Pacific Journal of Medical and Health Sciences
ISSN: 2456-7450 | Vol.4, No.4, 2022, pp - 135-145

PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

Review

COVID -19 and Cardiac Conduction System Abnormalities: A Review

Urvansh Mehta[1], Hiren Dangar[1], S.K. Verma[2]

[1]PG Resident, [2]Professor Emeritus and Director,

Department of General Medicine, Pacific Medical College and Hospital, Udaipur, Rajasthan, India

*Corresponding author Email: urvanshmehta@live.com

ABSTRACT

COVID-19 is a global pandemic caused by a strain of corona virus known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). It has affected billions of individuals worldwide. SARS-CoV-2 has common biological characteristics with SARS-CoV, which caused the 2002 outbreak of severe acute respiratory syndrome. This includes the system of cell entry, which is triggered by binding of the viral spike protein to angiotensin-converting enzyme 2. COVID-19 has been associated with cardiovascular disease, which can lead to worse outcomes and increased risk of death in patients with pre-existing cardiovascular disease. COVID-19 disease can cause cardiovascular derangement in form of cardiac arrhythmia, acute viral myocarditis or thrombogenic – ischaemic events. In this review, we have tried to summarise the current understanding of and pathophysiology of cardiac arrhythmias in COVID-19 and potentially finding out the root cause and management strategy.

KEYWORDS: Arrhythmia, Sudden Cardiac Death, SARS, SARS CoV-2, Q-T Interval

INTRODUCTION

We are still battling a global public health concern in form of a pandemic with COVID -19. The virus has wreaked havoc in the entire world and continues to do so. There is no end in sight, and we are still in the learning phase for the disease. What we have observed is that COVID -19 has propensity to affect almost any system in the body. Even though being a primary Respiratory Virus, COVID -19 has extensive cardiovascular manifestations. The severity of the disease has a strong association with co morbidities and complications, and specifically cardiac complications has been seen to have higher percentage of fatality[1]. The understanding and knowledge about the virus and the disease is increasing rapidly with newfound concepts being developed daily. The managing bodies are issuing newer and newer guidelines, and yet still the lacunae prevail.

COVID -19 patients are at an increased risk of developing specific cardiac arrhythmias and the prevalence is discernible throughout the population[2]. In a large chunk of patients there can be no clinical manifestations of any cardiovascular pathology presenting with COVID-19. Simple tachycardia can also be due to constitutional symptoms of the illness such as pyrexia, dyspnoea etc.

Previous faced outbreaks such as SARS – CoV, MERS CoV and the influenza virus spread has given us a similar picture of worsening severity when the disease was associated with underlying cardiovascular condition[3]. Before the humans were considered susceptible for CoV infections,

cardiomyopathies predominantly dilated cardiomyopathies were seen in rabbits infected with coronaviruses[4]. Similarly in human infection of above mentioned diseases sudden cardiac death, shock → hypotension and cardiac arrhythmias were seen[5].

Trying to understand a cause of sudden cardiac arrest in almost fifteen patients with severe acute respiratory syndrome, there was a study conducted in China by Pan *et al.*[6] and they concluded five hypotheses which were:

1. Hypoxemia due to acute lung injury leading to unsteady myocardial electrical activity.
2. Direct injury to the conducting cells of myocardium by the virus.
3. Worsening o pre-existing cardiac disease.
4. Excess catecholamine secretion due to stress leading to unstable myocardium.

Predisposition in COVID – 19

As per the current understanding the COVID-19 disease is extremely contagious however less the mortality be. Multiple cohorts have mentioned that prevalence of cardiac damage (7%), shock and hypotension (8.8%) and cardiac arrhythmias (16.8%), increased with disease severity[7].

An interesting concept can be proposed that diagnosing COVID-19 in early stages can be misled in patients with pre-

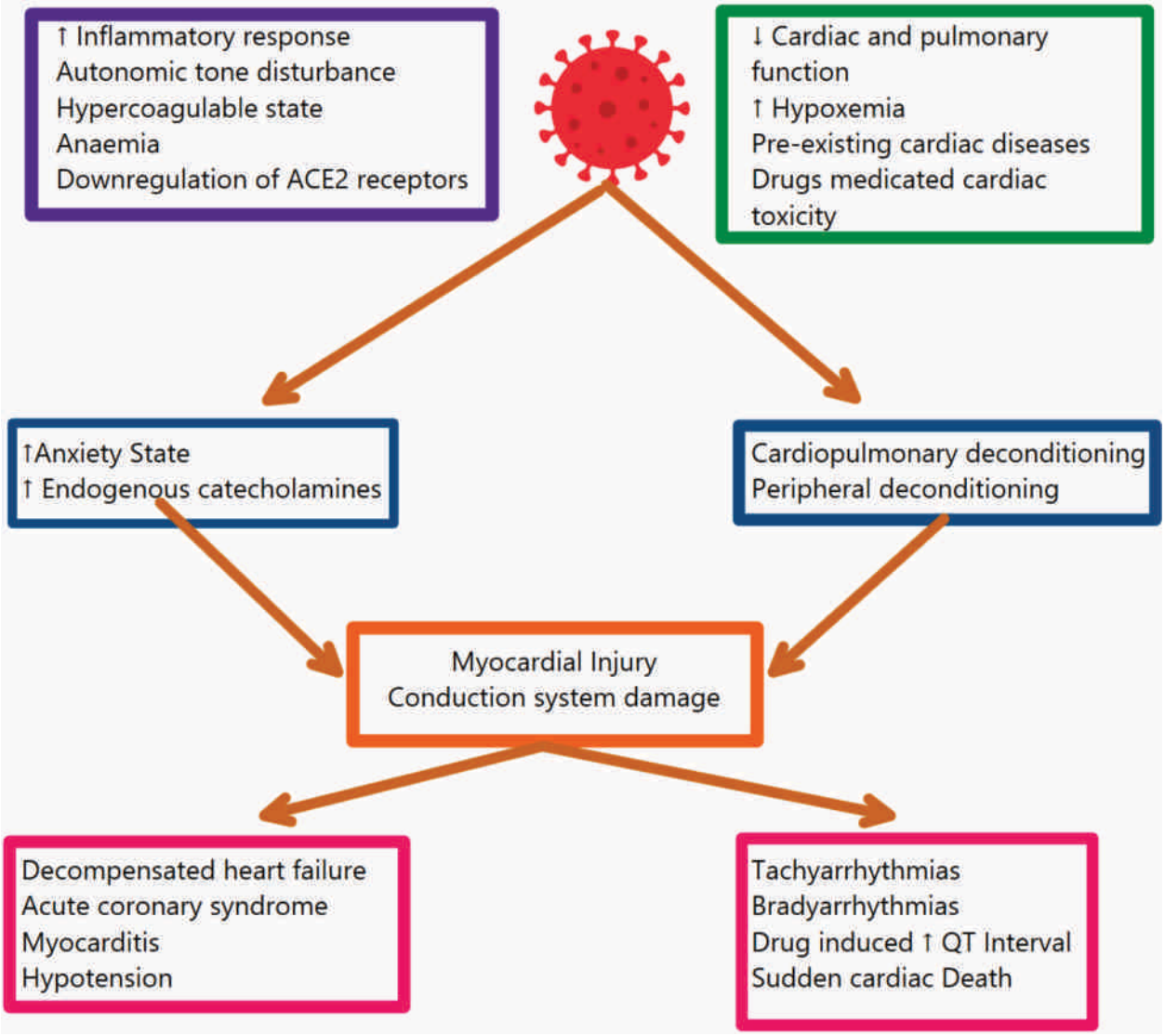

Figure 1: Cardiac Injury in COVID-19

existing cardiac conditions. Constitutional symptoms such as dyspnoea, cough, fever, easy fatigability can also be seen in as exacerbations of heart failure and arrhythmia[8]. This led to a report by NHC (National Health Commission – China) which stated that in diagnosed COVID-19 cases cardiac manifestations were the initial presenting features, this led to a delayed diagnosis of COVID – 19 due to overlapping symptoms. NHC mentioned in the report that amongst the fatal cases, about 11.8% of patients demonstrated widespread cardiac injury with elevated cardiac enzyme (predominantly Troponin I)[9].

The most accepted hypothesis for cardiac arrhythmia in COVID -19 can be the development of acute viral myocarditis[10]. Arrhythmogenic manifestations can be the result of cardiogenic shock developed due to myocarditis; this understanding is based on the concept that inflammation of the myocardium can cause novel re-entry points for the cardiac conduction circuit[11,12].

Ventilatory requirements increases with incidence of ventricular arrhythmia in COVID-19. What we can understand is these patients who exert a dysregulated immune response towards the infection also develop severe hypoxic lung injury, dyselectrolytaemia out of which potassium disorders causing cardiac arrhythmias[12].

Guo *et al.*[13] has done significant contribution in understanding the cardiac dysfunction caused by SARS viruses. They analyzed the Troponin levels of 187 COVID-19 confirmed patients and saw elevated Trop-I in 27.8% of patients. Elevated Trop–I was positively associated with ARDS (57.7% compared to 11.9%) and AKI (36.8% compared to 4.7%), more so even fatality was more with raised plasma TnT levels (59.6% compared to 8.9%).Ventricular arrhythmias along with viral myocarditis were seen initially in a COVID -19[14]. We saw in Italy that many home-quarantined patients succumbed to the injuries with Sudden Cardiac Deaths. Even after remission of COVID -19 there is strong possibility of residual atrial and ventricular fibrosis, subsequently causing long standing arrhythmias. The utility of Cardiac MRI is important here for stratification of the scar injury[15].

One more theory has been hypothesised that in COVID – 19 there is imbalance between the infection – induced increase in metabolic demand and reduced cardiac reserve, in the presence of such supply demand mismatch along with active inflammation and myocardial cell injury, there can be a rise in Arrhythmic events along with heart failure and coronary syndromes.7 In the initial surge of COVID-19 patients Anti malarial agents such as Hydroxychloroquine (HCQ) was used judiciously. HCQ is notorious for causing QT Prolongation. Although rare but it is a fatal complication. Hence HCQ has a pro-arrhythmic component which should be monitored in COVID patients[16].

These antimalarial drugs are stored in lysosomal cells; they act by directly blocking the phosphodiesterase activity, this results into formation of intra-cytoplasmic inclusion bodies. These inclusion bodies inactivates protein functions[17]. The most common ECG change seen in usage of Anti-Malarial drugs is heart block (fascicular) leading to AV block and syncope[18].

Cardiovascular conditions especially Hypertension and Coronary Artery Disease have predispose to higher mortality in COVID-19. Commonly used cardiovascular drugs such as ACE inhibitors and Angiotensin II Receptor Blockers can perhaps have impact in the managing COVID-19 also because of the viruses' higher affinity towards binding to ACE – II receptors[20].

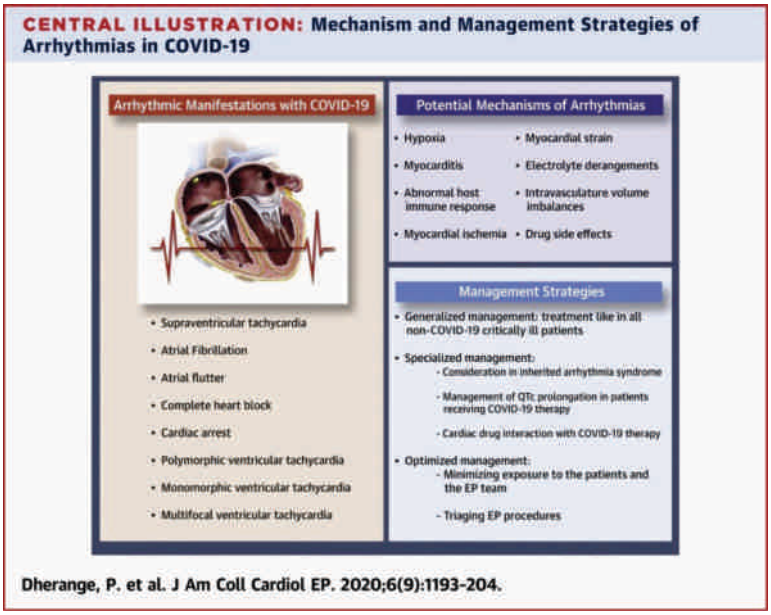

Figure 2: Potential mechanisms and management strategies of Cardiac Arrhythmias in COVID -19[19]

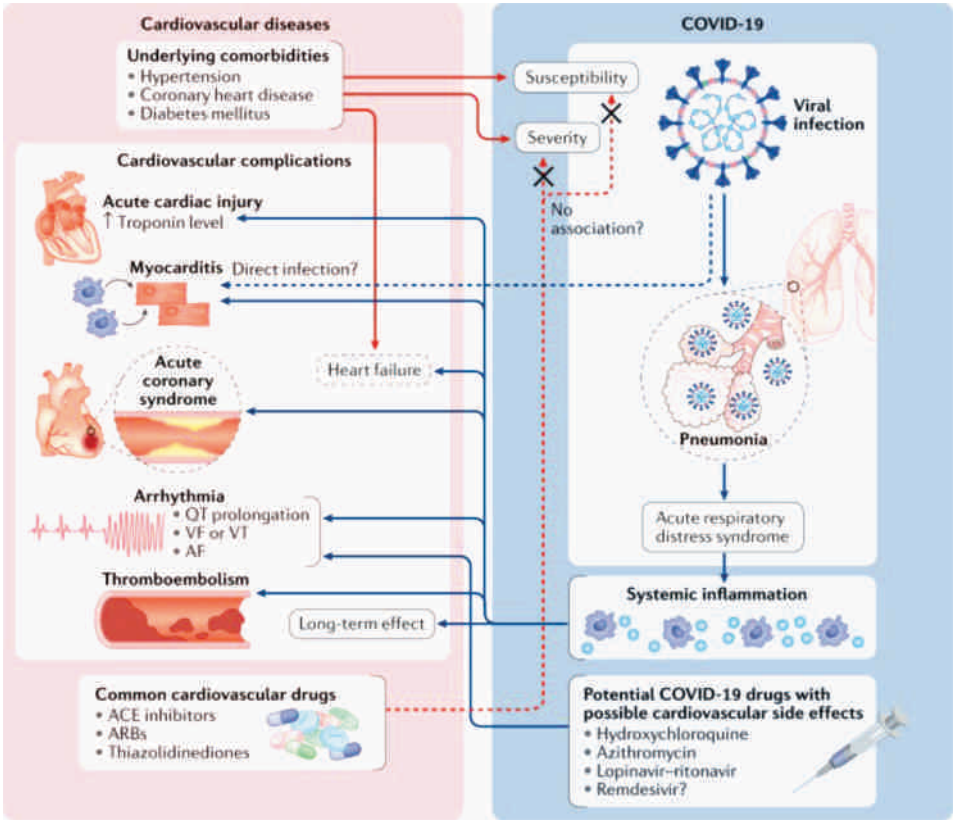

Figure 3: Association of Cardiovascular Disorders with COVID-19[21]

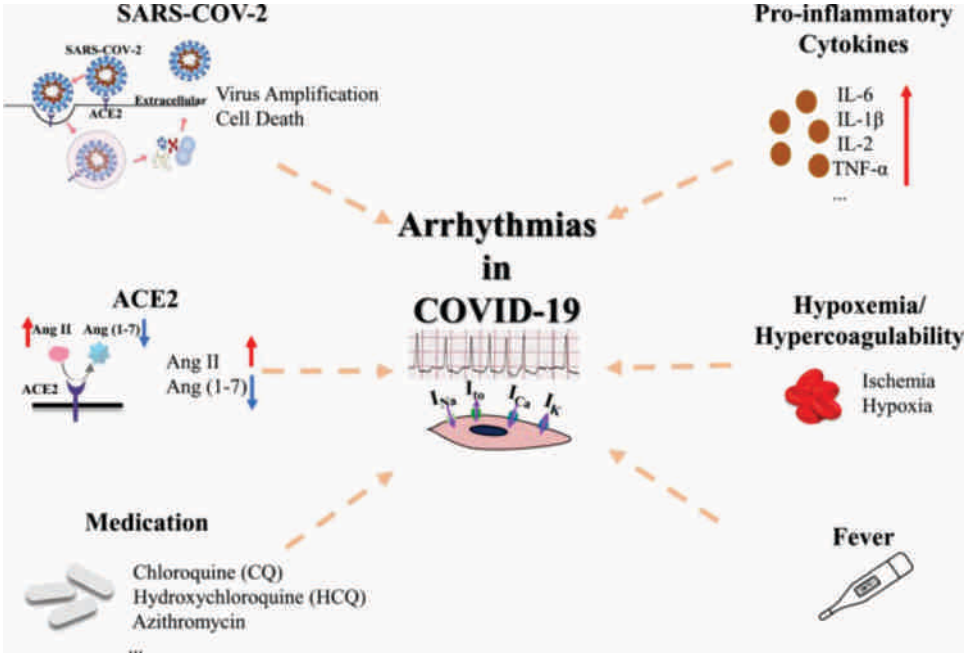

Figure 4: Purported Pathophysiology of Arrhythmias in COVID -19

Common Observations

- **QTc Prolongation –** In a New York multicentre cohort, they saw that out of 4250 patients enrolled in the study, 6.1% (260) patients reported a corrected QT of above 0.5s on initial presentation[22]. But in a different study of 84 patients, the baseline QTc of those patients before taking HCQ and Azithromycin was 435 ms[23].
- **Atrial Fibrillation -** 31,000 COVID-19 patients were studied in a large study conducted in USA saw 5.4% of them developing new onset AF while they were hospitalized for the first time[24]. A meta-analysis of various observational studies with around 21,653 patients of COVID-19, AF percentage was 11%[25].
- **Ventricular Tachycardia and Ectopic Conduction –** Non sustained VT was about 15.4% in a single centre study done on 143 patients, they also reported 1.4 percent patients of ventricular fibrillation and 28.8% of patients with ventricular tachycardia[26].
- **Brady arrhythmias –** Scarce data is available for Bradyarrhythmias in COVID-19, but a single centre study of 143 patients observed 1.4% patients developing atrio -ventricular block and 0.7% patients suffering from sinus arrest[27].
- **In Hospital Cardiac Events –** A study of 7000 COVID-19 patients from a single centre in United States – 9 patients suffered cardiac arrest[28]. In another cohort study conducted in China, there were 136 critically ill patients of COVID -19 enrolled. The study evaluated cardiac events in those patients, out of which majority of cardiac arrests were respiratory in origin, initially presenting with non-shockable rhythm. (Around 90% with asystole). Only 13% patients showed return of spontaneous circulation and as little as 1% patients survived with intact neurological function - Giving us an idea of the gravity of the situation[29].
- **Outpatient Cardiac Events –** A study from Italy states around 60% increase in outpatient cardiac arrest rates especially during the 2020 wave[30]. Around average incidence of Out – of – Hospital cardiac arrest was higher than 52% in the year 2020 according to a study conducted in France[31].

Pre existing cardiac conditions is the most common risk factor. Presence of any cardiovascular complication along with COVID -19 can predispose to developing arrhythmogenic events[32]. Atrial arrhythmias are more seen in severe COVID-19 pneumonia requiring mechanical ventilation. Predisposition to arrhythmia can be because of sepsis and septic shock, severe hypoxia or SIRS[33]. Electrolyte disturbances are more prone to develop into cardiac arrhythmias and even drugs that increase the QT intervals increases the risk to develop polymorphic VT.

Interestingly it is seen that Remdesivir, the most commonly, judiciously and relentlessly used antiviral in COVID-19 can be a risk for causing Bradycardia[34,35]. But the claim was also rejected in a series of large randomized trials[36,37]. Channelopathies (Such as Brugada Syndrome) can be dormant and gets precipitated in presence of fever leading to QT prolongation due to COVID -19[38,39].

Viral Cardiac Injury: A Possible Initiator

COVID-19 being a primary respiratory insult, symptoms usually begin with URTI mimics. But there are isolated reports, compiled by Inciardi et al which suggests that there can becases with solely cardiac symptoms[40]. Functional and structural heart alterations have been reported in COVID-19 by many authors. This includes Heart Failure[41,42] and also instances of Takotsubo cardiomyopathy[43,44] and the most dreaded of all Acute MI[42].

In the SARS infection, tachycardia was seen as the most prevalent ECG pattern, fortunately self limiting, but the incidence was high at around 72%[45].Bradycardia was much less seen, highest being 15%[46]. Along with these SARS also showed sudden cardiac death, QT prolongation, atrial fibrillation and ectopic conduction[47,48].

Cardiac Arrhythmia in COVID-19 was first described by Wang *et al.*[49] with an incidence of 17%. In critical patients, normal ECGs were only 26% according to a recent study[50]. Along with incidence, cardiac arrhythmia is associated with increased risk of hospital mortality when compared to sinus rhythm ECGs (Odds 1.95, CI 95% 1.33-2.86)[51].

Tachyarrhythmias

Just COVID-19 alone causes a base heart rate to increase at around 80-88 bpm even with a sinus rhythm[49,52]. Even average heart rate in critical COVID -19 patients was higher than asymptomatic or ward patients[49]. Confirming these findings, a study[53] reported 3 patients with tachycardia out of the 17 enrolled, and 2 patients with atrial fibrillation and heart rate around 160. Out of these two AF, one patient had persistent AF, but the other patient had the index finding. One can argue that due to pyrexia, base heart rate in COVID -19 can be elevated, but the author states that the increase is disproportionate to the rate of temperature rise.

Colon *et al.*[54], studied atrial arrhythmia related outcomes extensively. In his study, 19 patients out of 165 patients developed atrial tachyarrhythmias. Out of those 19 patients, 6 patients had hemodynamic collapse due to atrial flutter and 12 patients had atrial fibrillation, and 1 patient had atrial tachycardia.

The excerpt should be that atrial conduction abnormalities are very common in COVID-19 and they can also occur without a pre-existing cardiac dysfunction, maybe there are electrophysiological alterations by SARS-Cov-2 leading to such.

Conduction Blocks

According to a report50 incidence rate of cardiac arrhythmias is from 15-30% in COVID-19. Out of these AV conduction blocks were the most numerous (11.8%). A case study from Iran reported a child who suffered from severe left ventricular pathology and complete heart block[55]; another case talked about transient complete heart block in a COVID-19 patient[56]. Similarly a 21 year old female reported multiple VPC (Ventricular premature complexes) with non-specific conduction blocks[57]. Bradyarrhythmias however rare but has been reported as such in isolated instances.

ST-T Discordance

ST-T manifestations was commonly seen in ECGs (41%) reported by Wang *et al.*[58]. Out of those 5 patients developed Acute MI. ST elevation was seen in 18 COVID-19 patients, out of which 13 patients passed away (9 deaths were non-coronary) in a similar case series[59]. An interesting case report60 which wrote about a 61 year old male who presented to the hospital with Brugada syndrome morphology in ECG which transferred into a Atrioventricular Nodal Re-entrant Tachycardia (AVNRT), had no explanations of origins of this manifestation. Many reports of deaths are there due to ST Elevation in COVID -19[61].

Further Discussion on QT Prolongation

QT interval was around 454 ms in the study by Li *et al.*[50] As discussed earlier, antimicrobial and antiparasitic agents commonly used in COVID-19 are widely suspected to be the major cause of QT Prolongation in COVID-19. For HCQ even there is suggesting evidence available denoting prolonged QT[62].

In a double blinded parallel study Borba *et al.*[63] evaluated the risk of chloroquine. They found out that in corrected QT was prolonged in 11% patients out of the low dosage group (450 mg Twice daily for the first day and then once daily for the next 4 days), and 19% patients in the high dosage group (600 mg BD) developed QT prolongation. There were 3 patients in the high dose group who developed ventricular tachycardia, and out of the 5 with pre-existing heart conditions – 3 patients died.

As a common practice in SARS, eventually even followed in COVID-19, HCQ was given concurrently with Azithromycin, and the combination is proven to have higher risk of developing QT prolongation[64]. QTc more than 500 ms was observed after an average of 3.6 days of admission of HCQ+Azithromycin. Severely prolonged QT is a harbinger for malignant arrhythmias and sudden cardiac death[65].

Malignant Arrhythmias

Comorbidities along with COVID-19 worsen the disease progression, treatment effectiveness and outcomes significantly. Guo *et al.*[13] reported malignant arrhythmias initially in COVID-19 with an incidence of 5.9% comprising of ventricular fibrillation and VT. In a study by Du *et al.*[66] 2.46% of patients dying from COVID-19 had malignant arrhythmias as their primary cause SARS CoV-2 as compared to SARS is more likely to cause arrhythmic complications such as heart bocks, QT prolongation and malignant ventricular tachyarrhythmia as mentioned above.

There are currently only a few ECG records available for COVID-19 patients, and the reported rates of various arrhythmia types vary between researches. Due to the non-homogeneous characteristics of the cases that were chosen for investigations, the limited sample size, and the absence of continuous ECG monitoring data, this is probably the case. A single ECG analysis is not sufficient. To more accurately determine the kind of arrhythmias, dynamic ECG monitoring is necessary. According to the information that is currently available, COVID-19's clinical course progresses quickly, and ECG abnormalities found during hospitalisation may serve as an indicator of the disease's severity.

A serious COVID-19 patient's prognosis is likely to be bad if they exhibit pathophysiological alterations resembling severe myocardial injury or ECG manifestations such as heart blocks, QT interval prolongation, or ventricular arrhythmia. So, it is advised that clinicians carry out a thorough examination and that they be vigilant for potentially fatal ventricular arrhythmia storms.

Management Strategies

1.Diagnosis

Clinicians must keep a close lookout for any potential rhythm irregularities in COVID-19. 7% of COVID patients presented with palpitations initially[67]. About 4% of COVID-19 patients had a history of previous cardiac event, making them potentially more vulnerable to developing new rhythm problems[68]. Thus, it is necessary to gather crucial clinical data, including baseline ECGs, a thorough medication history, particularly for drugs that can cause electrocardiographic QT prolongation, previous incidence of arrhythmia, unexplained syncope, and family history of untimely SCD. In order to avoid negative clinical outcomes, patients with pre-existing cardiovascular illnesses need to have their ECG manifestations and possible risk of cardiac arrhythmias carefully monitored.

The evaluation of hospitalised individuals or those who may be more susceptible to cardiac arrhythmias requires a baseline examination. Close watch for cardiac arrhythmias should be carried out in patients with COVID-19 if they exhibit palpitations, light-headedness, or even unexplained syncope. A somewhat prolonged QTc on baseline ECG examination may be treated with medicine and electrolyte management. Medications that further prolong the QTc should be avoided if it is already considerably prolonged. Nonetheless, expert evaluation may allow administration with mitigating precautions.

ECG needs to be carefully watched over in order to provide early warning and action. To lessen the risk of infection for front-line healthcare providers and other patients during the pandemic, unnecessary testing, such as serial ECGs, should be avoided. Therefore, individuals with COVID-19, particularly those with cardiac comorbidities, should undergo continuous ECG monitoring more often. Some professionals believe it could be possible to employ a mobile continuous telemetry monitor (MCOT) and handheld ECG device as a QT screening tool in COVID-19 patients[69,70].

The following ECG signs might catch the attention of cardiologists and primary care doctors, according to researchers from the National Centre for Gerontology[71]: Continuous, coupled, pleomorphic, or multifocal premature contractions; Atrioventricular reentrant tachycardia; atrial flutter/atrial fibrillation; QRS complex low voltage; abnormal Q waves and wide QRS complex (QRS > 120ms); continuous ECG monitoring. ST-T changes accompanied by continuously dynamic changes in two or more leads (I, II, aVF, V5) with R waves dominance.

The presence of paroxysmal tachycardia or an increase in pulse rate that does not correspond to the illness severity status should also be taken into consideration in patients. Early detection of arrhythmia and high-risk ECGs, as well as prompt treatments, are very significant.

2. Prevention and Management

So far, no specific antiviral drugs or vaccines have been confirmed to benefit COVID-19 except for symptomatic relief and supportive treatments. The treatment guidelines for COVID-19 published by The National Institutes of Health (NIH) determined that no drug(s) has been proven to be safe and effective for treating COVID-19 at present. Although reports have appeared in the medical literature asserting successful treatment of COVID-19 by multiple medications[72,73], additional evidence from ongoing clinical trials will be needed to identify the optimal treatment. Several antiviral agents and immunomodulating therapies are currently under clinical investigation.

The COVID-19 Treatment Guidelines Panel recommends against the use of the following drugs for the treatment of COVID-19: the combination of HCQ plus azithromycin because of the potential for toxicities, except in the context of a clinical trial; Lopinavir/ Ritonavir or other human immunodeficiency virus (HIV) protease inhibitors because of unfavourable pharmacodynamics and negative clinical trial data[74].

Tempered with concerns of increased risks of QT prolongation and development of TdP, it is necessary to discontinue unnecessary medications which may also increase the risk of arrhythmias. If this combination proves to be life-saving for COVID-19 patients, monitoring the QT interval to allow patients to receive combination therapies will be critical.

Certainly, the use of combination therapies with azithromycin and CQ or HCQ in high-risk patients must be carefully weighed against the risks. The higher dosage of CQ should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. The late sodium channel-blocking drugs like mexiletine have been proposed to be used if the QT interval prolongs[75]. A temporary transvenous pacemaker may be necessary to overdrive pace if the patient is bradycardia with premature ventricular complexes. Careful attention to serum electrolytes, heart rate, and monitoring of QTc intervals may allow administration of a full course of these drugs.

Prevention or treatment of arrhythmias in COVID-19 patients should include optimization of supportive treatments, including bed rest, maintaining water and electrolyte balance, medication or physical cooling in patients with fever, oxygen supplementation in patients with hypoxia or dyspnoea, and non-invasive or invasive ventilator support treatment where indicated. For patients with sinus tachycardia, Ivabradine may be used for rate management[71]. Diltiazem, Propafenone, or Verapamil were also considered first in patients with atrial premature beats or tachycardia without cardiac disease[76]. Beta-blockers should be used with caution in patients with COVID-19 combined with sinus or atrial tachycardia. If the patient shows sustained VT, intravenous infusion of amiodarone and other antiarrhythmic medications may be given, electrical defibrillation can be used if it necessary. If VF occurs, cardiopulmonary resuscitation should be initiated and defibrillation should be initiated immediately. If patients with severe bradycardia resulting in dizziness, amaurosis, syncope and other symptoms, can be given atropine, isoproterenol, and other drugs to increase the heart rate or a temporary venous pacemaker may be placed.

CONCLUSION

Public health is at risk from COVID-19 outbreaks, but extrapulmonary symptoms and their long-term effects are frequently disregarded. One of the frequent and even life-threatening consequences of COVID-19 is cardiac arrhythmias. We recommend routine cardiac rhythm monitoring by front-line clinicians since the information may help determine whether arrhythmic problems from COVID-19 are a separate predictor of unfavourable outcomes. To lower mortality, prompt diagnosis and treatment are of utmost importance. Here, we offer a summary of possible pharmacological and interventional approaches to solving this issue. The antiviral properties of several drugs are now being studied, along with possible negative effects such QT prolongation.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

REFERENCES

1.Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. Zhonghua Xin Xue Guan Bing Za Zhi. 2020; 48(7):567-571. doi:10.3760/cma.j.cn112148-20200225-00123

2.Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020; 31(5):1003-1008. doi:10.1111/jce.14479

3.Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. Influenza Other Respir Viruses. 2017; 11(5):372-393. doi:10.1111/irv.12470

4.Alexander LK, Small JD, Edwards S, Baric RS. An experimental model for dilated cardiomyopathy after rabbit coronavirus infection. J Infect Dis. 1992; 166(5):978-985. doi:10.1093/infdis/166.5.978

5.Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J. 2020; 41(19):1798-1800. doi:10.1093/eurheartj/ehaa231

6.Pan SF, Zhang HY, Li CS, Wang C. Zhonghua Jie He He Hu Xi Za Zhi. 2003; 26(10):602-605.

7.Wang D, Hu B, Hu C, *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published correction appears in JAMA. 2021 Mar 16;325(11):1113]. JAMA. 2020; 323(11):1061-1069. doi:10.1001/jama.2020.1585

8.Yang J, Zheng Y, Gou X, *et al.* Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020. 10.1016/j.ijid.2020.03.017

9.Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020; 17(5):259-260. doi:10.1038/s41569-020-0360-5

10.Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Mohammed Y *et al.* Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020; S1547-5271:30422–7.

11.Lakkireddy, Dhanunjaya R *et al.* "Guidance for cardiac electrophysiology during the COVID-19 pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association." Heart rhythm vol. 17, 9 (2020): e233-e241. doi:10.1016/j.hrthm.2020.03.028

12.Wu CI, Postema PG, Arbelo E, *et al.* SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. Heart Rhythm. 2020; 17(9):1456-1462. doi:10.1016/j.hrthm.2020.03.024

13.Guo, Tao *et al.* "Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19)." JAMA cardiology vol. 5, 7 (2020): 811-818. doi:10.1001/jamacardio.2020.1017

14.Inciardi, Riccardo M *et al.* "Cardiac Involvement in a Patient with Coronavirus Disease 2019 (COVID-19)." JAMA cardiology vol. 5, 7 (2020): 819-824. doi:10.1001/jamacardio.2020.1096

15.Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020; 31(5):1003-1008. doi:10.1111/jce.14479

16.O'Laughlin, John P *et al.* "Life Threatening Severe QTc Prolongation in Patient with Systemic Lupus Erythematosus due to Hydroxychloroquine." Case reports in cardiology vol. 2016 (2016): 4626279. doi:10.1155/2016/4626279

17.Harris, L *et al.* "Antiarrhythmic potential of chloroquine: new use for an old drug." The Canadian journal of cardiology vol. 4, 6 (1988): 295-300.

18.Harris, L *et al.* "Antiarrhythmic potential of chloroquine: new use for an old drug." The Canadian journal of cardiology vol. 4, 6 (1988): 295-300.

19.Dherange, P. *et al.* J Am Coll Cardiol EP. 2020; 6(9):1193-204.

20.Shi S, *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020 doi: 10.1001/jamacardio.2020.0950.

21.Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020; 17(9):543-558. doi:10.1038/s41569-020-0413-9

22.Richardson, Safiya *et al.* "Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized With COVID-19 in the New York City Area." JAMA vol. 323, 20 (2020): 2052-2059. doi:10.1001/jama.2020.6775

23.Chorin E, Dai M, Shulman E, *et al.* The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020.

24.Rosenblatt, Anna G *et al.* "New-Onset Atrial Fibrillation in Patients Hospitalized With COVID-19: Results from the American Heart Association COVID-19

Cardiovascular Registry." Circulation. Arrhythmia and electrophysiology vol. 15, 5 (2022): e010666. doi:10.1161/CIRCEP.121.010666

25. Li, Zuwei *et al.* "Prevalence of Atrial Fibrillation and Associated Mortality among Hospitalized Patients with COVID-19: A Systematic Review and Meta-Analysis." Frontiers in cardiovascular medicine vol. 8 720129. 13 Oct. 2021, doi:10.3389/fcvm.2021.720129

26. Cho, Jae Hyung *et al.* "Cardiac arrhythmias in hospitalized patients with COVID-19: A prospective observational study in the western United States." PloS one vol. 15, 12 e0244533. 28 Dec. 2020, doi:10.1371/journal.pone.0244533

27. Cho JH, Namazi A, Shelton R, *et al.* Cardiac arrhythmias in hospitalized patients with COVID-19: A prospective observational study in the western United States. PLoS One. 2020; 15(12):e0244533. Published 2020 Dec 28. doi:10.1371/journal.pone.0244533

28. Bhatla, Anjali *et al.* "COVID-19 and cardiac arrhythmias." Heart rhythm vol. 17, 9 (2020): 1439-1444. doi:10.1016/j.hrthm.2020.06.016

29. Shao, Fei *et al.* "In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China." Resuscitation vol. 151 (2020): 18-23. doi:10.1016/j.resuscitation.2020.04.005

30. Baldi E, Sechi GM, Mare C, *et al.* Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy. N Engl J Med. 2020; 383(5):496-498. doi:10.1056/NEJMc2010418

31. Baldi E, Sechi GM, Mare C, et al. COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests. Eur Heart J. 2020; 41(32):3045-3054. doi:10.1093/eurheartj/ehaa508

32. Li Z, Shao W, Zhang J, *et al.* Prevalence of Atrial Fibrillation and Associated Mortality Among Hospitalized Patients With COVID-19: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2021; 8:720129. Published 2021 Oct 13. doi:10.3389/fcvm.2021.720129

33. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic Risk, and Inflammation: Mind the Gap! Circulation. 2020; 142(1):7-9. doi:10.1161/CIRCULATIONAHA.120.047293

34. Touafchia A, Bagheri H, Carrié D, *et al.* Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns [published online ahead of print, 2021 Feb 27]. Clin Microbiol Infect. 2021; 27(5):791.e5-791.e8. doi:10.1016/j.cmi.2021.02.013

35. Gubitosa JC, Kakar P, Gerula C, *et al.* Marked Sinus Bradycardia Associated With Remdesivir in COVID-19: A Case and Literature Review. JACC Case Rep. 2020; 2(14):2260-2264. doi:10.1016/j.jaccas.2020.08.025

36. Wang Y, Zhang D, Du G, *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2020 May 30; 395(10238):1694]. Lancet. 2020; 395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9

37. Spinner CD, Gottlieb RL, Criner GJ, *et al.* Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020; 324(11):1048-1057. doi:10.1001/jama.2020.16349

38. Amin AS, Herfst LJ, Delisle BP, *et al.* Fever-induced QTc prolongation and ventricular arrhythmias in individuals with type 2 congenital long QT syndrome. J Clin Invest. 2008; 118(7):2552-2561. doi:10.1172/JCI35337

39. Chang D, Saleh M, Garcia-Bengo Y, Choi E, Epstein L, Willner J. COVID-19 Infection Unmasking Brugada Syndrome. HeartRhythm Case Rep. 2020; 6(5):237-240. Published 2020 Mar 25. doi:10.1016/j.hrcr.2020.03.012

40. Inciardi RM, Lupi L, Zaccone G, *et al.* Cardiac Involvement in a Patient with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(7):819-824. doi:10.1001/jamacardio.2020.1096

41. Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7

42. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet. 2020; 395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

43. Meyer P, Degrauwe S, Van Delden C, Ghadri JR, Templin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. Eur Heart J. 2020; 41(19):1860. doi:10.1093/eurheartj/ehaa306

44. Sala S, Peretto G, Gramegna M, *et al.* Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J. 2020; 41(19):1861-1862. doi:10.1093/eurheartj/ehaa286

45. Yu CM, Wong RS, Wu EB, *et al.* Cardiovascular

complications of severe acute respiratory syndrome. Postgrad Med J. 2006; 82(964):140-144. doi:10.1136/pgmj.2005.037515

46. Duan Z, Zhang J, Shen L, Chen Y, Li S. Clinical features and mechanism of heart injury in patients suffered from severe acute respiratory syndrome. Zhong Hua Xin Xue Guan Bing Za Zhi. 2003; 31(10):727–30.

47. Li SS, Cheng CW, Fu CL, *et al.* Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. Circulation. 2003; 108(15):1798-1803. doi:10.1161/01.CIR.0000094737.21775.32

48. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J. 2020; 41(19):1798-1800. doi:10.1093/eurheartj/ehaa231

49. Wang D, Hu B, Hu C, *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published correction appears in JAMA. 2021 Mar 16;325(11):1113]. JAMA. 2020; 323(11):1061-1069. doi:10.1001/jama.2020.1585

50. Li Y, Liu T, Liu M, Li YJ, Yang Y, Zhao J, et al. Electrocardiogram abnormalities in patients with COVID-19. Zhong Hua Xin Lv Shi Chang Xue Za Zhi. 2020; 24(2):128–32. 10.3760/cma.j.cn.113859-20200302-00044

51. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19 [retracted in: N Engl J Med. 2020 Jun 4;:]. N Engl J Med. 2020; 382(25):e102. doi:10.1056/NEJMoa2007621

52. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020; 80(4):388-393. doi:10.1016/j.jinf.2020.02.016

53. Hui H, Zhang Y, Yang X, Wang X, He B, Li L, et al. Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia. medRxiv. 2020; 2020–2. 10.1101/2020.02.24.20027052

54. Colon CM, Barrios JG, Chiles JW, et al. Atrial Arrhythmias in COVID-19 Patients. JACC Clin Electrophysiol. 2020; 6(9):1189-1190. doi:10.1016/j.jacep.2020.05.015

55. El-Assaad I, Hood-Pishchany MI, Kheir J, *et al.* Complete Heart Block, Severe Ventricular Dysfunction, and Myocardial Inflammation in a Child with COVID-19 Infection. JACC Case Rep. 2020; 2(9):1351-1355. doi:10.1016/j.jaccas.2020.05.023

56. Azarkish M, Laleh Far V, Eslami M, Mollazadeh R. Transient complete heart block in a patient with critical COVID-19. Eur Heart J. 2020; 41(22):2131. doi:10.1093/eurheartj/ehaa307

57. Kim IC, Kim JY, Kim HA, Han S. COVID-19 related myocarditis in a 21-year-old female patient. Eur Heart J. 2020; 41(19):1859. doi:10.1093/eurheartj/ehaa288

58. Wang Y, Wang Z, Tse G, *et al.* Cardiac arrhythmias in patients with COVID-19. J Arrhythm. 2020; 36(5):827-836. Published 2020 Jul 26. doi:10.1002/joa3.12405

59. Bangalore S, Sharma A, Slotwiner A, *et al.* ST-Segment Elevation in Patients with Covid-19 - A Case Series. N Engl J Med. 2020; 382(25):2478-2480. doi:10.1056/NEJMc2009020

60. Vidovich MI. Transient Brugada-Like Electrocardiographic Pattern in a Patient with COVID-19. JACC Case Rep. 2020; 2(9):1245-1249. doi:10.1016/j.jaccas.2020.04.007

61. He J, Wu B, Chen Y, *et al.* Characteristic Electrocardiographic Manifestations in Patients with COVID-19. Can J Cardiol. 2020; 36(6):966.e1-966.e4. doi:10.1016/j.cjca.2020.03.028

62. Chorin E, Wadhwani L, Magnani S, *et al.* QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm. 2020; 17(9):1425-1433. doi:10.1016/j.hrthm.2020.05.014

63. Borba MGS, Val FFA, Sampaio VS, *et al.* Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020; 3(4):e208857. Published 2020 Apr 24. doi:10.1001/jamanetworkopen.2020.8857

64. Mercuro NJ, Yen CF, Shim DJ, *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) [published correction appears in JAMA Cardiol. 2020 Sep 1;5(9):1071]. JAMA Cardiol. 2020; 5(9):1036-1041. doi:10.1001/jamacardio.2020.1834

65. Chorin E, Dai M, Shulman E, *et al.* The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med. 2020; 26(6):808-809. doi:10.1038/s41591-020-0888-2

66. Du Y, Tu L, Zhu 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; 201(11):1372-1379. doi:10.1164/rccm.202003-0543OC

67. Liu K, Fang YY, Deng Y, *et al.* Clinical characteristics of

novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020; 133(9):1025-1031. doi:10.1097/CM9.0000000000000744

68. Zhang JJ, Dong X, Cao YY, *et al.* Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75(7):1730-1741. doi:10.1111/all.14238

69. Cheung CC, Davies B, Gibbs K, Laksman ZW, Krahn AD. Multilead QT Screening Is Necessary for QT Measurement: Implications for Management of Patients in the COVID-19 Era. JACC Clin Electrophysiol. 2020; 6(7):878-880. doi:10.1016/j.jacep.2020.04.001

70. Gabriels J, Saleh M, Chang D, Epstein LM. Inpatient use of mobile continuous telemetry for COVID-19 patients treated with hydroxychloroquine and azithromycin. HeartRhythm Case Rep. 2020; 6(5):241-243. Published 2020 Apr 1. doi:10.1016/j.hrcr.2020.03.017

71. National Center for Gerontology/ National Clinical Research Center for Geriatric Disorders. Expert recommendations for clinical management of myocardial injury associated with coronavirus disease 2019 (first edition). Zhong Guo Xun Huan Za Zhi. 2020; 35(4):1–5.

72. Gautret P, Lagier JC, Parola P, *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(1):105949. doi:10.1016/j.ijantimicag.2020.105949

73. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020; 14(1):72-73. doi:10.5582/bst.2020.01047

74. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. May 12, 2020. https://covid19treatmentguidelines.nih.gov/.

75. 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(5):244-248. Published 2020 Apr 1. doi:10.1016/j.hrcr.2020.03.016

76. Huang H, Wu G, Zhao Q, Liu Y, Xu Y. Recommendation for the diagnosis and treatment of arrhythmia complicated with COVID-19. Zhong Hua Xin Lv Shi Chang Xue Za Zhi. 2020; 24(2):123–27. 10.3760/cma.j.cn.113859-20200304-00052. [Epub ahead of print].