Rheumatology
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REVIEW

COVID-19, hydroxychloroquine and sudden cardiac death: implications for clinical practice in patients with rheumatic diseases

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Abstract

Sudden cardiac death is commonly seen due to arrhythmias, which is a common cardiac manifestation seen in COVID-19 patients, especially those with underlying cardiovascular disease (CVD). Administration of hydroxychloroquine (HCQ) as a potential treatment option during SARS-CoV-2, initially gained popularity, but later, its safe usage became questionable due to its cardiovascular safety, largely stemming from instances of cardiac arrhythmias in COVID-19. Moreover, in the setting of rheumatic diseases, in which patients are usually on HCQ for their primary disease, there is a need to scale the merits and demerits of HCQ usage for the treatment of COVID-19. In this narrative review, we aim to address the association between usage of HCQ and sudden cardiac death in COVID-19 patients. MEDLINE, EMBASE, ClinicalTrials.gov and SCOPUS databases were used to review articles in English ranging from case reports, case series, letter to editors, systematic reviews, narrative reviews, observational studies and randomized control trials. HCQ is a potential cause of sudden cardiac death in COVID-19 patients. As opposed to the reduction in CVD with HCQ in treatment of systemic lupus erythematous, rheumatoid arthritis, and other rheumatic diseases, safe usage of HCQ in COVID-19 patients is unclear; whereby, it is observed to result in QTc prolongation and *Torsades de pointes* even in patients with no underlying cardiovascular comorbidity. This is occasionally associated with sudden cardiac death or cardiac arrest; hence, its clinical efficacy needs further investigation by large-scale clinical trials.

Keywords COVID-19 · Pandemic · Hydroxychloroquine · Antimalarials · Cardiovascular risk

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
HCQ	Hydroxychloroquine
SCD	Sudden Cardiac Death
CVD	Cardiovascular disease
HTN	Hypertension
MI	Myocardial Infarction
HFpEF	Heart failure with preserved ejection fraction
CAD	Coronary artery disease
DM	Diabetes Mellitus
CCF	Congestive Cardiac Failure
ACE-2	Angiotensin-Converting Enzyme 2
RAAS	Renin–Angiotensin–Aldosterone System
AT II	Angiotensin II
RT-PCR	Reverse transcriptase-Polymerase Chain Reaction
iPSCs	Induced pluripotent stem cells
TnT	Cardiac troponin T
CRP	C-reactive protein
LDH	Lactate Dehydrogenase
ROS	Reactive oxygen species
vWF	Von Willebrand Factor
TCZ	Toclizumab

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CQ	Chloroquine
SLE	Systemic Lupus Erythematous
RA	Rheumatoid Arthritis
cGAS	Cyclic GMP–AMP synthase
FDA	Food and Drug Administration
EUA	Emergency Use Authorization
CDC	Centers for Disease Control and Prevention
RCT	Randomized Control Trial
AZT	Azithromycin
TdP	*Torsades de pointes*
hERG	Human ether-à-go-go-related gene
DMARDs	Disease-modifying anti-rheumatic drugs

Introduction

The Coronavirus disease 2 (COVID-19) pandemic has led to a disaster like situation, with widespread morbidity and mortality, not only due to the disease but also due to collateral damage to the economy, disrupted logistics of healthcare, and global negative impact on mental health. Despite being nine months into the pandemic and intensive exploration of therapeutic options, there is no successful drug for the condition yet [1]. While hydroxychloroquine (HCQ) seemed to be a promising option in the earlier days of the pandemic, emerging evidence has questioned its utility and also raised certain concerns on the safety of the drug. Most of these pertain to cardiovascular safety of HCQ, largely stemming from instances of cardiac arrhythmias in COVID-19 [2]. This assumes a larger relevance in the setting of rheumatic diseases, where patients are usually on HCQ for their primary disease. Since HCQ levels are likely to remain in the body for long after discontinuation, the events of cardiac toxicity call for re-examining the risk of sudden cardiac death in the event of COVID-19 infection. Furthermore, a recent review concluded that although the role of HCQ for treatment of COVID-19 shall be more clear following ongoing clinical trials, it is necessary to cautiously take into account the risk–benefit ratio before prescribing HCQ for COVID-19, particularly to high-risk populations to prevent adverse drug reactions [3]. Since there are limited data regarding the use of HCQ to treat rheumatic disease patients infected with COVID-19, rheumatologists may need to form appropriate management strategies on a case-by-case basis [4, 5]. Despite suggestions of severe disease course of COVID-19 infection in patients with RDs, the hospitalization rates and clinical features of such patients are similar to non-rheumatic disease patients [6, 7].

The manifestations of COVID-19 are diverse, ranging from anosmia and upper respiratory symptoms to respiratory distress. Existing literature suggests that COVID-19 infection results in new cardiovascular complications or

may aggravate underlying cardiovascular disease (CVD), leading to sudden cardiac death (SCD) [8, 9]. Common cardiac manifestations during severe acute respiratory syndrome coronavirus 2 (SARS-COV2) infection include myocardial infarction, arrhythmia, cardiac arrest, myocarditis, cardiomyopathy, heart failure with preserved ejection fraction (HFpEF), acute cardiac/myocardial injury, cardiogenic shock and venous and arterial thromboembolic complications [10–13]. Patients with a high cardiovascular risk profile are particularly susceptible to the latter complications, and such observations have been made in previous pandemics such as influenza as well [14–17]. SCD is the hardest outcome measure among all cardiovascular events. In this review, we hope to examine the association of COVID-19 with SCD and its intersection with HCQ usage.

Search strategy

A literature review was conducted in light of the review recommendations by Gasparyan et al. [18]. A search was conducted using the MEDLINE, EMBASE, ClinicalTrials. gov and SCOPUS databases to identify articles in English on the subject. All kinds of articles, ranging from case reports, case series, letter to editors, systematic reviews, narrative reviews, observational studies and randomized control trials published till November 14, 2020 were reviewed. The search terms included: "COVID-19 OR SARS-CoV2 OR SARS-COV-2 OR novel coronavirus OR nCOV", "Cardiac involvement OR Cardiac Injury OR Cardiovascular System OR Cardiovascular Complications OR Cardiovascular manifestations OR Myocardial Infarction OR arrhythmias OR Sudden Cardiac Death", "Hydroxychloroquine OR HCQ" and "Treatment OR therapy OR Pharmacology". Combinations of the above-mentioned terms were used to identify around 1600 articles. All articles were independently reviewed, and relevant information was extracted for this review.

Cardiovascular involvement in COVID-19 patients

Risk factors

Increased age (> 65 years), male gender and pre-existing comorbidities like hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), and congestive cardiac failure (CCF) are the main risk factors of cardiac involvement during infection with COVID-19 [19–23]. Wu et al. demonstrated increased mortality in elderly male patients with an underlying history of smoking and hypertension [24]. Studies suggest that pre-existing heart conditions are present in 8–25% of the infected population, with the disease being more severe in the elderly [25–27]. Furthermore,

a meta-analysis carried out by Bo Li et al. comprising of 1527 patients in China indicated the presence of hypertension, cardiac disease, and diabetes to be 17.1%, 16.4%, and 9.7%, respectively, amongst infected patients [28].

The more serious affliction of COVID-19 in those with an underlying CVD has been speculated to be linked to the enhanced interaction of the viral spike protein with the ACE-2 (Angiotensin-Converting Enzyme 2) receptor, which may be overexpressed in this population [17, 29, 30]. Therefore, concomitant CVD in elderly patients may make them more susceptible to worsening infection in COVID-19. Despite the initial conundrum resulting from a speculated higher risk of COVID-19 in those on ACEIs (Angiotensin-converting enzyme inhibitors) or ARBs (Angiotensin Receptor blockers) due to a postulated elevation in ACE receptor levels, a recent systematic review consisting of 11 studies with 33,483 patients failed to identify an increased risk of COVID-19 with anti-hypertensives targeting the RAAS. In fact, ACEI/ARB therapy showed a decreased risk of worsening of COVID-19 and, thus, reduced mortality [31]. Moreover, an advisory by the American Heart Association suggested that there is a heightened risk for individuals contracting COVID-19 by visiting their GP for a revised prescription of anti-hypertensives rather than continuing with ACEI [32]. Another retrospective cohort study showed similar findings concluding safe usage of ACEI in hypertensive patients with COVID-19 [33].

Pathogenic mechanisms

SARS-COV-2 can infect the cardiovascular system both directly and indirectly, considering the pronounced tropism of the virus for heart [34–36]. Several mechanisms underlie the worsening of symptoms in case of cardiac involvement:

ACE-2-mediated direct myocardial injury

SARS-COV2 gains entry into cells via binding of its spike protein to ACE-2 receptor, which is located on the heart, lungs, intestines and kidneys [17, 37–42]. ACE-2 regulates RAAS (Renin–Angiotensin–Aldosterone System) that is an important control mechanism of blood pressure [29]. This interaction inhibits the conversion of Angiotensin II (AT-II) into Angiotensin 1–7, which normally prevents inflammation, fibrosis and leads to vasodilation, thereby protecting the heart and lung from injury [43]. Hence, a decrease in ACE-2 results in the increased levels of AT-II, which is pro-inflammatory and increases the risk of heart failure [15]. These patients may have a higher mortality rate due to upregulation of ACE-2 receptor expression [39]. Furthermore, the infection is more critical as compared to SARS-COV-1, because SARS-COV-2 has a tenfold greater binding affinity due to its unique structure [10, 15]. Since greater than 7.5%

of heart cells carry the ACE-2 receptor-binding domain, the virus directly enters the heart, resulting in cardiotoxicity that eventually leads to acute myocardial injury and chronic heart damage [30, 38, 44]. This phenomenon was confirmed by the presence of viral particles in cardiac tissue found by RT-PCR (Reverse transcriptase-Polymerase Chain Reaction) in COVID-19 patients [40, 45].

Viral myocarditis

Infections by certain viruses like influenza and parvovirus B-19 are known to be some of the most common causes of myocarditis [46, 47]. Autopsy reports of COVID patients show the presence of myocyte necrosis with lymphocytes in vicinity, suggestive of viral myocarditis [48]. SARS-COV-2 seemingly carries the ability to replicate inside cardiomyocytes and pericytes, leading to inflammation [49]. Moreover, interstitial infiltrates have also been seen in non-survivors of COVID-19, further indicative of a virus attack on the myocardium [9]. In line with this, raised levels of cardiac troponin and creatine kinase in COVID patients also indicate the direct destruction of myocytes by the virus, leading on to myocarditis [34]. Further evidence is highlighted by in vitro studies whereby the SARS-Cov2 led to the destruction of contractile function and apoptosis of cardiac myocytes originated from induced pluripotent stem cells (iPSCs) leading to cardiac death within 72 h [36].

Cytokine storm

A cytokine storm is central to the immune pathogenesis of COVID-19 patients [50]. A massive release of cytokines consequent to T-cell activation (IL-1, IL-10, IL-12, IL-6, IL-7, IFN-γ, TNF-α, CXCL10, CSF, etc.) may lead to direct myocardial fiber injury [9–11, 29, 41, 46, 51, 52]. Cytokines such as TNF and IL-15 can directly induce myocardial fiber dysfunction, leading to stunning of the myocardium and poor contractile function [53]. Tao Guo et al. demonstrated a positive correlation between cardiac troponin T (TnT) levels and C-reactive protein (CRP) levels, objectively demonstrating an association of heart injury with inflammation [54]. Additionally, a study by PE et al. showed that IL-6 was also involved in QTc prolongation in COVID-19 patients [55]. Therefore, raised levels of inflammatory markers like CRP, ferritin, IL-6 and Lactate Dehydrogenase (LDH) may associate with elevated markers of myocardial injury like creatine kinase and myoglobin, which on a background of a cytokine storm may be associated with increased fatality [9, 22, 25].

Hypoxia and myocardial demand–supply mismatch

Inflammation of alveolar epithelial cells during SARS-COV-2 infection leads to respiratory distress and associated

impaired ventilation causing hypoxemia (low levels of oxygen in blood [17, 49, 56, 57]. The ensuing hypoxia results in acidosis and production of reactive oxygen species (ROS), which may damage the cell membrane of myocytes [28, 52]. This, in addition to an increased oxygen demand from the myocytes in the face of infection-induced fever and tachycardia, results in an oxygen demand–supply mismatch, which may be contributive towards a Type 2 myocardial infarction [12, 22, 25, 34, 41, 58, 59] Additionally, hypotension in a severe cytokine storm may further accentuate the ischemia due to poor coronary perfusion. Moreover, hypoxemia leads to the increased entry of calcium ions into cells that further aids the apoptotic cascade [28, 52]. These events would be the forerunners to arrhythmia, cardiogenic shock or even SCD [57].

Plaque rupture and coronary thrombosis

Recent insights suggest activation of the pro-thrombotic cascade as a key event in the pathogenesis of SARS-CoV2-mediated organ dysfunction. ACE-2 receptor is also located on the endothelial cells lining the vessels and hence serves as an entry point for the virus which then mediates inflammation (endothelitis) resulting in endothelial dysfunction [60]. This may ultimately lead to thrombogenesis in COVID-19 [61]. It has also been noticed that patients with severe infection had raised serum levels of vWF (Von Willebrand Factor), which mediates adhesion and aggregation of platelets

in vessel walls resulting in blockage [62]. Additionally, the cytokine storm in critically ill patients aids the development of a pro-coagulant and pro-thrombotic state, leading to the development of Disseminated Intravascular Coagulation (DIC) [34, 49]. Hence, thrombi in coronary vessels, together with an exaggerated inflammatory response, may contribute to rupture of unstable atherogenic plaques, manifesting as myocardial infarction [40, 44, 58, 59].
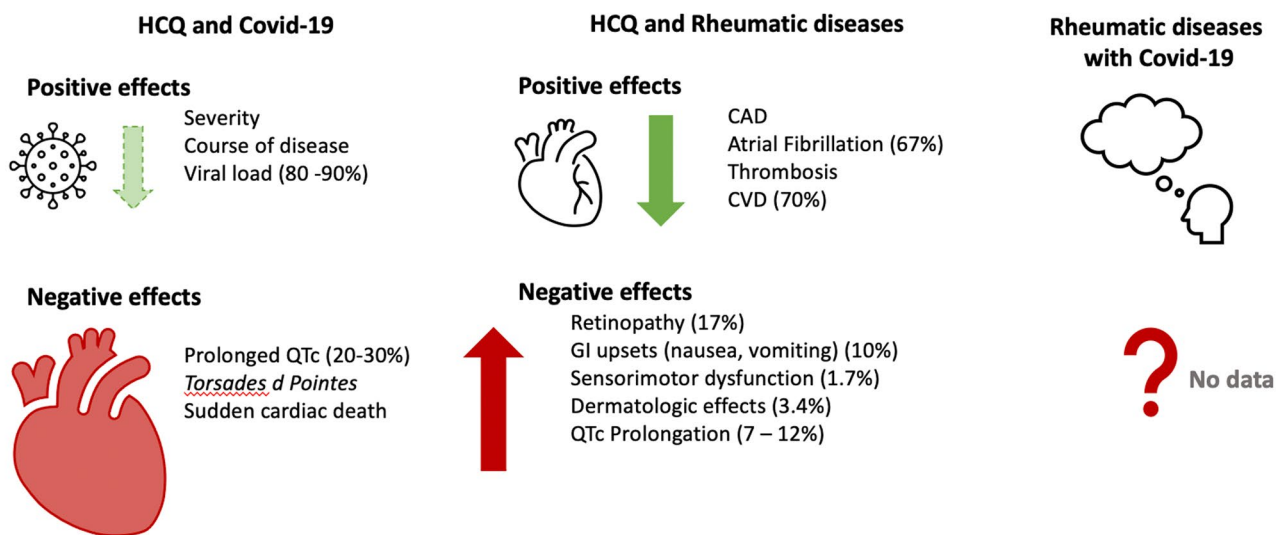
Anti-viral therapy-induced

Several anti-viral therapies have been employed to counter COVID-19 infection; however, some have shown to have damaging side effects on the cardiac system [10, 59]. Chloroquine and HCQ cause prolongation of the QT interval, which increases the risk of torsades de pointes [49] and predisposes to arrhythmia, especially when combined with azithromycin [29]. Other medications like Ritonavir and Ribavirin enhance hyperlipidemia; while, Tocilizumab (TCZ) and Interferon alpha 2B (IFN) result in hypertension all of which may result in cardiac complications [39] (Fig. 1).

Electrolyte imbalances

Electrolyte imbalances are known to be a common cause of arrhythmias, especially in patients with concomitant CVD [59]. Furthermore, during SARS-COV2 infection, the RAAS

Covid-19, Hydroxychloroquine and Sudden Cardiac Death: Implications for Clinical Practice in Patients with Rheumatic Diseases

HCQ and Covid-19

Positive effects
Severity
Course of disease
Viral load (80 -90%)

Negative effects
Prolonged QTc (20-30%)
Torsades d Pointes
Sudden cardiac death

HCQ and Rheumatic diseases

Positive effects
CAD
Atrial Fibrillation (67%)
Thrombosis
CVD (70%)

Negative effects
Retinopathy (17%)
GI upsets (nausea, vomiting) (10%)
Sensorimotor dysfunction (1.7%)
Dermatologic effects (3.4%)
QTc Prolongation (7 – 12%)

Rheumatic diseases with Covid-19

? No data

Usage of **HCQ in COVID-19 is of questionable safety** due to the prolongation of QTc which is associated with a risk of SCD.
Administration of **HCQ reduced the risk of CVD** when used in **rheumatic diseases.**
The safety and utility of HCQ in the setting of Covid-19 in rheumatic diseases is unknown.

Fig. 1 Summary of effects of hydroxychloroquine in COVID-19 and rheumatic diseases

is impaired due to interaction of the virus with ACE-2, hence resulting in hypokalemia which predisposes the patient to tachyarrhythmias [63].

Stress-induced cardiomyopathy (Takotsubo syndrome) and Overactivation of Autonomic Nervous System.

Severe SARS-COV2 infection with its associated fears, results in enhancement of physiologic stress in patients which stimulates the sympathetic system [64]. This leads to tachycardia, hypertension and vasoconstriction of coronary vessels, thus predisposing an individual towards arrhythmias and infarction [10], or even (HFpEF) [13]. Furthermore, stress causes increased aggregation of platelets leading to thrombus formation [65]. Apart from this, virus-induced vagal nerve injury, which leads to autonomic imbalances, can further exacerbate the catecholamine release causing negative effects such as stress-induced cardiomyopathy [12, 49, 66].

Hydroxychloroquine as a potential therapeutic agent

Hydroxychloroquine (HCQ), an analogue of Chloroquine (CQ), has been used as an antimalarial drug since 1955 [66–68]. It is also employed as an anti-inflammatory drug in the treatment of autoimmune diseases like Systemic Lupus Erythematous (SLE) and Rheumatoid arthritis (RA) [2, 29, 66–69]. Recently, several studies have shown it to be effective for the treatment of COVID-19 [70]. In fact, Yao et al. found HCQ to be more potent and safer than CQ in COVID-19 treatment; thus, it is considered as the drug of choice [71]. Due to similarities between the pathogenesis of rheumatic diseases and COVID-19, the use of HCQ can aid in controlling the virus, according to Najafi et al. [72].

Mechanism of action

HCQ has been found to mediate anti-viral and anti-inflammatory effects via several mechanisms. It blocks viral entry by raising the pH of endosomal vesicles which prevents fusion of SARS-COV2 with the host cell, and also by inhibiting Quinine reductase 2 which is required for the synthesis of sialic acid, thus preventing glycosylation of ACE2 receptors (binding site of SARS-COV2) [73–76]. Additionally, HCQ is known to interfere with the action of proteases required for modification of newly translated proteins. Using in silico prediction tools, a docking score of − 6.3 for HCQ for the COVID-19 main protease suggests higher ability to bind to and inhibit its function, as compared to the other tested drugs [77]. Moreover, it mediates its anti-inflammatory effects by inhibiting IL-6 and IFNα via reduction of T-cell activation, thus suppressing the cytokine storm [78, 79]. Apart from this, it blocks cGAS (cyclic GMP–AMP synthase)-mediated synthesis of type I interferon (IFNβ) and

also weakens NK cell cytotoxic function by controlling the conversion of perforins to its active form [80, 81]. Furthermore, in the disease course of COVID-19, zinc has shown to play a role in adaptive immunity and better disease outcomes [82]. Antimalarials such as chloroquine have shown to augment the efficacy of zinc by behaving as an ionophore, therefore aiding in the suppression of COVID-19 virus replication [83].

Pharmacokinetics

HCQ is a weak base, a property responsible for its main mechanism of alkalization of acidic vesicles [84]. It is widely preferred due to safety in adults as well as children, pregnant women, and those with normal renal function. However, it has a narrow therapeutic window, requiring caution in those with presumed altered pharmacodynamics. Furthermore, it can be given safely during pregnancy [85, 86]. It has also been shown to be severely toxic in cases of overdose [85]. Furthermore, the optimal dosage and course of therapy for COVID-19 are not yet known. Additional studies, especially randomized control trials, are needed to determine the ideal dosage, ensuring both therapeutic and safety profiles [73].

Adverse effects

HCQ affects several organ systems adversely, particularly the heart and retina [70]. QTc prolongation, arrhythmias particularly torsades de pointes, cardiomyopathy, cardiac arrest and other cardiotoxicities are the most common cardiovascular manifestations [67, 74, 78, 85, 87]. The effects on the ocular system are also pronounced, ranging from retinopathy and blurry vision to possible blindness [67, 74, 78, 86]. HCQ can also lead to gastrointestinal upsets presenting as nausea, vomiting, abdominal cramps, pancreatitis and hepatitis [67, 86]. At times, neurologic and musculoskeletal manifestations like headache, dizziness, confusion, insomnia, sensorimotor dysfunction, hearing loss and mental disturbances can also be experienced by few patients [67, 85]. Apart from this, HCQ may interfere with metabolic function leading to hypoglycemia and may also cause idiosyncratic reactions, anaphylaxis and skin infections like Pruritis and Stevens-Johnson syndrome in severe cases [67, 74, 85]. Furthermore, the hematologic system might be affected in certain patients presenting as neutropenia, Lymphopenia and eosinophilia [85, 86].

Usage in COVID-19

Usage of hydroxychloroquine in SARS-COV2-infected patients was authorized by FDA on 28th March 2020 [2, 88]. However, in March 2020, the FDA (U.S. Food and Drug

Administration) issued an Emergency Use Authorization (EUA) of HCQ. The suggested dose was 800 mg on day one, followed by 400 mg once daily for a week [79]. But later, due to the adverse cardiovascular events associated with the usage of HCQ in COVID patients, FDA revoked the EUA of HCQ [89]. On the other hand, the CDC (Centers for Disease Control and Prevention) recommends avoidance of high-dosage HCQ to avoid untoward effects [79]. However, the existing BSR guidelines do not consider CVD a contraindication when administering HCQ or other DMARDs [90].

Existing data supporting the use of HCQ as a potential therapy against COVID-19 is limited to in-vitro tests showing its anti-viral and anti-inflammatory properties [71, 88, 91–96]. These are summarized in Table 1. However, the larger emerging concern is the continuation of HCQ in patients with RDs when they contract COVID-19. Due to initial attributions of HCQ toxicity in COVID-19 to the higher doses used, rheumatologists may be tempted to speculate that it is safe to continue the drug at lower doses in these patients when they get the viral illness.

Benefits of HCQ treatment for COVID-19

Since the onset of the pandemic, several centers around the world have closely examined the utility of HCQ in the management of COVID-19 infection, and as prophylaxis. While this translated into a tendency of rheumatologists to overprescribe HCQ in the early pandemic period, the initial enthusiasm faded when a slew of flawed publications failed to demonstrate valid efficacy (as seen in Table 1) [97, 98].

Due to a lack of large-scale clinical trials and small sample sizes; the safety and efficacy of the drug are still not conclusive [66, 67, 73, 79, 86, 99]. More RCTs are needed for validating the therapeutic benefits of HCQ treatment in COVID-19 [100]. Furthermore, in terms of prophylaxis, a single study showed that individuals administered with prophylactic HCQ had a lower percentage of testing positive for the virus and did not show any mortality [92]. Additionally, a systematic review also showed efficient usage of HCQ as prophylactic therapy for COVID-19 in pre-clinical studies, but the absence of clinical studies limits the study finding [101]. Nonetheless, the prophylactic role may be evaluated further keeping in view the safety profile of the drug [101, 102].

Although initial studies pointed towards positive therapeutic effects of HCQ, more recently conducted studies failed to do so. In fact, a recent clinical trial conducted by Self et al. concluded that HCQ did not improve clinical status at day 14 of COVID-19 patients; thus, its use was not supported [103]. However, several reasons may be associated with this trend, such as different in vitro and in vivo results and conduction of recent studies in critically ill patients and, hence, the administration of HCQ in the later

stage of the disease; while, most of its mechanisms of inhibition of viral replication are effective during early disease [104]. Therefore, the data available for HCQ show both promising early therapeutic benefits and existing concerns. In fact, an observational study recently published in Lancet, showing a higher risk to benefit ratio of HCQ usage, was later retracted upon critique. Hence, no convincing results are available yet [73]. More research is needed regarding this field, especially in the context of treating COVID-19 with HCQ in rheumatic disease patients [105].

Risk of adverse cardiac effects with the usage of hydroxychloroquine in COVID-19 patients

In light of the poor evidence supporting the use of immunosuppressive drugs for treatment in COVID-19, it becomes all the more important to examine the toxicity with HCQ in COVID-19. Several studies have been conducted to investigate cardiotoxicity associated with HCQ usage in both non-COVID and COVID-infected patients [106–110] as shown in Table 2.

Evidence in support of increased risk

HCQ is not only known to mildly block the human ether-à-go-go related gene (hERG) aka KCNH2 that codes for delayed rectifier potassium channel, but also the inward-rectifier potassium channel [111]. This interferes with ventricular repolarization, resulting in a continuous action potential which causes significant prolongation of QT interval [104, 112]. Thus, HCQ is proarrhythmic, increasing the risk of torsades de pointes and other ventricular arrhythmias [66]. In a systematic review comprising of 1515 patients treated with HCQ, about 10% experienced QT prolongation [112]. A complete atrioventricular block was also noticed in some cases [113]. It is suggested that these findings are more common when high doses are used for a shorter duration and, hence, are said to be dose dependent [79]. This is evident by an RCT conducted by Borba et al. in Brazil, where patients given a high dose of HCQ experienced arrhythmias within 2–3 days of the administration, while 11 patients died on the 6th day. Over 25% of the high-dose patients developed a prolonged QTc > 500 ms, with increased mortality in comparison to the other group (17% vs 13.5%) [114]. In addition, a report of 3 cases also showed sudden cardiac death in all three patients who initially had normal ECG and were administered HCQ, along with lopinavir/ritonavir and other regimens addressing their existing comorbidities. Hence, it is suggested that the cardiac arrest was due to the proarrhythmic effects of HCQ which along with Lopinavir/Ritonavir could have led to QTc prolongation and development of TdP. However, the ECG of patients prior to death was not available to confirm the hypothesis [46]. Thus, prolonged

Table 1 Evidence for and against HCQ usage in the treatment of COVID-19 infection

Author (year, study design, country)	Population	Key findings	Study limitations
Gao et al. [147] (2020, Multicenter clinical report, China)	100 patients treated with CQ phosphate	Effective treatment of pneumonia. Decreased course of disease without any side effects. Improvement in pulmonary imaging	Details of findings in patients were not specified in the report
Gautret et al. [91] (2020, Open labeled RCT, France)	Total = 36 patients Control group = 16 patients Treatment group (HCQ) = 20 patients 6 patients excluded	PCR testing on day 6 showed significant reduction in viral load in HCQ group as compared to control group This finding led to mass usage of HCQ around the world for the treatment of COVID-19	Small sample size of 36. One of the patients showed a recurrence of infection (tested back as positive on day 8), 6 excluded (1 died, 1 withdrew, 3 ICU admission, 1 lost follow-up). Due to flawed methods used, this study became a target of critique leading to the publishing society declaring its inability to meet the required standards
Gautret al al [148] (2020, Uncontrolled non-comparative observational study, France)	80 patients given HCQ	Negative viral cultures in 83% of cases by day 7, and in 93% cases by day 8. Clinical improvement and rapid discharge	No comparison group. One death reported and one patient developed GI side effects and required ICU admission
Chen Z et al. [149] (2020, RCT, China)	Total = 62 patients Control group with standard treatment = 31 patients HCQ group = 31 patients	quicker clinical recovery from pneumonia (80.60% vs. 54.8%), faster restoration of normal body temperature and earlier disappearance of cough symptoms in HCQ group	The authors excluded 80 patients from the study, violating their original study plan. Furthermore, the description regarding the standard therapy was not sufficient enough and neither was any data related to fatality and viral load reduction provided
Million et al. [150] (2020, Uncontrolled non-comparative observational study, France)	1061 patients given HCQ	Around 91.7% had negative RT-PCR by 10th day of HCQ administration, while only 10 patients (0.9%) were transferred to the ICU and 8 (0.75%) deaths were reported Significant reduction in mortality	Study design is poor (no comparison group). Incomplete data of few patients. Diagnostic reports were not synchronized properly. Majority patients (95%) had non-complicated disease. HCQ was used in conjunct with AZT
Barbosa et al. [151] (2020, Retrospective cohort study, USA)	63 patients	No reduction in mortality in HCQ group, in fact a significant need for respiratory support was required	No control groups. Small sample size
Chen J et al. [152] (2020, Open label randomized controlled trial, China)	30 patients (15 in control group and 15 in HCQ group) 400 mg HCQ given for 5 days	No marked difference in reduction of clinical course and restoration of normal body temperature in HCQ group as compared to control group (93.3% vs 86.7%). Also, lesser improvement on CT of chest was noted in HCQ patients as compared to control (33.3% vs 46.7%) and adverse effects like diarrhea and hepatic dysfunction were more pronounced in HCQ group (26.7% vs 20%)	Small sample size
Geleris et al. [153] (2020, Observational study, USA)	1446 hospitalized patients whereby 70 patients were excluded due to death, intubation or early discharge; while the remaining were treated with HCQ	Although deaths were reported but no significant correlation was noted between the usage of HCQ and mortality	No control group

Table 1 (continued)

Author (year, study design, country)	Population	Key findings	Study limitations
Molina et al. [154] (2020, Uncontrolled non-comparative observational study, France)	11 patients given HCQ+AZT	Lack of evidence of viral clearance in complicated cases given HCQ. 80% showed positive cultures, i.e., 8 showed positive cultures and 2 showed negative cultures on day 6 HCQ was withdrawn for one patient due to prolonged QTc. 1 patient died	Poor study design (No comparative group). Small sample size. HCQ given along with AZT
Magagnoli et al. [155] (2020, Retrospective cohort study, USA)	368 patients administered HCQ	Increased mortality	No comparison group
Cipriani et al. [156] (2020, Observational case–control study, Not Available)	22 patients given HCQ+AZT for 3 days	ECG showed prolonged QTc interval (>480 ms) after treatment with HCQ in comparison to before therapy	Small sample size

intake of HCQ has shown to result in heart conduction defects, hypotension, cardiomyopathy, cardiac arrest and sudden cardiac death.

Evidence against an increased risk

Although, apart from the usage of drugs that prolongs QT, several other reasons might be associated with cardiac complications that occur in COVID-19 patients on HCQ therapy. It has been noticed that in general, patients with a pre-existing CVD tend to have longer QT intervals. Additionally, studies have also shown that COVID-19 patients usually have a higher than normal baseline QT levels, even before the start of HCQ therapy [115, 116]. This could be due to underlying comorbidities, such as diabetes which, along with the medications, may be responsible for longer QT intervals [117, 118]. Furthermore, as mentioned previously, the cytokine storm in SARS-COV-2-infected patients, marked by inflammatory cytokines like IL-1, IL-6, is also known to prolong QT intervals [55]. Impaired RAAS in such patients could also lead to hypokalemia which affects ventricular repolarization [119]. Hence, these factors may be the culprits behind cardiac complications in COVID-19 patients receiving HCQ therapy, rather than the drug itself.

Cardiac safety of Quinolines in non-COVID population

While the evidence to support an increased risk is limited a handful of case reports from the previous decade, large well-controlled studies have demonstrated a decreased CV risk with the administration of HCQ (Table 3) [120–122].

The risk of QTc prolongation is nearly one-third (7% versus 25%) of that described in the setting of COVID-19, with a mere 1.5% exhibiting a QTc > 500 ms. In fact, in a subset of 591 patients who also had a pretreatment electrocardiogram, mean QTc increased from 424.4 ± 29.7 ms to 432.0 ± 32.3 ms (P < 0.0001) during HCQ treatment. QTc > 470 ms during HCQ treatment was associated with greater mortality risk in univariable but not in multivariable analysis [123]. Furthermore, a systematic review in 35,548 patients sealed the argument with no documented risk of adverse cardiac effects [124].

Cardio-protective effect of Quinolines in the non-COVID population

A systematic review by Liu et al. whereby HCQ was given to 19,679 patients with rheumatic disease showed a 30% reduction in risk of developing CVD [125].

Table 2 Risk of adverse cardiac effects with usage of hydroxychloroquine in COVID-19 patients

Author (year, study design)	Population	Key findings	Study limitations
Asli et al. [157] (2020, Case report)	1 patient given HCQ	Developed prolonged QTc interval and a right bundle block	Single patient
Borba et al. [114] (2020, Randomized double-blinded parallel phase IIb trial)	Total = 81 High dose (600 mg CQ BD for 10 days) group = 41 Low dose group (450 mg BD on day 1 and OD for 4 days) = 40	Arrhythmias with high dose CQ within 2–3 days of administration, while 11 patients died on the 6th day. Increased mortality in high-dose group in comparison to low-dose group (39% vs. 15%). More instance of a prolonged QTc interval (> 500 ms) in high-dose group—18.9%, than the low-dose group [11.1%]. Ventricular arrhythmia in 2 patients (2.7%)	Limited sample size. Only hospitalized patients with severe SARS-CoV-2 infection
Chorin et al. [158] (2020, Retrospective cohort study)	251 patients Given HCQ in conjunct to AZT	Development of prolonged QTc (> 500 ms) in 23% of patients with one presenting as polymorphic ventricular tachycardia that was suspected as torsades de pointes	No comparison group
Mahévas et al. [159] (2020, Comparative observational study)	181 hospitalized patients on supplemental oxygen HCQ group = 84 Non HCQ group = 89	No difference in survival rates between patients receiving HCQ with those not being treated by HCQ (89% vs 91%). 10% in HCQ group had adverse changes in ECGs due to which HCQ had to be withdrawn. ECG changes included QTc prolongation (> 60 ms in 7 patients and > 500 ms in 1 patient), first degree AV block in 1 patient and left bundle branch block in 1 patient	Potential confounders since treatment was not given randomly. Only hospitalized patients considered
Mercuro et al. [160] (2020, Retrospective cohort study)	Total = 90 53: HCQ + AZT 37: HCQ only	Demonstrated the prolongation of QTc (> 500 ms in 7 patients and > 50 ms in 3 patients). One case of torsades de pointes was also reported	Attributable risk unclear: Most had a pre-existing CVD. No control group
Shirazi et al. [46] (2020, Case series)	3 patients given HCQ along with lopinavir/ritonavir and other regimens	Sudden cardiac death in all three patients. (It is suggested that the cardiac arrest was due to the proarrythmatic effects of HCQ which along with liponavir/ritonavir could have led to QTc prolongation and development of TdP)	ECG of patients prior to death was not available to confirm the hypothesis. Small sample size
Bessière et al. [161] (2020, Retrospective cohort study)	40 patients given HCQ and AZT vs HCQ only	93% patients showed an increase in QTc interval; however, the prolongation was greater in the group receiving HCQ + AZT as compared to HCQ only (33% vs 5%)	Treatment was stopped in most patients before completion
Lane JCE et al. [162] (2020, Cohort self-controlled case series)	Total = 1,941,802 956,374 and 310,350 users of hydroxychloroquine + sulfasalazine 323,122 and 351,956 users of hydroxychloroquine–azithromycin and hydroxychloroquine–amoxicillin	Higher risk of 30-day cardiovascular mortality upon using HCQ along with AZT in comparison to HCQ alone	No control arm without HCQ

Table 2 (continued)

Author (year, study design)	Population	Key findings	Study limitations
Saleh et al. [163] (2020, Prospective observational study)	201 patients given HCQ + AZT	Patients had increased rates of QTc prolongation when used in combination,, however, no case of *torsades de pointes* was noted	No control arm with HCQ alone or without HCQ

HCQ and RA

CVD is a major cause of death in patients with RA [126]. Studies suggest that HCQ is used as an effective treatment in patients with rheumatic diseases and has shown to lower the risk of diabetes, atherosclerosis and CVD in such patients, thus improving survival rates [125, 126]. However, it is noted that the clinical efficacy of HCQ in improving cardiovascular and metabolic outcomes in RA patients is more enhanced when combined with other disease-modifying anti-rheumatic drugs (DMARDs) [127].

Moreover, in a population-based retrospective cohort study, it was found that lesser risk of coronary artery disease occurred in 173 rheumatoid patients treated with HCQ [128]. A similar finding was noted in the retrospective cohort by Yang et al. investigating 795 SLE patients receiving HCQ [129]. Apart from this, another prospective cohort study by involving 169 rheumatoid arthritis patients showed that 42 patients on HCQ therapy had lower levels of serum LDL and triglyceride, and therefore were at a lower risk of CVD [130]. Also, van Halm et al. demonstrated a decreased risk of CVD 613 rheumatoid arthritis patients, 214 of which were HCQ recipients. [131]

Similarly, a retrospective cohort by Sharma et al. involving HCQ usage in 547 rheumatoid arthritis patients also showed a 72% reduction in CVD [132]. Additionally, a study by Shapir et al. showed that the 241 rheumatoid patients using HCQ had a reduced risk of arterial and venous CVD [133]. Nonetheless, a recent review published on managing RA in COVID-19 times concluded that since the evidence is still evolving, the use of DMARDs for RA in exposed or confirmed COVID patients remains on the clinical assessment of the treating rheumatologist [134].

HCQ and SLE

It has been seen that discontinuation of HCQ in patients with RA and SLE, most commonly due to ocular toxicity, can lead to a relapse of the disease [135–137] Moreover, discontinuation of HCQ in pregnant women with lupus incurs a higher risk of neonatal lupus and complete congenital heart block [138].

Furthermore, a prospective cohort in 812 SLE patients showed that usage of HCQ led to a decreased risk of venous and arterial thrombosis [139]. Ruiz-Irastorza et al. also reported similar findings in a prospective cohort study on 104 SLE patients treated with HCQ [140]. Similarly, Gupta et al. also reported a decreased risk of atrial fibrillation in 754 SLE patients receiving HCQ therapy [141]. Moreover, a possible concern for rheumatologists is the rise of future SLE cases, since due to the presence of antinuclear and antiphospholipid antibodies found in patients who contract COVID-19 infection, COVID patients may possibly be at a

Table 3 Risk of sudden cardiac death with usage of HCQ in non-COVID-19 patients

Author (year, study design)	Population	Key findings	Study limitations
Chen et al. [120] (2006, Case report)	1 patient given 200 mg daily HCQ given for 1 year along with prednisolone	Prolonged QTc interval. Progressing to *Torsades de Pointes*. After discontinuing HCQ, the QT interval was shorter, and the patient recovered after treatment with lidocaine and isoproterenol	Single patient
Morgan et al. [121] (2013, Case report)	1 patient given HCQ	QTc prolongation	Single patient
O'laughlin et al. [122] (2016, Case report)	1 patient given HCQ	Increased QTc interval	Single patient
Hooks et al. [122] (2020, Retrospective cohort study)	819 patients with RD given HCQ	HCQ was associated with QT prolongation in a significant proportion, especially in CKD, AF and heart failure. 55 (7%) had QTc 470–500 ms, 12 (1.5%) had QTc > 500 ms. In 591 (subset with pretreatment ECG), QTc increased from 424.4 ± 29.7 ms to 432.0 ± 32.3 ms (P < .0001) while on HCQ treatment. QTc > 470 ms during HCQ treatment was associated with a higher mortality risk in univariable but not in multivariable analysis	No clear limitations given. No comparison group
Haeusler et al. [124] (2018, Systematic review)	35,548 malaria patients given quinoline and its structural derivatives	Did not present any finding of cardiac complications	
Hung et al. [128] (2018, Retrospective cohort)	173 RA patients given HCQ	Lower CAD risk	No clear limitations given. No comparison group
Liu et al. [125] (2018, Systematic review)	19,679 patients with RD given HCQ/CQ	30% CVD risk reduction	No clear limitations given. No comparison group
Konig et al. [139] (2020, Prospective cohort study)	812 SLE patients given HCQ	Decreased risk of thrombosis, and hence lesser damage to heart	No clear limitations given. No comparison group
Ruiz-Irastorza et al. [140] (2006, Prospective cohort study)	104 SLE patients given HCQ	Reduced thrombosis	No comparison group. Allocation bias
Rho et al. [130] (2009, Prospective cohort study)	169 RA patients, of which 42 used HCQ	Those using HCQ had lower levels of serum LDL and triglyceride, and therefore a lower risk of CVD	No comparison group. Allocation bias
Van Halm et al. [131] (2006, Retrospective cohort study)	613 patients, 214 of which were HCQ recipients	Decreased risk of CVD	No clear limitations given. No comparison group
Sharma et al. [132] (2016, Retrospective cohort study)	547 RA patients given HCQ	72% CVD risk reduction	No comparison group. Sampling bias
Shapiro et al. [133] (2016, Retrospective cohort study)	541 RA patients, from which HCQ was given to 241. 273 were non-treated	Reduced risk of arterial and venous CVD	No clear limitations given. No comparison group
Gupta et al. [141] (2016, Retrospective cohort study)	1646 SLE Patients, from which HCQ usage by 754 patients	67% decreased risk of atrial fibrillation	No clear limitations given. No comparison group
Yang et al. [129] (2019, Retrospective cohort study)	795 SLE patients given HCQ	Lower risk of coronary artery disease, however no lowering of stroke	No clear limitations given. No comparison group

higher risk of developing lupus spectrum disease later on in life [142]. Overactivation of the interferon axis in the immune response against COVID-19, more so in women due to the location of numerous immune response elements on the X chromosome, may possibly trigger autoimmune diseases such as SLE in genetically predisposed individuals.

Ongoing clinical trials

Due to the concerns associated with safe therapeutic usage of HCQ during COVID-19 treatment and lack of RCTs to provide conclusive evidence, several clinical trials have been proposed across the globe to investigate the aforementioned dilemma. A total of 3237 studies are currently registered at US NIH's National Library of Medicine portal (https://www.clinicaltrials.gov/ct2/home) from 114 countries, of which 793 are investigating various treatment options in COVID-19. Amongst these, a total of 68 studies refer to HCQ usage in COVID-19, of which 49 are recruiting, not yet recruiting or active but not recruiting, 12 have been suspended/terminated or withdrawn, while 7 are completed. Some of the ongoing trials are listed in Supplementary Table 1 as given in Online Resource 1.

COVID-19 as the forerunner to SCD in COVID-19 in patients not exposed to HCQ

It is noticed that majority of the sudden deaths are associated with an underlying cardiovascular manifestation, mainly coronary artery disease (CAD) [143]. In a retrospective cohort study in China, comprising of 191 hospitalized adult patients, the majority with a pre-existing CVD, 23% experienced a heart failure, while 17% were also noted to have raised troponin levels [144]. Therefore, SCD and sudden cardiac arrest are not uncommon features and is usually related to abnormalities in the conduction system of heart, such as prolonged QT interval, or a structural dysfunction of cardiac system, such as ischemic heart disease, thus leading to arrhythmias [145].

Similarly, SARS-Cov2 is known to cause both direct and indirect injury to cardiac cells, with arrhythmias being the most common associated complication [146]. This is seen to be further aggravated in patients with a pre-existing CVD and those being administered medications like HCQ, which prolong the QT interval resulting in TdP and sudden cardiac death [66].

Conclusion

Therefore, evidently, the usage of HCQ in treatment of SLE, rheumatoid arthritis, and other rheumatic diseases showed a reduced risk of CVD, as opposed to its usage in COVID-19 patients; whereby, it is observed to result in QTc prolongation and TdP even in patients with no underlying cardiovascular comorbidity. This is occasionally associated with sudden cardiac death or cardiac arrest, more so when used in combination with other drugs. Although we do not have substantial evidence yet of COVID-19 implications in rheumatic diseases treated with HCQ, the benefits of HCQ usage in rheumatic disease treatment still may outweigh the risks, yet this is pending further validation. Nonetheless, although cardiac complications are less frequently reported, HCQ still may potentially cause mortality. Hence, its clinical benefit needs to be further investigated and justified by future large-scale RCTs.

Compliance with ethical standards

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