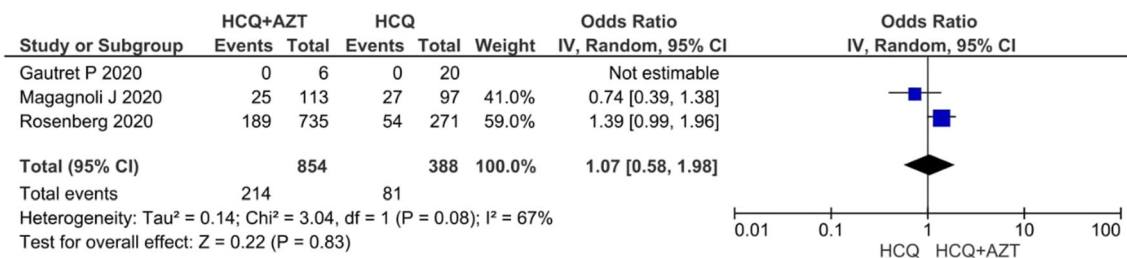


Fig. 5 Meta-analytic summary of mortality data(Hydroxychloroquine+Azithromycin versus Hydroxychloroquine) through random effect model

Hydroxychloroquine with respect to virological cure (Chen et al. 2020a; Tang et al. 2020). They showed conflicting results with the symptomatic relief (Chen et al. 2020a; Tang et al. 2020). Chen J et al. did not observe a difference in alleviation of fever between hydroxychloroquine and supportive care. Chen Z et al. and Tang W et al. observed an earlier symptomatic relief in hydroxychloroquine-treated than supportive care treated patients.

This study has several limitations. The findings are based on observational studies. Baseline characteristics are less likely to be comparable in observational than clinical trials. The currently published RCTs of Hydroxychloroquine were of open labelled in design and of the small sample size to report mortality data. We have not studied other parameters like virological and clinical improvements. Our findings on mortality should be interpreted cautiously due to the inclusion of studies with differences in age group, co-morbidity, co-interventions and severity of disease in Hydroxychloroquine and supportive care patients. Evidence from multi-centric double blind randomized controlled trial should be confirmatory in this regards.

In conclusion, current evidence suggests hydroxychloroquine did not improve mortality outcome in COVID-19 patients. Patients who received Hydroxychloroquine and Azithromycin are at higher risk of mortality than those who received neither of these drugs. This combination should be avoided in the treatment of COVID-19 patients.

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Author Contributions TKP, MB, BDK, PBP and HLB designed the systematic review. TKP and MB conducted the literature search and extracted the data. TKP, MB and PBP analyzed the data. TKP, MB, BDK, PBP and HLB interpreted the data. TKP wrote the first draft and revised subsequent drafts with the inputs of MB, BDK, PBP and HLB.

Compliance with Ethical Standards

Conflict of Interest None to declare.

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