**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 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. 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. Their incidence varies significantly between study populations, with arrhythmia recognised as the second most common complication after acute respiratory distress syndrome (ARDS). 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.

Structurally, the main difference between these three viruses is in the prominent spike (S) protein, responsible for its virulence. 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. This is thought to play a crucial role in the pro-arrhythogenic 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. 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 (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) ≥ 500 milliseconds (ms) or ΔQTc by ≥60 ms, as these are patients at greatest risk of TdP. 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, and randomised control designs were discussed according to guidelines provided within the CONSORT statement.
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
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 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., the underpowered sample sizes across the remaining studies are a potential
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, whilst in other studies patients with all degrees of severity were included based on unspecified clinical criteria. Quantitative markers of severity like viraemia were not used. In addition, some studies included patients without a baseline electrocardiogram (ECG), whilst in other studies, all patients without a baseline ECG

**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) | 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) | USA | VT | Electrical cardioversion and adrenaline | Cardiac arrest and death |
| Kochav S et al (2020) | 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) | 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) | USA | Patient 1: AF | Intravenous and oral diltiazem. | Discharged |
| | | Patient 2: AF | Intravenous diltiazem | Discharged |
| Mitra R et al (2020) | 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) | 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) | 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.
TABLE 3 Summary of incidence of acquired LQTS and VA amongst SARS-CoV-2 patients and treatment regimens used across studies in 2020

| Author et al (2020) | Study design (Setting) | COVID-19–directed therapy | Incidence of acquired LQTS and VA (%) | Management of arrhythmia | Cumulative incidence of LQTS (%) |
|---------------------|------------------------|---------------------------|--------------------------------------|--------------------------|----------------------------------|
| Monotherapy         |                        |                           |                                      |                          |                                  |
| Tang W et al11       | 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 al17    | Prospective cohort study (France) | HCQ (200 mg three times daily, for 10 d) | LQTS: 2/13 (15.4) | Discontinuation of therapy |                                  |
| Mahevas M et al26    | 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 al21 | 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 al24      | 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) | Discontinuation of therapy, intravenous lidocaine for mVT patient |
| Ramireddy A et al25  | 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 | Not reported |
| Combination therapy  | Ramireddy A et al25      | 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 | Not reported |
| Saleh M et al24      | 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 intravenously) | LQTS: 11/119 (9.2) | QTc > 600 ms: 1/119 (0.5) | Discontinuation of therapy, intravenous lidocaine for QTc > 600 ms patient |
| Molina et al18       | 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 al23     | 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 al15     | 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 |
were excluded. 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. 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.

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. Although repeat testing improves accuracy, all studies did not address whether further PCR testing was utilised. 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.

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

### 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). In comparison, Guo et al 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.

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 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. In another case series of nine patients infected by MERS, one developed VT and another supra-ventricular tachycardia. 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.

| Author (2020) | Study design (Setting) | COVID-19-directed therapy | Incidence of acquired LQTS* and VA (%) | Management of arrhythmia | Cumulative incidence of LQTS (%) |
|---------------|------------------------|---------------------------|--------------------------------------|--------------------------|---------------------------------|
| Borba M et al | 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.

*QTc ≥ 500 ms or ∆QTc ≥ 60 ms.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{11} Overall, one patient had monomorphic VT, three had critical QTc prolongation (≥600 ms)\textsuperscript{24,30,31} and two had TdP.\textsuperscript{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.\textsuperscript{15} Comparatively, this is four times the estimated risk of TdP for patients on sotalol. Other electrophysiological disturbances that occurred include AV block\textsuperscript{26} and new onset AF.\textsuperscript{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,\textsuperscript{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-protection 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 dil-tiazem. 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 erythematosus 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 al41 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 (≥2600 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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### APPENDIX 1

#### Comparison of three novel beta-coronaviruses

|            | 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 000⁴ | 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.

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## 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, I²) 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 2.2

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                                                | • Animals                                                                           |
|                                                         | • Children (Age < 18 y of age)                                                     |
| Time                                                    | • Published articles before year 2000 or after 01/06/2020                           |
| Study types                                             | • 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                                              | • All other infections                                                              |
| Arrhythmias                                             | • Physiologic sinus tachycardia                                                     |
|                                                         | • Inherited Arrhythmia Syndromes                                                    |
|                                                         | • Alternative definitions of LQTS                                                    |
| Study findings                                          | • 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)

| Study Authors | Wang D | Guo T | Colon C | Zhang G | Saad M | Yu CM | Seecheran R | Beri A | Kochav S | Peigh G | Taha M |
|----------------|--------|-------|---------|---------|--------|-------|-------------|--------|---------|---------|-------|
| Sample Frame Appropriate to Address Target Population? | Y Y Y Y Y Y Y Y Y Y NA NA NA NA NA NA NA NA NA NA |
| Study Participants Sampled in an Appropriate Way? | 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 |
| Sample Size Adequate? | 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 |
| Study Subjects and 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 Y Y Y Y |
| Data Analysis Conducted with Sufficient Coverage of Identified Sample? | Y Y Y Y Y Y Y Y Y Y Y Y NA NA NA NA NA NA NA NA NA NA |
| Valid Methods Used for Identification of Condition? | U U U U Y Y Y Y U Y U U Y Y Y Y Y Y Y Y Y Y |
| 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 |
| Appropriate Statistical Analysis? | Y Y Y Y Y Y Y Y Y Y Y Y NA NA NA NA NA NA NA NA NA |
| 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 NA NA NA |

**Notes:**
- **Y** indicates yes, **NA** indicates not applicable, **U** indicates uncertain.
| Chorin E | Perinel S | Voisin O | Saleh M | Mahevas M | Ramireddy A | Tang W | Mitra R | Szekely E | Gabriele J | Molina J | Borba et al | Van den Broek M |
|----------|-----------|---------|---------|-----------|-------------|--------|---------|-----------|------------|----------|-------------|-----------------|
| MM       | TK        | MM      | TK      | MM        | TK          | MM     | TK      | MM        | TK         | MM       | TK          | MM              |
| 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      | 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        | 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       | 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         | 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         | 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       | 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          | Y        | Y           | Y               |
| Y        | Y         | Y       | Y       | Y         | Y           | Y      | Y       | Y         | Y          | Y        | Y           | Y               |
| 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         |

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 (harm)s 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     |

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/   | Number: 7 (of 600 reports)                                             |
| hydroxychloroquine            | 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