Lethal Arrhythmia (*Torsade de Pointes*) in COVID-19: An Event Synergistically Induced by Viral Associated Cardiac Injury, Hyperinflammatory Response, and Treatment Drug?

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ABSTRACT: Arrhythmias in patients with coronavirus disease 2019 (COVID-19) are prevalent and deserve special attention because they are associated with an increased risk of fatal outcome. The mechanism of arrhythmia in COVID-19 remains unclear. Here, we report our first case of confirmed COVID-19 with documented Torsade de Pointes (TdP). A 64-year-old woman, previously healthy, presented to our emergency department with progressive shortness of breath, dry cough, and 1 week of fever. She was treated with chloroquine phosphate, meropenem, and ciprofloxacin. After 5 days of admission, her condition deteriorated and she was admitted to the intensive care unit. The patient had two episodes of malignant arrhythmias within 24 hours. The former was TdP, and the latter was a fatal pulseless ventricular tachycardia that occured even after chloroquine was discontinued. There was evidence of cardiac injury shown by increased serum level of troponin I. We propose a synergistic concept of lethal arrhythmia due to direct severe acute respiratory syndrome coronavirus (SARS-CoV)-2-associated cardiac injury, hyperinflammatory response, and drug-induced arrhythmia.

KEYWORDS: COVID-19, cardiac injury, arrhythmias, chloroquine, hydroxychloroquine

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Introduction

Coronavirus disease 2019 (COVID-19) is associated with cardiac injury and arrhythmias. COVID-19-related arrhythmia may occur in up to 44% patients in the intensive care unit (ICU) and 6.9% in non-ICU patients.[1] The arrhythmia resulting from cardiac injury is associated with increased fatal outcome in COVID-19. The 4-aminoquinoline antimalarial drugs, hydroxychloroquine and chloroquine, have been widely used to treat COVID-19.[2] However, these drugs are currently under global scrutiny because of controversy regarding their potential to prolong QT interval, induce fatal arrhythmias, and sudden cardiac death.[2-4] The mechanism of cardiac arrhythmia in COVID-19 remains unclear.[5,6] It needs to be determined whether the cardiac arrhythmias are caused by cardiac injury associated with direct invasion of SARS-CoV-2, hyperinflammatory response, a drug-induced event, or the synergistic activity of all causes.[6-8] Here, we report our first case of COVID-19 with documented Torsade de Pointes (TdP) and fatal pulseless ventricular tachycardia within 24 hours apart.

Case Report

A 64-year-old woman presented to our emergency department with progressive shortness of breath, dry cough, and fever. She had a contact history with a confirmed COVID-19 patient. She was otherwise healthy with no known comorbidities and was not being treated with any medication. Her physical examination on admission revealed tachypnea, bilateral intercostal retraction, and hypoxia (peripheral oxygen saturation was 88% in room air). A chest X-ray showed bilateral peripheral opacities suggesting interstitial inflammatory lung disease without cardiomegaly. Her baseline electrocardiogram (ECG) (Figure 1) showed a normal sinus rhythm of 94 bpm with QT interval and Fridericia's corrected QT interval (QTc) of 380 and 441 ms (475 ms with Bazett's formula), respectively. Her initial complete blood count showed a normal hemoglobin level and white blood cell count (14.0 g/dL and 4500 cell/μL, respectively), but low absolute lymphocyte of 1000 cell/μL, and mild thrombocytopenia of 136 000 cell/μL (Table 1). SARS-CoV-2 infection was later confirmed by qualitative reverse transcription polymerase chain reaction test of the nasopharyngeal and oropharyngeal specimens, and diagnosis of COVID-19 pneumonia was established. Initial treatments were oral chloroquine phosphate 500 mg BID, intravenous (IV) meropenem 1 g TID, IV ciprofloxacin 400 mg BID, and subcutaneous unfractionated heparin (UFH) 5000 IU BID as pulmonary embolism prophylaxis.

On the fifth day of hospitalization, her respiratory condition deteriorated (Figure 2). She required intensive care, invasive mechanical ventilation, and continuous ECG monitoring. Her blood tests showed a total white cell count of 9800 cell/μL,

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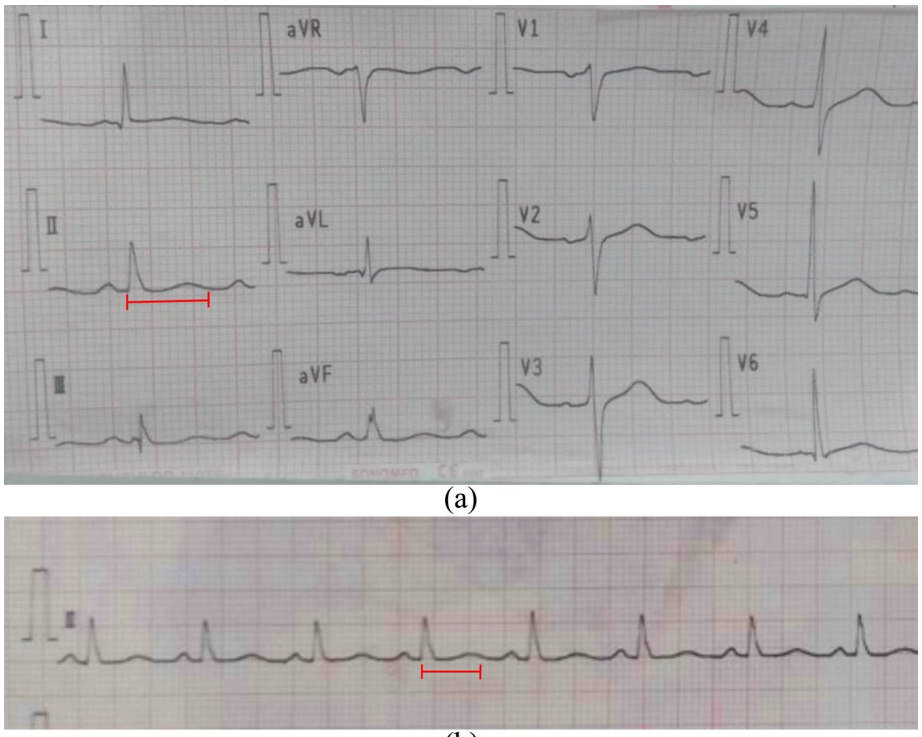

Figure 1. Baseline electrocardiogram (ECG) of lead I – V6 (A) and lead II (B). QT = 380 ms, RR = 640 ms and QTc = 441 ms (Fridericia), 475 (Bazett). Red vertical bars are showing where the beginning of the QRS and the end of T wave.

Table 1. Normal reference range for laboratory parameters.

LABORATORY PARAMETERS	UNIT	REFERENCE RANGE
Hemoglobin	g/dL	14-17.4
White blood cells (WBC) count	cell/μL	4400-11 300
Platelets	cell/μL	1 50 000-4 50 000
Differentials count		
Basophil	%	0-1
Eosinophil	%	0-4
Neutrophils, Rod	%	3-5
Neutrophils, Segmented	%	45-73
Lymphocytes	%	18-44
Monocytes	%	3-8
Sodium	mEq/L	135-145
Potassium	mEq/L	3.5-5.1
Calcium	mg/dL	4.5-5.6
Magnesium	mg/dL	1.8-2.4
Urea	mg/dL	15-39
Creatinine	mg/dL	0.8-1.3
Aspartate aminotransferase (AST)	U/L	15-37
Alanine aminotransferase (ALT)	U/L	16-63
Troponin I	ng/mL	<0.01
C-reactive protein	mg/dL	<0.3
Procalcitonin	ng/mL	<0.1
Ferritin	ng/mL	30-400

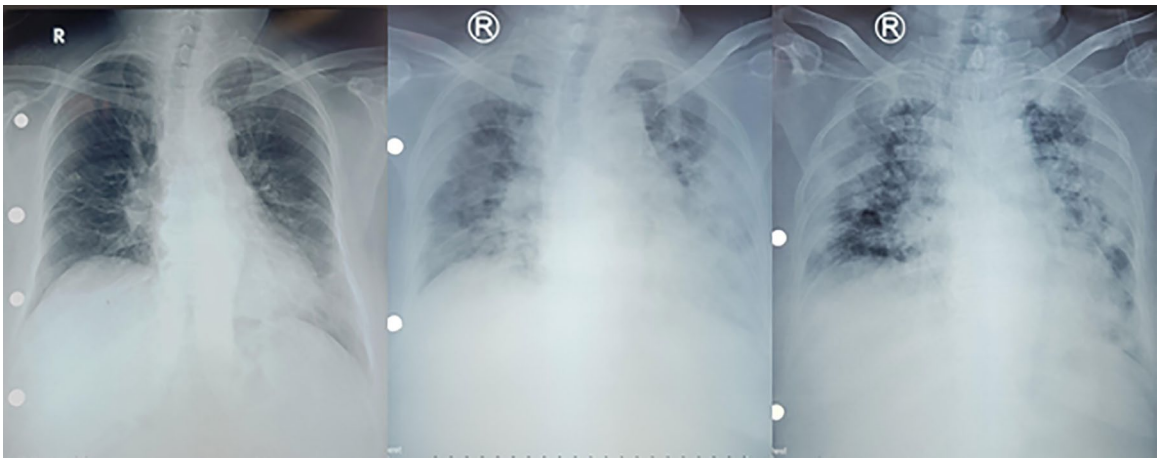

Figure 2. Chest X-ray (CXR) on admission (left). CXR on the third day of admission (middle). CXR before admitted to the intensive care unit.

a low absolute lymphocyte count of 490 cell/μL with an increased neutrophil percentage of 91%, low serum potassium of 3.0 mEq/L, low serum calcium of 3.65 mEq/L, and serum procalcitonin of 0.1 ng/mL. IV potassium and calcium were administered for serum electrolyte correction. Continuous ECG monitoring did not yield any significant changes from the baseline ECG.

The patient's overall condition in the ICU was stable until two sudden episodes of malignant arrhythmias ensued within 24 hours apart, which were on the day 13 of illness (day 9 of admission and antibiotic treatment). The first arrhythmia was TdP (Figure 3A), which was preceded by sinus tachycardia (Figure 3B) with Fridericia QTc of 292 ms (353 ms with Bazett). We performed cardiopulmonary resuscitation (CPR) as soon as TdP was documented and prepared the defibrillator. It was not long before the rhythm spontaneously turned to asystole, then CPR was continued. After 2 minutes of CPR, the patient was on return of spontaneous circulation with sinus tachycardia and evident T-wave alternans (Figure 3C). Intravenous magnesium sulfate and potassium were given, along with termination of chloroquine phosphate administration. The serum electrolytes upon the episode of TdP showed relatively normal values (Na 146 mEq/L, K 3.6 mEq/L, Ca 4.53 mEq/L, Mg 1.9 mEq/L), but with increased serum troponin I level of 0.42 ng/mL. The blood samples were taken after CPR. The second episode of arrhythmia was a fatal pulseless ventricular tachycardia which occured within 20 hours from the onset of TdP. Unfortunately, even after vigorous resuscitation the patient could not be saved. The final blood examination before she succumbed to the disease showed the following: lymphopenia (290 cell/μL), and signs of multiorgan failure, including acute kidney injury (increased serum creatinine 1.33 mg/dL and urea 75.6 mg/dL), liver injury (serum alanine aminotransferase 100 IU/L), coagulopathy (serum D-dimer 11.22 mg/L), and increased proinflammatory markers (serum ferritin 1237 ng/mL, serum procalcitonin 32.4 ng/mL, and serum C-reactive protein 0.85 mg/dL).

Discussion

Arrhythmias in patients with COVID-19 deserve special attention, because they are found in up to 48% of severe COVID-19 cases and are associated with an increased risk of poor outcome.[9] These findings may be attributed to wide range of etiologies, including adverse drug reaction, electrolyte abnormalities, inflammation, hypoxia, or neurohormonal stress associated with COVID-19 infection.[3,10] SARS-CoV-2 has been shown to cause direct cardiac injury through angiotensin-converting enzyme (ACE)2, which is highly expressed in cardiac pericytes.[11] Guo et al[7] showed that lethal arrhythmias were found in 11 out of 187 (5.9%) hospitalized COVID-19 patients, and of those patients, 81.8% had laboratory-confirmed evidence of cardiac injury. It is hypothesized that the mechanism of arrhythmia due to COVID-19-induced cardiac injury might be similar to that in other virus-induced myocarditis, which is caused by the interaction between host factors and pathogenic characteristics.[12] These mechanisms consist of abnormal conduction and prolonged repolarization due interstitial edema and cardiac fibrosis, and abnormal $Ca^{2}+$ handling and downregulation of K^{+} channels, respectively.[13]

Both hydroxychloroquine and chloroquine are widely known as antimalarials and anti-rheumatic drugs.[14] These drugs have gained attention in treating COVID-19 after an early study by Gautret et al[15] showed some benefits in reducing viral loads of SARS-CoV-2. It is hypothesized that chloroquine and hydroxychloroquine inhibit viral entry of SARS-CoV-2 by interfering with ACE2 receptor glycosylation and sialic acid biosynthesis.[16] However, these drugs are known to cause QT prolongation and may trigger a fatal ventricular arrhythmia commonly known as TdP.[17] Chloroquine and hydroxychloroquine cause QT prolongation through the inhibition of hERG, which encodes a K^{+} channel protein that mainly regulates cardiac repolarizing current.[18] Several established risk factors may contribute to the development of TdP, includes myocardial ischemia and infarction, heart failure with reduced ejection fraction, bradycardia, electrolyte imbalances

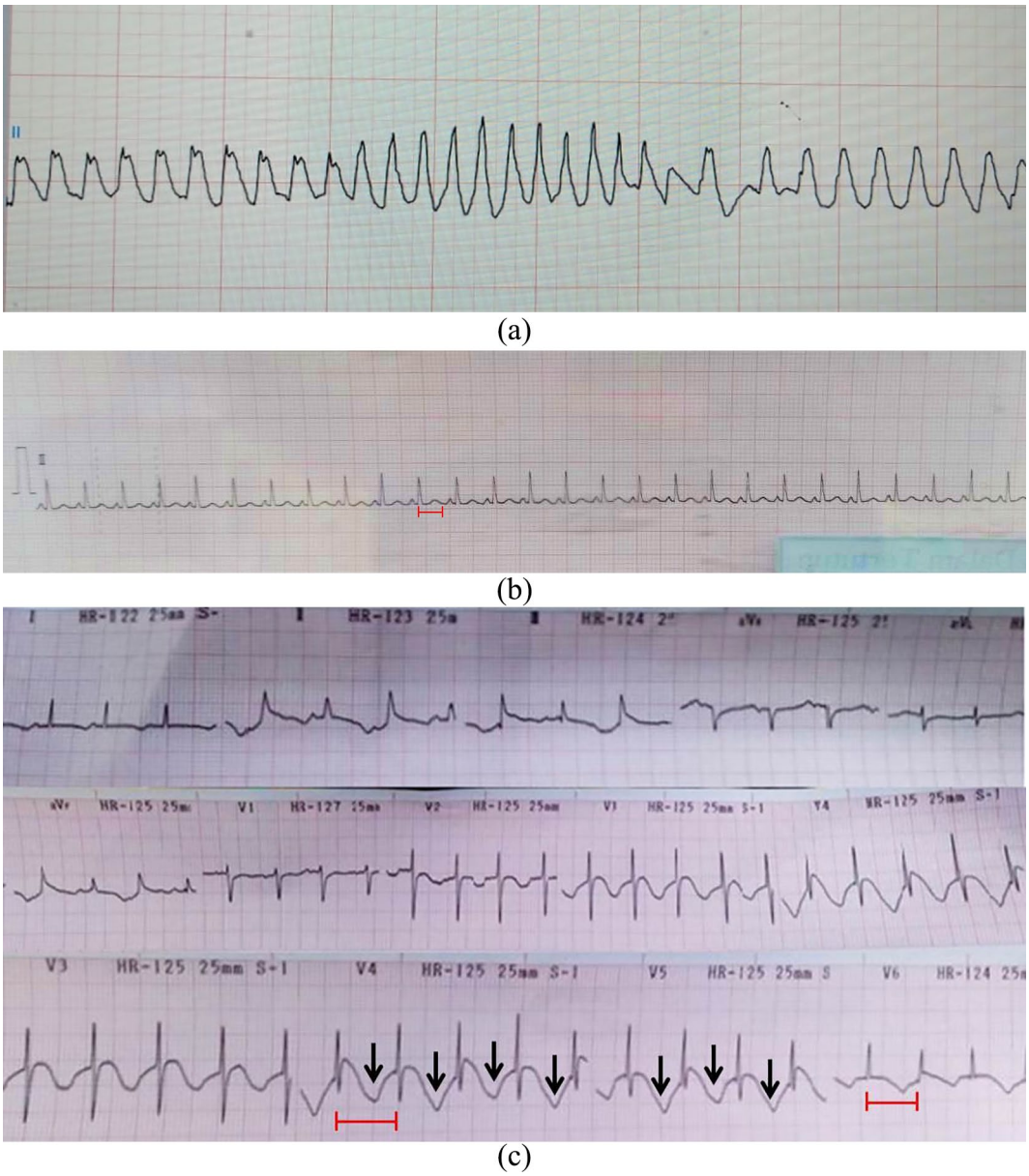

Figure 3. (A) Torsade de pointes (TdP), (B) The lead II of electrocardiogram (ECG) 1 hour preceding the torsade de pointes (TdP). QT = 200 ms, RR = 320 ms and QTc = 292 ms (Fridericia), 353 (Bazett), and (C) The electrocardiogram (ECG) after the torsade de pointes (TdP). The ECG was taken 10 minutes after the return of spontaneous circulation (ROSC). Macroscopic T-wave alternans are shown by the vertical arrows. QT = 520 ms, RR = 240 ms and QTc = 664 ms (Fridericia), 751 ms (Bazett).

(hypokalemia, hypomagnesemia, and hypocalcemia), concurrent QT-interval-prolonging drugs, renal impairment, sepsis, female sex, advanced age, and congenital LQTS.[17,19]

Hyper-inflammatory state, a specific characteristic of severe COVID-19, is hypothesized to have a pivotal role in inducing arrhythmia.[6,20] Increased of interleukin-6, which is a crucial cytokine in hyper-inflammatory state, could promote QT prolongation by different mechanisms, including direct blockade of the human ether-a-go-go-related gene (*hERG*)-K^+-channel and cytochrome p450-3A inhibition which increase bioavailability of several QT-prolonging drugs.[21,22] Moreover, systemic inflammation could cause cardiac sympathetic system hyperactivation, which is a well-recognized trigger for life-threatening arrhythmic events in patients with long-QT-syndrome (LQTS).[23] The impact of systemic inflammation on the risk of ventricular arrhythmias due to acute infection, irrespective of concomitant QT-prolonging drugs, was recently reported by Lazzerini et al.[24] They evidently showed that during acute infections, QT prolongation can occur directly through the modulation of specific K^+ channels expression in the ventricles caused by systemic inflammation.

The case presented here was our first experience with a lethal arrhythmia in a severe COVID-19 patient with laboratory-confirmed evidence of cardiac injury showing increased troponin I values after TdP. Although this evidence makes it plausible that the fatal arrhythmias may have been caused

directly by SARS-CoV-2 infection, the patient was also on the ninth day of treatment with chloroquine when the arrythmias occurred. Furthermore, the evidence of hyperinflammatory response, as depicted by the increased of pro-inflammatory markers, makes it difficult to conclude whether the fatal arrythmia was drug-induced, or caused by systemic hyperinflammatory response, direct cardiac injury due to SARS-CoV-2 infection, or the synergistic activity of all causes.

Noteworthily, drug-induced QT interval prolongation leading to a TdP is commonly occur when the QTc interval exceeds 500 ms and it is considered rare when QTc interval is <500 ms.[19,25] Based on a study by Sasaoka et al[26] the pattern of drug-induced LQTS might differ among drugs. For example, quinolone (eg, moxifloxacin) and clarithromycin could induce LQTS in the range of 0 to 6 days and 3-21 days in the time-to-onset analysis, respectively. A systematic review by Jankelson et al[17] showed that 3 days of chloroquine phosphate could increase baseline QTc by 18.4-35 ms on day 3 of administration. Even though in our patient the TdP occur when the QTc was less than 500 ms, it was still possible that the drug-induced arrhythmia may play a role, considering the presence of risk factors which consist of female, advanced age, and the use of two arrhythmogenic drugs (quinolone and chloroquine). Another thing worthy to be considered was the presence of macroscopic T-wave alternans in this patient. Although this rare sign of impending TdP was not evident before the occurrence of TdP, it was clearly visible soon after the episode. The presence of this phenomenon is well-known for its association with TdP and LQTS,[27] but has never been reported in a viral myocarditis.

It was also worth noting the presence of hypokalemia in this patient (on the fifth day of hospitalization). Chen et al[28] reported that hypokalemia was highly prevalent among hospitalized patients with COVID-19 and was associated with severity of the disease. While they proposed the etiology of hypokalemia in COVID-19 was due to the disordered renin-angiotensin system (RAS) activity, hypokalemia can also be caused by medications. Although not as common as diuretics in inducing hypokalemia, several types of antibiotics could cause hypokalemia, including amphotericin B, penicillin, aminoglycosides and capreomycin.[29] Meropenem could also be considered as as one of the possible cause hypokalemia, as several authors has reported previously.[30] Even though the cause of hypokalemia was still inconclusive, the development of TdP in this patient could not be explained by the hypokalemia, as the value was 3.6 mEq/L when TdP ensued.

The nature of dynamic ECG changes of the patient along with the increased of cardiac troponin may also signify the possibility of COVID-induced myocarditis. Although TdP commonly takes place in the setting of either hereditary or acquired LQTS due to drug or toxins, several reports had documented its occurrence in the setting of viral myocarditis.[31,32] It was unfortunate that we did not conduct a cardiovascular magnetic resonance (CMR) scanning or endomyocardial biopsy to confirm the diagnosis. Echocardiography may provide clues for myocarditis if there is a wall motion abnormalities or other structural and or functional defects. Regrettably, the nature of a first case during pandemic with unfamiliarity with the illness leading us to incomprehensive investigations.

Szekely et al[33] reported a case of chloroquine-induced TdP in a COVID-19 patient, where the TdP occurred after 5 days of CQ treatment and was preceded by an extremely prolonged QTc (Baseline QTc values of 462 ms to 627 ms before the onset of TdP) that returned to normal after the administration of magnesium sulphate and potassium. However, the blood troponin level was not increased; In contrast with our case, the blood troponin level was elevated, showing evidence of cardiac injury. Mercuro et al[8] reported one case of TdP out of 90 COVID-19 patients treated with hydroxychloroquine (53 patients received combination treatment with azithromycin). The TdP patient was administered concurrent hydroxychloroquine with azithromycin and exhibited a QTc prolongation of 499 ms. Around 27.8% of patients in that study showed increased levels of troponin-T. Another study by Chorin et al[34] of 84 COVID-19 patients receiving hydroxychloroquine and azithromycin, no TdP events were noted even with severely prolonged QTc or more than 500 ms. Nevertheless, no data of cardiac injury were given in the study. Both studies by Mercuro et al[8] and Chorin et al[34] used the same dose of hydroxychloroquine which was 400 mg twice daily on day 1, then 200 mg twice daily on days 2 through 5.

It was unfortunate that we did not conduct a cardiac pathology study in this patient, therefore, the definitive cause of lethal arrhythmia remains unknown. However, based on this case report and the latest evidence, we suggest that the risk of lethal arrhythmia from solely chloroquine or hydroxychloroquine might be low. The risk may be augmented in patients with evidence of cardiac injury marked by increased blood troponin levels. Moreover, the hyperinflammatory response, as depicted by the increased of pro-inflammatory marker, may further increasing the risk of lethal arrhythmia. We propose a synergistic concept of lethal arrhythmia in COVID-19 due to direct cardiac injury caused by SARS-CoV-2 infection, hyperinflammatory response, and drug-induced arrhythmia. However, further study is needed to confirm our hypothesis. We also encourage further studies to create a prognostic model that incorporates the presence of arrhythmia along with other established risk factors and comorbidities for prognostication in severe COVID-19.[35-40]

Since we began treating COVID-19, the majority of international, national,[41] and our hospital guidelines have recommended the administration of chloroquine or hydroxychloroquine for the initial treatment of COVID-19. However, the Center for Disease Control and Prevention (CDC) and the National Institute of Health (NIH) have recently updated the previous recommendation concerning the use of chloroquine or hydroxychloroquine due to unclear

efficacy and potential cardiotoxic adverse effects.[42] This issue is of importance, especially during this pandemic when physicians are trying to use the best treatment available that they think may save their patients.[43-45] In the COVID-19 scenario where chloroquine or hydroxychloroquine is considered, whether due to ongoing trials or due to the unavailability of other promising drugs (eg, remdesivir),[46] the Tisdale risk score may be useful. Despite the fact prolonged QTc was not found in this case, TdP generally occurs in this specific manner. Therefore, a simple risk prediction score to predict which patients are at greater risk for QT prolongation may be beneficial in reducing the risk of fatal arryhthmia.[47] Frequent ECG monitoring in patients treated with chloroquine or hydroxychloroquine is also suggested. If frequent monitoring can not be achieved, we suggest not to use chloroquine or hydroxychloroquine due to exposing patients to possible life-threatening adverse effect.[48] In cases in which TdP ensues, the management should be based on the current recommendation by European Society of Cardiology which consists of withdrawal of all QT-prolonging drugs, maintenance of blood potassium levels (target of > 4.5 mEq/L), administration of IV magnesium, and increasing the heart rate by withdrawing bradycardic agents or administering IV isoproterenol.[49]

Author Contributions

NYK, IH, and ESN: wrote the initial draft of the manuscript.
NYK, IH, EM, TAS, ESN, and SP: performed extensive research on the topic and gave expert advice based on theory and experience.
EM, LH, and YH: supervised and critically reviewed the manuscript.
All authors read and approved the final version of the manuscript.

Informed Consent

The written consent to publish the article was obtained from the patient next of kin.

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