Clinical Evidences and Pathophysiology of Cardiac Arrhythmia in the Era of Coronavirus Disease-2019

Adel Khalifa Sultan Hamad
Mohammed Bin Khalifa Al Khalifa Cardiac Centre, Awali, Bahrain

ABSTRACT

The coronavirus disease-2019 (COVID-19) is primarily caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been a challenge to the clinician. Epidemiological studies unveiled the involvement of the cardiovascular system during the course of SARS-CoV-2 infection. The cardiac complications in patients with COVID-19 include myocarditis, heart failure, acute coronary syndrome, and cardiac arrhythmia. The pathophysiological states of the disease and multiple concurrent medications (unfamiliar to the clinicians) lead to a significant threat to arrhythmia. This review article hopes to elucidate the mechanisms of arrhythmias in COVID-19.

Key words: Arrhythmia, coronavirus, electrocardiography, severe acute respiratory syndrome

INTRODUCTION

The coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is highly contagious. An increased number of COVID-19 cases have increased exponentially ever since it was first reported cases in Wuhan, China, in December 2019. By March 2020, the World Health Organization declared COVID-19 as a pandemic. As of this writing, with more than 37.8M confirmed cases and more than one million mortalities, the global spread of this viral disease has affected more than 210 countries.

It has been reported that the fatality rate of the COVID-19 varies from 1.4% to 4.3%.[1-3]

The majority of patients are asymptomatic or have mild symptoms. However, a considerable number of patients develop acute respiratory distress syndrome necessitating intensive care treatment, mechanical ventilation, and extracorporeal membrane oxygenation. A growing body of evidence indicates the involvement of extrapulmonary system also.

Epidemiological studies highlighted the cardiac consequences of COVID-19 and stimulated research.[2,4] Retrospective analysis of 137 patients admitted to respiratory departments of nine tertiary hospitals in Hubei province revealed that 7.3% of the patients presented with palpitation.[5] A descriptive study of 85 fatal cases of COVID-19 showed that arrhythmia was observed in 60% of cases.[6]

Shi et al. also observed that the electrocardiography (ECG) of patients with cardiac injury showed T-wave depression and inversion, ST-segment depression, and Q waves of myocardial ischemia when it was performed during the periods of elevation of cardiac biomarkers.[7]

Subsequently, a case series of 187 patients demonstrated that the patients who exhibited myocardial injury were more likely to experience malignant arrhythmia.[8] Although arrhythmias are frequently reported in COVID-19, it is more prevalent among critically ill patients. Wang et al. observed that the patients...
admitted to an intensive care unit were more likely to experience arrhythmia as compared to patients admitted to non-intensive care units (44.4% vs. 6.9%; \(P < 0.001\)).[2]

Similarly, retrospective analysis of 416 patients also showed a higher mortality rate among patients with cardiac injury as compared to non-cardiac (51.2% vs. 4.5%; \(P < 0.001\)).[7] ECG performed in patients (\(n = 14\)) with a cardiac injury during the periods of elevation of cardiac biomarkers showed evidence T-wave depression and inversion, ST-segment depression, and Q-waves of myocardial ischemia.[7]

In this review, we shed light on the available clinical evidence related to cardiac arrhythmia during the course of SARS-CoV-2 infection and the pathophysiology of cardiac arrhythmias in hospitalized patients with COVID-19, and the role of available treatment options for COVID-19 disease in arrhythmia.

**CLINICAL EVIDENCES OF ARRHYTHMIA DURING THE COURSE OF CORONAVIRUS DISEASE-2019**

There is a scarcity in the medical literature as to the characteristics of arrhythmias in COVID-19. The Heart Rhythm Society performed a worldwide cross-sectional survey of electrophysiology professionals (physicians, scientists, and allied professionals) to assess cardiac arrhythmic manifestations and treatment strategies employed in hospitalized COVID-19 patients.[9]

Of 905 professionals who reported to have COVID-19 patients in their hospitals, atrial fibrillation (21%) was reported most commonly, followed by sinus bradycardia (8%) and complete heart block (8%).

Other reported tachyarrhythmias include atrial tachycardia (5.7%), paroxysmal supraventricular tachycardia (5.7%), and atrial flutter (5.4%), respectively. Ventricular tachycardia/fibrillation arrest and pulseless electrical activity were reported by 4.8% and 5.6% of respondents, respectively. The Brugada-like electrocardiographic pattern was also reported in COVID-19 patients.[10]

A large study which included 700 patients (mean age 50 ± 18 years) showed higher incidences of cardiac arrest among patients admitted in intensive care units. A considerable number of patients reported atrial fibrillation (\(n = 25\)), clinically significant bradycardias (\(n = 9\)) and nonsustained ventricular tachycardias (\(n = 10\)).[11]

A single-day snap-shot survey demonstrated a 9% (12/132) incidence of arrhythmias, limited to atrial fibrillation (\(n = 8\)) and supraventricular tachycardia (\(n = 4\)) among clinically stable patients with COVID-19.[12] Amaratunga et al. reported two cases of cardiac arrhythmia in COVID-19, of which one patient presented temporary SIQIIITIII morphology followed by reversible nearly complete atrioventricular block.

In contrast, ECG of the other patient demonstrated ST-segment elevation accompanied by multifocal ventricular tachycardia.[13]

While assessing the cardiac rhythm of 170 COVID-19 patients who showed the evidence of cardiac disease, arrhythmias were noted in 25.9% of patients.[14] Among these 44 patients, 35 had only atrial arrhythmias, two had only ventricular arrhythmias, and seven had both atrial and ventricular arrhythmias. Guo et al. reported the occurrence of ventricular tachycardia/fibrillation in 6% of hospitalized patients.[8] While assessing the etiology of cardiopulmonary arrest, Sho et al. found asystole as initial rhythm in 90% of patients, ventricular fibrillation/tachycardia in 6%, and pulseless electrical activity in 4% of the patients.[15]

Atrial fibrillation, a common sequela of critical illness, affects approximately 3.6% to 6.7% of the patients with COVID-19.[16] Taha et al. reported two cases of new-onset atrial fibrillation occurring in middle-aged men who were tested positive for SARS-CoV-2 infection.[17] The patients were not having significant past medical history suggestive of cardiovascular disease.[17] Seecheran et al. reported another case report of a middle-aged Caribbean-COVID-19 patient who was initially presented with atrial flutter with two to one atrioventricular block and transitioned to atrial fibrillation with a rapid ventricular response.[18]

The occurrence of bradyarrhythmia, a warning sign of the onset of a serious cytokine storm, is another reason for close monitoring of patients with COVID-19.[19] It may occur also in patients even in the absence of underlying cardiovascular disease.[13] Kir et al. reported a case of a patient with moderate COVID-19 who experienced bradycardia with intermittent high-degree atrioventricular block.[20] The authors speculated that subclinical myocarditis or isolated involvement of the AV node and infra-Hisian block secondary to SARS-CoV-2 virus infection could be a possible mechanism for the conduction disturbances in the patient.

Bradycarrhythmias during the clinical course of COVID-19 result in poor outcomes among patients who require pacing support. Chinitz et al. reported high short-term mortality (57% inhospital and 71% mortality within 3 months of presentation) despite prompt management among seven patients presented with or developed severe bradycarrhythmias requiring pacing support.[21] Similar findings are observed in a retrospective cohort study (\(n = 756\) COVID-19 patients) performed by McCullough et al.[22]

The multivariable logistic regression analysis demonstrated increased odds of death when the electrocardiogram showed the presence of one or more atrial premature contractions and a right bundle branch block or intraventricular block.[22]
PATHOPHYSIOLOGY OF CARDIAC ARRHYTHMIA IN CORONAVIRUS DISEASE-2019

The disease progression is believed to occur across three distinct phases: the entry and proliferation of the virus which ultimately activates the host immune system (Phase-I). Activation of the host immune system attenuates viral proliferation. However, persistent activation of the host immune system triggers Phase-2 of the disease which is characterized by T-cell activation, cytokine production, and cross-reacting antibodies formation. The inability of the immune system to eradicate the virus in a productive and protective manner yields Phase-3 of the disease, cardiac remodeling and progressive cardiac dilatation.

Cardiac arrhythmia during COVID-19 is assumed to be multifactorial, which not only includes various modes of myocardial injury but also occurs as a result of the extracardiac process.

It is postulated that hypoxia caused by direct viral tissue involvement of lungs, myocarditis, and abnormal host immune response may result in arrhythmia. Hypoxia due to acute respiratory failure can activate anaerobic glycolysis along with a generation of oxygen free radicals, reduction of intracellular pH, and thereby resulting in the increased concentration of cytosolic calcium. Intracellular acidosis and oxygen free radicals may destroy the phospholipid layer of the cell membrane. Increased level of cytosolic calcium facilitates early and late depolarizations and temporal alterations in the action potential duration. Hypoxia also decreases the threshold for depolarization due to increased levels of extracellular potassium.

Myocarditis during COVID-19 has been described in the literature. SARS-CoV-2 virus binds with an angiotensin-converting enzyme (ACE) 2 receptors on the myocardial cell membrane through spike protein resulting in downregulation of the ACE-2 receptors and subsequent accumulation of Angiotensin-II. Angiotensin-II leads to adverse myocardial remodeling through Angiotensin-II Type 1 receptors. The accessory proteins of SARS-CoV-2 virus may impair stress granule formation. Absence of the stress granule facilitates replication of the virus and damage of the cell.

Cell-mediated cytotoxicity also plays an important role in which primed CD8+ T lymphocytes migrate to the cardiomyocytes and cause myocardial inflammation. As a result of cytokine storms release of interleukin (IL)-1 β, IL-2, IL-6, IL-7, interferon-gamma (IFN-γ), IFN-inducible protein-10, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1a, T-lymphocyte activation is altered which further releases cytokines resulting in a positive-feedback loop of immune activation and myocardial injury.

Inflammatory cytokines further stimulate the cardiac sympathetic system through central hypothalamus-mediated (inflammatory reflex) and peripheral (left stellate ganglia activation) pathways and increase the susceptibility of arrhythmic events in patients with preexisting long QT-interval. Of these released cytokines during COVID-19, cytokines IL-6, TNF-α, and IL-1 have the ability to prolong ventricular action potential.

Lazzerini et al. observed inhibitory effects of IL-6 on hERG-K+ channel, which subsequently prolongs action potential duration in ventricular myocytes. Furthermore, during a hyperinflammatory storm, coronary atherosclerotic plaques are prone to rupture, causing acute cardiac injury and increasing the susceptibility for arrhythmias.

Siripanthong et al. illustrated the mechanism of arrhythmia that occurred during COVID-19. Arrhythmia during COVID-19 occurs during acute myocarditis as a result of (1) direct injury to cardiomyocytes disrupting the plasma membrane and electrical conduction; or (2) infection of the pericardium causing massive edema; or (3) ischemia from microvascular disease due to possible infection of the pericytes. Chronic myocarditis may also lead to the occurrence of arrhythmia.

Furthermore, pulmonary hypertension which induces myocardial strain imbalance and myocardial ischemia also plays a significant role in the development of arrhythmia.

Heart failure or sepsis as a consequence of acute respiratory distress leads to intravascular volume imbalance which is believed to result in cardiac arrhythmia, particularly atrial fibrillation.

Acute kidney injury which was reported in as high as 27% of the patients and diarrhea cause electrolyte imbalance, a triggering factor for cardiac arrhythmia. Another study in which arrhythmia was noted in 56.5% of patients (fatal cases). Furthermore, the binding of SARS-CoV-2 with ACE-2 receptors results in their downregulation. As the effects of ACE-2 receptors on the renin-angiotensin system are hampered, there will be increase reabsorption of sodium and excretion of potassium.

Hypokalemia was reported in up to 61% of hospitalized COVID-19 patients. Patients with hypokalemia are prone to the development of arrhythmia as hypokalemia increases resting membrane potential and accelerate depolarization in cardiac cells (Figure 1).

ROLE OF CORONAVIRUS DISEASE-2019 TREATMENT IN CARDIAC ARRHYTHMIA

Currently, there is no definite treatment available for COVID-19 patients. Chloroquine or hydroxychloroquine

HEART VIEWS
Volume 22 / Issue 2 / April-June 2021
is believed to possess antiviral efficacy against SARS-CoV-2. Intracellular drugs create alkalinization of the intracellular phagolysosome, which ultimately prevent fusion of the virus to the cell membrane. The drugs also affect the binding and uncoating of SARS-CoV-2 due to impaired glycosylation of ACE-2 receptors. Early clinical trial results confirmed the efficiency of hydroxychloroquine in patients infected with SARS-CoV-2 and reinforced the physicians to treat COVID-19 patients with this antimalarial agent. Furthermore, the addition of azithromycin intensified viral load reduction efficiency of hydroxychloroquine.

However, hydroxychloroquine is a known inhibitor of the KCNH2-encoded hERG/Kv11.1 potassium channel present in the heart. The hERG channel plays a vital role during the repolarization of the cardiac action potential and inhibition of it potentially increases QT interval and predisposing the patient to fatal ventricular tachyarrhythmias (torsades de pointes). The risk of arrhythmia is amplified in the presence of electrolyte imbalance (hypokalemia, hypocalcemia, and hypomagnesemia), renal impairment, and polypharmacy (particularly other QT-prolonging medications). Moreover, IL-6 generated during cytokine storms increases the bioavailability of QT-prolonging drugs through inhibition of cytochrome p450, particularly CYP3A4.

In a cohort of 201 COVID-19 patients who were treated with either monotherapy with chloroquine/hydroxychloroquine \( (n = 201) \) or combination therapy chloroquine/hydroxychloroquine and azithromycin \( (n = 119) \), 9% of patients had QT prolongation of more than 500 ms. Chorin et al. observed corrected QT-interval prolongation in 84 patients treated with combination therapy of hydroxychloroquine/azithromycin for COVID-19 patients. It is noteworthy that five of nine patients who developed QT-prolongation of more than 500 ms had normal QT-interval at baseline.

Recently, the US FDA has mentioned the risk of arrhythmia with the use of hydroxychloroquine/azithromycin combination therapy. Hence, to mitigate the risk of arrhythmia, the Heart Rhythm Society outlines a practical approach related to the use of QT-prolonging medications. Lidocaine and mexiletine which block the \( I_{Na+} \) channel can be proved useful as they shorten the QT interval and suppress torsades de pointes.

Ritonavir/Lopinavir are protease inhibitors which are prescribed for the treatment of human immunodeficiency virus infection. The drugs are currently being used for the treatment of SARS-CoV-2 infection. However, one should also consider the QT and PR interval prolongation risk of the drugs while considering the treatment of COVID-19. Second-or third-degree atrioventricular block with the use of these drugs warns their usage in patients with underlying structural heart disease and preexisting conduction system abnormalities.

Moschini et al. have observed a significant increase in corrected QT interval (from baseline) when the COVID-19 patients were treated with either hydroxychloroquine plus ritonavir/darunavir \( (438 \text{ vs. } 452 \text{ ms}; P=0.001) \) or hydroxychloroquine plus azithromycin \( (433–440 \text{ ms}; 0.001) \). It is hypothesized that cytokine storm as a consequence of SARS-CoV-2 infection could be responsible for the development of acute respiratory distress.

Tocilizumab, a monoclonal antibody against IL-6 receptor, is believed to be a promising approach. Tocilizumab in combination with methylprednisolone is able to lower increased C-reactive protein and IL-6 in patients infected with SARS-CoV-2. Favipiravir, a competitive inhibitor of RNA-dependent RNA polymerase, is currently being investigated for the treatment of COVID-19 disease. The drug has a risk of QT prolongation.

**CONCLUSION**

Cardiac arrhythmia is one of the common cardiac manifestations of the COVID-19. This review provides a current state of knowledge on arrhythmia in COVID-19 condition. However, our understanding about the mechanism of cardiac arrhythmia as a consequence of SARS-CoV-2 infection is still in infancy.

Knowledge of arrhythmia risk with novel minimally investigated drugs enables clinicians to ensure adequate monitoring of the QT interval and management of...
Hamad, et al. Arrhythmia during COVID-19

arrhythmic risk, maximizing safety for the patients infected with SARS-CoV-2 infection in this challenging time.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
3. World Health Organization. "Coronavirus disease 2019 (COVID-19): situation report, 73." (2020).
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
5. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020;133:1025-31.
6. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. Am J Respir Crit Care Med 2020;191:1372-9.
7. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802-10.
8. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811-8.
9. Gopinathannair R, Merchant FM, Lakkireddy DR, Etheridge SP, Feiglsky S, Han JK, et al. COVID-19 and cardiac arrhythmias: A global perspective on arrhythmia characteristics and management strategies. J Interv Card Electrophysiol 2020;59:329-36.
10. Vidovich M. Transient brugada-like electrocardiographic pattern in a patient with COVID-19. JACC Case Rep 2020;2:1245-9.
11. Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm 2020;17:1439-44.
12. Sala S, Peretto G, De Luca G, Farina N, Campochiaro C, Tresoldi M, et al. Low prevalence of arrhythmias in clinically stable COVID-19 patients. Pacing Clin Electrophysiol 2020;43:891-3.
13. Amarutunga EA, Corwin DS, Moran L, Snyder R. Bradycardia in patients with COVID-19: A calm before the storm? Cureus 2020;12:e8599.
14. Si D, Du B, Ni L, Yang B, Sun H, Jiang N, et al. Death, discharge and arrhythmias among patients with COVID-19 and cardiac injury. CMAJ 2020;192:E791-8.
15. Shao F, Xu S, Ma X, Xu Z, Lin J, Ng M, et al. In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China. Resuscitation 2020;151:18-23.
16. Gawalko M, Kaplon-Cieslicka A, Hohl M, Dobrev D, Linz D. COVID-19-associated atrial fibrillation: Incidence, putative mechanisms and potential clinical implications. Int J Cardiol Heart Vasc 2020;30:100631.
17. Taha ME, Alsafi W, Taha M, Eljake A, Ibrahim H. Coronavirus disease and new-onset atrial fibrillation: Two cases. Cureus 2020;12:e8066.
18. Seecheran R, Narayansingh R, Giddings S, Rampaul M, Furlonge K, Abdool K, et al. Atrial arrhythmias in a patient presenting with coronavirus disease-2019 (COVID-19) Infection. J Investig Med High Impact Case Rep 2020;8:2324709620925571.
19. Manolis AS, Manolis AA, Manolis TA, Apostolopoulos EJ, Papatheou D, Melita H. COVID-19 infection and cardiac arrhythmias. Trends Cardiovasc Med 2020;30:451-60.
20. Kir D, Mohan C, Sancassani R. Heart brake: An unusual cardiac manifestation of COVID-19. JACC Case Rep 2020;2:1252-5.
21. Chinitz JS, Goyal R, Harding M, Veseli G, Gruberg L, Jadonath R, et al. Bradyarrhythmias in patients with COVID-19: Marker of poor prognosis? Pacing Clin Electrophysiol 2020;43:1199-204.
22. McCullough SA, Goyal P, Krishnan U, Choi JI, Safford MM, Okin PM. Electrocardiographic findings in coronavirus disease-19: Insights on mortality and underlying myocardial processes. J Card Fail 2020;26:626-32.
23. Liu PP, Mason JW. Advances in the understanding of myocarditis. Circulation 2001;104:1076-82.
24. Dherange P, Lang J, Qian P, Oberfeld B, Sauer WH, Koplan B, et al. Arrhythmias and CardioVIRUS -19: A review. JACC Clin Electrophysiol 2020;6:1193-204.
25. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic risk, and inflammation: mind the gap! Circulation 2020;142:7-9.
26. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khani MY, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020;17:1463-71.
27. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-3.
28. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653-9.
29. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: Lessons from rheumatoid arthritis. Eur Heart J 2017;38:1717-27.
30. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: The role of autoimmune and inflammatory cardiac channelopathies. Nat Rev Immunol 2019;19:63-4.
31. Birchak J, Khan A, Singh G, Schuger C, Maskoun W. An unusual case of sustained ventricular tachycardia from acute pulmonary embolism. J Am Coll Cardiol 2020;75:2820.
32. Diao B, Wang C, Wang R et al. Human kidney is a target for SARS-CoV-2 infection. Nat Commun 2020;12:e8066.
33. Chen D, Li X, Song Q, Hu C, Su F, Dai J, et al. Assessment of hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in Wenzhou, China. JAMA Netw Open 2020;3:e2011122.
34. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). J Infect Dis 2020;71:732-9.
35. Gauthier P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhythm Electrophysiol 2020;13:e008662.

37. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020;26:808-9.

38. Mitra RL, Greenstein SA, Epstein LM. An algorithm for managing QT prolongation in coronavirus disease 2019 (COVID-19) patients treated with either chloroquine or hydroxychloroquine in conjunction with azithromycin: Possible benefits of intravenous lidocaine. HeartRhythm Case Rep 2020;6:244-8.

39. Johannesen L, Vicente J, Mason JW, Erato C, Sanabria C, Waite-Labott K, et al. Late sodium current block for drug-induced long QT syndrome: Results from a prospective clinical trial. Clin Pharmacol Ther 2016;99:214-23.

40. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020;382:1787-99.

41. Soliman EZ, Lundgren JD, Roediger MP, Duprez DA, Temesgen Z, Bickel M, et al. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. AIDS 2011;25:367-77.

42. Puech R, Gagnieu MC, Planus C, Charpiait B, Boibieux A, Ferry T, et al. Extreme bradycardia due to multiple drug-drug interactions in a patient with HIV post-exposure prophylaxis containing lopinavir-ritonavir. Br J Clin Pharmacol 2011;71:621-3.

43. Moschini L, Lozzi 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 2021;36:115-20.

44. Pedersen SF, Ho YC. SARS-CoV-2: A storm is raging. J Clin Invest 2020;130:2202-5.

45. Chinello P, Petrosillo N, Pitallo S, Biava G, Ippolito G, Nicastri E, et al. QTc interval prolongation during favipiravir therapy in an Ebola virus-infected patient. PLoS Negl Trop Dis 2017;11:e0006034.