Indonesian Journal of Pharmacy

VOL 32 (3) 2021: 266–279 | REVIEW ARTICLE

Narrative Review: Risk-Benefit Analysis of Hydroxychloroquine and Chloroquine Treatment in COVID-19

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Info Article

Submitted: 13-01-2021
Revised: 20-07-2021
Accepted: 14-09-2021

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ABSTRACT

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are highly prescribed as medications for COVID-19 infection, although no robust or convincing data has yet been published about their efficacy in COVID-19 patients. Therefore, risk and benefit assessment is necessary for deciding to prescribe these drugs in COVID-19 patients in hospital settings. We systematically searched from the MEDLINE Database, investigating the benefits and risks of HCQ and CQ among COVID-19 patients. All records were searched using the search terms Hydroxychloroquine, Chloroquine, COVID-19, and SARS-CoV-2. The selection criteria include all clinical trials and observational studies. We found 11 records on benefits and 7 records on risks of HCQ and CQ in COVID-19 patients after following inclusion and exclusion criteria. Clinical trial and observational studies have shown that HCQ is very limited, particularly in reducing mortality or proving clinical improvement. Similarly, seven observational studies have estimated the cardiac event in the use of HCQ or CQ in COVID-19. Even though there was no increase in death, these studies reported an increased risk of prolonging QT-interval in high proportion and other cardiac events such as arrhythmia, *torsade de pointes*, and conduction block. We conclude that the beneficial effect of HCQ and CQ in COVID-19 remains very limited. However, both medications have independently been shown to increase the risk for QT-interval prolongation, drug-induced torsades de pointes/TdP (a form of polymorphic ventricular tachycardia), and drug-induced other cardiac events in other populations

Keywords: Chloroquine, Hydroxychloroquine, COVID-19, risk, benefits

INTRODUCTION

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are quinoline drugs widely used to treat malaria. But recently it has been used also to treat rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). CQ and HCQ are currently highly prescribed as medications for COVID-19 infection, although no robust or convincing data has yet been published about these drug's efficacy in COVID-19. CQ/HCQ is used for COVID-19 given for a 10-14-day course in many places across the countries. CQ and HCQ have potential benefits in treating COVID-19 due to their antiviral, immunomodulator, and anti-inflammatory effects (Jorge *et al*., 2018; Lim *et al*., 2009; Schrezenmeier & Dörner, 2020). Nevertheless, establishing the safety of these drugs, related to QT interval prolongation on the electrocardiogram, remains challenging in COVID-19 patients who use many drug regimens and had several comorbidities. Even though the cumulative dose and duration of this drug in COVID-19 was not relatively low, but the low-risk management could lead to a cardiac adverse event. Moreover, the toxic effect in cardiac may occur even when it is used in low cumulative doses. Therefore, risk and benefit assessment is necessary to decide whether to prescribe these drugs in patients with COVID-19 in clinical practice. This review aimed to assess the risk and benefits of use CQ/HCQ in COVID-19.

Methods

We systematically searched a major medical database (MEDLINE Database) to investigate the benefits and risks of hydroxychloroquine and chloroquine in COVID-19 patients. All records were searched using the following search terms: ((((("Hydroxychloroquine"[Mesh]) OR ("Chloroquine"[Mesh])) OR (Hydroxychloroquine[Title/Abstract])) OR (Chloroquine[Title/Abstract])) AND ((((("COVID-19"[Mesh]) OR ("SARS-CoV-2"[Mesh])) OR (SARS-CoV-2[Title/Abstract])) OR (COVID-19[Title/Abstract])). The selection criteria include all clinical trials and observational studies. We found 11 records on benefits and 7 records on risks of HCQ / CQ in COVID-19 patients after following inclusion and exclusion criteria. Searches are current as of November 30th, 2020.

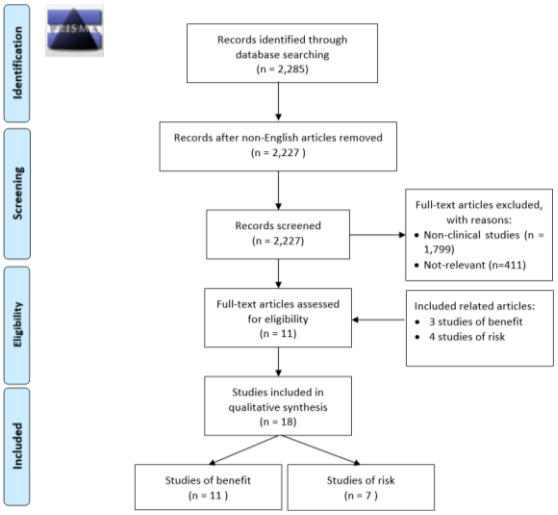

Figure. 1. PRISMA Flowchart

The Benefits of Chloroquine and Hydroxychloroquine in COVID-19 patients

HCQ and CQ are widely used for more than several decades, and it is part of list of essential medicines the World Health Organization (WHO). These drugs are also low-cost, and their clinical safety profiles have been established (Colson *et al*., 2020). However, safety data of HCQ and CQ for COVID-19 treatment remains unclear.

The studies *in-vitro* shave detected the benefit of the CQ/HCQ as antiviral drugs. These studies have demonstrated that these regimens have properties as broad-spectrum antiviral. The mechanism ction of this drug was interfering the fusion process of virus in macrophages, and also other antigen-presenting cells through decreasing the pH. In addition, CQ could also change the glycosylation at the receptors of coronaviruses (Lim *et al*., 2009). HCQ is similar to CQ but more soluble, and acts by increasing the pH and confers antiviral effects. Moreover, hydroxychloroquine has effect on modulating the activated immune cells, caused downregulates the expression of Toll-like receptors (TLRs) including TLR-mediated signal transduction, and reduction of the production of interleukin-6 (Jorge *et al*., 2018; Schrezenmeier & Dörner, 2020).

The *in vitro* study of HCQ and CQ in SARS-CoV-2 has been published recently. This study showed HCQ (EC50=0.72μM) was fmore potent than chloroquine. Therefore, based on the Physiologically Based Pharmacokinetic (PBPK) model, recommended dose for COVID-19 is 400mg orally twice daily for loading dose of HCQ, and 200mg twice daily for four days for maintenance dose, and when it is given at 500mg two times for 5 days would reach three times the potency of CQ (Yao *et al*., 2020).

Two recent trials suggested that the HCQ may have a positive effect on the viral load (Gautret *et al*., 2020a), clinical improvement, and time to recovery (Z. Chen *et al*., 2020). Nevertheless, these two clinical trials had several limitations. The limitations of the first study were a relatively small cohort of patients, only 20 patients received HCQ (six of whom also received azithromycin) and 16 controls; with 6 days observation period; and non-randomized trial. Another issue is selection bias, imbalance of patient's characteristics at baseline between HCQ and control group, and there was no clinical improvement in outcome measured (Taccone *et al*., 2020). And second study showed that additional hydroxychloroquine into the standard treatment was shorter time to clinical recovery (fever and cough) compared to standard treatment alone; considering 13 patients had mild symptom, so it could not be extrapolated this result into critically ill patients. Another study with small number of patients (11 patients) with COVID-19 has reported a persistence of SARS-CoV-2 in nasopharyngeal swab in 8 out of 10 patients receiving HCQ. Furthermore, three randomized controlled trials (RCT) suggested that the HCQ/CQ may have no significant effect on conversion rate of SARS-CoV-2 (Huang *et al*., 2020), clinical status improvement (Cavalcanti *et al*., 2020), and mortality (RECOVERY Trial, 2020). Two of those randomized controlled open-label trials (Cavalcanti *et al*., 2020; RECOVERY Trial, 2020) had involved many patients comparing HCQ and

standard of care, while one trial had a small number of patients comparing chloroquine and lopinavir/ritonavir. Even though a combined randomized clinical trial (RCT) and observational retrospective study in Taiwan showed the reduction of median time to reach negative COIVD-19 test in the HCQ intervention group compared to the standard care only (5 days vs. 10 days), but the difference was not significant (C.-P. Chen *et al*., 2020).

A cohort study with HCQ (800mg + 400mg as loading dose, followed by a 400mg a day as maintenance dose additional to standard treatments (antiviral, immunomodulatory, and anti-inflammatory drugs) compared to standard treatment alone have higher mean survival by 1.4-1.8 times in patients with any severity of COVID-19 (de Novales *et al*., 2020). Another cohort study in China also favored HCQ use (200mg two times day for 7-10 days) in addition the standard treatment (antibiotics and anti-viral) on reducing mortality in critically ill patients and improving cytokines IL-6 compared to standard treatment alone (Yu *et al*., 2020). On the other hand, a French study (case series report), although larger, had no control arms and no outcome on viral loads of infected patients. This study has shown clinical improvement of patients and made this regimen used by clinicians worldwide. Another study from four French tertiary care centers in acute respiratory distress syndrome (ARDS) patients caused by COVID-19 has shown that HCQ has no association with improvement of overall survival at day 21 (Mahévas *et al*., 2020) (Table I).

For prophylaxis purposes, HCQ was also unproven to prevent the COVID-19 infection. Therefore, a clinical trial in the US and Canada was conducted in adults with high risk of exposure, as defined of who have household or occupational contact with someone confirmed COVID-19 at ≤6 feet within ≥10 minutes without wearing face mask or face shield. The study showed that the incidence of COVID-19 did not significantly differ between participants receiving HCQ and placebo, with an absolute difference was −2.4% points (95%CI −7.0-2.2; P = 0.35) (Boulware *et al*., 2020).

However, based on the limitations of the clinical trial design and observational studies above, the beneficial effects of CQ/HCQ in COVID-19 remain unclear. Therefore, WHO has initiated the Solidarity Trial in hundreds of countries to evaluate the safety and efficacy of CQ/HCQ on COVID-19. This large randomized clinical trial, open-label, had been stopped earlier because hydroxychloroquine showed no benefit in reducing mortality in all severity hospitalized patients with COVID-19. (Mahase, 2020)

The Risk of HCQ and CQ

Adverse drug reactions of HCQ/CQ are known for many years, including their cardiotoxicity. This ADR is due to dysfunction of lysosomal and glycogen and phospholipids accumulation (Thomé *et al*., 2013). The effect on cardiotoxic of HCQ/CQ was related to the cumulative dose. High dosages of CQ/HCQ have shown increase risk cardiac events such as atrioventricular blocks and cardiac arrest. (Ladipo *et al*., 1983)

In some reported cases, if baseline QT interval was found prolonged, closed monitoring should be performed to mitigate the risk of ventricular arrhythmias. If hypokalemia causes QTc interval prolongation, low-level potassium in severe COVID-19 may increase potential arrhythmogenic activity of CQ/HCQ. It has been know that CQ was more frequently causing conduction defects in comparison with HCQ. An observational study in 85 patients treated with HCQ for minimum one year, and had no history of cardiac disease, HCQ was approved safe, and was reported developing of right bundle branch block (RBBB) in only 2 patients, and one patient was developing of left bundle branch block (Costedoat-Chalumeau *et al*., 2007)

There was no instance of QT prolongation or blocking atrioventricular. Abnormalities of echocardiograms (ECG) were reported among patients using high doses of CQ/HCQ. An systematic review reported that cardiac complications associated with CQ/HCQ were frequently in female (65%), median age of 56 years old (Chatre *et al*., 2018), and it was estimated for almost 85% from all cardiac complications cases. Other adverse effects were also reported such as heart failure (27%), follow by hypertrophy in left ventricular (22%), dysfunction of valvular (7%), and pulmonary hypertension (4%).

Four recent observational studies have reported the cardiac event attributed with the use of HCQ/CQ in COVID-19. Even though there was no increased death, these studies reported an increased risk of prolonging QT-interval in high proportion and other cardiac events such as arrhythmia, conduction block, or other cardiac events (Supplement Table II, number 1-4). (Chorin *et al*., 2020; Gérard *et al*., 2020; Gevers *et al*., 2020;

Table I. Studies on the benefit of hydroxychloroquine and chloroquine in patients with COVID19

Authors and year	Criteria and number of study subjects	Study design and setting	Intervention & comparison	Study outcomes	Effect on Intervention arm	Effect on a Control arm	Relative Risk and NNT (95% CI)
(Gautret. , 2020a)	Patient's criteria: · Hospitalized patients age >12 years confirmed COVID-19 Exclusion criteria: · Contraindication HCQ/CQ, · Breastfeeding and pregnant Number of patients: 42	Study design: non-randomized, open trial Setting · The Mediterranean University Hospital Institute, Marseille, Nice, Avignon, and Briançon centers	Intervention arm: · HCQ 200 mg, 3x/day for 10 days. · Six patients received Azithromycin 500 mg at first day, and 250 mg per day for 4 days Control arm · 16 patients did not receive HCQ	Virological cure day 6 post-intervention	Absolute effect: · 14/20 (70%) Absolute effect HCQ only · 8/14 (57%) Absolute effect HCQ + Azithromycin: · 6/6 (100%)	Absolute effect: · 2/16 (12.5%)	· Virological cure: RR 5.60 (1.48-21.13) and NNT 1.7 (1.2-3.3) · HQ only RR 4.57 (1.16-18.05) and NNT 2.2 (1.3-6.7); HQ & Azithromycin RR 8.00 (2.19-29.25) and NNT 1.1 (1.0-1.6)
(Z. Chen *et al*., 2020)	Patient's criteria · Adult with positive SARS-CoV-2, Chest CT pneumonia; ratio SaO2/SPO2 > 93% or ratio PaO2/FIO2 > 300 mmHg · The exclusion: Severe/ critical illness, Cardiac problem, liver disease, pregnant, or breastfeeding. Number of patients: 62	Study design: Randomized, open-label trial. Setting · Renmin Hospital at Wuhan University	Intervention arm: · Standard care (oxygen, antibacterial, antiviral, immunoglobulin, and/or corticosteroids) · and oral HCQ 400 mg/d (200 mg, twice a day) between 1-5 days Control arm · Only standard treatment	· Pneumonia improvement in Day 5 after enrolment · Time to clinical recovery	Absolute effect · Improvement of pneumonia: = 25/31 (80.6%) Body temperature recovery time [2.2 (±0.4) days].	Absolute effect: · Improvement of pneumonia: = 17/31 (54.8%) Body temperature recovery time [3.2 (±1.3) days].	Improvement pneumonia: · RR 1.47 (1.02-2.11) and NNT 3.9 (2.1-29.1) Time to clinical recovery · Time for body temperature recovery and cough remission were reduced in HCQ treatment. And 4/62 progressed to severe (all in control group)
(de Novales *et al*., 2020)	Inclusion Criteria: · Adult hospitalized patient COVID-19 · Severity: mild, moderate, and severe Number of patients: 166 (83 mild, 48 moderate, 35 severe)	Study design: · Observational cohort Study center and recruitment · Central Defense Hospital "Gómez Ulla", Madrid, Spain	Intervention arm: · HCQ 800 mg + 400 mg, maintenance dose 400 mg, and lopinavir/ ritonavir, interferon beta, and/or anti-inflammatory · Comparison: No HCQ	Survive/death · 118 patients survived · 48 patients died.	Absolute effect (survived): · 96/123 (78.0%) Mean survival (days) (95%CI): Mild: 14.4 (13.7-15.2); Moderate: 10.9 (9.3-12.5); Severe: 6 (3.3-8.5)	Absolute effect (survived): · 22/43(51.2%) Mean survival (days) (95%CI): Mild: 8.2 (6.5-9.9; Moderate: 7.7 (4.4-10.90); Severe: 4 (1.7-6.1)	Survive · RR 1.53 (1.12-2.07) · NNT 3.7 (2.4-8.6) Mean survival (days) Difference: Mild: 6.2 (p = 0.032); Moderate: 3.1 (p = 0.205); Severe: 2 (p = 0.297).

Authors and year	Criteria and number of study subjects	Study design and setting	Intervention & comparison	Study outcomes	Effect on Intervention arm	Effect on a Control arm	Relative Risk and NNT (95% CI)
(Yu *et al.*, 2020)	Inclusion criteria: · COVID-19 patients, critically ill and need mechanical ventilation Number of patients 550 patients:	Study design · Observational cohort Setting · Tongji Hospital at Wuhan, 1 Feb-4 April 2020.	Intervention arms: · HCQ (200 mg two times a day for 7–10 days) in addition to the standard care. Comparison: · standard treatments (antiviral drugs and antibiotics)	· Fatality · duration of hospital stay before death · inflammatory cytokine levels	Absolute effect (fatalities) · 9/48 (18.8%) Time hospitals stay before death: 15 (10–21) days. Cytokine IL-6: 22.2 (8.3-118.9) baseline to 5.2 (3.0–23.4) (P<0.05)	Absolute effect (fatalities) : · 238/502 (47.4%) The time of hospital stay before death: · 8 (4–14) days The levels of inflammatory cytokine IL-6: no change	Fatalities: · RR 0.40 (0.22-0.72) · NNT 3.5 (2.3-7.1) Duration hospitals stay before patient death P<0.05.
(Gautret *et al.*, 2020b)	Patient's criteria · Patients with upper and lower respiratory tract infection (URTI and LRTI) with pneumonia or bronchitis Number of patients: 80	Study design: · Observational cohort Setting: The Mediterranean University Hospital Institute, Marseille.	Intervention arm: · Combination 200 mg oral HCQ, 3x per day for 10 days and azithromycin (500 mg at day 1, 250 mg per day for 4 days). Patients and NEWS score≥5 was added Ceftriaxone · No Comparison	· Requiring O_2 therapy. · Contagious-ness as assessed by PCR · (LoS)	· 15% required O_2 · 1.2% required ICU · The number of contagious decreased and zero on Day 12. · average length of stay of 4.6 days.	No control group	No relative risk and NNT
(Mahévas *et al.*, 2020)	Patients criteria: · Adult COVID patient who required Oxygen Number of patients: 181	Study design: · Comparative observational study Setting: Four French tertiary centers between 12 March and 31 March 2020.	Intervention arm: · HCQ 600 mg per day within 48 hours of hospital admission Control arm: · Standard care without HCQ	· Overall survival day21 · Survival w/o ARDS day21 · Weaned oxygen day21	· Overall survival = 89% · Survival without ARDS = 69% · oxygen waning = 21.8%	· Overall survival = 91% · Survival without ARDS = 74% · oxygen waning = 76%	· Overall survival; RR and 95%CI = 1.2 (0.4-3.3). · Survival without ARDS = 1.3 (0.7-2.6). · Oxygen waning = 1.1, (0.9-1.3).
(Boulware *et al.*, 2020)	Patient criteria: · Adults with high risk of exposure (the one who had household or occupational contact with someone confirmed Covid-19 at ≤6 ft for ≥10 minutes without face	Study design: · randomized, placebo-controlled trial, double-blind, Setting: United States and Canada	Intervention arm: · HCQ 800 mg once, continue with 600 mg in 6-8 hours, and then 600 mg per day 4 days Control arm: · Placebo	Number of laboratory-confirmed Covid-19 or illness compatible with COVID-19 within 14 days	Incidence of illness compatible with COVID-19 = 49/414 (11.8%)	· Incidence of illness compatible with COVID-19 = 58/407 (14.3%)	There were no statistically different on incidence COVID-19 between HCQ and placebo. Absolute difference was −2.4% (95%CI −7.0-2.2; p value = 0.35).

Authors and year	Criteria and number of study subjects	Study design and setting	Intervention & comparison	Study outcomes	Effect on Intervention arm	Effect on a Control arm	Relative Risk and NNT (95% CI)
	mask or eye shield) or moderate risk of exposure (wearing face mask but no eye shield) · Number of participants: 821						
(Cavalcanti *et al.*, 2020)	Patient Criteria: · Patients ≥18 years, hospitalized due to Covid-19 within 14 or less since symptom onset. Exclusion criteria: · use supplemental oxygen ≥4 liters/minute by a nasal cannula or ≥40% with Venturi mask; · use a high-flow nasal cannula oxygen · use invasive or noninvasive ventilation; · had a history of severe ventricular tachycardia or ECG findings with a corrected QT interval (QTc) of at least 480 msec. Number of patients: 667 (504	Study design: Multicenter, randomized controlled trial, open label, Setting: 55 hospitals in Brazil	Intervention arm: · HCQ 400 mg bid and standard of care for 7 days · HCQ 400 mg bid and azithromycin 500 mg and standard of care for 7 days Control arm: Standard treatment without HCQ	Primary: · Clinical improvement using 7-level ordinal scale at 15d	Median (IQR) of clinical improvement at 15 days of HCQ: 1 (1-2) Median (IQR) of clinical improvement at 15 days of HCQ plus Azithromycin: 1 (1-2)	Median (IQR) of clinical status at 15 days: 1 (1-2)	Effect estimates of clinical improvement at 15 days of HCQ vs control: 1.21 (0.69-2.11)

Authors and year	Criteria and number of study subjects	Study design and setting	Intervention & comparison	Study outcomes	Effect on Intervention arm	Effect on a Control arm	Relative Risk and NNT (95% CI)
	confirmed COVID-19)						
(Huang *et al*., 2020)	Patient Criteria: · Patients ≥18 years with COVID-19 Exclusion criteria: · Pregnant women · History of allergic to CQ, hematological system disease, chronic liver and kidney disease, cardiac arrhythmia or chronic heart disease, retina or hearing dysfunction, mental illnesses · Use of digitalis in previous disease Number of patients: 22	Study design: · Randomized controlled trial Setting: China 27 January- 15 February 2020	Intervention group: Chloroquine 500 mg per oral two times per day for 10 days Control group: Lopinavir/Ritonavir 400/100 mg per oral two times per day for 10 days	A negative conversion rate of SARS-CoV-2 using RT-PCR at day 10th and 14th	Negative conversion at 10th day: 9/10 (90%) Negative conversion at 14th day: 10/10 (100%)	Negative conversion at 10th day: 9/12 (75%) Negative conversion 14th day: 11/12 (91.67%)	Risk Ratio at 10th day: 1.20 (0.84-2.00) Risk Ratio 14th day: 1.09 (1-1.33)
(RECOVERY Collaborative Group, 2020)	Patient inclusion: Hospitalized patients were eligible for the trial if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put	Study design: Randomized controlled trial, open label Setting: 176 hospitals in the UK.	Intervention group: Standard of care plus HCQ sulfate 200 mg orally at baseline, followed with 400 mg per 12 hours for 9 days Control group: Standard care	Mortality of any caused within 28 days post randomization	Death at 28 days: 421/1561 (27.0%)	Deaths at 28 days: 790/3155 (25.0%)	Rate ratio: 1.09 (95%CI: 0.97-1.23)

Authors and year	Criteria and number of study subjects	Study design and setting	Intervention & comparison	Study outcomes	Effect on Intervention arm	Effect on a Control arm	Relative Risk and NNT (95% CI)
	patients at substantial risk if they were to participate in the trial. Number of patients: 4716						
(C.-P. Chen *et al.*, 2020)	Patient inclusion: - patients COVID-19 confirmed RT-PCR - randomized at a 2:1 ratio and stratified by mild or moderate illness. Number of subjects: 33 in RCT and 37 cases in retrospective	Study design: - Randomized Controlled Trial - Retrospective Study. Setting: 11 public hospitals in Taiwan (1 April - 31 May 2020)	Intervention group: Standard of care plus HCQ 400 mg two tablets in a day or HCQ 200 mg two tablets in a day for 6 days. Control group: Standard care	Proportion of negative RT-PCR on 14th day and time to negative	Proportion of negative RT-PCR on 14th day: 17 (81%) Median time to negative: 5 days (95%CI: 1-9)	Proportion of negative RT-PCR on 14th day: 9 (75%) Median time to negative: 10 days (95%CI: 2-12)	No significant difference in the proportion of negative negative RT-PCR on 14th day and time to negative between the intervention group & control group. No relative risk and NNT.

Table II. Studies on the risk of Hydroxychloroquine and Chloroquine in patients with COVID19

Authors and year	Database and number of study subjects	Study design and setting	Intervention & comparison	Adverse Drug reaction reported
(Sarayani et al., 2020)	Database · All data from FDA's Adverse Event Reporting System (FAERS) 1969 2019 The number of data: Over 13.3 million FAERS reports were analyzed.	Study design: Cross-sectional study, The risk of adverse effects was calculated using the Proportional Reporting Ratio (PRR). The PRR measures disproportionality outcome in the exposed compared to the unexposed. Study center: University of Florida,	Exposure: · HCQ/CQ alone · HCQ/CQ combined azithromycin HCQ/CQ combined Amoxicillin Non-exposure Other drugs on FAERS	HCQ or CQ alone · PRR for Death 0.66 (95%CI 0.48-0.90) · PRR for TdP/QT prolongation = 1.43 (95%CI 1.29 -1.59) Combination of HCQ/CQ with Azithromycin · PRR for Death 0.46 (95%CI 0.44-0.47) · PRR for TdP/QT prolongation 3.77 (95%CI 1.80 7.87) Combination of HCQ/CQ with Amoxicillin · Not available
(Gérard et al., 2020)	Database · French pharmacovigilance database (FPVD), ADR from 27th March 27April 2020 in COVID19 patients. The number of data: · 131 ADR (120 cardiac events), 103 on HCQ, 60 on azithromycin, 1 on Lopinavir	Study design: Case reports/survey Study center: Center Pharmaco vigilance, France	Exposure: · HCQ · Azithromycin and lopinavir. Non exposure: · Not available	Cardiac events on HCQ is 103/131 (79%): · QTc prolongations representing = 67/103 (65%) · Ventricular arrythmia: 6/103 (6%) · Conduction block: 7/103 (7%) · Other cardiac events: 4/103 (3.3%) Cardiac events on Azithromycin is 60/131 (46%) Cardiac events on Lopinavir is 1/131 (0.8%)
(Chorin et al., 2020)	Database · Hospital database from hospitalized adult patients with COVID19 The number of patients: · 251 consecutive COVID patients with normal baseline ECG	Study design: Retrospective observational study Study center: NYU Langone Health, New York, USA, San Paolo University Hospital, Milan, Italy	Exposure: · HCQ 400 mg twice in one day (loading dose) followed by 200 mg twice a day for 4 days. · Azithromycin 500 mg daily for 5 days. Non-exposure: Not available	· Mortality: 44/251 (17.5%) · Extreme new QTc interval prolongation to >500 ms = 58/251 (23%) · Ventricular tachycardia suspected TdP = 1/251 (0.4%)
(Gevers et al., 2020)	Database Data of WHO pharmacovigilance database (www.vigiaccess.org) for system organ classes relevant to patients with COVID 19 (access date April 9, 2020) The number of data: · For CQ and HCQ VigiAccessTM with total of 5,797 and 22,138 records, resp.	Study design: Case series reports Study centers: Dutch Medicines Evaluation Board, Utrecht, the Netherlands	Exposure: CQ and HCQ	CQ: cardiac events were tachycardia (1.6%), cardiomyopathy (0.7%), · palpitations (0.6%), cardiac arrest (0.6%), · atrioventricular block complete (0.5%) HCQ: cardiac events were · cardiomyopathy (0.7%), palpitations (0.6%), · cardiac failure (0.4%), tachycardia (0.3%), · cardiac failure congestive (0.3%)
(Rosenberg et al., 2020)	Database: · Random samples of hospitalized confirmed COVID 19 the New York City (NYC) metropolitan region between 15-28 March, 2020 Number of patients: 1438	Study design: Observational study Study centers: NYC, Nassau County, Suffolk County.	Exposure: HCQ, azithromycin, or both	· Mortality (95%CI): HCQ + azithromycin was 189/735 (25.7% (22.3-28.9; HCQ alone: 54/271 (19.9% [15.2 24.7]); Azithromycin alone, 21/211 (10.0% [5.9-14.0]); neither drug, 28/221 (12.7% [8.3-17.1]). · HCQ + Azithromycin: (HR, 1.35 [0.76-2.40]), HCQ alone (HR, 1.08 [0.63 1.85]),

Authors and year	Database and number of study subjects	Study design and setting	Intervention & comparison	Adverse Drug reaction reported
				· Azithromycin alone (HR, 0.56 [0.26-1.21]). · no significant differences in relative likelihood of abnormal electrocardiogram.
(Geleris et al., 2020)	Patient's criteria: · hospitalized patients with Covid-19, excluding were intubated, dead, or discharged within 24 hours Number of patients: 1446	Study design: · Observational study Study centers: · NYC medical centers	Exposure: HCQ and Azithromycin	The composite endpoint: · Respiratory failure: 346/1376 (25.1%); · 180 patients were intubated, and 166 died without intubation. · No association between HCQ and the composite endpoint (HR, 1.04 [0.82 to 1.32]) · No association between Azithromycin and the composite endpoint (HR. 1.03 [0.81 to 1.31]).
(Friedman et al., 2020)	Patient's criteria: - pregnant women with anti-SSA/Ro - with or without anti-SSB/La antibodies irrespective of rheumatologic maternal diagnosis - previous pregnancy has at least one of these following complications: fetal 2° or 3° CHB, serious cardiac injury - presence of severe endocardial fibroelastosis (EFE) associated with cardiac dysfunction seen on fetal echocardiography.	Study design: open-label single-arm study Study center: School of Medicine, New York University	HCQ 400mg, or 200mg escalated to 400mg by 10 weeks.	· 5/45 infants had prolongation of the QTc (11% [4-24]).

Sarayani *et al*., 2020). Prolonged QTc was also reported in an open-label single-arm study in 5/45 (11%) infants from the gestation of pregnant mothers taking HCQ. Still, they were asymptomatic, and there was no correlation with maternal or cord HCQ levels (Friedman *et al*., 2020).

In contrast, two observational studies using the hospital database in the New York region showed that the used of HCQ, azithromycin, or both, compared with no treatment, was not significantly differences in in-hospital mortality, and none of patients was found to have an abnormal electrocardiogram. However, the interpretation of these findings must be done carefully because of the limitation of the observational design (Geleris *et al*., 2020; Rosenberg *et al*., 2020).

Most of those observational studies using the pharmacovigilance database rely on spontaneous adverse drug reactions (ADR) reporting. This method is one of the critical data sources in the field of pharmacovigilance worldwide. Although these spontaneous ADR reports help detect rare or un-expected ADRs occur in post marketing authorization, but several reporting biases occurred. Therefore, limiting applicability of these reports for estimating the true incidence of ADR. The common types of limitation in spontaneous reporting are underreporting, or there is the tendency that health professionals reported more frequently for serious events (Weber effect) in compare with non-serious adverse drug reaction, and notoriety bias. It is then very important to understand which factors could affect ADR reporting, so it would improve the data interpretation. Some studies have shown some factors related to healthcare professional's decision to report an ADR is a play an important role in this reporting bias.

The largest observational study was recently published in Lancet, included more than 90,000 patients in 671 hospitals worldwide, compared patients outcomes with COVID-19 who treated with HCQ/CQ only or combination with azithromycin (around 14,800 patients) with control group of who do not receive these agents. This study showed that HCQ/CQ alone or with azithromycin combination, increased risk of death during hospitalization. Mortality rates in treated group was ranged between 16-24% compared with about 10% only in control group patients. Group of HCQ combination with azithromycin showed increase the risk of serious cardiac arrhythmias. Even after adjusted for confounding factors such as demographic and other comorbidities, this treatment combination was still more than 5-fold increase for developing serious arrhythmia. The World Health Organization (WHO) temporarily halted its Solidarity Trial in group of patients using HCQ to treat COVID-19 because the concerns that the drug may do more harm than good. But, soon after that, the WHO resumed the use of HCQ in the Solidarity trial, and Lancet's article was retracted due to data integrity. (Mahase, 2020)

Data Safety of the use of HCQ/CQ in Indonesia is limited. One case report showed that a young Indonesian adult male with suspected COVID-19 pneumonia who treated with HCQ combination with Azithromycin, during the 24-hour experienced deterioration of atrioventricular block. However, an observational study in 10 hospitals in Indonesia has been done to evaluate the prolonged QT interval among COVID-19 patients who received HCQ alone or combined with a macrolide. (Pratama *et al*., 2020)

Risk management in the administration of Chloroquine and Hydroxychloroquine in COVID-19 patients

When prescribing HCQ and CQ with or without macrolide, healthcare professionals should consider pre-existing heart conditions. These concomitant medications also prolong QT interval and uncorrected potassium or magnesium imbalance. These factors may cause patients to be more prone to have heart rhythm disorders. In addition, healthcare professionals and clinicians should also be aware that heart rhythm disorders are more likely or more severe if HCQ and CQ are used at higher doses than those recommended for their authorized indications or combined with certain antibiotics such as azithromycin.

Several factors are conrtibuted increasing the risk for drug-induced QTc interval prolongation and/or TdP. Those factors among others are female gender, age≥68 years, had history of hepatic/renal failure, has current heart disease, had congenital long-QT syndromes, current electrolyte disturbances, , and use of concomitant medications associated with QTc interval-prolonging (WHO, 2017). The safety use of medications which causing QT-prolongation would be maximized by monitoring closely and take into account of these factors when use the medication. A risk score has been validated and use to predict QTc interval prolongation because the drug associated adverse events among hospitalized patients with risk of cardiac events (Table III) (Tisdale *et al*., 2013).

Table III. Tisdale Score

Risk Factors	Points
Age 68 years or more	1
Female gender	1
Use of Loop diuretic	1
Serum Potassium level ≤3.5 mEq/L	2
Baseline QTc ≥450 ms	2
History of Acute Myocardial Infarction	2
Use of ≥2 QTc-interval prolonging drugs	3
Sepsis	3
Heart Failure	3
Use of one QTc interval-prolonging drug	3

When the score of ≤ 6 predicts as low risk, 7-10 as medium risk, and ≥ 11 as high risks of drug-associated QTciInterval prolongation

Below is the guideline from American College of Cardiology for monitoring CQ/HCQ in COVID-19 patients (Vandenberk *et al*., 2016): At the baseline; Stop and do not use all QTc-interval prolonging agents; Monitoring ECG, hepatic and renal function, level of serum potassium and magnesium before giving the treatment; Measure QTc interval and ask pharmacist input when using the drug in patients with in acute renal or hepatic failure; Relative contraindications (only for therapy with potential benefits); patient has history of syndrome QTc interval prolongation, or . patients has QTc interval >500 msec at baseline (or >530-550 msec in patients with QRS wave in electrocardiography greater than >120 msec)

Monitoring closely, adjust the dose, and discontinue the drugs: Monitor serum potassium level daily; Place telemetry prior to therapy; Check ECG 2-3 hours after the second dose HCQ and continue check daily after that; If QTc increases >60 msec, or absolute>500msec (or >530-550 msec if QRS wave >120 msec), stop azithromycin (if used), and reduce HCQ dose, and repeat ECG daily; If QTc still >60 msec and/or absolute >500 msec (or >530-550 msec if QRS wave >120 msec), consdider the risk/benefit of the therapy, consult electrophysiologist, and stop of HCQ.

By following this risk management, the healthcare professional will be able to reduce the risk of HCQ/CQ use in patient with COVID-19.

CONCLUSIONS

The beneficial effect of CQ/HCQ in COVID-19 remains unclear. However, these medications have shown to increase the risk for QTc-interval prolongation, induced torsades de pointes (TdP) (a form of polymorphic ventricular tachycardia), and other cardiac events. Therefore, risk management is important to reduce the cardiac risk due to CQ/HCQ in patients with COVID-19 or non-COVID-19.

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