Received: 7 September 2020 | Revised: 22 December 2020 | Accepted: 22 December 2020

DOI: 10.1111/jcpt.13356

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

QT prolongation associated with hydroxychloroquine and protease inhibitors in COVID-19

Hui Moon Koh BPharm, MClinPharm[1] | Pei Feng Chong MPharm, MClinPharm[1] | Ju Nee Tan MPharm, MClinPharm[1] | Suresh Kumar Chidambaram MBSS, MRCP, PG Dip (Epid)[2] | Hiu Jian Chua MBBS, MRCP[3]

[1]Department of Pharmacy, Sungai Buloh Hospital, Ministry of Health, Sungai Buloh, Malaysia

[2]Department of Medicine and Infectious Disease, Sungai Buloh Hospital, Ministry of Health, Sungai Buloh, Malaysia

[3]Department of Medicine, Sungai Buloh Hospital, Ministry of Health, Sungai Buloh, Malaysia

Correspondence
Hui Moon Koh, Inpatient Pharmacy Department, Hospital Sungai Buloh, 47000 Sungai Buloh, Selangor, Malaysia.
Email: kohhuimoon@moh.gov.my

Funding information
This work was supported by the Ministry of Health, Putrajaya, Malaysia and Clinical Research Centre, Hospital Sungai Buloh, Selangor, Malaysia

Abstract

What is known and Objective: Hydroxychloroquine and protease inhibitors were widely used as off-label treatment options for COVID-19 but the safety data of these drugs among the COVID-19 population are largely lacking. Drug-induced QTc prolongation is a known adverse reaction of hydroxychloroquine, especially during chronic treatment. However, when administered concurrently with potential pro-arrhythmic drugs such as protease inhibitors, the risk of QTc prolongation imposed on these patients is not known. We aim to investigate the incidence of QTc prolongation events and potential factors associated with its occurrence in COVID-19 population.

Methods: We included 446 SARS-CoV-2 RT-PCR-positive patients taking at least one treatment drug for COVID-19 within a period of one month (March–April 2020). In addition to COVID-19-related treatment (HCQ/PI), concomitant drugs with risks of QTc prolongation were considered. We defined QTc prolongation as QTc interval of ≥470 ms in postpubertal males, and ≥480 ms in postpubertal females.

Results and Discussion: QTc prolongation events occurred in 28/446 (6.3%) patients with an incidence rate of 1 case per 100 person-days. A total of 26/28 (93%) patients who had prolonged QTc intervals received at least two pro-QT drugs. Multivariate analysis showed that HCQ and PI combination therapy had five times higher odds of QTc prolongation as compared to HCQ-only therapy after controlling for age, cardiovascular disease, SIRS and the use of concurrent QTc-prolonging agents besides HCQ and/or PI (OR 5.2; 95% CI, 1.11-24.49; $p = 0.036$). Independent of drug therapy, presence of SIRS resulted in four times higher odds of QTc prolongation (OR 4.3; 95% CI, 1.66-11.06; $p = 0.003$). In HCQ-PI combination group, having concomitant pro-QT drugs led to four times higher odds of QTc prolongation (OR 3.8; 95% CI, 1.53-9.73; $p = 0.004$). Four patients who had prolonged QTc intervals died but none were cardiac-related deaths.

What is new and conclusion: In our cohort, hydroxychloroquine monotherapy had low potential to increase QTc intervals. However, when given concurrently with protease inhibitors which have possible or conditional risk, the odds of QTc prolongation increased fivefold. Interestingly, independent of drug therapy, the presence of

systemic inflammatory response syndrome (SIRS) resulted in four times higher odds of QTc prolongation, leading to the postulation that some QTc events seen in COVID-19 patients may be due to the disease itself. ECG monitoring should be continued for at least a week from the initiation of treatment.

KEYWORDS
COVID-19, drug interaction, hydroxychloroquine, protease inhibitor, QTc prolongation

1 | WHAT IS KNOWN AND OBJECTIVE

Hydroxychloroquine (HCQ) and protease inhibitors (PI) were two of the most commonly repurposed drugs used as investigational therapeutics for COVID-19.

Hydroxychloroquine possesses antiviral properties in vitro[1,2] by inhibiting ACE2-mediated viral entry (i.e. pre-infection prophylaxis) and has been postulated for having a role in attenuating the viral cytokine storm in severe COVID-19 patients. Due to the promising in vitro data, chloroquine or hydroxychloroquine had been extensively used in various countries as a COVID-19 treatment[3,4]. Although exhibiting relatively favourable safety profiles, hydroxychloroquine blocks potassium channels and can potentially prolong corrected QT(QTc) intervals[5], causing known risk of drug-induced torsades de pointes (DI-TdP) or drug-induced sudden cardiac death (DI-SCD). Several recent reviews have highlighted the risk of cardiac toxicity when used for the treatment of COVID-19[6–8].

Commonly used boosted protease inhibitors in the treatment of COVID-19 include lopinavir/ritonavir[9] and atazanavir/ritonavir[10]. Similar to hydroxychloroquine, protease inhibitors do not independently prolong QTc intervals. However, the risk of QTc prolongation is increased with other risk factors such as multiple concurrent drugs that may prolong QTc and/or have multiple comorbidities[5]. Therefore, protease inhibitors when combined with hydroxychloroquine may potentiate DI-TdP. Lopinavir/ritonavir has possible TdP risk whereas atazanavir/ritonavir has conditional TdP risk when hypokalaemia is present or when taken with interacting drugs[11].

Concomitant pro-QT drugs or drugs that cause electrolyte disturbances such as diuretics and digoxin[12] can lead to pharmacokinetic and pharmacodynamic drug interactions. Each pro-QT drug is highly dependent on the circumstances of its use and on each patient's clinical characteristics. There were mainly three risk categories—known risk (KR), possible risk (PR) and conditional risk (CR)[11]. The known risk category encompasses drugs that prolong QT intervals and are clearly associated with a known risk of TdP, even when taken as recommended. The possible risk category encompasses drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended, whereas the conditional risk category refers to drugs associated with TdP but only under certain conditions of their use (e.g. excessive doses, in patients with conditions such as hypokalemia or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

Additionally, QTc interval may be elevated by patient-related risk factors such as age, gender, hypokalemia, sepsis and presence of pre-existing comorbidities especially cardiovascular dysfunction[12]. National Health Services (NHS) UK defines cardiovascular dysfunction as conditions affecting the heart or blood vessels, and these conditions include coronary heart disease, stroke or transient ischaemic attack, peripheral arterial disease and aortic disease.

Given the extensive but yet experimental use of these drugs in the treatment of COVID-19, our study aimed to investigate the incidence of QTc prolongation event and potential factors associated with its occurrence in the COVID-19 population. This study was also pivotal to provide an insight to targeted recommendation of 12-lead electrocardiogram (ECG) screening in patients on pro-QT COVID-19 therapy, especially in resource-limited settings. This study has been approved by the Medical Research and Ethics Committee Malaysia and registered with the National Medical Research Register (NMRR-20-798-54728).

2 | METHODS

2.1 | Design and study population

We established a retrospective study including 446 patients who were RT-PCR positive for COVID-19 from Sungai Buloh Hospital, the largest referral hospital for the treatment of COVID-19 in Malaysia. This large single centre admitted approximately 70% of the country's COVID-19 inpatient cases. All data were collected from electronic medical records (EMR).

All patients who received inpatient COVID-19 care were screened for a period of one month from 30 March 2020 to 30 April 2020. We included all adult patients (18 years old and above) diagnosed with COVID-19 who were on treatment for at least 1 day. The treatment provided was either hydroxychloroquine (400mg twice daily on day 1 followed by 200mg twice daily from day 2 onwards) or boosted protease inhibitors (lopinavir/ritonavir 400mg/100mg twice daily or atazanavir/ritonavir 300 mg/100 mg once daily) alone or in combination, all of which are classified as showing known risk (KR), possible risk (PR) or conditional risk (CR) for increasing QTc (AZCERT, Inc., Oro Valley, AZ)[11]. Other investigational COVID-19 pharmacotherapies used were interferon beta-1b and ribavirin. Patients who had 12-lead ECG done within two weeks from the start of these drugs were included in the study. The ECG findings for QTc prolongation were reported by the attending physician

either in actual time units or as prolonged or not in the EMR. We excluded patients whose ECG results were unavailable or unrecorded, patients whose ECG recorded prolonged QTc at baseline prior to starting drugs, patients who were recruited into the WHO Solidarity Trial, and pregnant women. We also excluded patients with underlying atrial fibrillation as QTc measures might be unreliable. After screening for eligibility, patients were screened for QTc prolongation events. Systemic inflammatory response syndrome (SIRS) was included as a potential risk factor for increasing QTC. SIRS was defined by two or more criteria, such as temperature >38.3˚C or <36˚C, heart rate of <90bpm, respiratory rate >20 breaths/min or PaCO2<32mmHg and white blood cell (WBC) >12,000 cells/mm^3, <4000 cells/mm^3 or >10% immature bands[13]. Patients were observed for hospital outcome measures until discharge, death or up until 30th May 2020.

2.2 | Outcome measures

The primary outcome is the clinical documentation of QTc prolongation. All ECG data were directly recorded from the EMR. QTc prolongation was defined as any QTc interval exceeding 470 ms in postpubertal males, and 480 ms in postpubertal females, or a QTc increase of ≥ 60 ms from baseline. The interval has to be preceded by any pro-QT drug within 24 hours. In local practice, for QTc comparisons to be made, QTc was calculated from lead II of the 12-lead electrocardiogram and corrected for heart rate using Bazett's formula[14].

2.3 | Data analysis

Dichotomous variables were expressed using proportions; continuous variables were expressed as medians with interquartile ranges (IQRs) and means with standard deviation (SD), where appropriate. The associations between QTc prolongation and potential risk factors were assessed using chi-square and logistic regression analysis. Variables for univariate analysis were chosen based on review of published literature. After univariate analysis, multivariate logistic regression was used to ascertain the relationship between risk factors and QT prolongation events. Multicollinearity among the independent variables was tested after recoding categorical variables into dummy variables. Statistical analyses were performed using SPSS version 22 (IBM). All levels of significance were set at 0.05.

3 | RESULTS

A total of 446 patients were included in the study (Figure 1). The baseline demographics and clinical characteristics of the study population are shown in Table 1. In terms of COVID treatment drug regimens, 437/446 (98.0%) were put on HCQ-based treatment and about half of them were receiving PI in addition to HCQ. The median hospital stay duration was 9 days (IQR 6-13).

The incidence of QTc prolongation events was 28/446 (6.3%) with a rate of 1 case per 100 person-days. The proportion of prolonged QTc events in the HCQ-only group, PI-only group, and

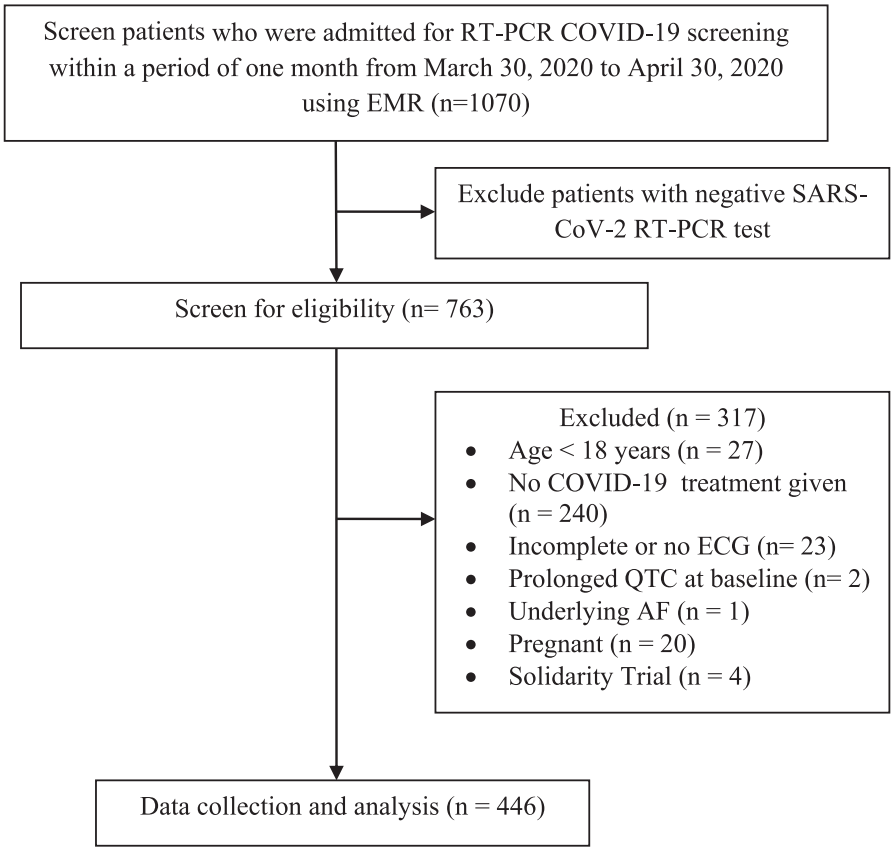

FIGURE 1 Study recruitment following eligibility according to inclusion and exclusion criteria. EMR: electronic medical records; RT-PCR: real-time reverse-transcriptase polymerase chain reaction; AF: atrial fibrillation

TABLE 1 Baseline characteristics of study population (N = 446)

Characteristic	n (%) unless otherwise specified
Age (years), median (IQR)	52 (34-60)
Gender	
Male	297 (66.6)
Female	149 (33.4)
Patients with underlying chronic medical conditions	208 (46.6)
Hypertension	145 (32.5)
Cardiovascular dysfunction	37 (8.3)
Diabetes mellitus	108 (24.2)
Severe kidney disease (Stage 4-5)	23 (5.2)
Thyroid dysfunction	7 (1.6)
COVID-19-associated pneumonia	348 (78)
Serum potassium ≤ 3.5 mEq/L	136 (30.5)
Patients requiring admission to intensive care units	54 (12.1)
COVID-19 pharmacotherapy	
HCQ-only regimen	219 (49.1)
PI-containing regimen without HCQ	9 (2)
Both HCQ and PI-containing regimen	218 (48.8)
Interferon beta-1b	71 (15.9)
Ribavirin	2 (0.4)
Number of patients on PIs	227 (50.9)
Lopinavir/ritonavir	126 (28.3)
Atazanavir/ritonavir	101 (22.6)
Total number QTc-prolonging drugs	
1 pro-QT drug	209 (46.9)
2 or more pro-QT drugs	237 (53.1)

Abbreviations: HCQ, hydroxychloroquine; PI, protease inhibitor

HCQ-PI combination group were 2/219 (0.9%), 2/9 (22%) and 24/218 (11%), respectively. Among the 24 patients who developed QTc prolongation while being put on the HCQ-PI combination, 13(54%) and 11 (45.8%) were receiving lopinavir/ritonavir and atazanavir/ritonavir respectively. Out of nine patients in the PI-only group, only one patient was on atazanavir/ritonavir and this patient was one of the two patients who had QTc prolongation. The estimated mean time from the commencement of HCQ or/and PI-based treatment to the development of QTc prolongation was 6 days (SD 3.3).

All concurrent drugs that had known, possible or conditional risk of QTc prolongation were considered in the analyses (Table 2). We found that 237/446 (53.1%) were exposed to two or more QTc-prolonging agents. Among the 28 patients who developed QTc prolongation, 19 (67.9%) had received concomitant QTc-prolonging drugs besides HCQ and/or PI,and 26 (92.9%) had received at least two pro-QT drugs be it HCQ, PI or other concomitant drugs (Table 3).

The results for univariate and multivariate regression analyses are shown in Table 4. In multivariate analysis, combination therapy containing both HCQ and PI was associated with five times higher odds of QTc prolongation events as compared to HCQ-only therapy after controlling for age, concomitant cardiovascular disease, SIRS and the use of concurrent QTc-prolonging agents besides HCQ and/or PI (OR 5.2; 95% CI, 1.11-24.49; $p = 0.036$). There was no difference in events between the use of either HCQ-only regimens and PI-containing regimens without HCQ. The use of lopinavir/ritonavir and atazanavir/ritonavir showed similar occurrence of events. Independent of drug therapy, the presence of SIRS resulted in four times higher odds of QTc prolongation (OR 4.3; 95% CI, 1.66-11.06; $p = 0.003$). There was no multicollinearity among the predictor variables (VIF=1).

In a subgroup analysis of patients who had combination therapy with HCQ and PI, patients who had concomitant drugs with any risk of QTc prolongation were associated with almost four times higher odds of QTc events as compared to those who had no concomitant drugs (OR 3.8; 95% CI, 1.53-9.73; $p = 0.004$).

Up until the end of the follow-up process, 431/446 (96.6%) were discharged home. There were 8/446 (1.8%) documented deaths. Half of those who died had documented prolonged QT intervals but none were cardiac-related deaths. Seven (1.6%) patients remained hospitalized for infective complications and rehabilitation issues.

4 | DISCUSSION

Drugs are the commonest cause of acquired long QT syndrome. Yu et al. reported that 6% of patients with prolonged QTc developed syncope and life-threatening ventricular arrhythmia and this group of patients also had a higher all-cause mortality[15].

Our study reported a 0.9% incidence of QTc prolongation in patients taking onlyhydroxychloroquine. This is in line with the study by Gerard et al. which reported an estimated incidence of 0.77% to 1.54% for cardiac adverse drug reaction secondary to hydroxychloroquine, with prolonged QTc being the commonest cause[16]. However, there were differences in the study populations in which our study population was of a younger age group (median age 52 vs 65 years old) and with less severe disease (ICU admission 12% vs 45.8%). Bessiereet al. and Mercuroet al. recently reported QTc ≥ 500 ms in 1/22 (5%) and 7/37 (19%) patients receiving HCQ alone, respectively, albeit both studies had relatively small sample sizes

TABLE 2 Concomitant drugs with QTc prolongation risk (N=446)

Known risk (n=13)	Possible risk (n=3)	Conditional risk (n=109)
Azithromycin, fluconazole, chlorpromazine, levofloxacin	Venlafaxine, efavirenz, tramadol	Loperamide, metoclopramide, omeprazole, pantoprazole, esomeprazole, metronidazole, frusemide, indapamide, risperidone, piperacillin–tazobactam, sertraline, fluoxetine, olanzapine, famotidine

TABLE 3 Subgroup analysis of 28 patients who developed QTc prolongation

n (%)	HCQ only	PI only	HCQ+PI	Total
Prolonged QTc interval	2 (7.1)	2 (7.1)	24 (85.7)	28 (100)
Patient outcomes				
Survived	2 (7.1)	2 (7.1)	20 (71.4)	24 (85.7)
Died	0	0	4 (14.3)	4 (14.3)
Concomitant pro-QT drugs	1 (3.6)	1 (3.6)	17 (60.7)	19 (67.9)
KR	0	1 (3.6)	5 (17.9)	6 (21.4)
PR	0	0	1 (3.6)	1 (3.6)
CR	1 (3.6)	1 (3.6)	16 (57.1)	18 (64.3)
Total pro-QT drugs of ≥ 2	1 (3.6)	1 (3.6)	24 (85.7)	26 (92.9)

Abbreviations: CR, conditional risk of QTc prolongation; HCQ, hydroxychloroquine; KR, known risk of QTc prolongation; PI, protease inhibitor; PR, possible risk of QTc prolongation.

which may overestimate the magnitude of the association[17,18]. One systematic review reported that a severe increase in the QTc interval occurred 1% to 18% of patients[8]. Yet, there was insufficient evidence from controlled trials to conclude that hydroxychloroquine resulted in significant QTc prolongation or torsades de pointes.

We also reported an estimated mean time of 6 days from the commencement of HCQ and/or PI-based treatment to the development of QTc prolongation. One potential postulation for this finding might be due to the prolonged half-life of hydroxychloroquine (22.4 days in blood, 123.5 days in serum)[19]. In addition, Moschini et al found that HCQ combined with PIs darunavir/ritonavir developed QTc prolongation of >500ms at 7 days[20]. Therefore, this would support the need to extend the ECG surveillance for at least one week or throughout the prolonged duration of treatment, especially if combination pro-QT drugs are used.

Our multivariate analysis reported higher odds for combination therapy of hydroxychloroquine with PIs to develop QTc prolongation when compared to hydroxychloroquine alone. Boosted PIs such as lopinavir/ritonavir have been reported to cause a dose-dependent block of HERG-K+ potassium channels leading to QT prolongation[21]. Similarly, hydroxychloroquine is also a hERG-K blocker and drug–drug interaction occurring with the combination of both therapies could explain the result of this finding[22]. This is supported by another study which reported that HCQ given together with PIs significantly increase QTc interval of >500ms with an increase of >40ms by day 3 of therapy[20]. However, PIs do not appear to independently predispose patient to QTc prolongation[23,24]. Our study showed no difference in the occurrence of QTc event between the different PI-based regimens, similar to the findings in the SMART study[24].

Our study has shown that HCQ and/or PI-based treatments with other concomitant pro-QT drugs had a higher chance of causing QTc prolongation when compared to those patients on treatments with no other concomitant pro-QT drugs. The increase in risk has been highlighted in other studies whereby the concurrent usage of a pro-QT drug like azithromycin increased the risk of QTc prolongation by 3% to 28% as compared to treatments with HCQ alone[17,18]. In critically ill patients, concurrent pro-arrhythmic drugs given together such as macrolides, fluoroquinolones, typical and atypical antipsychotics were associated with QTc prolongation[25]. This explains the association of QTc prolongation with some of the concomitant pro-arrhythmic drugs given in our study in Table 2. QTc prolongation was likely due to the drugs' mechanism of action or through the interaction with other drugs which prolongs the repolarization phase. Moreover, the wide extent of underlying clinical conditions predisposes patients to higher risk of developing TdP, especially in the critically ill. This underscores the importance of drug reconciliation to enable early identification of QTc-prolonging drugs that patients have been taking and discontinuation of them if deemed unnecessary prior to the initiation of pro-QT drugs used for COVID-19 treatments.

Interestingly, we found that systematic inflammatory response (SIRS) is an independent factor/variable in prolonging QTc. COVID-19 is known to cause an accentuated immune response in some individuals resulting in a more severe disease[26]. This explains that COVID-19 patients reportedly have a longer baseline QTc due to metabolic and physiological sequelae of the illness[20]. Additionally, critically ill

TABLE 4 Results from logistic regression of factors associated with QTc prolongation

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age ≥ 65 years	3.41 (1.46-7.94)	0.004	1.75 (0.67-4.55)	0.255
Female gender	0.786 (0.34-1.83)	0.576	-	
Cardiovascular dysfunction	3.40 (1.29-9.02)	0.014	2.23 (0.74-6.69)	0.152
SIRS	9.37 (3.99-21.99)	0.000	4.28 (1.66-11.06)	0.003
(PI) vs HCQ	31.29 (3.83-255.34)	0.001	5.74 (0.57-57.71)	0.138
(PI+HCQ) vs HCQ	13.69 (3.19-58.67)	0.000	5.22 (1.11-24.49)	0.036
Use of concomitant QTc-prolonging agents other than HCQ and/or PI	7.18 (3.14-16.39)	0.000	3.03 (1.23-7.42)	0.016

Abbreviations: CI, confidence interval; HCQ, hydroxychloroquine; OR, odds ratio; PI, protease inhibitor; SIRS, systemic inflammatory response syndrome.

COVID-19 patients with acute respiratory distress syndrome (ARDS) would meet clinical SIRS criteria (tachypnea, fever and lymphopenia), further enhanced by elevated inflammatory markers and pro-inflammatory cytokines[27]. In the event of SIRS, this explicably describes the association of widespread increase in pro-inflammatory cytokines with myocarditis[28]. Independent of the drugs used to treat COVID-19, the infection itself could be a risk factor for QTc prolongation due to myocardial injury[7,29]. There are several proposed mechanisms of injury, including direct myocardial injury by the virus through ACE2 entry, hypoxia-induced myocardial injury, microvascular damage and endothelial shedding, and cytokine / inflammation-mediated damage[29,30]. Therefore, with SIRS being one of the main manifestations in the critically ill, the incidence of QTc prolongation in severely ill COVID-19 patients should be attentively anticipated and monitored, particularly when HCQ and/or PIs were being administered concurrently.

Of the eight deaths that were reported in our study, four developed QTc prolongation. However, none of the deceased patients developed TdP during hospitalization. The cause of death was due to multi-organ failure related to COVID-19. Pneumonia and acute respiratory distress were reported as the main causes of death in COVID-19 patients, but sudden cardiac deaths were reported in patients with pre-existing cardiovascular conditions[31–33]. Reports of severe cardiac complications due to hydroxychloroquine in COVID-19 patients were rare[8,17,18]. No ventricular arrhythmias were identified by Bessiereet al., and one case of TdP (1/90) was reported by Mercuroet al. As current evidence is inconclusive, more reliable drug safety data in COVID-19 from ongoing large randomized trials is anticipated[7,8].

Despite having the highest number of admissions for COVID-19 in the country, single-centred studies such as ours lacked external validity. There were no cardiac-related morbidity and mortality in our cohort, which warrants a further validation through multi-centred, controlled trials. Another limitation to our study was the absence and non-feasibility of continuous ECG monitoring. Ill patients were monitored daily whereas fitter patients were monitored periodically within the treatment period. This means the actual start time of QTc prolongation was not known.

5 | WHAT IS NEW AND CONCLUSION

In this cohort, HCQ-only regimens had low potential for QTc prolongation but the risk was increased with combined use of QTc-prolonging drugs. ECG monitoring for QTC prolongation should be done periodically for at least a week from the initiation of treatment. Drug reconciliation is essential to avoid overlapping toxicities.

6 | APPROVAL OF INSTITUTIONAL REVIEW BOARD

This study has been approved by the Medical Research and Ethics Committee Malaysia and registered with the National Medical Research Register (NMRR-20-798-54728).

7 | PATIENT CONSENT STATEMENT

Due to the nature of the retrospective chart review, the need for informed consent from individual patients was waived.

8 | PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

All authors accept the terms and conditions of the editorial for publication.

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We would also like to record our deepest gratitude to our Pharmacy Head of Department, Dr Syamhanin Adnan, for her support throughout the entire research period and to Professor Karuthan A/L Chinna from Taylor's University for his assistance with the statistical analysis of the research. We are grateful to Dr Kalairasu Periasamy and his team at CRC Hospital Sungai Buloh for their unwavering support with our work. Lastly, we also thank Dr Kuldip Kaur, Director of Sungai Buloh Hospital, for her permission to allow the research to be conducted in this facility.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

AUTHOR CONTRIBUTIONS

Study concept and design, critical revision of the manuscript for important intellectual content, and study supervision: Koh HM and Chidambaram S K. Acquisition of data, and analysis and interpretation of data: Koh HM, Chong PF and Tan JN. Statistical analysis: Koh HM. Drafting the manuscript: Koh HM, Chong PF, Tan JN and Chua HJ.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Hui Moon Koh https://orcid.org/0000-0001-7078-5091

REFERENCES

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269–271.
2. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimize dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;71(15):732–739. https://doi.org/10.1093/cid/ciaa237
3. Zhang Q, Wang Y, Qi C, et al. Clinical trial analysis of 2019-nCoV therapy registered in China. *J Med Virol*. 2020;92:540–545. https://doi.org/10.1002/jmv.25733

4. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care*. 2020;57:279–283. https://doi.org/10.1016/j.jcrc.2020.03.005
5. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). *Mayo Clinic Proceedings*. 2020;95 (6):1213–1221.
6. Kamp TJ, Hamdan MH, January CT. Chloroquine or Hydroxychloroquine for COVID-19: Is Cardiotoxicity a Concern?. *Journal of the American Heart Association*. 2020;9 (12). https://doi.org/10.1161/jaha.120.016887
7. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. *Heart Rhythm*. 2020;17(9):1472–1479. https://doi.org/10.1016/j.hrthm.2020.05.008
8. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review. *Ann Intern Med*. 2020;173(4):287–296.
9. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382:1787–1799.
10. Joseph T, Ashkan M. International Pulmonologist's Consensus on COVID-19. 1st ed. https://www.researchgate.net/publication/340666754_International_Pulmonologist%27s_consensus_on_COVID-19. Accessed March 20, 2020.
11. Woosley R, Heise CW, Romero KA.QT drugs list. 2015. CredibleMeds website. www.crediblemeds.org. Assessed April 14, 2020.
12. Tisdale JE, Jaynes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*. 2013;6:479–487.
13. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644–1655. https://doi.org/10.1378/chest.101.6.1644
14. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121:1047–1060.
15. Yu H, Zhang L, Liu J, et al. Acquired long QT syndrome in hospitalized patients. *Heart Rhythm*. 2017;14:974.
16. Gérard A, Romani S, Fresse A, et al. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapies*. 2020;75(4):371–379. https://doi.org/10.1016/j.therap.2020.05.002
17. Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. *JAMA Cardiol*. 2020;5(9):1067–1069. https://doi.org/10.1001/jamacardio.2020.1787
18. Mercuro NJ, Christina FY, David JS, et al. Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1036–1041.
19. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res*. 2018;46(D1):D1074–D1082. https://doi.org/10.1093/nar/gkx1037
20. Moschini L, Loffi M, Regazzoni V, Di Tano G, Gherbesi E, Danzi GB. Effects on QT interval of hydroxychloroquine associated with ritonavir/darunavir or azithromycin in patients with SARS-CoV-2 infection. *Heart Vessels*. 2020;1–6.
21. Anson BD, Weaver JGR, Ackerman MJ, et al. Blockade of HERG channels by HIV protease inhibitors. *Lancet*. 2005;365:682–686.
22. Capel RA, Herring N, Kalla M, et al. Hydroxychloroquine reduces heart rate by modulating the hyperpolarization-activated current if: novel electrophys- iological insights and therapeutic potential. *Heart Rhythm*. 2015;12(10):2186–2194.
23. Hunt K, Hughes CA, Hills-Nieminen C. Protease inhibitor-associated QT interval prolongation. *Ann Pharmacother*. 2011;45(12):1544–1550. https://doi.org/10.1345/aph.1Q422
24. Soliman EZ, Lundgren JD, Roediger MP, et al. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. *AIDS*. 2011;25(3):367–377. https://doi.org/10.1097/QAD.0b013e328341dcc0
25. Etchegoyen CV, Keller GA, Mrad S, Cheng S, Di Girolamo G. Drug-induced QT Interval Prolongation in the Intensive Care Unit. *Curr Clin Pharmacol*. 2017;12(4):210–222. https://doi.org/10.2174/1574884713666180223123947
26. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–1034. https://doi.org/10.1016/S0140-6736(20)30628-0
27. Hanidziar D, Bittner EA. Hypotension, systemic inflammatory response syndrome, and coronovirus disease 2019: a clinical conundrum. *Anesth Analg*. 2020;131(3):e175–e176. https://doi.org/10.1213/ANE.0000000000005062
28. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;S1547–5271(20):30422–30427. https://doi.org/10.1016/j.hrthm.2020.05.001
29. Zhu H, Rhee JW, Cheng P, et al. Cardiovascular complications in patients with covid-19: consequences of viral toxicities and host immune response. *Curr Cardiol Rep*. 2020;22(5):32. https://doi.org/10.1007/s11886-020-01292-3
30. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury with mortality in hospitalized patients with COVID-19 in Wuhan. *China. JAMA Cardiol*. 2020;1–8.
31. Shirazi S, Mami S, Mohtadi N, et al. Sudden cardiac death in COVID-19 patients, a report of three cases. *Future Cardiol*. 2021;17(1):113–118.
32. Liu R, Ming X, Zhu H, et al. Association of cardiovascular manifestations with in-hospital outcomes in patients with COVID-19: a hospital staff data. https://www.medrxiv.org/content/10.1101/2020.02.29.20029348v5.full.pdf.Accessed June 22 2020.
33. Keeley P, Buchanan D, Carolan C, Pivodic L, Tavabie S, Noble S. Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary. *BMJ Support Palliative Care*. 2020;10(4):381–384.

How to cite this article: Koh HM, Chong PF, Tan JN, Chidambaram SK, Chua HJ. QT prolongation associated with hydroxychloroquine and protease inhibitors in COVID-19. *J Clin Pharm Ther*. 2021;46:800–806. https://doi.org/10.1111/jcpt.13356