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Worldwide Survey of COVID-19 Associated Arrhythmias

Running title: *Coromilas et al.; Worldwide COVID-19 arrhythmia cases*

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Abstract:

Background - COVID-19 has led to over 1 million deaths worldwide and has been associated with cardiac complications including cardiac arrhythmias. The incidence and pathophysiology of these manifestations remain elusive. In this worldwide survey of patients hospitalized with COVID-19 who developed cardiac arrhythmias, we describe clinical characteristics associated with various arrhythmias, as well as global differences in modulations of routine electrophysiology practice during the pandemic.

Methods - We conducted a retrospective analysis of patients hospitalized with COVID-19 infection worldwide with and without incident cardiac arrhythmias. Patients with documented atrial fibrillation (AF), atrial flutter (AFL), supraventricular tachycardia (SVT), non-sustained or sustained ventricular tachycardia (VT), ventricular fibrillation (VF), atrioventricular block (AVB), or marked sinus bradycardia (HR<40bpm) were classified as having arrhythmia. De-identified data was provided by each institution and analyzed:

Results - Data was collected for 4,526 patients across 4 continents and 12 countries, 827 of whom had an arrhythmia. Cardiac comorbidities were common in patients with arrhythmia: 69% had hypertension, 42% diabetes mellitus, 30% had heart failure and 24% coronary artery disease. Most had no prior history of arrhythmia. Of those who did develop an arrhythmia, the majority (81.8%) developed atrial arrhythmias, 20.7% developed ventricular arrhythmias, and 22.6% had bradyarrhythmia. Regional differences suggested a lower incidence of AF in Asia compared to other continents (34% vs. 63%). Most patients in in North America and Europe received hydroxychloroquine, though the frequency of hydroxychloroquine therapy was constant across arrhythmia types. Forty-three percent of patients who developed arrhythmia were mechanically ventilated and 51% survived to hospital discharge. Many institutions reported drastic decreases in electrophysiology procedures performed.

Conclusions - Cardiac arrhythmias are common and associated with high morbidity and mortality among patients hospitalized with COVID-19 infection. There were significant regional variations in the types of arrhythmias and treatment approaches.

Key words: atrial fibrillation; arrhythmia; torsade de pointes; ventricular tachycardia; ventricular fibrillation; COVID-19; SARS-CoV-2

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Nonstandard Abbreviations and Acronyms:

AF: Atrial fibrillation

AFL: Atrial Flutter

AVB: Atrioventricular block

CHF: congestive heart failure

CAD: Coronary artery disease

EP: Electrophysiology

ICD: Implantable cardioverter defibrillator

IL-6: Interleukin 6

LV: Left ventricle

LVEF: Left ventricular ejection fraction

NSVT: Non-sustained ventricular tachycardia

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2

SVT: Supraventricular tachycardia

VF: Ventricular fibrillation

VT: Ventricular tachycardia

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the virus that causes COVID-19 has affected over 50 million people worldwide since late December 2019, leading to over 1 million deaths.[1] COVID-19 is known to affect nearly every organ system and the heart is no exception.[2] The Heart Rhythm Society (HRS), American College of Cardiology (ACC), and the American Heart Association (AHA) released a joint statement with recommendations regarding exposure risks, triage, cardiac arrhythmias as well as how to manage electrophysiology (EP) procedures, clinic visits, and device interrogations.[3]

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Although the underlying pathophysiology has remained elusive, various single-center studies and surveys around the world have reported a spectrum of EP issues associated with the disease and its therapies, specifically atrioventricular heart block (AVB), atrial fibrillation (AF), and polymorphic ventricular tachycardia (VT).[4-7] Coexisting hypoxia, electrolyte disarray, and the administration of arrhythmogenic medications (e.g. hydroxychloroquine, azithromycin) make it difficult to ascertain the direct and indirect contribution of COVID-19 on cardiac arrhythmias. A 58% increase in out-of-hospital cardiac arrest in the Lombardy region of Italy during the first 40 days of the COVID-19 pandemic raised concerns regarding the risk of arrhythmia associated with SARS-CoV-2 infection.[8] In the United States, a large single-center study of 700 patients demonstrated that admission to the intensive care unit was independently associated with a 10-fold increase in arrhythmia risk.[9] While cardiac arrest was associated with in-hospital mortality, most were due to non-shockable rhythms and incident AF, bradycardia, and non-sustained ventricular tachycardia (NSVT) were not associated with mortality.[8]

In this global case series, including 29 institutions across 4 continents, 12 countries, and 28 cities (Figure 1, Table 1), we aimed to survey the experiences of institutions from multiple continents to better understand the type of arrhythmias associated with COVID-19 infection, as well as global differences in modulations of routine EP practice due to the pandemic. Patient care of COVID-19 infection has varied across the globe due to differences in rhythm manifestations and its management of the disease but also due to differences in non-COVID-19 medical care and resources available to physicians. The incidence, diagnosis, and management of arrhythmias and conduction system disease has varied across populations, cities, countries and continents worldwide. We will also describe how COVID-19 affected routine EP practice and procedural volume.

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Methods

We conducted a retrospective, international, multicenter analysis of patients ≥18 years of age with a clinical diagnosis of SARS-CoV-2 (confirmed by nasopharyngeal PCR testing) with and without incident cardiac arrhythmias while hospitalized with COVID-19 infection. Patients were classified as having arrhythmia if they had documented AF, atrial flutter (AFL), supraventricular tachycardia (SVT), NSVT, sustained monomorphic or polymorphic VT, sustained ventricular fibrillation (VF), AVB, or marked sinus bradycardia (heart rate of <40bpm). De-identified clinical data including demographics, co-morbidities, baseline electrocardiographic and echocardiographic findings, antiviral therapy, use of hydroxychloroquine with or without azithromycin and presence of arrhythmia during hospitalization was provided by each treating institution. Patient admissions ranged from January 4, 2020 (Modena and Padova, Italy) through August 7, 2020 (Porto Alegre, Brazil), and varied based upon the timing of peak infection rate in each region. Information was also collected regarding the volume of EP procedures at each center during the pandemic. The data that support the findings published in this study are available from the corresponding author on request.

Cardiac electrophysiologists at medical centers throughout the world were contacted and asked to participate in a survey of cardiac arrhythmias occurring in patients hospitalized with COVID-19 infection. Patient level data was collected and reported by each collaborating center utilizing a pre-specified excel spreadsheet; the categories collected are included in Supplemental Table 1.

Columbia University Medical Center served as the coordinating center. Study data were collected and managed using REDCap electronic data capture tools hosted at Columbia University.[10, 11] The study protocol conforms to the ethical guidelines of the 1975 Declaration of

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Helsinki as reflected in *a priori* approval by the Columbia University Institutional Review Board. The study was approved by each participating center's respective Institutional Review Board.

Descriptive statistics were computed. Values for continuous variables are presented as mean ± standard deviation or median [interquartile range] as appropriate. Categorical variables were presented as counts and percentage. Where appropriate, Pearson chi-square test and analysis of variance (ANOVA) were used to compare proportions and group means, respectively. Statistical analysis was performed using SPSS Version V27**.**

Results

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COVID-19 across the globe

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Data was submitted for 4,526 patients hospitalized with COVID-19 infection across the world for whom data was available, and we further analyzed 827 patients who had a cardiac arrhythmia as a result of COVID-19 infection. Overall, the mean age of the total cohort with and without arrhythmias was 62.8 ± 17.0 years and 57% were men (Table 2). The prevalence of medical comorbidities was high (e.g. 55% had hypertension and 35% had diabetes mellitus); however, among the 4 continents surveyed, patients from Asia were generally healthier, as only 29% and 16% reported a history of hypertension and diabetes mellitus, respectively. Likewise, compared with Europe, North America, and South America, patients from Asia had lower body mass indices (23.7 ± 4.6 kg/m^2 vs. mean body mass index >27 kg/m^2 in all other continents represented). As expected, the majority of patients from Europe, North America, and South America identified as Caucasian or Hispanic, while 97% of the population from Asia identified as Asian. Treatment regimens for COVID-19 varied considerably with over 50% of patients in

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Europe and Asia receiving antiviral agents (oseltamivir or remdesivir) compared with only 6-7% of patients in North and South America. Additionally, over 60% of patients in Europe and North America received hydroxychloroquine while fewer than 20% did in Asia and South America. Ten percent of patients worldwide were treated with interleukin-6 (IL-6) receptor inhibitors such as tocilizumab or sarilumab, and these medications were used rarely in Asia and South America.

The majority of sites contributing did not send information on all patients admitted to their hospital with COVID-19, and thus incidence of arrhythmia cannot be estimated on the full cohort. Four institutions (International Medical University in Kuala Lampur, Malaysia; NYP-Columbia and NYP-Queens in New York, USA; and Hospital de Clínicas de Porto Alegre) contributed data on all patients admitted to their institutions. Among 2,762 patients admitted to these institutions with COVID-19 infection, the incidence of cardiac arrhythmia AF, AFL, SVT, NSVT, VT, VF, marked sinus bradycardia, AVB, or pauses >3 seconds) was 12.9%.

827 patients across all institutions developed cardiac arrhythmia while hospitalized for COVID-19 infection (Table 3). Among this cohort, the mean age was 71.1 ± 14.1 years and 65% were men. Cardiac comorbidities were common, as 69% had hypertension, 42% had diabetes mellitus, 30% had congestive heart failure (CHF) and 24% had coronary artery disease (CAD). The majority of patients with SARS-CoV-2 infection who developed a cardiac arrhythmia had no prior history of arrhythmia. Similar to what has been previously reported, cardiac arrhythmias were associated with significant morbidity and mortality;[6] 43% of patients who developed arrhythmia were mechanically ventilated, and only 51% survived to hospital discharge. Of the 359 patients who were mechanically ventilated, 146 (41%) survived to discharge. Similar regional variations in medical management were noted in patients with arrhythmia as in the entire cohort.

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Due to evolving understanding of the disease process and efficacy of medical therapies, we compared treatments and outcomes among patients admitted from January through April and May through August. While the majority of patients (65%) were treated with hydroxychloroquine early in the pandemic, only 13% of patients admitted after April received this therapy. Azithromycin was used as therapy for 47% of patients early in the pandemic, compared to 31% later in the pandemic. There was no similar decrease in the use of antiviral medications over time, with 21% of patients receiving this therapy in the early period of the pandemic, compared to 17% later in the pandemic. Despite increasing experience treating the disease, there was no significant change in survival or number of patients ventilated seen in this cohort, with 49% of patients admitted January through April surviving to discharge, compared to 52% of patients admitted after April 2020. These trends were similar both in the cohort of patients with arrhythmia and the full cohort of patients with and without cardiac arrhythmia.

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Of patients who developed an arrhythmia, the majority (81.8%) developed atrial arrhythmias including AF, AFL, or another SVT (Table 4). However, these arrhythmias occurred less often among patients in Asia, where only 34% of patients had AF and a larger proportion of patients had bradyarrhythmia or AVB. The incidence of ventricular arrhythmias was less common than other dysrhythmias across all regions, with 21% of patients having NSVT, VT or VF. Of patients with VT, there was an equal distribution of monomorphic and polymorphic morphology. 22.6% of patients with COVID-19 infection developed bradyarrhythmias.

Table 5 compares the clinical characteristics and medical therapies among patients by type of arrhythmia. Ventricular arrhythmia was associated with significant mortality, and only 38% of these patients survived to discharge. Rates of mechanical ventilation and mortality were high regardless of type of arrhythmia, though patients who developed VT were 1.3 times more

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likely to be mechanically ventilated and 1.4 times more likely to die during the hospitalization than patients with atrial or brady arrhythmias.

Forty five percent of patients had their left ventricular (LV) function assessed with an echocardiogram in the 2 years prior to admission, with a mean left ventricular ejection fraction (LVEF) of 51.7 ± 13**%.** Among 827 patients who developed cardiac arrhythmia, only 32% had echocardiographic assessments during their hospitalization; this may be due to substantial resource limitation, in particular at the height of the pandemic. Of those patients who underwent assessment of LV assessment during their hospitalization, the mean LVEF was 52.5 ± 13%. At the time of hospital admission with COVID-19 infection, the corrected QT interval (Bazett) was borderline prolonged in this population, with a mean QTc of 446.5 ± 43.2 msec. The QTc at the time of admission was similar across the world regardless of type of arrhythmia, though the maximum QTc developed during admission was highest among patients with ventricular arrhythmias.

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While the majority of patients were treated with QTc prolonging medications, including hydroxychloroquine, azithromycin, and quinolone antibiotics, there was no difference in treatment based on type of arrhythmia. Regarding antiarrhythmic therapy, amiodarone was commonly used in patients with arrhythmia, and in particular patients with tachyarrhythmias. Permanent pacemakers were uncommon, and were present in about 5% of patients.

Among the 67 patients who had ventricular arrhythmias, 30 (44.8%) were specified as having monomorphic VT (MMVT) and 33 (49.2%) had polymorphic VT (PMVT) or torsade de pointes (Table 6); the remaining 4 patients did not have the morphology of ventricular tachycardia specified**.** Patients with both PMVT and MMVT were treated with hydroxychloroquine and azithromycin. Almost half of the patients with VT were hypoxic with a

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measured oxygen saturation of less than 90% or hypotensive with systolic blood pressure of less than 90 mmHg at the time of their arrhythmia; this was similar for patients with both monomorphic and polymorphic VT. About 1/3 of patients were in renal failure or acidotic at the time of their arrhythmia. Patients with ventricular arrhythmias had prolonged maximum QTc, however patients with PMVT did not have significantly longer QT intervals than patients with MMVT.

Of the 1420 patients in the cohort who died, 35 (2.4%) had VT or VF recorded as the rhythm at the time of death. The rhythm at time of death was recorded as bradycardic in 38 cases (2.7%), pulseless electrical activity in 78 patients (5.5%), and asystole in 220 patients (15.5%). The remainder (73.9%) were either not receiving rhythm monitoring at the time of death or had an unknown rhythm at the time of death. Five-hundred and sixty-two (39.6%) of the patients who died were mechanically ventilated during their hospitalization.

Impact of COVID-19 on electrophysiologists around the world

Institutions throughout the world reported drastic decreases in EP procedures including ablations and device insertions, ranging from a 20 to 95% decrease in these procedures. In Milan, a primarily cardiac hospital was completely devoted to caring for patients with COVID-19, and no EP procedures were performed. Consistent with the guidelines released by HRS/AHA/ACC, most institutions reported a suspension of elective procedures and only performed procedures which were emergent or immediately-life threatening which included pacemaker for complete heart block or asystole, ablations for VT storm, or lead extraction for endocarditis, We have summarized the changes in EP procedural volume and use of personal protective equipment at each center in Supplemental Table 2.

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Discussion

In a large cohort of patients hospitalized with COVID-19 across the globe, arrhythmias were common and associated with high morbidity and mortality. Atrial arrhythmias were most common, occurring in 80% of patients with arrhythmia. Patients with cardiac arrhythmias had a high burden of medical comorbidities, even though most did not have a known prior history of arrhythmia. Patients were often critically ill and had considerable mortality, with only half of the those surviving to hospital discharge.

Our finding that patients with COVID-19 infection and cardiac arrhythmia had a high burden of cardiovascular comorbidities is consistent with prior reports documenting high rates of these conditions, in particular among critically ill patients.[5, 12, 13] A global survey of EP professionals conducted by the Heart Rhythm Society in March and April similarly found that atrial arrhythmias were the most common cardiac arrhythmia noted in patients with COVID-19.[7]

We noted significant regional differences in the incidence of these comorbidities, and in particular metabolic syndrome. Patients in Asia had a lower burden of these diseases, and also had a unique distribution of arrhythmia, with a lower incidence of tachyarrhythmias compared to other regions, and a more significant burden of bradyarrhythmia. This is consistent with prior analyses which have noted a lower prevalence of AF in the Asia Pacific region.[14] The reason for this regional difference is unclear, though plausibly could be related to a decreased prevalence of metabolic syndrome and obesity observed in this cohort. Both inflammation and oxidative stress have been implicated in the pathogenesis of AF and metabolic syndrome, and patients with metabolic syndrome have been shown to have a higher risk of AF. [12, 13, 15] Additionally, a pro-inflammatory state has been repeatedly implicated in the pathogenesis of severe COVID-19

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infection, with several treatments proposed to mitigate the inflammatory cascade, including hydroxychloroquine, corticosteroids, and IL-6 receptor inhibition.[16-18]

COVID-19 treatment protocols varied significantly across the globe, likely due to differences in mechanisms of care, burden of illness in the community, and timing of the peak infection rate. For example, hydroxychloroquine was not standard therapy for COVID-19 in the early months of infection. However, several retrospective studies suggesting a beneficial effect of hydroxychloroquine and chloroquine were published in March and April, concurrent to the peak infection in much of Europe and the northeast United States.[19-21] The majority of patients in these regions were treated with hydroxychloroquine in our series. However, as ongoing investigations have not confirmed benefit of this treatment regimen, patients in South America may have been less likely to receive this medication given the later onset of peak infection in this region of the world. While antivirals such as oseltamivir and remdesivir were used in almost all patients in Asia and the majority of patients in Europe, patients in North and South America were infrequently treated with these medications. While dexamethasone has recently showed some promise in treating patients hospitalized with COVID-19 infection, data regarding frequency of steroid use in this cohort was unavailable and cannot be commented on.[17]

The majority of patients with COVID-19 infection and cardiac arrhythmia were treated with systemic anticoagulation. The primary indication for anticoagulation is not known; many patients may have been anticoagulated to prevent thromboembolic events related to atrial arrhythmias. Others may have had a prior history of thromboembolism or developed acute complications in the setting of critical illness, especially given concern for a disease-related hypercoagulable state.[22, 23] Indeed, during the pandemic there was interest in the utilization of

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therapeutic dose anticoagulation in patients critically ill with COVID-19 infection, which may account for some of the use of therapeutic anticoagulation in this population.[24, 25]

At the start of the pandemic, there was substantial concern regarding the risk of ventricular arrhythmia, and in particular torsade de pointes given the frequent use of both hydroxychloroquine and azithromycin, both of which are known to prolong the QTc. Indeed, 40% of patients who developed polymorphic VT were treated with hydroxychloroquine and many had severe prolongation of their QTc, with a max QTc of 514.8 ± 70.5 ms (Bazett correction). Of note, patients who developed monomorphic VT also tended to have prolonged QTc about 25% of patients were treated with hydroxychloroquine, and in both cohorts, patients commonly had reduced LV function at baseline. Taken together, this data suggests that although treatment of hydroxychloroquine may have contributed to the incidence of polymorphic VT in patients with severe COVID-19 infection, the majority of these patients were likely at high risk for this arrhythmia due to pre-existing cardiac disease and critical illness. Patient with ventricular arrhythmias tended to be critically ill with a high prevalence of mechanical ventilation, renal failure, hypoxia, and severe hypotension at the time that the arrhythmia occurred.

Among those patients who died, ventricular arrhythmias were rarely noted to be the rhythm at the time of death. Only 2.4% of had VT or VF recorded at the time of death, while 23.7% had non-shockable rhythms including bradycardia, pulseless electrical activity, or asystole noted at the time of death. This is suggestive of severe hypoxemia and critical illness being the primary driver of cardiac arrest in this population, rather than myocardial injury or electrical derangements leading to primary cardiac arrest.

The causes of arrhythmias in patients with COVID-19 have not been fully elucidated and are likely multifactorial. The majority of patients in our cohort with arrhythmias had co-morbid

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conditions, including CHF and CAD, and likely were predisposed to the development of cardiac arrhythmias. The possibility of direct and indirect myocardial injury in the setting of SARS-CoV-2 infection has also been extensively discussed, and may play a role in the etiology of cardiac arrhythmia in this population[12, 23] Myocardial injury, as assessed by cardiac biomarkers, has been reported in up to 25% of patients with severe COVID-19 infection, and both acute myocardial injury and dysfunction associated with cardiogenic shock and myocardial injury that develops as illness severity intensifies have been described. Stress-induced myopathy, hypoxia-mediated cardiac apoptosis, pro-arrhythmic inflammatory state and cytokine storm, and myocardial injury due to viral invasion via angiotensin-converting enzyme 2 have all been implicated in the pathogenesis of COVID-19 associated myocardial injury.[26-29]

However, our ability to infer the importance of SARS-CoV-2 related myocardial injury on the development of cardiac arrhythmia is limited by incomplete assessment of histopathological analysis of viral induced injury on the cardiac conduction system as well as limited understanding of how focused or diffuse inflammation due to COVID-19 infection may affect the conduction system. Whether or not the incidence of cardiac arrhythmias is higher in patients with COVID-19 infection as compared to patients with other viral illnesses or other critically ill populations remains unclear.

Institutions that participated in this study reported significant reductions in EP procedures consistent with the guidelines released by HRS/AHA/ACC. Several collaborators have published detailed reports of the effect of the COVID-19 pandemic on procedural volume. In the Lombardy and Veneto regions of Italy, rates of urgent pacemaker implantation decreased by 30% during the lockdown.[30] Ancona, Italy reported a decrease in EP procedural volume to a median 12 procedures per week compared to a median of 24 per week in the preceding 6 month period,

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primarily attributed to the postponement of nonurgent interventions.[31] Consistent with our findings, a survey of 84 centers by the Italian association of Arrhythmology and Cardiac Pacing found that more than 90% of the centers saw a significant decrease in elective device implantation, 77% saw a significant decrease in elective ablations, 70% saw a significant decrease in emergent device implantations, and 55% saw a significant decrease in emergent ablations compared to the same period in 2019.[32]

This is the largest worldwide survey of cardiac arrhythmia occurring in patients hospitalized with COVID-19 infection. We acknowledge that our ability to make conclusions or direct comparisons is limited due to its retrospective nature, the heterogeneous data collection and variation in the available data at each site. Additionally, some regional differences in treatment may be due to changes in our understanding of the disease process and treatment outcomes over time. This cohort was limited to cases that were submitted by each institution and often was not fully representative of all cases in that particular hospital, city, state, country, or continent. The majority of cases of arrhythmia (60%) were submitted by institutions in North America, and 40% were submitted by institutions in New York City which primarily saw patients early in the pandemic. This may skew the results and limit the generalizability of the results. Because data was collected by cardiac electrophysiologists, data in the full cohort is likely skewed towards patients with cardiac arrhythmia. Additionally, resources during the pandemic were scarce, and not all patients received 12-lead electrocardiograms or routine cardiac rhythm monitoring as part of their care, which limited the ability to identify the true burden of arrhythmia in this population. Similarly, other evaluations such as echocardiography or computed tomography were performed sparingly in this population, even in patients who were critically ill, limiting the ability to make inferences regarding the causes of the arrhythmia. Due

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to these limitations, we did not conduct comparative statistical analysis in order to avoid making comparisons among heterogeneous groups.

Conclusion

COVID-19 has had a profound effect on the lives of millions of people across the globe. Many patients hospitalized with COVID-19 infection developed cardiac arrhythmia, which was associated with high morbidity and mortality and highlights the need for electrophysiologists to be involved in COVID-19 care. Regional differences in the type of arrhythmias affecting these patients may provide important insights into the pathophysiology of both SARS-CoV-2 infection and of the arrhythmia itself. Future investigations regarding the mechanisms of the cardiac complications of SARS-CoV-2 infection may aid in our understanding of arrhythmia in this population.

American Heart Association.

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Table 1. Worldwide cases contributed to this case series

Country	City	Institution	# Cases	# Arrhythmia Cases
Asia				
China	Wuhan	Wuhan Asia General Hospital	123	25
Hong Kong	Hong Kong	Hospital Authority of Hong Kong	77	6
Iran	Tehran	Tehran University of Medical Sciences	25	6
Japan	Tokyo	Kyorin University School of Medicine	40	4
Malaysia	Taiping	Taiping Hospital	13	0
South Korea	Daegu	Keimyung University Dongsan Hospital	4	3
Europe				
Italy	Ancona	Marche Polytechnic University - University Hospital 'Ospedali Riuniti'	21	20
Italy	Bergamo	ASST Papa Giovanni XXIII	40	7
Italy	Milan	San Luca Hospital	137	34
Italy	Modena	University of Modena and Reggio Emilia	24	24
Italy	Padova	University of Padova	22	3
Italy	Parma	University Hospital of Parma	1	1
Italy	Siena	University of Siena - Azienda Ospedaliera Universitaria Senese	4	4
Spain	Léon	University of Léon	1	1
Spain	Madrid	Hospital General Universitario Gregorio Marañón	97	88
Switzerland	Basel	University Hospital	185	16
Switzerland	Lugano	Fondazione Cardiocentro Ticino	6	6
United Kingdom	London	Imperial College Healthcare NHS Trust	34	30
North America				
Mexico	Mexico City	UMAE Hospital de Especialidades Centro Médico Nacional La Raza IMSS, CDMX	50	10
USA	Dallas, TX	University of Texas, Southwestern	3	3
USA	Greenville, NC	East Carolina University	16	10
USA	New Brunswick, NJ	Rutgers University	21	21
USA	New Haven, CT	Yale University	378	21
USA	New York, NY	New York Presbyterian/Columbia University Irving Medical Center*	1311	227
USA	New York, NY	New York-Presbyterian Queens	1167	108
USA	Stanford, CA	Stanford University	19	16
USA	Washington, DC	George Washington University	406	83
South America				
Brazil	Porto Alegre	Hospital de Clínicas de Porto Alegre	269	21
Brazil	São Paulo	InCor Insituto do Coração, University of São Paulo	32	29

*Coordinating Center

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Table 2. Clinical characteristics of COVID-19 patients with and without arrhythmia worldwide

	All n=4526	Asia n=282	Europe n=572	North America n=3371	South America n=301	P value
Demographics						
Age (years)	62.8 ± 17.0	54.2 ± 19.6	64.9 ± 16.4	63.7 ± 16.7	56.4 ± 15.1	<0.001
Sex (% Male)	2591 (57.0)	161 (57.1)	370 (64.7)	1910 (56.7)	150 (49.8)	<0.001
BMI (kg/m^2)	28.6 ± 6.9	23.7 ± 4.6	27.7 ± 4.7	28.7 ± 7.1	29.8 ± 6.3	<0.001
Race						
White/Caucasian	1287 (28.3)	6 (2.1)	544 (95.1)	497 (14.7)	240 (79.7)	<0.001
Black	439 (9.7)	1 (0.4)	7 (1.2%)	387 (11.5)	44 (14.6)	
Hispanic	1280 (28.2)	0 (0.0)	5 (0.9%)	1275 (37.8)	0 (0.0)	
Asian	549 (12.1)	273 (96.8)	9 (1.6%)	266 (7.9)	1 (0.3)	
Other	186 (4.1)	2 (0.7)	4 (0.7%)	166 (5.0)	14 (4.7)	
Medical Comorbidities						
Hypertension	2499 (55.0)	81 (28.7)	297 (51.9)	1973 (58.5)	148 (49.2)	<0.001
Diabetes Mellitus	1577 (34.7)	44 (15.6)	123 (21.5)	1327 (39.4)	83 (27.6)	<0.001
CHF	766 (16.9)	9 (3.2)	55 (9.6)	654 (19.4)	48 (15.9)	<0.001
CAD	598 (13.2)	25 (8.9)	95 (16.6)	444 (13.2)	34 (11.3)	<0.001
AF/AFL	408 (9.0)	4 (6.1)	125 (21.9)	243 (7.2)	34 (11.3)	<0.001
VT	27 (0.6)	4 (6.1)	4 (0.7)	12 (3.6)	5 (1.7)	<0.001
Vascular Disease	167 (3.7)	1 (0.3)	23 (4.0)	131 (3.9)	12 (4.0)	<0.001
Stroke	276 (6.1)	11 (3.9)	36 (6.3)	208 (6.2)	21 (7.0)	<0.001
CKD	617 (13.6)	7 (2.5)	67 (11.7)	503 (14.9)	40 (13.3)	<0.001
Lung Disease	653 (14.4)	2 (0.7)	95 (16.6)	495 (14.7)	61 (20.3)	<0.001
Medications						
Hydroxychloroquine	2618 (57.6)	44 (15.6)	394 (68.9)	2137 (63.4)	43 (14.3)	<0.001
Azithromycin	2262 (49.8)	32 (11.3)	167 (29.2)	1861 (55.2)	202 (67.1)	<0.001
Antiviral	696 (15.3)	224 (79.4)	256 (44.6)	196 (5.8)	20 (6.6)	<0.001
IL-6 Inhibitor	436 (9.6)	1 (0.4%)	99 (17.3)	336 (10.0)	0 (0.0)	<0.001
Anticoagulation	1334 (29.4)	41 (14.5)	313 (54.7)	913 (27.1)	67 (22.3)	<0.001

*Data is presented as mean ± standard deviation for quantitative variables, and n (%) for categorical variables

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Table 3. Clinical characteristics of COVID-19 patients with cardiac arrhythmia worldwide

	All n=827	Asia n=44	Europe n=234	North America n=499	South America n=50	P value
Demographics						
Age (years)	71.1 ± 14.1	70.7 ± 13.1	72.4 ± 12.6	71.5 ± 14.6	60.8 ± 14.6	<0.001
Sex (% Male)	535 (64.7)	31 (70.5)	159 (67.9)	317 (63.5)	28 (56.0)	0.15
BMI (kg/m^2)	28.8 ± 10.6	23.8 ±3.5	27.6 ± 4.5	29.6 ± 12.6	27.1 ± 5.1	0.15
Race						<0.001
White/Caucasian	361 (43.7)	0 (0.0)	211 (90.2%)	109 (21.8)	41 (82.0)	
Black	60 (7.3)	0 (0.0)	5 (2.1%)	52 (10.4)	3 (6.0)	
Hispanic	161 (19.5)	0 (0.0)	3 (1.3%)	158 (31.7)	0 (0.0)	
Asian	91 (11.0)	44 (100)	9 (3.8%)	38 (7.6)	0 (0.0)	
Other	35 (4.2)	0 (0.0)	3 (1.3%)	26 (5.2)	6 (12.0)	
Medical Comorbidities						
Hypertension	567 (68.6)	24 (54.5)	149 (63.7%)	359 (71.9)	35 (70.0)	0.03
Diabetes Mellitus	344 (41.6)	11 (25.0)	66 (28.2%)	247 (49.5)	20 (40.0)	<0.001
CHF	255 (30.8)	2 (4.5)	42 (17.9%)	180 (36.1)	31 (62.0)	<0.001
CAD	201 (24.3)	8 (18.2)	56 (23.9%)	123 (24.6)	14 (28.0)	0.79
AF/AFL	282 (34.1)	4 (9.1)	107 (45.7%)	144 (29.5)	27 (54.0)	<0.001
VT	20 (2.4)	4 (9.1)	4 (1.7%)	8 (1.6)	4 (8.0)	0.001
Vascular Disease	53 (6.4)	0 (0.0)	13 (5.6%)	38 (7.6)	1 (2.0)	0.11
Stroke	90 (10.9)	6 (13.6)	20 (8.5%)	57 (11.4)	7 (14.0)	0.57
CKD	174 (21.0)	1 (2.3)	43 (18.4%)	119 (23.8)	11 (22.0)	0.007
Lung Disease	151 (18.3)	0 (0.0)	46 (19.7%)	95 (19.0)	10 (20.0)	0.02
Medications						
Hydroxychloroquine	474 (57.3)	10 (22.7)	173 (73.9%)	288 (57.7)	3 (6.0)	<0.001
Azithromycin	369 (44.6)	5 (11.4)	76 (32.5%)	270 (54.1)	18 (36.0)	<0.001
Antiviral	197 (23.8)	41 (93.2)	119 (50.9%)	35 (7.0)	1 (2.0)	<0.001
IL-6 Inhibitor	115 (13.9)	1 (2.3)	54 (23.1%)	60 (12.0)	0 (0.0)	<0.001
Anticoagulation	507 (61.3)	16 (36.4)	182 (77.8%)	277 (55.5)	32 (46.0)	<0.001
Clinical Outcomes						
Survival to Discharge	425 (51.4)	32 (72.7)	149 (63.7%)	221 (44.3)	23 (46.0)	<0.001
Ventilated	358 (43.3)	12 (27.3)	110 (47.0%)	207 (41.5)	30 (60.0)	<0.001

*Data is presented as mean ± standard deviation for quantitative variables, and n (%) for categorical variables

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Table 4. Types of cardiac arrhythmias in COVID-19 patients worldwide

	All n=827	Asia n=44	Europe n=234	North America n=499	South America n=50	P value
AF	509 (61.5)	15 (34.1)	151 (64.5)	310 (62.1)	33 (66.0)	0.004
AFL	86 (10.4)	1 (2.3)	15 (6.4)	63 (12.6)	7 (14.0)	0.02
SVT	80 (9.7)	8 (18.2)	24 (10.3)	42 (8.4)	6 (12.0)	0.14
NSVT	78 (9.4)	3 (6.8)	28 (4.9)	45 (9.2)	2 (4.0)	0.11
VT	67 (8.1)	0 (0.0)	17 (7.3)	41 (8.2)	9 (18.0)	0.02
Monomorphic	30 (3.6)	0 (0.0)	6 (2.6)	19 (4.1)	4 (8.0)	0.09
Polymorphic	33 (4.0)	0 (0.0)	10 (4.3)	20 (4.3)	4 (8.0)	0.28
VF	28 (3.4)	1 (2.3)	3 (1.3)	20 (4.0)	4 (8.0)	0.07
Bradycardia	106 (12.8)	9 (20.5)	25 (10.7)	68 (13.6)	4 (8.0)	0.17
AV Block	71 (8.6)	10 (22.7)	19 (8.1)	35 (7.0)	7 (14.0)	0.001
Pause >3 Seconds	10 (1.2)	0 (0.0)	0 (0.0)	6 (1.2)	0 (0.0)	0.66

*Data is presented as mean ± standard deviation for quantitative variables, and n (%) for categorical variables

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Table 5. Clinical characteristics and arrhythmia management of COVID-19 patients with arrhythmia

	All N= 827	AF, AFL, SVT N=599	NSVT, VT, VF N=164	Bradycardia N= 172
Clinical Information				
Survival to Discharge	424 (51.4)	305 (50.9)	62 (37.8)	103 (59.9)
Ventilated	358 (43.4)	263 (43.9)	86 (52.4)	62 (36.0)
QTc (ms)	446.5 ± 43.2	447.3 ± 43.7	447.8 ± 45.0	444.0 ± 40.2
Max QTc (ms)	479.4 ± 48.6	480.4 ± 48.2	490.6 ± 56.0	473.2 ± 50.8
LVEF prior to admit (%)	51.7 ± 13.4	52.0 ± 13.4	46.6 ± 17.1	53.5 ± 8.4
LVEF during admit (%)	52.5 ± 13.3	52.7 ± 12.7	45.9 ± 15.8	55.1 ± 11.8
Treatment				
Hydroxychloroquine	474 (57.3)	355 (59.3)	89 (54.3)	88 (51.2)
Azithromycin	369 (44.6)	265 (44.2)	74 (45.1)	74 (43.0)
Quinolones	84 (10.2)	57 (9.5)	12 (7.3)	20 (11.6)
Amiodarone	248 (30.0)	218 (36.4)	64 (39.0)	22 (12.8)
Sotalol	13 (1.6)	10 (1.7)	3 (1.8)	1 (0.6)
Other AAD	85 (10.3)	67 (11.2)	22 (13.4)	10 (5.8)
Pacemaker	40 (4.8)	30 (5.0)	6 (3.7)	13 (7.6)

*Data is presented as mean ± standard deviation for quantitative variables, and n (%) for categorical variables

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Table 6. Types of ventricular arrhythmias in COVID-19 patients worldwide

	Monomorphic VT N=30	Polymorphic VT N=33
Medications		
Hydroxychloroquine	8 (26.7)	13 (39.4)
Azithromycin	5 (16.7)	6 (18.2)
Inotrope	8 (26.7)	7 (21.2)
Clinical		
Hypokalemia (K<3.5 mmol/L)	3 (10.0)	6 (18.2)
Hypotension (SBP<90 mmHg)	12 (40.0)	12 (36.6)
Hypoxia (SpO2<90%)	13 (43.3)	12 (36.6)
Ventilated	12 (40.0)	20 (60.1)
Acidosis/Renal Failure	6 (20.0)	11 (33.3)
Max QTc (ms)	502.6 ± 62.0	514.8 ± 70.5
Baseline LVEF (%)	36.1 ± 20.0	46.4 ± 14.8

*Data is presented as mean ± standard deviation for quantitative variables, and n (%) for categorical variables

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Figure Legend:

Figure 1. Map of cases contributed to this worldwide survey

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What Is Known?

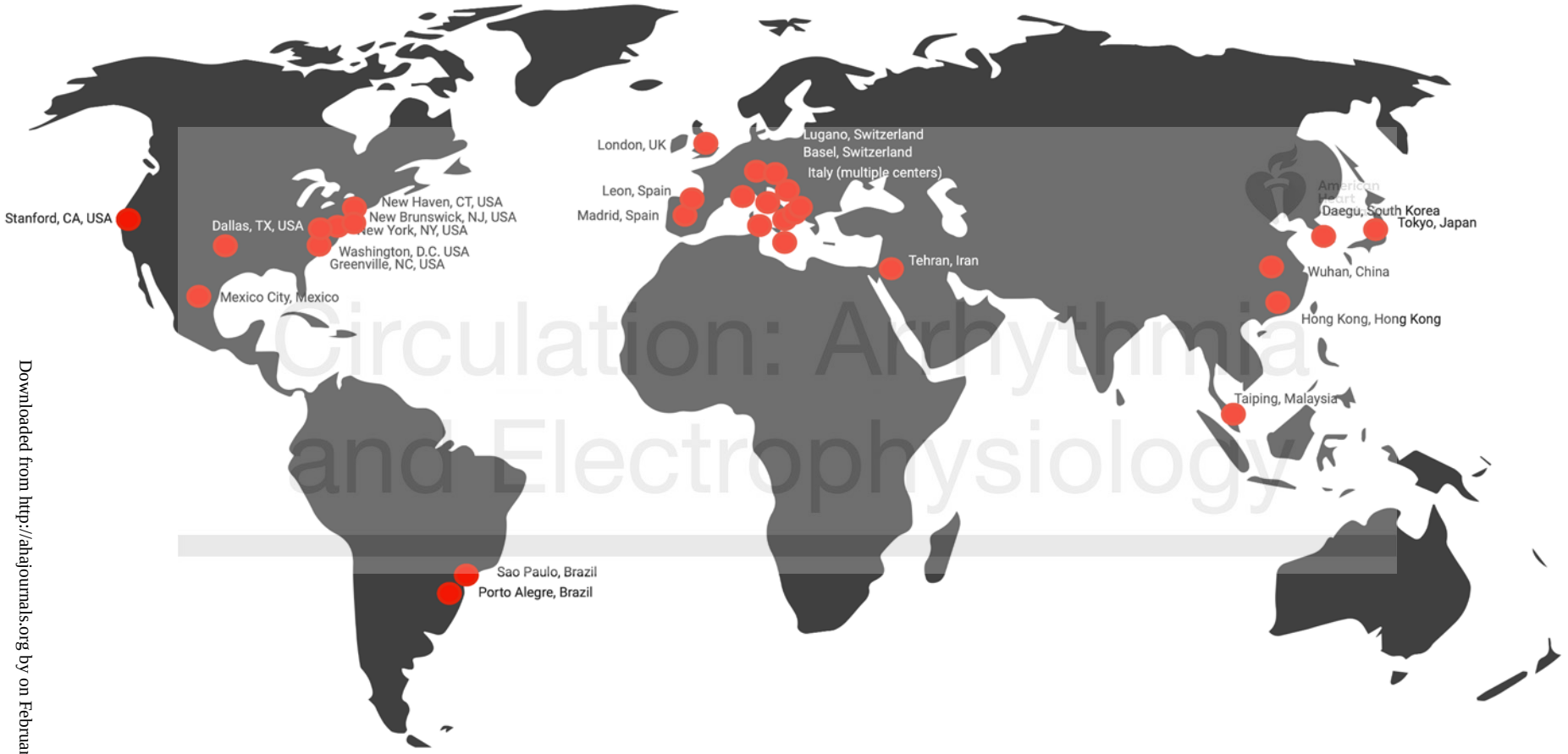
- COVID-19 infection has become a leading cause of hospitalization and death worldwide, and cardiac arrhythmias have been noted in these patients.
- Pre-existing co-morbidities, such as hypertension, diabetes, heart failure and coronary artery disease, are common in hospitalized COVID-19 patients.

What the Study Adds?

- Of 827 hospitalized COVID-19 patients who developed a cardiac arrhythmia, most (7 in 10) developed atrial arrhythmias. 1 in 5 hospitalized COVID-19 patients developed ventricular arrhythmias and a similar proportion developed bradyarrhythmias.
- The presence of arrhythmia was associated with significant morbidity and mortality; about 4 in 10 patients who developed an arrhythmia were mechanically ventilated and only one half survived to hospital discharge.

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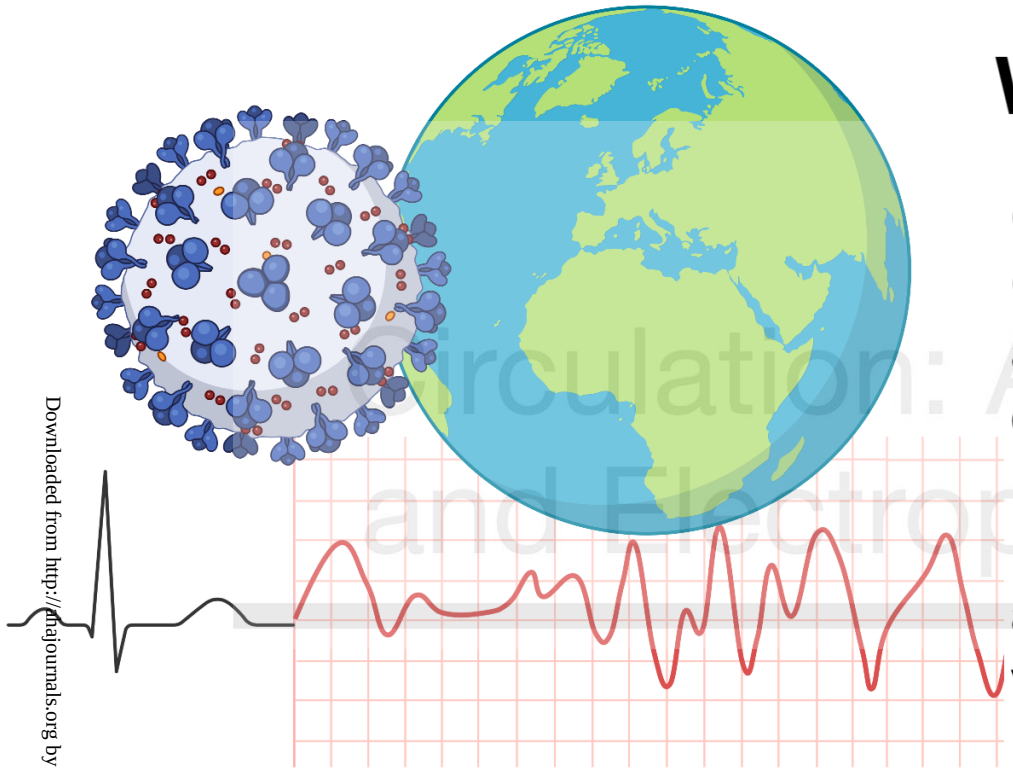
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Graphic Abstract



Worldwide Case Survey

Of hospitalized patients with COVID-19 infection, 7 in 10 had atrial arrhythmias, and 1 in 5 developed ventricular arrhythmias.

Four out of 10 patients with arrhythmia were mechanically ventilated, and only half survived.

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