Arrhythmia may contribute to neuropsychiatric symptoms in COVID-19 patients

Dear Editor,

Forero-Peña et al. described immediate and long-term neuropsychiatric complications following the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and discussed the possible roles of (hydroxy)chloroquine and dexamethasone on these neuropsychiatric symptoms. The patients demonstrated multiple psychiatric symptoms, including bipolar I disorder, major depressive episodes, and brief psychotic disorder. This is consistent with a previous report that depression and anxiety were the most common psychological distresses across patients infected by SARS-CoV-2.

For (hydroxy)chloroquine administration, in four of the five patients presented, the rapid onset of symptoms after initiation of the drug and remission shortly after discontinuation, supporting (hydroxy)chloroquine as a potential trigger for their neuropsychiatric symptoms. And the overall psychiatric impacts of corticosteroids in COVID-19 patients presented, the rapid onset of symptoms after initiation of the drug and remission shortly after discontinuation, supporting (hydroxy)chloroquine and dexamethasone as potential triggers for neuropsychiatric symptoms.

However, arrhythmia may also contribute to neuropsychiatric symptoms in COVID-19 patients and should not be neglected. Through a literature search, we summarized abnormal electrocardiographic findings in COVID-19 patients. Sinus tachycardia was the most common arrhythmia found in the patients, with frequencies of 16.9%–70.4% (Table 1). Atrial fibrillation (AF) may be the secondary common arrhythmia. However, its occurrence rates vary greatly between different reports, ranging from 1.9% to 62.5% (Table 1). Premature beat, ST-T segment and T wave changes, non-sustained ventricular tachycardia, QT-interval (QTc) prolongation, paroxysmal supraventricular tachycardia, atrioventricular block, bifascicular block, and left anterior hemi-block may also occur in the patients with frequencies higher than 10% (Table 1).

In many cases of sinus tachycardia, cognitive and behavioral factors, somatic hypervigilance associated with anxiety, depression, and behavioral amplification contributes to symptom chronicity. And a previous study indicated that, for the patients with inappropriate sinus tachycardia, the most common comorbid conditions were depression (25.6%) and anxiety (24.6%). Although no evidence of an association between symptoms of anxiety or severe depression and AF risk, a significant association of symptoms of mild to moderate depression with increased AF risk has been identified. Moreover, anxiety and depression may be associated with worsened AF.

Thus, antiarrhythmic drugs, such as amiodarone and metoprolol may be used for COVID-19 patients with ventricular arrhythmia. We should pay attention to the COVID-19 patients with psychiatric disorders before COVID-19, as the infection may exacerbate pre-existing mental symptoms. The antiarrhythmic drugs should be applied to these patients, if they showed arrhythmia after the infection, since that arrhythmia may worsen the neuropsychiatric symptoms.

Chloroquine and hydroxychloroquine have been widely used in COVID-19 treatments. However, there is compelling evidence that chloroquine and hydroxychloroquine induce significant QTc prolongation and potentially increase the risk of arrhythmia (such as Torsade de pointes) (Table 2). Actually, among COVID-19 patients, approximately 10% developed QTc prolongation to a degree that generally leads to withdrawal of the drug. Although clinicians did not find evidence that occurrence of either depressive or anxiety disorder is associated with abnormalities in QTc, increased anxiety scores were associated with prolonged QTc intervals. Therefore, (hydroxy)chloroquine should not be used for COVID-19 patients with anxiety disorders to avoid severe QTc prolongation.

Neither psychiatric symptoms nor arrhythmia in COVID-19 patients undergoing steroid treatments has been well described in the literature. Corticosteroid-induced psychosis is a rare but well-documented disorder when corticosteroid was applied at a high dose. And a rare case study in lupus previously reported that high dose corticosteroid was associated with increased AF. However, no such side effects have been reported at lower doses. Indeed, low-dose corticosteroids have been shown in septic shock and prophylactic use for AF postcardiac surgery or ventilator-induced. Although there is no direct evidence that corticosteroids can prevent arrhythmia, they are likely safe in low or moderate dosages and may have a role in preventing AF development in COVID-19. Corticosteroids might be applied to the COVID-19 patients with psychiatric disorders, if they showed AF after the infection, as AF may worsen neuropsychiatric symptoms.

DOI: 10.1002/jmv.27583
| Reference | Reference | Reference | Reference |
|-----------|-----------|-----------|-----------|
| Cho et al., PLoS One 2020; 15: e0244533 | Song et al., Front Cardiovasc Med 2020; 7: 150 | Kunal et al., Indian Heart J 2020; 72: 593-598 | Chen et al., Clin Cardiol 2020; 43: 796-802 |
| Hsieh et al., SAGE Open Med 2021; 9: 20503121121054973 | Mesquita et al., Rev Port Cardiol (Engl Ed) 2021; 40: 573-580 | Antwi-Amoabeng et al., Ann Noninvasive Electrocardiol 2021; 26: e12833 |
| Cho et al., PLoS One 2020, 15: e0244533 | Song et al., Front Cardiovasc Med 2020; 7: 150 | Kunal et al., Indian Heart J 2020; 72: 593-598 | Chen et al., Clin Cardiol 2020; 43: 796-802 |
| Hsieh et al., SAGE Open Med 2021; 9: 20503121121054973 | Mesquita et al., Rev Port Cardiol (Engl Ed) 2021; 40: 573-580 | Antwi-Amoabeng et al., Ann Noninvasive Electrocardiol 2021; 26: e12833 |
| | | | |
| Reference | Arrhythmia in COVID-19 patients | Frequency | |
| Cho et al., PLoS One 2020, 15: e0244533 | Sinus tachycardia | 39.9% (57/143) | |
| | Premature ventricular complexes | 28.7% (41/143) | |
| | Non-sustained ventricular tachycardia | 15.4% (22/143) | |
| | Sustained ventricular tachycardia | 1.4% (2/143) | |
| | Ventricular fibrillation | 0.7% (1/143) | |
| Song et al., Front Cardiovasc Med 2020; 7: 150 | ST-T segment and T wave changes | 33.3% (7/21) | |
| | Sinus tachycardia | 19.0% (4/21) | |
| Kunal et al., Indian Heart J 2020; 72: 593-598 | QT-interval (QTc) prolongation | 17.6% (19/108) | |
| | Sinus tachycardia | 16.9% (18/108) | |
| | First degree atrioventricular (AV) block | 4.6% (5/108) | |
| | Ventricular tachycardia/ventricular fibrillation (VT/VF) in two | 1.8% (2/108) | |
| | Sinus bradycardia | 0.9% (1/108) | |
| Chen et al., Clin Cardiol 2020; 43: 796-802 | Sinus tachycardia | 70.4% (38/54) | |
| | Premature beat | 18.5% (10/54) | |
| | Ventricular tachycardia (VT) | 5.6% (3/54) | |
| | Sinus bradycardia | 5.6% (3/54) | |
| | Atrioventricular (AV) block | 3.7% (2/54) | |
| | Atrial fibrillation (AF) | 1.9% (1/54) | |
| Hsieh et al., SAGE Open Med 2021; 9: 20503121121054973 | Sinus tachycardia | 41.1% (97/236) | |
| Mesquita et al., Rev Port Cardiol (Engl Ed) 2021; 40: 573-580 | Atrial fibrillation (AF) or flutter | 62.5% (40/64) | |
| | Paroxysmal supraventricular tachycardia | 26.6% (17/64) | |
| | Increased QTc interval | 10.9% (7/64) | |
| | Sinus bradycardia | 7.8% (5/64) | |
| | Ventricular tachycardia | 3.1% (2/64) | |
| Antwi-Amoabeng et al., Ann Noninvasive Electrocardiol 2021; 26: e12833 | T-wave abnormalities | 38.7% (72/186) | |
| | Sinus tachycardia | 30.1% (56/186) | |
| | Atrial fibrillation (AF) or flutter | 12.9% (24/186) | |
| | Atrioventricular (AV) block | 11.8% (22/186) | |
| | ST depression | 8.6% (16/186) | |
| | ST elevation | 8.1% (15/186) | |
| | Sinus bradycardia | 7.5% (14/186) | |
| | Right bundle branch block | 7.5% (14/186) | |
| | Premature atrial contraction | 5.9% (11/186) | |
| | Premature ventricular contraction | 5.4% (10/186) | |
| | Supraventricular tachycardia | 1.6% (3/186) | |
| | Left bundle branch block | 1.6% (3/186) | |
### TABLE 1  (Continued)

| Reference | Arrhythmia in COVID-19 patients | Frequency |
|-----------|--------------------------------|-----------|
| Aghajani et al., Arch Acad Emerg Med 2021; 9: e45 | Sinus tachycardia | 35.5% (317/893) |
| | Abnormal T wave | 24.7% (221/893) |
| | ST depression | 19.1% (171/893) |
| | Prolonged QT interval | 18.2% (162/893) |
| | Bifascicular block | 17.2% (154/893) |
| | Left anterior hemi-block | 13.2% (118/893) |
| | Supraventricular arrhythmia | 9.9% (88/893) |
| | Sinus bradycardia | 6.2% (55/893) |
| | Q wave in inferior leads | 5.6% (50/893) |
| | Abnormal R wave progression | 4.8% (43/893) |
| | Right bundle branch block | 4.6% (41/893) |
| | ST elevation | 4.0% (36/893) |
| | Ventricular arrhythmia | 3.1% (28/893) |
| | Interventricular conduction delay | 3.0% (27/893) |
| | Q wave in precordial leads | 3.0% (27/893) |
| | Left bundle branch block | 2.9% (26/893) |
| | Incomplete right bundle branch block | 2.8% (25/893) |
| | Incomplete left bundle branch block | 1.2% (11/893) |
| | Q wave in lateral leads | 0.3% (3/893) |
| | Left posterior hemi-block | 0.2% (2/893) |

### TABLE 2  Arrhythmia in COVID-19 patients treated with (hydroxy)chloroquine

| Reference | Arrhythmia in COVID-19 patients treated with (hydroxy)chloroquine | Frequency |
|-----------|---------------------------------------------------------------|-----------|
| Chang et al., J Am Coll Cardiol 2020; 75: 2992-2993 | Atrial fibrillation with a rapid ventricular response | 53.6% (15/28) |
| | QT-interval (QTc) > 500 ms | 17.9% (5/28) |
| | First-degree atrioventricular block | 14.3% (4/28) |
| | Nonsustained ventricular tachycardia | 7.1% (2/28) |
| | Ventricular bigeminy | 3.6% (1/28) |
| | Supraventricular tachycardia | 3.6% (1/28) |
| Becker et al., Cardiovasc Toxicol 2021; 21: 314-321 | QTc > 500 ms or the change in QTc > 60 ms | 27.1% (19/70) |
| Jiménez-Jáimez et al., Sci Rep 2020; 10: 21417 | QTc > 460 ms | 14.2% (31/219) |
| Gopinathannair et al., J Interv Card Electrophysiol 2020; 59: 329-336 | QTc > 500 ms | 16.8% (80/477) |
| | Torsade de pointes | 4.1% (20/489) |
| Saleh et al., Circ Arrhythm Electrophysiol 2020; 13: e008662 | QTc > 500 ms | 9.0% (18/201) |
| | The change in QTc > 60 ms | 12.9% (26/201) |
| | New-onset atrial fibrillation | 8.5% (17/201) |
| | Nonsustained, monomorphic ventricular tachycardia | 3.5% (7/201) |
| | Sustained, monomorphic ventricular tachycardia | 0.5% (1/201) |

(Continues)
CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Shu Yuan conceptualized the analysis. All authors contributed to literature search, writing, and revision of the manuscript. All authors approved the final version.

DATA AVAILABILITY STATEMENT
Data are available from the corresponding author on a reasonable request.

ORCID
Shu Yuan http://orcid.org/0000-0001-6565-6914

REFERENCES
1. Forero-Peña DA, Hernandez MM, Mozo Herrera IP, et al. Remitting neuropsychiatric symptoms in COVID-19 patients: viral cause or drug effect? J Med Virol. Epub ahead of print doi:10.1002/jmv.27443
2. Zhang J, Lu H, Zeng H, et al. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav Immun. 2020;87:49-50. doi:10.1016/j.bbi.2020.04.031
3. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc. 2012;87:1214-1225. doi:10.1016/j.mayocp.2012.08.013
4. Shabtaie SA, Witt CM, Asirvatham SJ. Natural history and clinical outcomes of inappropriate sinus tachycardia. J Cardiovasc Electrophysiol. 2020;31:137-143. doi:10.1111/jce.14288
5. Feng T, Malmo V, Laugsand LE, et al. Symptoms of anxiety and depression and risk of atrial fibrillation—the HUNT study. Int J Cardiol. 2020;306:95-100. doi:10.1016/j.ijcard.2019.11.107
6. Thompson TS, Barksdale DJ, Sears SF, Mounsey JP, Pursell I, Gehi AK. The effect of anxiety and depression on symptoms attributed to atrial fibrillation. Pacing Clin Electrophysiol. 2014;37:439-446. doi:10.1111/pace.12292
7. Gopinathannair R, Merchant FM, Lakkireddy DR, et al. COVID-19 and cardiac arrhythmias: a global perspective on arrhythmia characteristics and management strategies. J Interv Card Electrophysiol. 2020;59:329-336. doi:10.1007/s10840-020-00789-9
8. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: systematic review of the current evidence. Brain Behav Immun. 2020;89:531-542. doi:10.1016/j.bbi.2020.03.048
9. 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;17:1472-1479. doi:10.1016/j.hrthm.2020.05.008
10. Hu MX, Lamers F, Penninx BWJH, de Geus EJC. Association between depression, anxiety, and antidepressant use with T-wave amplitude and QT-interval. Front Neurosci. 2018;12:375. doi:10.3389/fnins.2018.00375
11. Fava M, Abraham M, Pava J, Shuster J, Rosenbaum J. Cardiovascular risk factors in depression. The role of anxiety and anger. Psychosomatics. 1996;37:31-37. doi:10.1016/S0033-3182(96)71595-5

12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed.; 2013. ISBN 978-0-89042-554-1

13. Yamamura K, Ohga S, Nishiyama K, et al. Recurrent atrial fibrillation after high-dose methylprednisolone therapy in a girl with lupus-associated hemophagocytic syndrome. Lupus. 2011;20:871-875. doi:10.1177/0961203310392429

14. Launey Y, Lasocki S, Asehnoune K, et al. Impact of low-dose hydrocortisone on the incidence of atrial fibrillation in patients with septic shock: a propensity score-inverse probability of treatment weighting cohort study. J Intensive Care Med. 2019;34:238-244. doi:10.1177/0885066617696847

15. Stone E, Kiat H, McLachlan CS. Atrial fibrillation in COVID-19: a review of possible mechanisms. FASEB J. 2020;34:11347-11354. doi:10.1096/fj.202001613