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REVIEW

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Incidence and treatment of arrhythmias secondary to coronavirus infection in humans: A systematic review

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has affected millions of people worldwide resulting in significant morbidity and mortality. Arrhythmias are prevalent and reportedly, the second most common complication. Several mechanistic pathways are proposed to explain the pro-arrhythmic effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A number of treatment approaches have been trialled, each with its inherent unique challenges. This rapid systematic review aimed to examine the current incidence and available treatment of arrhythmias in COVID-19, as well as barriers to implementation.

Methods: Our search of scientific databases identified relevant published studies from 1 January 2000 until 1 June 2020. We also searched Google Scholar for grey literature. We identified 1729 publications of which 1704 were excluded.

Results: The incidence and nature of arrhythmias in the setting of COVID-19 were poorly documented across studies. The cumulative incidence of arrhythmia across studies of hospitalised patients was 6.9%. Drug-induced long QT syndrome secondary to antimalarial and antimicrobial therapy was a significant contributor to arrhythmia formation, with an incidence of 14.15%. Torsades de pointes (TdP) and sudden cardiac death (SCD) were reported. Treatment strategies aim to minimise this through risk stratification and regular monitoring of corrected QT interval (QTc).

Conclusion: Patients with SARS-CoV-2 are at an increased risk of arrhythmias. Drug therapy is pro-arrhythmogenic and may result in TdP and SCD in these patients. Risk assessment and regular QTc monitoring are imperative for safety during the treatment course. Further studies are needed to guide future decision-making.

KEYWORDS

arrhythmia, coronavirus, COVID-19, long QT syndrome, sudden cardiac death

1 | INTRODUCTION

The *Coronaviridae* are a family of spherical single-stranded, positive-sense ribonucleic acid (RNA) viruses further categorised into four genera namely alpha-, beta-, gamma- and delta-coronaviruses. Of the strains infecting humans, alpha-coronaviruses including human coronavirus (HCoV) HL63 and 229E, and beta-coronaviruses including HCoV OC43 and HKU1, result in mild, self-limiting respiratory illnesses accounting for 15%-30% of common colds.[1,2] In

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contrast, the three novel beta-coronaviruses—severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2—result in severe illness responsible for large outbreaks during the twenty-first century.[1,2] Unlike SARS-CoV and MERS-CoV which affected a relatively small number of people, 8096 and 2494, respectively, SARS-CoV-2 has infected over 10 million people with over 490 000 deaths (Coronavirus disease (COVID-19) Situation Report—161 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200629-covid-19-sitrep-161.pdf?sfvrsn=74fde64e_2 (Appendix 1)).

Several cardiovascular complications in COVID-19 have been identified including arrhythmia, myocardial injury, thromboembolism and cardiomyopathy which correlate with poorer outcomes.[2,3] Their incidence varies significantly between study populations, with arrhythmia recognised as the second most common complication after acute respiratory distress syndrome (ARDS).[2] Whilst 7.3% of Wuhan patients presented with palpitations, arrhythmia was established in 44% of intensive care unit (ICU) admissions suggesting they are associated with severe illness and largely asymptomatic on presentation.[3]

Structurally, the main difference between these three viruses is in the prominent spike (S) protein, responsible for its virulence.[1] In SARS-CoV-2, the S protein is 20-30 amino acids longer accounting for higher affinity to zinc peptidase angiotensin-converting enzyme-2 (ACE-2), found on numerous host cells including myocytes, pneumocytes, endothelial cells and leucocytes.[1,2,4,6] This is thought to play a crucial role in the pro-arrhythmogenic properties of SARS-CoV-2. Figure 1 illustrates the mechanisms implicated in myocardial inflammation and fibrosis forming a substrate for arrhythmia formation.

Arrhythmias in SARS-CoV-2 infections are associated with poorer outcomes.[3] The exact contribution of each of the mechanistic pathways (Figure 1) to arrhythmia formation is unknown, and therefore, treatment is not well established in literature. The aim of this rapid systematic review is to examine the current incidence and available treatment for arrhythmias in hospitalised patients with SARS-CoV-2 infection.

2 | METHODS

This review was conducted according to Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) guideline[5] (Appendix 2) which conforms to the broad EQUATOR guidelines (Simera et al January 2010 issue of EJCI). We registered our study protocol with the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42020186332 (https://www.crd.york.ac.uk/prospero/#recordDetails).

2.1 | Data sources and search strategy

Three authors (AA, TK and MM) completed a comprehensive search of online databases from the year 2000 to June 2020. Our search included databases Scopus, Ovid Medline, CINAHL, ScienceDirect, ProQuest Health & Medicine and Embase. A broad timeline was selected to capture all relevant available literature. The search terms and key search strategies are listed in Appendix 3. Google Scholar was searched for available grey literature and other relevant publications.

2.2 | Selection criteria

All study designs, if available in the English language, including systematic literature reviews and meta-analysis, narrative reviews, randomised control trials (RCTs), non-RCT or quasi-experimental study designs, cross-sectional cohort studies, case reports and case series were included. Articles were required to report either on incidence or prevalence of cardiac arrhythmias due to coronavirus infection in adults, use of drug therapy in patients with SARS-CoV-2 infection as well as management strategies available to address arrhythmias. We defined LQTS as a corrected QT interval (QTc) $\geq$ 500 milliseconds (ms) or ΔQTc by $\geq$60 ms, as these are patients at greatest risk of TdP.[6] Patients with physiologic sinus tachycardia or inherited arrhythmia syndromes were excluded. Non-peer-reviewed studies, editorials, conference article proceedings, theses, studies describing animal models or with alternate definition of LQTS, studies that did not report arrhythmia and published articles before year 2000 were excluded.

2.3 | Literature retrieval and selection

An initial limited search of Medline and Google Scholar was undertaken followed by analysis of text words contained in the titles and abstracts, and index terms used to describe identified articles. A second search using all identified key words and index terms was undertaken across all included databases. Finally, reference lists of identified articles were manually searched for additional relevant studies, using defined inclusion and exclusion criteria (Appendix 4). Two authors (TK and MM) independently carried out initial screening of titles and abstracts, which were independently approved by a third author (MK) for inclusion. Any disagreements were resolved through mutual discussions before finalising literature summary Tables 1-3. Non-randomised designs were discussed according to guidelines provided within the Transparent Reporting of Non-randomised Designs (TREND) statement,[7] and randomised control designs were discussed according to guidelines provided within the CONSORT statement.[8]

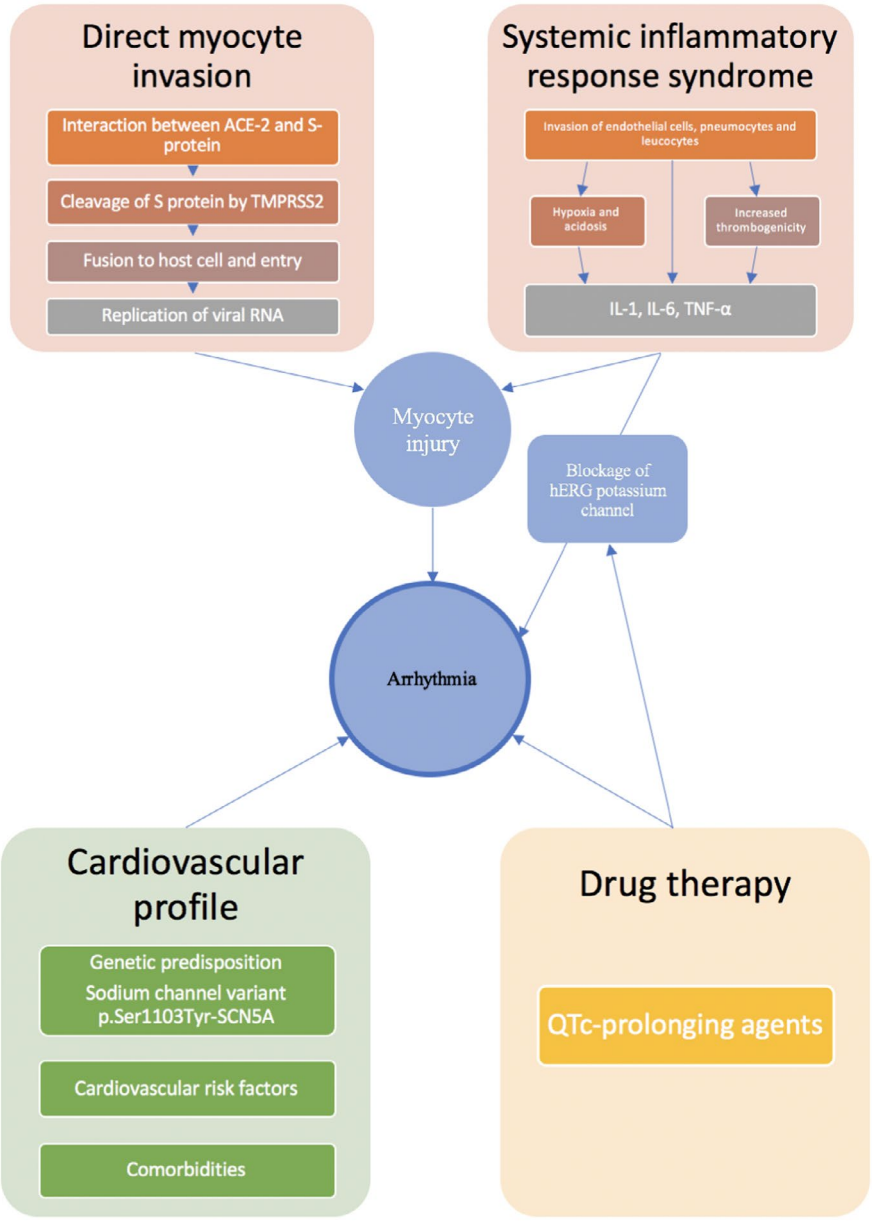

FIGURE 1 Pathogenesis of arrhythmias in SARS-CoV-2. Cleavage of viral S protein via an enzyme TMPRSS2 results in fusion of viral and host membrane leading to entry of virus into host cytoplasm. Direct infiltration of myocytes ensues which has been established in 35% of SARS-CoV patients.[1,3,47] Due to the genomic similarity between SARS-CoV and SARS-CoV-2, direct invasion by SARS-CoV-2 may also occur. Indirect myocardial injury results from systemic inflammatory response syndrome (SIRS). The sum of microvascular and macrovascular dysfunction, increased thrombogenicity, acidosis and hypoxia as well as the imbalance of T-helper 1 and 2 responses leads to an intense release of cytokines and chemokines, particularly interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α). The heightened catecholaminergic response amplifies this process. In fact, hyper-inflammation due to high levels of IL-6 results in hERG potassium channel blockade and QT prolongation, facilitating formation of unstable arrhythmias.[47] Traditional cardiovascular risk factors such as type II diabetes mellitus, hypertension and hypercholesterolaemia, as well as comorbidities such as ischaemic heart disease and chronic renal failure, also contribute to arrhythmia formation by altering cardiac structure and also responsible for clinically severe disease.[12,13] Another potential contributor for arrhythmia formation in the setting of COVID-19 is the common SCN5A-encoded Nav1.5 sodium channel variant p.Ser1103Tyr-SCN5A which results in a lack of 'repolarisation reserve'. ACE-2, angiotensin-converting enzyme 2; hERG, human ether-a-go-go–related gene; p.Ser1103Tyr-SCN5A, SCN5A-encoded Nav1.5 sodium channel variant; QTc, corrected QT; RNA, Ribonucleic acid; S protein, Spike protein; TMPRSS2, enzyme transmembrane protease serine 2

TABLE 1 Incidence of arrhythmias in SARS-CoV-2, MERS-CoV and SARS-CoV found across retrospective observational studies

Pathogen	Author and setting (Year)	Incidence of arrhythmia (%)	Type of arrhythmia	Outcome of arrhythmia group	Cumulative incidence (%)
SARS-CoV-2	Wang D et al Wuhan, China (2020)[a 13]	Total: 23/138 (16.7) ICU: 16/36 (44.4)	Not specified	Not reported	337/4911 (6.9)
	Guo T et al Wuhan, China (2020)[a 16]	Total: 11/187 (5.9)	VT/VF	Not reported	
	Colon C et al Birmingham, USA (2020) [a 48]	Total: 19/115 (16.5)	AF, AT, Atrial flutter	10 reverted to sinus rhythm with treatment 4 remained in AF 5 died	
	Zhang G et al Wuhan, China (2020)[a 20]	Total: 24/221 (10.9) ICU: 22/55 (40)	Not specified	Not reported	
	Richardson S et al New York, USA (2020)[10]	Total: 260/4250 (6.1)	Long QT syndrome (QTc ≥ 500 ms)	Not reported	
MERS-CoV	Saad M et al Riyadh, Saudi Arabia (2014)[14]	11/70 (15.7)	Variable tachyarrhythmias and severe bradycardia	Not reported	11/70 (15.7)
SARS-CoV	Yu CM et al Hong Kong (2005)[19]	1/121 (0.8)	AF	1 self-reverted to sinus rhythm	1/121 (0.8)

Abbreviations: AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; AT, atrial tachycardia; ICU, intensive care unit; MERS-CoV, Middle East respiratory syndrome coronavirus; QTc, corrected QT interval; SARS-CoV, severe acute respiratory syndrome coronavirus; USA, United States of America; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]Received a combination of antiviral, antibacterial, glucocorticoid therapy and/or human immunoglobulin therapy, in addition to supportive care.

2.4 | Quality appraisal of the selected studies for the review

The risk of bias within and across the selected studies was assessed independently by two authors (TK and MM) using the Joanna Briggs Institute Critical Appraisal tools[9] for assessing prevalence data, randomised control trials and case reports/series (Appendices 5-7). This process afforded increased methodological rigour and evaluated potential bias and threats to validity (Joanna Briggs Institute 2017 https://reviewersmanual.joannabriggs.org/). Both reviewers were trained in use of the appraisal tool prior to this process.

3 | RESULTS

3.1 | Search results

We identified 1598 records after duplicates were removed. A total of 1528 articles were removed on basic screening of title and abstract. Seventy full-text articles were then assessed for eligibility, of which 25 records met the inclusion criteria (Appendix 4). Figure 2 demonstrates the study selection flow chart, the types of studies included and reasons for exclusion.

3.2 | Study characteristics

Included studies are summarised in tables 1, 2 and 3. A total of 4911 SARS-CoV-2 cases were extracted for assessment of the incidence of arrhythmias (Table 1). A total of 961 patients were evaluated to calculate the incidence of long QT syndrome (LQTS) and ventricular arrhythmias (VA) due to drug therapy with azithromycin (AZ) and/or hydroxychloroquine (HCQ) or chloroquine (CQ) (Table 3). Several case reports were included (Table 2) to illustrate the range of arrhythmias found secondary to SARS-CoV-2 infection and drug therapy but were not included in the cumulative incidences as establishing causality is difficult.

3.3 | Risk of bias

Quality appraisals of included studies are presented in Appendices 5-7. Except for Richardson et al,[10] the underpowered sample sizes across the remaining studies are a potential

TABLE 2 Summary of arrhythmias, LQTS and VA in case reports and case series in patients with SARS-CoV-2 infection with or without drug therapy

Author (Year)	Study setting	Arrhythmic condition reported	Treatment (in addition to supportive care)	Outcome
Seecheran R et al (2020)[49]	Trinidad and Tobago	Atrial flutter with 2:1 block and AF	Electrical cardioversion, atenolol 50 mg three times daily, amiodarone 200 mg twice daily	Reverted to sinus rhythm. Discharged.
Beri A et al (2020)[50]	USA	VT	Electrical cardioversion and adrenaline	Cardiac arrest and death
Kochav S et al (2020)[27]	USA	Patient 1: High grade AV block	Dopamine infusion resulted in reversal of bradycardia.	ICU admission Hypoxic respiratory arrest and death
		Patient 2: Symptomatic bradycardia with high grade AV block	Permanent pacemaker implantation	Discharged
		Patient 3: AF	Cardioversion	ICU Admission then discharge
		Patient 4: Polymorphic VT with baseline QTc of 528 ms	Intravenous magnesium, defibrillation, cessation of intravenous AZ.	ICU admission then discharge
		Patient 5: CHB followed by PEA arrest. Baseline ECG LBBB with QTc 479 ms	Discontinuation of azithromycin and hydroxychloroquine	ICU admission CHB followed by VF which disintegrated into PEA arrest and death
Peigh G et al (2020)[28]	USA	Patient 1: Sinus bradycardia	Inotropes	ICU admission then discharge
		Patient 2: Sinus bradycardia, accelerated idioventricular rhythm	Inotropes	ICU admission then discharge
Taha M et al (2020)[34]	USA	Patient 1: AF	Intravenous and oral diltiazem.	Discharged
		Patient 2: AF	Intravenous diltiazem	Discharged
Mitra R et al (2020)[30]	USA	QTc prolongation to 620 ms whilst receiving combination therapy with HCQ and AZ. Dosages not reported	Discontinuation of AZ. Continuation of HCQ. Commencement of Intravenous lidocaine.	ICU admission the discharged.
Szekely E et al (2020)[31]	Israel	QTc prolongation to 627 ms with TdP, whilst receiving CQ 500 mg twice daily, for 5 d	Discontinuation of CQ, electrolyte replacement, continuous ECG monitoring, intravenous lidocaine and isoproterenol	ICU admission then discharged.
Gabriels J et al (2020)[42]	USA	QTc prolongation > 500 ms whilst receiving HCQ (400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 d), AND, AZ (500 mg daily for 5 d, intravenously)	No intervention required	Discharged

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; AV, atrioventricular block; AZ, Azithromycin; CHB, complete heart block; ECG, electrocardiogram; HCQ, Hydroxychloroquine; ICU, intensive care unit; LBBB, left bundle branch block; PEA, pulse electrical activity; QTc, corrected QT interval; TdP, Torsades de Pointes; USA, United States of America; VF, ventricular fibrillation; VT, ventricular tachycardia.

for bias. Across all studies, the total number of patients analysed was 5872, which is a small representation of the total number of SARS-CoV-2 patients. There was marked non-uniformity within the selected cohorts; 99% of one cohort represented mild disease,[11] whilst in other studies patients with all degrees of severity were included based on unspecified clinical criteria.[12,13] Quantitative markers of severity like viraemia were not used.[13,14] In addition, some studies included patients without a baseline electrocardiogram (ECG), whilst in other studies, all patients without a baseline ECG

TABLE 3 Summary of incidence of acquired LQTS and VA amongst SARS-CoV-2 patients and treatment regimens used across studies in 2020

	Author (2020)	Study design (Setting)	COVID-19–directed therapy	Incidence of acquired LQTS[a] and VA (%)	Management of arrhythmia	Cumulative incidence of LQTS (%)
Monotheraphy	Tang W et al[11]	Multicentre, randomised controlled trial (China)	HCQ (1200 mg daily for 3 d, then 800 mg daily for 2-3 wk)	0/75 (0)	Not applicable	43/376 (11.44)
	Perinel S et al[17]	Prospective cohort study (France)	HCQ (200 mg three times daily, for 10 d)	LQTS: 2/13 (15.4) VA: not reported	Discontinuation of therapy	
	Mahevas M et al[26]	Prospective cohort study (France)	HCQ (600 mg daily. Duration not specified)	LQTS: 7/84 (8.3) VA: Not reported	Not reported	
	Van den Broek M et al[21]	Retrospective cohort study (Netherlands)	CQ (600 mg loading dose, then 300 mg twice daily starting 12 h after the loading dose, total treatment duration of 5 d)	LQTS: 22/95 (23) VA: 0	Discontinuation of therapy	
	Saleh M et al[24]	Prospective cohort study (Netherlands)	CQ (500 mg twice daily day 1, then 500 mg once daily day 2-5), OR HCQ (400 mg twice daily day 1, then 200 mg twice daily days 2-5)	LQTS: 7/82 (8.5) mVT 1/201 (0.5) [Total LQTS: 18/201 (9)]	Discontinuation of therapy, intravenous lidocaine for mVT patient	
	Ramireddy A et al[25]	Retrospective cohort study (USA)	AZ (500 mg daily for 5 d or 500 mg on day 1 followed by 250 mg daily on days 2-5, orally or intravenously)	LQTS: 5/27 (19) VA: 0 [Total LQTS: 12/98 (12)]	Not reported	
Combination theraphy	Ramireddy A et al[25]	Retrospective cohort study (USA)	AZ (500 mg daily for 5 d or 500 mg on day 1 followed by 250 mg daily on days 2-5, orally or intravenously), AND HCQ (400 mg twice daily day 1, then 200 mg twice daily on days 2-5)	LQTS: 7/61 (21) VA: 0 [Total LQTS: 12/98 (12)]	Not reported	93/585 (15.90)
	Saleh M et al[24]	Prospective cohort study (Netherlands)	CQ (500 mg twice daily day 1, then 500 mg once daily day 2-5), OR HCQ (400 mg twice daily day 1, then 200 mg twice daily days 2-5) AND AZ (500 mg daily for five days, orally or intravenous)	LQTS: 11/119 (9.2) QTc > 600 ms: 1/119 (0.5) [Total LQTS: 18/201 (9)]	Discontinuation of therapy, intravenous lidocaine in QTc > 600 ms patient	
	Molina et al [18]	Retrospective cohort study (France)	HCQ (200 mg three times a day for 5 d), AND AZ (500 mg on day 1, 250 mg on days 2-5)	LQTS: 1/11 (9.1) VA: 0	Discontinuation of therapy	
	Voisin O et al [23]	Retrospective cohort study (France)	HCQ (600 mg daily for 10 days), AND AZ (500 mg day 1, then 250 mg daily days 2-5)	LQTS: 6/50 (12) VA: 0	Discontinuation of therapy	
	Chorin E et al [15]	Retrospective cohort study (USA/Brazil)	HCQ (loading dose 400 mg twice daily, day 1 followed by maintenance dose of 200 mg twice daily, day 2-5), AND AZ (500 mg daily for 5 d, orally)	LQTS: 58/251 (23) TdP: 1/251 (0.4)	Discontinuation of therapy. Urgent defibrillation for TdP	

	Author (2020)	Study design (Setting)	COVID-19–directed therapy	Incidence of acquired LQTS[a] and VA (%)	Management of arrhythmia	Cumulative incidence of LQTS (%)
	Borba M et al [22]	*CloroCovid-19*. Parallel, double-blinded, randomised, phase IIb clinical trial (Brazil)	Low dose: CQ (2.7g over 5 d) OR High dose: CQ (12g over 10 d) AND Ceftriaxone and AZ with or without oseltamivir	Total: 10/56 (17.9) Low-dose arm: 3/28 (10.7) High-dose arm: 7/28 (25)	Study was terminated early	
All therapy incidence						136/961 (14.15)

Abbreviations: AZ, Azithromycin; CQ, Chloroquine; ECG, electrocardiogram; HCQ, Hydroxychloroquine; ICU, intensive care unit; LQTS, long QT syndrome; mVT, monomorphic ventricular tachycardia; QTc, corrected QT Interval; TdP, Torsades de Pointes; USA, United States of America; VA, ventricular arrhythmia.

[a]QTc ≥ 500 ms or ΔQTc ≥ 60 ms.

were excluded.[11,15] These factors limit generalisability to the population.

Most studies were retrospective monocentric observational studies, with biases in incomplete data collection and variations in reporting. The method used to diagnose arrhythmias and to calculate QT interval was not reported in some studies which may lead to reporting bias.[10,12,15,19,26-28] Furthermore, the retrospective study design lends itself to selection bias. We note large numbers of patients were initially screened in some studies and only a small population included for analysis.[16,20]

The diagnosis of infection was based on polymerase chain reaction (PCR) testing of samples taken from the upper respiratory tract which could lead to false-negative results and therefore result in exclusion of infected patients.[11] Although repeat testing improves accuracy, all studies did not address whether further PCR testing was utilised.[11] In two studies, non–PCR-confirmed SARS-CoV-2 cases were included in the final analysis which may cause dilution of results in the event that patients without SARS-CoV-2 infection were included.[21,22]

Drug regimens differed in terms of combination, dosages and duration (Table 3). Drug levels were not widely measured except by Perinel et al[17]; however, assessment of LQTS was not their primary outcome. Hence, it is unclear if QTc measurements were taken at maximum drug levels.[21] Only four of 10 studies reported drug-induced LQTS (DI-LQTS) as the main outcome, another potential for reporting bias.[15,23-25] In one study, the duration of treatment was not specified.[26]

3.4 | Synthesis of results

3.4.1 | Arrhythmias in coronavirus infection

The incidence and nature of arrhythmias amongst patients with SARS-CoV-2 were poorly documented. We retrieved data on arrhythmias in SARS-CoV-2 in only five of 13 published retrospective studies, but many did not elaborate on the type of arrhythmias elicited, nor on the specific treatment regimens prescribed. This included a combination of antiviral, antibacterial, glucocorticoid therapy or human immunoglobulin therapy, in addition to supportive care (Table 1). The types of arrhythmias when specified across all studies included 13 cases of ventricular arrhythmias—ventricular tachycardia (VT) and fibrillation (VF); 23 cases of atrial arrhythmias—atrial fibrillation (AF), atrial flutter and atrial tachycardia; five cases of bradyarrhythmias—atrioventricular (AV) block, sinus bradycardia and complete heart block; and 260 cases of LQTS (Tables 1 and 2).

Compared with non-ICU admissions, there was a larger proportion of arrhythmias found in ICU admissions in two studies (1.2%-16.7% and 40%-44% respectively).[13,20] In comparison, Guo et al[16] reported malignant VA in 5.9% of all patients and in 11.5% of patients with concurrent troponin elevation, suggesting arrhythmia occurs more commonly in this subset. In addition to tachyarrhythmias, sinus nodal disease and AV block have been described, requiring permanent pacemaker insertion (Table 2). It is postulated this occurs due to diffuse conduction system involvement with possible infiltration into conductile myocytes.[27,28]

Compared to COVID-19, the prevalence of arrhythmias in patients infected by SARS and MERS is significantly less, albeit this is based on data from occasional observational studies. An estimated cumulative incidence 6.9% of hospitalised SARS-CoV-2 patients develops an arrhythmia. Saad et al[14] found 15.7% of MERS patients developed either a tachyarrhythmia or bradyarrhythmia. Although they detail temporary pacing wire insertion as management of bradyarrhythmias, treatments of tachyarrhythmias and patient outcomes were not specified.[14] In another case series of nine patients infected by MERS, one developed VT and another supra-ventricular tachycardia.[29] Similarly, AF has been reported in SARS, although poorly documented across all studies. The calculated cumulative incidence of arrhythmia in SARS is 0.7% (Table 1), which is likely an underestimation.

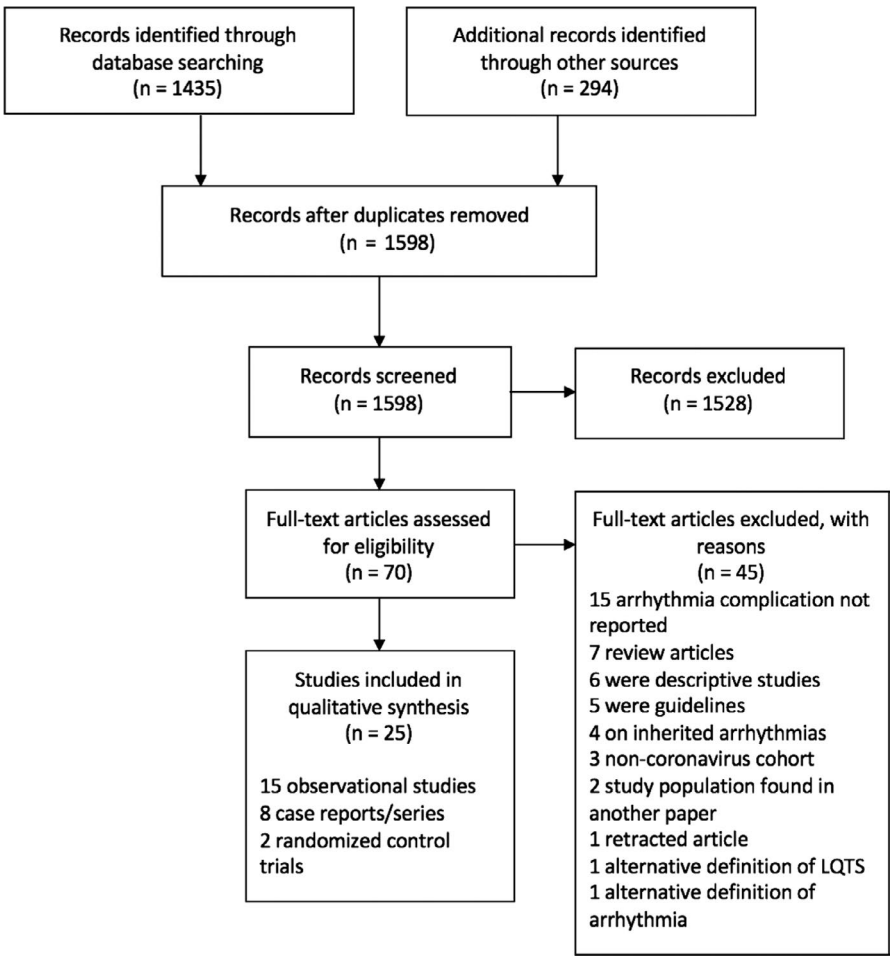

FIGURE 2 Literature search results

3.4.2 | Drug-induced LQTS in SARS-CoV-2 infection

Table 3 summarises incidences of unstable VA and DI-LQTS. Several agents have been used as viral load lowering therapy, including lopinavir/ritonavir, HCQ/CQ and AZ.[13,16,20] However, our search yielded results relating to arrhythmias secondary to HCQ, CQ and AZ. Of note, the CloroCovid-19 Study comparing low- to high-dose CQ in combination with antimicrobial therapy found 25% in the high-dose arm developed DI-LQTS with two patients (3.5%) having SCD. Hence, this study was terminated early.[22]

Incidence of DI-LQTS amongst SARS-CoV-2 patients was 14.15% across all studies. DI-LQTS was more frequent in combination therapy with AZ and either HCQ or CQ compared to monotherapy with either HCQ or CQ or AZ (15.90% and 11.44%, respectively). This difference may be due to inclusion of a large subset of mild to moderate disease patients from Tang et al and the additive effect of these agents on potassium channel disruption.[11] Overall, one patient had monomorphic VT, three had critical QTc prolongation (≥600 ms)[24,30,31] and two had TdP.[15,31] This was not limited to combination therapy. All received lidocaine infusion, in addition to discontinuation of QT-prolonging therapy (Tables 1 and 2).

Incidence of TdP is approximately 0.4% amongst hospitalised SARS-CoV-2 patients on combination therapy.[15] Comparatively, this is four times the estimated risk of TdP for patients on sotalol. Other electrophysiological disturbances that occurred include AV block[26] and new onset AF.[24]

4 | DISCUSSION

4.1 | Arrhythmias in coronavirus infection

Our results demonstrate significant morbidity and mortality associated with arrhythmias (Tables 1-3). Based on cumulative incidence of 6.9%, we project 690 000 of 10 million people infected with SARS-CoV-2 would have developed an arrhythmia, making it more arrhythmogenic than SARS and MERS. Some literature hypothesises this to be due to increased virus affinity for ACE-2 but overall the exact reason for this remains unknown.

Due to poor reporting of arrhythmias, as exemplified by retraction of two major studies,[32,33] our findings are likely an

underestimation of the absolute prevalence of arrhythmias in this cohort. We postulate this to be due to still rising numbers of infected patients and subsequent demands placed on healthcare systems. Performing an ECG may be overlooked if patients lack symptoms suggestive of arrhythmia, in an attempt to reduce transmission and preserve scarce personal-protective equipment (PPE).

Management of arrhythmias in the setting of COVID-19 is not straightforward, and evidence for conventional anti-arrhythmic agents is limited. Using AF as an example, patients were treated successfully with cardioversion or diltiazem. Amiodarone was avoided due to its QT-prolongation properties, particularly with concomitant use of other QT-prolonging agents. Beta-blockers were avoided due to risk of bronchospasm, especially in light of pneumonia or ARDS. Another concern is increased risk of thromboembolic events associated with SARS-CoV-2, and perhaps anticoagulation should be used irrespective of yearly stroke risk.[27,34] There are no large trials addressing arrhythmia management in the setting of SARS-CoV-2 infection. Hence, these decisions are made after assessment of risk and benefit on a case-by-case basis.

4.2 | LQTS in SARS-CoV-2 infection secondary to drug therapy

Based on our calculated incidence of DI-LQTS, more than 1 million of the currently infected SARS-CoV-2 patients are at an increased risk of TdP. Treatment is aimed at targeting each of the pathways implicated in arrhythmia formation (Figure 1). This is complicated as there is conflicting evidence regarding efficacy of HCQ, CQ and AZ as SARS-CoV-2 viral load-reducing therapy. Whilst one series of six patients found reductions in viral load with AZ and HCQ, with low rates of adverse events,[35] their cohort lacked critically ill patients with comorbidities and multi-organ failure. In severe disease, another group found no evidence of clinical benefit with combination therapy.[18]

Moreover, combination antimalarial and AZ therapy is associated with high rates of adverse cardiac events in SARS-CoV-2 patients compared to other clinical situations where these agents are commonly used. In the long-term management of systemic lupus erythematous and rheumatoid arthritis, as well as in resistant malaria management, SCD has not been reported.[30] The risk of drug-induced, life-threatening arrhythmia secondary to these agents varies between 0.001% and 8%.[36,37] Consequently, both American and European Rheumatology societies do not recommend ECG monitoring.[31] Based on this, the Food and Drug Administration (FDA) issued emergency use authorisation for HCQ in the treatment of SARS-CoV-2 in April 2020.[23]

Approximately 14.15% of SARS-CoV-2 patients developed DI-LQTS which is significantly higher than the number of cases reported to the FDA Adverse Event Reporting System (FAERS) amongst non-SARS-CoV-2 patients (Appendix 8). The sum of virus, host and drug-related factors have been used to explain this occurrence. As previously mentioned, SARS-CoV-2 is more virulent than other coronaviruses due to its unique S protein and higher affinity for ACE2, explaining its pro-arrhythmogenic potential. Comorbidities such as inherited arrhythmia, polypharmacy, cardiomyopathy, ischaemic heart disease and renal failure result in a lack of 'repolarisation reserve', which predispose patients to developing LQTS.[38] Similarly, these are the same risk factors for severe respiratory compromise in SARS-CoV-2 infection, which are also the target population for combination antimalarial and AZ therapy.[38]

The pharmacokinetics and pharmacodynamics of antimalarial therapy in SARS-CoV-2 infection also increase susceptibility to LQTS. The mechanism is not fully understood but thought to occur from inhibition of potassium repolarising currents.[39,40] HCQ and CQ concentrations continually increase through the first week of use and may lead to human ether-a-go-go–related gene (hERG) channel saturation, as blockade is concentration dependent.[21] Furthermore, monotherapy with HCQ or CQ, which are both Cytochrome P450 3A4 (CYP3A4) substrates, results in mild QT prolongation, but if used with inhibitors of CYP3A4 such as AZ, higher plasma levels of HCQ or CQ occur and result in significant QT prolongation.[21,41] Hence, the goals of management are to minimise risk of DI-LQTS and to prevent deterioration into malignant arrhythmias.

Stratification of patients according to their risk of developing LQTS in SARS-CoV-2 infection is imperative and depends on assessment of baseline QTc, baseline serum electrolyte levels, comorbidities and concurrent use of other QT-prolonging agents (Appendix 9). Whilst this is performed in some studies, it is unclear in what manner each of these components was addressed. Consequently, there is non-uniformity on how monitoring proceeds, particularly after patients have been deemed infection-free.[15,23-25] Risk stratification tools such as one developed by Tisdale et al[41] are useful as a guide, but it is unclear if it is validated for use in COVID-19.

As ECG acquisition is resource intensive in COVID-19, some guidelines do not recommend baseline and follow-up ECGs whilst on antimalarial and AZ therapy for individuals with previously documented normal QTc, who do not have other risk factors for arrhythmia.[37] The majority of studies in our review did not outline how QTc was calculated. Other studies adopted alternative methods for QT interval measurement, by utilising telemetry units or mobile devices.[21,42] Although they are more costly and depend on availability, a baseline measurement of QTc is imperative in hospitalised

patients to ensure those who lack 'repolarisation reserve', QTc ≥ 500 ms, are identified prior to commencement of therapy.[42] Viral load-reducing therapy should be commenced if the potential benefit outweighs arrhythmia risk, particularly in those patients with a higher risk of respiratory compromise. For those patients with critical QTc prolongation (≥600 ms) or unstable VA, intravenous lidocaine was utilised to inhibit late sodium current, shorten QT interval and prevent deterioration into TdP.[24,30,31] Together with optimisation of electrolytes, this allows continuation of antimalarial and AZ therapy in the short term and focus on addressing the inflammatory component of arrhythmia formation.

Although combination therapy may be of benefit in inducing viral suppression, it seems safer to employ a monotherapy treatment strategy to reduce the risk of DI-LQTS and potential sequelae. This decision will be less difficult after RCTs such as RECOVERY (EudraCT Number 2020-001113-21), DisCoVeRy (NCT04315948) and SOLIDARITY (EudraCT Number 2020-000982-18) have demonstrated the effectiveness and safety of various viral load-reducing drug regimens.[43] In our included studies, there was no mention of how patients with a baseline prolonged QTc were managed, but all studies demonstrated resolution of QTc with discontinuation of therapy (Table 3).

Finally, the lack of 'repolarisation reserve' is of great concern particularly if genes such as p.Ser1103Tyr-SCN5A variant are present. In hypoxia and acidosis, there is increased late sodium current activity by 10-fold, which in turn increases risk of LQTS, TdP and SCD, accounting for up to 43% of deaths.[40,44] This puts patients with inherited channelopathies such as inherited LQTS and Brugada syndrome (BrS) at an increased risk of malignant arrhythmias. Several case reports have demonstrated unmasking of BrS by fever secondary to SARS-CoV-2 infection.[44-46] For this subgroup of patients, it is imperative that the above recommendations (Appendix 9) are strictly followed together with a consultation to an electrophysiologist.[37,44]

5 | LIMITATIONS

The majority of the data extracted was from retrospective studies and case series. Most were not designed to primarily assess the incidence or treatment of arrhythmias in SARS-CoV-2 infection. Our search strategy was broad to include all agents trialled for treatment of SARS-CoV-2 infection; however, all but one paper included the antiviral oseltamivir (Table 3). Despite the arrhythmogenic properties of lopinavir and ritonavir, there were no studies within our search assessing DI-LQTS or arrhythmias secondary to these agents. Furthermore, our exclusion criteria in limiting studies to only the English language may have omitted eligible studies. We could not perform further statistical analysis for these reasons. Our data may therefore represent an underestimation of the true incidence of arrhythmias.

6 | CONCLUSION

Arrhythmias are under-recognised part of the clinical spectrum of SARS-CoV-2. Hence, limited data are available on treatment approaches. Larger, multicentre epidemiological studies and randomised control trials are needed to truly appreciate the impact of arrhythmias, including DI-LQTS, to direct further therapy in this group of patients.

CONFLICT OF INTEREST

The authors report no relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

AA, MM and TT developed the study protocol. AA, MK, MM and TK completed literature search, collected data and drafted the manuscript. Figures were designed by MM and TK. Data analysis and tabulation were completed by MM and TK. All authors were involved in the interpretation of the data and edited the manuscript. Critical revision and final approval of the article was by RM and TT.

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REFERENCES

1. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: immunology and treatment options. *Clin Immunol*. 2020;215:108448.
2. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*. 2020;116:1666-1687.
3. Cheng P, Zhu H, Witteles RM, et al. Cardiovascular risks in patients with COVID-19: potential mechanisms and areas of uncertainty. *Curr Cardiol Rep*. 2020;22:34.
4. Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol*. 2003;52:715-720.
5. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
6. Roden D, Harrington R, Poppas A, et al. Considerations for drug interactions on QTc in exploratory COVID-19 treatment. *Heart Rhythm*. 2020;17(7):231-232.
7. Des Jarlais D, Lyles C, Crepaz N. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *Am J Public Health*. 2004;94(3):361-366.

8. Pandis N, Chung B, Scherer R, Elbourne D, Altman D. CONSORT 2010 statement: extension checklist for reporting within person randomised trials. *BMJ*. 2010;2017:2835.
9. JBI manual for evidence synthesis - JBI manual for evidence synthesis - JBI GLOBAL WIKI [Internet]. Doi.org. 2020. https://doi.org/10.46658/JBIMES-20-01. Accessed June 12, 2020.
10. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052-2059.
11. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849.
12. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *New Engl J Med*. 2020;382:1708-1720.
13. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-1069.
14. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis*. 2014;29:301-306.
15. 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;17:1425-1433.
16. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:811-818.
17. Perinel S, Launay M, Botelho-Nevers É, et al. Towards optimization of hydroxychloroquine dosing in intensive care unit COVID-19 patients. *Clin Infect Dis*. 2020;ciaa394. https://doi.org/10.1093/cid/ciaa394
18. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50:30085-30088.
19. Yu C, Wong RS, Wu E, et al. Cardiovascular complications of severe acute respiratory syndrome. *Postgrad Med J*. 2006;82:140-144.
20. Zhang G, Hu C, Luo L, et al. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. *MedRxiv*. 2020;https://doi.org/10.1371/journal.pone.0233147
21. van den Broek M, Möhlmann J, Abeln B, Liebregts M. van Dijk V, van de Garde V. Chloroquine-induced QTc prolongation in COVID-19 patients. *Neth Heart Journal*. 2020;28:406-409.
22. Borba M, de Almeida VF, Sampaio VS, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). *MedRxiv*. 2020. https://doi.org/10.1101/2020.04.07.20056424
23. Voisin O, le Lorc'h E, Mahé A, et al.Acute QT interval modifications during hydroxychloroquine-azithromycin treatment in the context of COVID-19 Infection. Mayo Clinic Proceedings; 2020;95 (8):1696-1700. https://doi.org/10.1016/j.mayocp.2020.05.005
24. Saleh M, Gabriels J, Chang D, et al. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythm Electrophysiol*. 2020;13:e008662.
25. Ramireddy A, Chugh H, Reinier K, et al. Experience with hydroxychloroquine and azithromycin in the COVID-19 pandemic: implications for QT interval monitoring. *J Am Heart Assoc*. 2020;9:e017144.
26. Mahévas M, Tran V-T, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020;369.
27. Kochav SM, Coromilas E, Nalbandian A, et al. Cardiac arrhythmias in COVID-19 infection. *Circ Arrhythm Electrophysiol*. 2020;13:579–585.
28. Peigh G, Leya MV, Baman JR, Cantey EP, Knight BP, Flaherty JD. Novel coronavirus 19 (COVID-19) associated sinus node dysfunction: a case series. *Eur Heart J Case Rep*. 2020;4;1–6. https://doi.org/10.1093/ehjcr/ytaa132
29. Al-Abdallat MM, Payne DC, Alqasrawi S, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. *Clin Infect Dis*. 2014;59:1225-1233.
30. 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. *Heart Rhythm Case Reports*. 2020;6:244.
31. Szekely Y, Lichter Y, Shrkihe BA, Bruck H, Oster HS, Viskin S. Chloroquine-induced torsades de pointes in a patient with coronavirus disease 2019. *Heart Rhythm*. 2020;17:1452-1455.
32. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. *New Engl J Med*. 2020;382;e102. https://www.nejm.org/doi/full/10.1056/NEJMoa2007621
33. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)31180-6
34. Taha ME, Alsafi W, Taha M, Eljack A, Ibrahim H. Coronavirus disease and new-onset atrial fibrillation: two cases. *Cureus*. 2020;12(5):e8066. https://doi.org/10.7759/cureus.8066
35. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Travel Med Infect Dis*. 2020;34:101663.
36. Almalki ZS, Guo JJ. Cardiovascular events and safety outcomes associated with azithromycin therapy: a meta-analysis of randomized controlled trials. *Am Health Drug Benefits*. 2014;7:318.
37. Sapp JL, Alqarawi W, MacIntyre CJ, et al. Guidance on minimizing risk of drug-induced ventricular arrhythmia during treatment of COVID-19: a statement from the Canadian Heart Rhythm Society. *Can J Cardiol*. 2020;36:948-951.
38. Kapoor A, Pandurangi U, Arora V, et al. Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: a scientific statement from the Indian Heart Rhythm Society. *Indian Pacing Electrophysiol J*. 2020;20:117-120.
39. Taccone FS, Gorham J, Vincent J-L. Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. *Lancet Respir Med*. 2020;8(6):539–541. https://doi.org/10.1016/S2213-2600(20)30172-7

40. Giudicessi JR, Roden DM, Wilde AA, Ackerman MJ. Genetic susceptibility for COVID-19–associated sudden cardiac death in African Americans. *Heart rhythm*. 2020;17(9):1487–1492. https://doi.org/10.1016/j.hrthm.2020.04.045
41. Tisdale JE, Jaynes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*. 2013;6:479-487.
42. 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 Reports*. 2020;6:241-243.
43. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46:854-887.
44. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239-1242.
45. Chang D, Saleh M, Garcia-Bengo Y, Choi E, Epstein L, Willner J. COVID-19 infection unmasking Brugada syndrome. *HeartRhythm Case Reports*. 2020;6:237-240.
46. Sorgente A, Capulzini L, Brugada P. The known into the unknown: Brugada syndrome and COVID-19∗. *JACC Case Rep*. 2020;2(9):1250–1251. https://doi.org/10.1016/j.jaccas.2020.04.006
47. Oudit G, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest*. 2009;39:618-625.
48. Colon CM, Barrios JG, Chiles JW, et al. Atrial Arrhythmias in COVID-19 patients. *JACC Clin Electrophysiol*. 2020;6:1189-1190.
49. Seecheran R, Narayansingh R, Giddings S, et al. Atrial arrhythmias in a patient presenting with coronavirus disease-2019 (COVID-19) infection. *J Investigat Med High Impact Case Rep*. 2020;8:2324709620925571.
50. Beri A, Kotak K. Cardiac injury, arrhythmia, and sudden death in a COVID-19 patient. *HeartRhythm Case Rep*. 2020;6:367-369
51. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). *Mayo Clinic Proceedings*. 2020;95(6):1213–1221. https://doi.org/10.1016/j.mayocp.2020.03.024

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APPENDIX 1

Comparison of three novel beta-coronaviruses[1-3]

	Time of conception	Place of spread	Natural reservoir	Intermediate hosts	Number affected	Percentage requiring intensive care support	Mortality rate
SARS-CoV	November 2002	Foshan, Guangdong, China	Bats	Masked palm civet	8096	20%	9.6%
MERS-CoV	June 2012	Riyadh, Saudi Arabia	Bats	Dromedary camels	2494	—	30%-40%
SARS-CoV-2	December 2019	Wuhan, Hubei Province, China	Bats	Pangolin	10 000 000[a]	5%	2.3%-14.8%

Note: Numbers affected as of 29/06/2020.Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus.

APPENDIX 2.1

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	5,6
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	6,7
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-12

(Continues)

APPENDIX 2.1 (Continued)

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	13-17
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	1

APPENDIX 2.2

Synthesis without meta-analysis (swim) reporting items (equator guidelines)

SWiM is intended to complement and be used as an extension to PRISMA

SWiM reporting item	Item description	Page in manuscript where item is reported	Other
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (eg, groupings of populations, interventions, outcomes, study design)	5,6	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	–	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	–	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	5-7	
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (eg, based on study design, risk of bias assessments, directness in relation to the review question)	5-7	
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	6-7	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	6-7	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (eg, tables, forest plots, harvest plots). Specify key study characteristics (eg, study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	8	
Results			
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	8-12	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	13-18	

APPENDIX 3

Search planner

Concepts	Similar search terms	Limits
Coronavirus	Coronavirus OR Covid19 OR Covid-19 OR SARS-CoV-2 OR infection OR "Coronavirus Infect*" OR MERS-CoV OR "Middle East respiratory syndrome" OR MERS OR "Severe Acute Respiratory Syndrome" OR SARS OR "2019 novel coronavirus" OR SARS-CoV OR MERS-CoV OR HCoV NL63 OR HCoV HKU1	English Language 2000-June 2020
Arrhythmia	Arrhythmia OR "sinus tachycardia" OR tachyarrhythmia OR "pathological arrhythmia" OR "atrial fibrillation" OR "atrial flutter" OR "atrial tachycardia" OR "supraventricular tachycardia" OR "ventricular tachycardia" OR "ventricular fibrillation" OR AF OR SVT OR AVNRT OR VT OR VF OR "sinus node disease" OR "escape rhythm" OR "AV node conduction disease" OR "complete heart block" OR "Mobitz type 1" OR "Mobitz type 2" OR "long QT syndrome" OR LQTS OR "New-onset atrial fibrillation" OR "Auricular Fibrillation" OR "Paroxysmal Atrial Fibrillation" OR "Persistent Atrial Fibrillation" OR "Cardiac arrhythmia" OR "New-onset auricular Fibrillation"	
Consequence	"Haemodynamic compromise" OR "haemodynamic instability" OR "sudden cardiac death*" OR SCD OR cardioversion* OR "early intervention*" OR "Medical intervention*" OR "Sudden arrest" OR "Sudden cardiac arrest"	
Treatment	Drugs OR antivirals OR chloroquine OR hydroxychloroquine OR azithromycin OR antiarrhythmic OR beta-blockers OR calcium channel blockers OR amiodarone OR digoxin OR procainamide OR flecainide OR ibutilide OR cardioversion OR direct current cardioversion OR DC cardioversion OR DCCV OR ablation OR catheter ablation	

Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, middle east respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019; HCoV, human coronavirus; AF, atrial fibrillation; SVT, supraventricular tachycardia; AVNRT, Atrioventricular nodal re-entrant tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; LQTS, long QT syndrome; SCD, sudden cardiac death; DCCV, direct current cardioversion.

APPENDIX 4

Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Patients	• Human adults ≥18 y of age	• Animals • Children (Age < 18 y of age)
Time	• Published articles between 01/01/2000-01/06/2020	• Published articles before year 2000 or after 01/06/2020
Study types	• English Language • Peer-reviewed: systematic literature reviews and meta-analysis, narrative reviews, RCTs, non-RCT or quasi-experimental study designs cross-sectional cohort studies, case reports and case series	• Non-English Language • Non-peer reviewed systematic literature reviews and meta-analysis, narrative reviews, RCTs, non-RCT or quasi-experimental study designs cross-sectional cohort studies, case reports and case series • Editorials • Conference article proceedings • Theses
Infections	• Infections with SARS-CoV, MERS-CoV, SARS-CoV-2	• All other infections
Arrhythmias	• All pathological arrhythmias including LQTS (QTc ≥ 500 ms or ΔQTc by ≥ 60 ms)	• Physiologic sinus tachycardia • Inherited Arrhythmia Syndromes • Alternative definitions of LQTS
Study findings	• Report either on incidence or prevalence of cardiac arrhythmias due to coronavirus infection • Management strategies available to address arrhythmias	• Studies that did not report arrhythmias

Abbreviations: LQTS, long QT syndrome; QTc, corrected QT interval; RCT, randomised control trial.

APPENDIX 5

Critical appraisal of observational and randomised studies (the Joanna Briggs Institute critical appraisal instrument for studies reporting prevalence data)

	Wang D		Guo T		Colon C		Zhang G		Saad M		Yu CM		Seecheran R		Beri A		Kochav S		Peigh G		Taha M	
	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK
Was the sample frame appropriate to address the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were study participants sampled in an appropriate way?	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Was the sample size adequate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the data analysis conducted with sufficient coverage of the identified sample?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were valid methods used for the identification of the condition?	U	U	U	U	Y	Y	Y	Y	U	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants?	U	U	U	U	Y	Y	Y	Y	U	Y	U	U	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y
Was there appropriate statistical analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Was the response rate adequate, and if not, was the low response rate managed appropriately?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Chorin E		Perinel S		Voisin O		Saleh M		Mahevas M		Ramireddy A		Tang W		Mitra R		Szekely E		Gabriels J		Molina J		Borba et al		Van den Broek M	
MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	Y	U	Y	U
Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y
Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	Y	Y	Y	Y	Y
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

APPENDIX 6

Critical appraisal of case reports (the Joanna Briggs Institute critical appraisal checklist for case reports)

	Seecheran R		Beri A		Mitra R		Szekely E		Gabriels J	
	MM	TK	MM	TK	MM	TK	MM	TK	MM	TK
1. Were patient's demographic characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the patient's history clearly described and presented as a timeline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the current clinical condition of the patient on presentation clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were diagnostic tests or assessment methods and the results clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was the intervention(s) or treatment procedure(s) clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA
6. Was the post-intervention clinical condition clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Were adverse events (harms) or unanticipated events identified and described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Does the case report provide takeaway lessons?	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA

APPENDIX 7

Critical appraisal of case series (the Joanna Briggs Institute critical appraisal checklist for case series)

	Kochav S		Peigh G		Taha M	
	MM	TK	MM	TK	MM	TK
1. Were there clear criteria for inclusion in the case series?	Y	Y	N	N	Y	Y
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Y	Y	Y	Y	Y	Y
3. Were valid methods used for identification of the condition for all participants included in the case series?	Y	Y	NA	NA	NA	NA
4. Did the case series have consecutive inclusion of participants?	Y	Y	Y	Y	Y	Y
5. Did the case series have complete inclusion of participants?	Y	Y	Y	Y	Y	Y
6. Was there clear reporting of the demographics of the participants in the study?	Y	Y	Y	Y	Y	Y
7. Was there clear reporting of clinical information of the participants?	Y	Y	Y	Y	Y	Y
8. Were the outcomes or follow up results of cases clearly reported?	Y	Y	Y	Y	Y	Y
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Y	Y	Y	Y	Y	Y
10. Was statistical analysis appropriate?	NA	NA	NA	NA	NA	NA

APPENDIX 8

Faers reported rates of LQTS and TDP for agents used in SARS-COV-2 infection

Agent	Reported number of TdP and QT prolongation according to FAERS. 1964 –2019
Chloroquine/hydroxychloroquine	Number: 344 (of 78 848 reports) Incidence: 0.44% Proportional Reporting Ratios 1.4 95% CI 1.29-1.59
Azithromycin	Number: 667 (of 53 378 reports) Incidence: 1.25% Proportional Reporting Ratios 4.10 95% CI 3.80-4.42
Azithromycin + Chloroquine/ hydroxychloroquine	Number: 7 (of 600 reports) Incidence: 1.2% Proportional Reporting Ratios 3.77 95% CI 1.80-7.87

Abbreviations: TdP, Torsades de Pointes; CQ, Chloroquine; HCQ, Hydroxychloroquine; AZ, Azithromycin; CI, confidence interval; FAERS, FDA Adverse Event Reporting System.

APPENDIX 9

Strategy for reducing the risk of drug-induced LQTS and its sequel

*May be more frequent if clinically relevant.

QTc, corrected QT interval; ECG, electrocardiogram; Ca^{2+}, Calcium; Mg^{2+}, Magnesium; K^{+}, Potassium; TdP, Torsades de pointes; BrS, Brugada syndrome

Adapted from Giudicessi et al[51].