ELECTROPHYSIOLOGY

PACE〰〰 WILEY

Arrhythmias and electrocardiographic findings in Coronavirus disease 2019: A systematic review and meta-analysis

Sebastian Garcia-Zamora MD[1] ⓘ | Sharen Lee MD[2] ⓘ | Sohaib Haseeb Bsc[3] ⓘ |
George Bazoukis MD[4] ⓘ | Gary Tse MD[5] ⓘ | Jesus Alvarez-Garcia MD[6,7] ⓘ |
Enes Elvin Gul MD[8] ⓘ | Göksel Çinier MD[9] ⓘ | Bryce Alexander MD[10] ⓘ |
Marcelo Martins Pinto-Filho MD[11] ⓘ | Tong Liu MD[5] ⓘ | Adrian Baranchuk MD[10] ⓘ

[1] Cardiology Department, FLENI, Buenos Aires, Argentina

[2] Laboratory of Cardiovascular Physiology, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China

[3] College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia

[4] Second Department of Cardiology, General Hospital of Athens "Evangelismos", Athens, Greece

[5] Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China

[6] Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, Bronx, New York, USA

[7] Cardiology Department, Hospital de la Santa Creui Sant Pau, CIBERCV, Barcelona, Spain

[8] Division of Cardiac Electrophysiology, Madinah Cardiac Centre, Madinah, Saudi Arabia

[9] Department of Cardiology, Dr.SiyamiErsek Hospital Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

[10] Heart Rhythm Service, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada

[11] Cardiology Department at Hospital das Clinicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Correspondence
Adrian Baranchuk, MD, FACC, FRCPC, FCCS, FSIAC, Cardiac Electrophysiology and Pacing, Kingston Health Science Center K7L 2V7, Queen's University, Canada.
Email: barancha@kgh.kari.net

Registration: PROSPERO ID: CRD42020184448

Abstract

Background: Coronavirus disease 2019 (COVID-19) primarily causes lung infection, but recent studies have shown that cardiac involvement is associated with a worse prognosis.

Objectives: We conducted a systematic review and meta-analysis to examine the prevalence of cardiac arrhythmias detected by the electrocardiogram and their relationships with adverse outcomes in patients with COVID-19.

Methods: PubMed and Google were searched for studies that reported on cardiac arrhythmias and/or examined the relationship between arrhythmias and adverse outcomes.

Results: Thirty studies with 12,713 participants were included in the systematic review, and 28 studies ($n = 12,499$) in the meta-analysis. The mean age was 61.3 ± 16.8 years; 39.3% were female. In 25 studies with 7578 patients, the overall prevalence of cardiac arrhythmias was 10.3% (95% confidence interval [CI]: 8.4%–12.3%). The most common arrhythmias documented during hospitalization were supraventricular arrhythmias (6.2%, 95% CI: 4.4%–8.1%) followed by ventricular arrhythmias (2.5%,

95% CI: 1.8%–3.1%). The incidence of cardiac arrhythmias was higher among critically ill patients (relative risk [RR]: 12.1, 95% CI: 8.5–17.3) and among non-survivors (RR: 3.8, 95%, CI: 1.7–8.7). Eight studies reported changes in the QT interval. The prevalence of QTc > 500 ms was 12.3% (95% CI: 6.9%–17.8%). ST-segment deviation was reported in eight studies, with a pooled estimate of 8.7% (95% CI: 7.3% to 10.0%).

Conclusion: Our meta-analysis showed that QTc prolongation, ST-segment deviation, and various other cardiac arrhythmias were observed in patients hospitalized with COVID-19. The presence of cardiac arrhythmias was associated with a worse prognosis.

KEYWORDS
atrial fibrillation, COVID-19, ECG, ventricular tachyarrhythmias.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially life-threatening infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 as the host receptor to gain entry into the cell. Recent studies have reported significant cardiac involvement in patients infected with COVID-19,[3,4] and this presence has been associated with a worse prognosis.[5,6] The surface electrocardiogram (ECG) is one of the leading tools to assess potential cardiac involvement in hospitalized patients with COVID-19.[4] Existing data shows that cardiac arrhythmias area common complication of a COVID-19 infection, although their association with adverse outcomes remains to be fully defined.[7] The aim of our systematic review and meta-analysis was to estimate the prevalence of ECG abnormalities and cardiac arrhythmias in hospitalized patients with COVID-19 and to further evaluate the association of arrhythmias with patient outcomes.

2 | METHODS

2.1 | Study design and data sources

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] The protocol was registered in the PROSPERO database of systematic reviews (registration number: CRD42020184448). PubMed was searched for studies that reported the prevalence of cardiac arrhythmias detected by the ECG and/or reported the relationship between cardiac arrhythmias and adverse outcomes in COVID-19. The search was performed from database inception to August 30, 2020 without language restrictions. Search terms used were: "COVID" AND ("electrocardiogram" OR "ECG" OR "QT" OR "fibrillation" OR "arrhythm*" OR "LBBB" OR "RBBB" OR "bundle branch block" OR "QRS"). Gray literature and bibliographies of included studies were also searched to extend the search cover-

age. The exclusion criteria were: case reports, case series, reviews, preclinical studies, and preprints publications. Once duplicates were removed, two reviewers (YL and SGZ) independently screened titles and abstracts to ensure the capture of all relevant studies. Disagreements were resolved by discussion to achieve consensus.

2.2 | Data extraction and quality assessment

Data were extracted into predetermined tables using a standardized protocol. The data extracted were: first author, country of study, number of included patients, study design, age of participants, gender, prevalence of risk factors, previous cardiovascular events, history of arrhythmias, pharmacological treatments for COVID-19, type of ECG changes or arrhythmias, complications, and mortality during hospitalization for COVID-19.

Two reviewers (GB and GT) independently completed a risk of bias assessment using the Newcastle–Ottawa scale (NOS).[9] The NOS point scoring scale uses a star system in which each study is judged based on three domains: selection of the study groups (four items); comparability of the groups (one item); and exposure (ascertainment of the outcome; three items). A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, and a maximum of two stars for comparability.

2.3 | Patient and public involvement

We performed this meta-analysis based on published data, and there were no patients or public involvement in this project.

2.4 | Statistical analysis

For the outcomes of interest, mean differences with 95% confidence interval (CI) were extracted and subsequently pooled.[10] If the standard

error (SE) or 95% CIs were not reported, calculations were made using the following formula:

$SE = \sqrt{\text{prevalence (1-prevalence)} / n}$, &

95% CI = $p \pm 1.96 \times SE$

where "n" is the sample size.

Heterogeneity across studies was determined using the variance between the studies (Tau-square, τš) and the Iš statistic. The Iš statistic, determined from the standard chi-square test, describes the total variance explained by heterogeneity rather than chance. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. If $I^2 < 50\%$, a fixed effects model was used; otherwise, the random-effects model using the inverse variance heterogeneity method was used.[11–13] To identify the source of the heterogeneity, sensitivity analysis using the leave-one-out method was used. To assess for possible publication bias, funnel plots, Begg's, and Egger's test were used.[14] Data analysis was performed using Review Manager (RevMan) (Version 5.3) and Stata (Version 13.0).

3 | RESULTS

3.1 | Study selection

The search identified 488 records. After the removal of duplicates ($n = 37$), 451 records were screened based on titles and abstracts. Of these, 316 records were excluded because they were editorials, position papers from scientific societies, or reviews. Subsequently, full texts of 135 articles were reviewed. Of these, 102 articles were non related to the topic of interest; three articles were excluded because the ECG data were out of the scope of this review[15-17]; Pavri et al.[15] were excluded because they evaluated the PR interval in hospitalized patients with COVID-19; Shi et al.[16] were excluded because they described the frequencies of patients with abnormal ECG findings but did not further delineate the abnormalities observed; and Lei et al.[17] were excluded because they included all patients who underwent elective surgeries, but the diagnosis of COVID-19 was made after the procedure. Finally, 30 studies were included in the qualitative review (Figure 1). Of these, 19 studies reported relevant ECG and/or arrhythmia findings.[18–36] The other 11 studies only specified cardiac arrhythmias in general without further elaboration.[37–47] For the meta-analysis, two studies (from the 30 included studies) were excluded as they only provided qualitative data on QT intervals.[30,32] The quality assessment of the included studies are summarized in **Table S1**.

3.2 | Characteristics of the included studies and study participants

We included 30 studies with 12,713 participants. The sample size varied from 16 to 5700 patients (median: 128 patients, interquartile range: 90–380). The mean age was 61.3 ± 16.7 years, and 42.0% were female. All of the included studies were cohort studies, with the exception of Borba et al.[20] who reported the findings of a randomized con-

Key messages

What is already known about this subject?
Coronavirus disease-2019 (COVID-19) is a novel viral infection with a wide spectrum of presentations, ranging from asymptomatic or mild symptomatic to severe forms. Cardiac involvement during COVID-19 has been associated with significant morbidity and mortality. However, the frequency of cardiac arrhythmias or electrocardiographic abnormalities and their prognostic implications in patients with COVID-19 remains uncertain.

What does this study add?
We found that new-onset cardiac arrhythmias, ST-segment deviation, and QTc prolongation were common findings in hospitalized patients with COVID-19. These findings were seen in about one in 10 patients and occurred more frequently in critical care patients. Supraventricular arrhythmias were the most common, but any types of arrhythmias were associated with a worse prognosis.

How might this impact clinical practice?
Our findings suggest that the electrocardiogram can be a useful tool in the risk stratification of hospitalized patients with COVID-19. Telemetry can also be considered for all critically ill patients to detect new-onset cardiac arrhythmias.

trolled trial. Most studies originated from the United States ($n = 13$) and China ($n = 11$). All but one study[34] included adult patients, with most participants over 40 years of age. Samuel et al.[34] included pediatric and adolescent patients, with a mean age of 13 ± 6 years.

All studies reported medical comorbidities. The most common was hypertension (45%), followed by obesity (34%), and diabetes mellitus (24%). Obesity was most commonly reported among patients from the United States.[18,19,25,27–29,32,33,37,41–43] Overall, 11% of the patients had coronary artery disease. There were variations in the mortality rates amongst the studies (12% ± 2%, range: 0%–27.2%). There were variations in the disease severity of COVID-19—ranging from stable to severe or critical patients requiring mechanical ventilation or cardiac support—and differences in the treatments offered (Tables 1 and 2).

In our meta-analysis of 28 studies,[18–29,31,33–47] a total of 12,499 patients (mean age: 61.3 ± 16.8 years; 39.3% female) were included. Prior history of cardiac arrhythmias was only reported in 10 studies,[19–21,23,24,27,29,32,33,46] which showed a prevalence of 8.7% ± 2.5% (Tables 1 and 2). Atrial fibrillation was the most observed arrhythmia in eight of the mentioned studies.

The overall prevalence of cardiac arrhythmias during COVID-19 hospitalization was 10.3% (95% CI: 8.4%–12.3%) amongst

TABLE 1 Demographic and baseline characteristics of included studies with electrocardiographic data

Author	Sample size	Country	Age	Female sex	Risk factors/Comorbidities	Prior CV events and Arrhythmias	Treatments	Severity / evolutions	Mortality
Angeli F[18]	50	Italy	64 ± 15	38%	BMI 26.8 ± 4,4 kg/m²; 50% HTN; 12% DM; 2% COPD; 10% smoker	10% CAD; 6% CHF;	82% HCQ 56% Macrolides54% antiviral	4% ICU	None
Bhatla A[19]	700	United States	50 ± 18	55%	BMI 31 ± 9 kg/m²; 50% HTN; 26% DM; 9% COPD; 11% CKD; 9% smoker	11% CAD; 13% CHF;6% AF	25% HCQ8% RDV	11% ICU; 8% remained hospitalized	4%
Borba MGS[20]	81	Brazil	51.1 ± 13.9	24.7%	45.5% HTN; 25.5% DM; 7.4% CKD; 8.3% smoker	3.6% CAD; 3.6% CHF; 1.9% Atrioventricular block	100% Chloroquine 100% Macrolides86.4% antiviral	45.7% ICU	27.2%
Chen Q[21]	54	China	56.1 ± 13.5 61.7 ± 9.6$^{\lambda}$	33.3%	29.6% HTN; 46.3% DM; 0% COPD	11.1% CAD; 0% CHF; 1.9% CeVD; 1.9% AF	NA	27.8% critical patients[1]	NA
Chorin E[22]	251	United States & Italy	64 ± 13	25%	54% HTN; 27% DM; 7% COPD; 11% CKD	12% CAD; 3% CHF	100%HCQ100% Macrolides	NA	20%
Colon CM[23]	115	United States	56 ± 17	46%	70% HTN; 39% DM; 13% COPD; 14% CKD; 42% smoker[ε]	16% CAD; 4.4% AF	6.1% HCQ 43.5% Macrolides7% RDV	60% ICU	4.4%
Deng Q[24]	112	China	65(49–70.8)	49.1%	32.1% HTN; 17% DM; 3.6% COPD	13.4% CAD; 3.6% AF	NA	23.2% ICU; 54.5% remained hospitalized	12.5%
Goyal P[25]	393	United States	62,2(48.6–73.7)	39.4%	35.8% obesity; 50.1% HTN; 25.2% DM; 5.1% COPD; 5.1% smoker	13,7% CAD	64% HCQ4.3% RDV	33.1% mechanical ventilation	10.2%
Guo T[26]	187	China	58.5 ± 14.7	51.3%	32.6% HTN; 15% DM; 3.2% CKD	11.2% CAD; 4.3% CHF	98% antibiotics89% antiviral	24.1% mechanical ventilation	23%

(Continues)

TABLE 1 (Continued)

Author	Sample size	Country	Age	Female sex	Risk factors/Comorbidities	Prior CV events and Arrhythmias	Treatments	Severity/evolutions	Mortality
Jain S[27]	459	United States	68.2 ± 15.2	37.9%	16.5% morbid obesity; 59.2% HTN; 48.5% DM; 31.1% CKD	18.4% CAD; 15.5% CHF; 13.6% CeVD; 19.4% AF/AFL	90.4% HCQ 2.9% Macrolides 20.5% antiviral*5.7% RDV*	58.3% ICU during hospitalization	NA
McCullough SA[28]	756	United States	63.3 ± 16	36.8%	37.3% obesity; 56.5% HTN; 29.4% DM; 18.8% pulmonary disease; 9.5% renal disease	14.4% CAD; 7.3% CHF; 7.3% CeVD	None	NA	11.9%
Mercuro NJ[29]	90	United States	60.1 ± 16.7	48.9%	BMI 31.5 ± 6.6 kg/m^2; 53.3% HTN; 28.9% DM; 20% COPD	11.1% CAD; 10% CHF; 13.3% AF	100% HCQ58.9% Macrolides	33.3% ICU; 50% remained hospitalized	4.4%
Öztürk F[30]	91[£]	Turkey	49.2 ± 16.7	43.1%	11.8% HTN; 11.7% DM; other risk factors excluded	Prior CV disease and arrhythmias excluded	NA	NA	5.9%
Ramireddy A[31]	98	United States	62.3 ± 17	39%	60% HTN; 22% DM; 26% COPD; 14% CKD	20% CHF; prior arrhythmias excluded	72.5% HCQ89.8% Macrolides	49% ICU	NA
Rath D[32]	123	Germany	68 ± 15	37.4%	19.5% obesity; 69.9% HTN; 24.4% DM; 11.4% CKD; 0.8% smoker[€]	22.8% CAD22.8% AF	NA	45.5% ICU	13%
Sala S[33]	132	Italy	65 ± 14	NA	14% obesity; 45% HTN; 20% DM; 6% COPD	7% CAD12% AF; 0.9% PSVT	100% HCQ100% Macrolides	All clinically stable patients	NA
Samuel S[34]	36	United States	12.6 ± 6	44.4%	5.5% obesity; 17% malignancy; 8% asthma; 11% sickle cell;	55.5% on home medications; 8% cerebral palsy /seizures	69.4% HCQ 25% Macrolides5.6% RDV	58% ICU	2.8%
Si D[35]	1159	China	61.5 (32–69) vs 64 (24–70)[Ω]	45.3%	55.9% HTN; 21.8% DM; 5.3% CKD; 6.5% COPD	17.7% CAD; 3.5% CeVD	NA[2]	NA	1.6%
Yenercag M[36]	75	Turkey	55.5 ± 17.1	48%	BMI 24.1 ± 3.5 kg/m^2; 52% HTN; 36% DM; 37% smoker	CAD, CHF, AF, CeVD and CKD were excluded	NA	NA	NA

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HCQ, hydroxycloroquine; HTN, hypertension; ICU, intensive care units; IQR, interquartile range; NA, not available; PSVT, paroxysmal supraventricular tachycardia; RDV, Remdesivir; vs, versus.

[1] Any one of the following: respiratory failure and an artificial airway required for invasive mechanical ventilation; shock; combining failure of other organs which requires ICU monitoring and treatment.

[2] Reported only for a subset of patients.

[λ] Severe and critical patients, respective.

*Could be slightly overestimated due to some treatments were reported in combination.

[€] Current or former smoker.

[£] 51 COVID-19 patients and 40 controls.

[Ω] Discharged alive and died in hospital, respective.

TABLE 2 Demographic and baseline characteristics of included studies without electrocardiographic data

Author	Sample size	Country	Age	Female sex	Risk factors / Comorbidities	Prior CV events	Treatments	Severity / evolutions	Mortality
Aggarwal S[37]	16	United States	67(38–95)	25%	50% obesity; 57% HTN; 31% DM; 38% CKD; 13% COPD; 0% smoker	19% CAD; 25% CHF; 13% CeVD	69% HCQ43% Macrolides	50% ICU	19%
Cao J[38]	102	China	54(37–67)	48%	BMI IQR 21.8–26; 27.5% HTN; 10.8% DM; 3.9% CKD; 9.8% respiratory disease	4.9% CVD disease; 5.9% CeVD	99% antibiotics98% antiviral	17.6% ICU	16.7%
Du Y[39]	85	China	65.8 ± 14.2	27.1%	37.6% HTN; 22.4% DM; 3.5% CKD; 2.4% COPD	11.8% CVD; 8.2% CeVD	90.6% antibiotics91.8% antiviral	Include all fatal cases in 2 hospitals	100%
Hou W[40]	101	China	50.9 ± 20.1	56.4%	20.8% HTN; 5.9% DM; 4% COPD	10.9% CAD; 3% CeVD	34.7% antiviral	10% ICU	5%
Mani VR[41]	184	United States	64.7 ± 14.9	39.7%	38.6% obesity; 65.8% HTN; 43.5% DM; 17.4% CKD; 9.2% COPD	20.1% CAD	70.7% HCQ 61.4% Macrolides	16.3% mechanical ventilation	17.4%
Richardson S[42]	5700	United States	63(52–75)	39.7%	41.7% obesity; 56.6% HTN; 33.8% DM; 5% CKD; 5.4% COPD; 15.6% smoker[€]	11.1% CAD; 6.9% CHF	NA	14.2% ICU; 53.8% remained hospitalized	21%
Rosenberg ES[43]	1438	United States	63.4 (IQR NA)	40.3%	30.5% obesity; 56.8% HTN; 35.1% DM; 13% CKD; 18% respiratory disease	12% CAD; 6.7% CHF	69.9% HCQ65.8% Macrolides	22.8% ICU	20.3%
Wang D[44]	138	China	56(42–68)	45.7%	31.2% HTN; 10.1% DM; 2.9% CKD; 2.9% COPD	14.5% CVD; 5.1% CeVD	18.1% Macrolides89.9% antiviral	26.1% ICU; 61.6% remained hospitalized	4.3%
Wang L[45]	339	China	69(65–76)	51%	40.8% HTN; 16% DM; 3.8% CKD; 6.2% COPD	15.7% CVD; 6.2% CeVD	NA	NA	19.2%
Zeng JH[46]	416	China	45(33–57) 64(60–68)[¥]	52.4%	14.4% HTN; 5.5% DM; 0.5% CKD; 1.2% COPD	3.1% CAD;1% prior arrhythmias	NA	8.4% ICU	0.7%
Zhang G[47]	221	China	55(39–66.5)	51.1%	24.4% HTN; 10% DM; 2.7% CKD; 2.7% COPD	10% CVD; 6.8% CeVD	88.7% antiviral	19.9% ICU	5.4%

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HCQ, hydroxychloroquine; HTN, hypertension; ICU, intensive care units; IQR, interquartile range; NA, not available; RDV, Remdesivir.
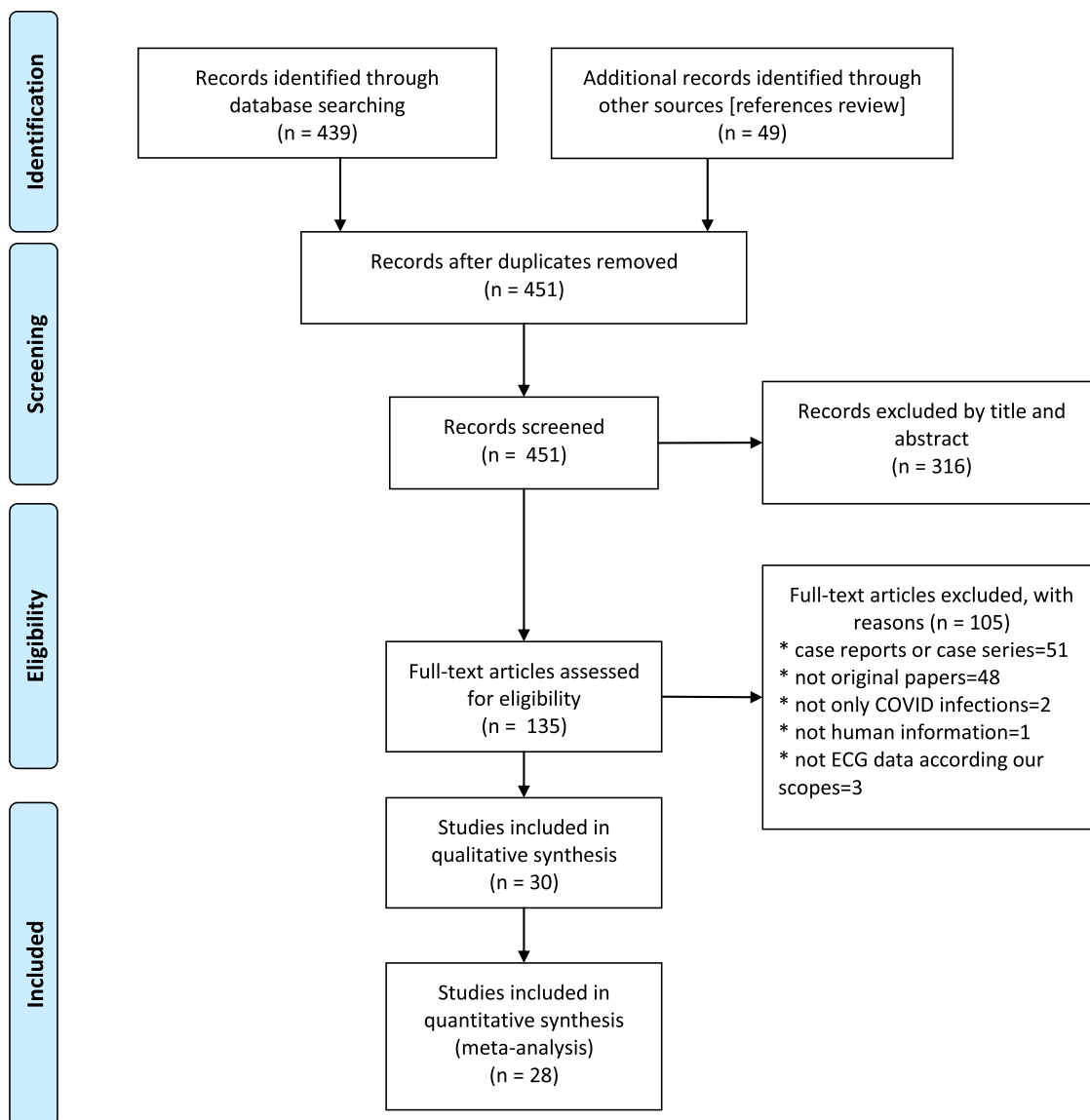
FIGURE 1 Flow diagram of included studies [Color figure can be viewed at wileyonlinelibrary.com]

25 studies (*n* = 7578), though there was substantial heterogeneity between the studies (*I*² = 100%) (Figure 1A). Sensitivity analysis, excluding data from pediatric and adolescent patients, did not significantly alter the overall frequency of arrhythmias (10%, 95% CI: 8.1%–12%) (Figure S1).

Specific types of arrhythmias were reported by 15 studies (Table 3). The most common was supraventricular tachyarrhythmias (*n* = 3395 from nine studies, 6.2%, 95% CI: 4.4%–8.1%; *I*² = 100%) (Figure 1B),[18,19,21,23,25,28,33–35] followed by ventricular tachyarrhythmias (*n* = 3485 from 11 studies, 2.5%, 95% CI: 1.8%–3.1%; *I*² = 100%) (Figure 1C).[19–22,25–27,29,34–36] Bradyarrhythmias were the least common (*n* = 1560 from four studies, 1.8%, 95% CI: 1.0%–2.5%; *I*² = 100%) (Figure S2).[18,19,21,28]

3.3 | ST-segment changes and QT interval prolongation

Changes in the QT interval during COVID-19 hospitalization were reported by 16 studies (Table 4).[18,20,22,27–36,41–43] The most frequent criteria to define substantial QTc prolongation was QTc duration > 500 ms when the QRS duration was < 120 ms and QTc > 550 ms when the QRS duration was ≥120 ms. Due to disparities in the reported data, only six studies (*n* = 4812) were included in our meta-analysis for QT prolongation.[18,20,22,29,31,42] The overall prevalence of QTc > 500 ms was 12.3% (95% CI: 6.9%–17.8%; *I*² = 100%) (Figure 2A).

The presence or absence of ST-segment deviation was reported in eight studies (*n* = 1598) with a pooled estimate of 8.7% (95% CI: 7.35%–10.0%; *I*² = 100%) (Figure 2B).[18,21,23,24,27,34,37]

TABLE 3 Arrhythmias observed in the included studies

Study	Supraventricular	Ventricular	Bradyarrhythmias	Combined
AngeliF[18]	3 AF	–	1 tachy/brady	–
BhatlaA[19]	25 incident AF	9 cardiac arrests, 10 NSVTs	9 bradyarrhythmias	–
BorbaMGS[20]	–	2 VT	–	–
Chen Q[21]	1 AF 1	3 VT	2 complete AV block	–
ChorinE[22]	–	1 TdP	–	–
Colon CM[23]	12 AF, 6 AFL, 1AT	–	–	–
Goyal P[25]	28*	1 VT	–	–
Guo T[26]	–	11 VT/VF	–	–
Jain S[27]	–	2 VT	–	–
McCullough SA[28]	42 AF or AFL	–	1 complete AV block	–
Mercuro NJ[29]	–	1 TdP	–	–
Sala S[33]	8 AF, 3 AT & 1 PSVT	–	–	–
Samuel S[34]	1 AT	5 VT	–	–
Si D[35]	22 AT/AF	3 VT/VF	–	3 AT/AF + VT/VF
Yenercag M[36]	–	2 VT	–	–

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia.; AV block, atrioventricular block; NSVT, non sustained ventricular tachycardia; tachy/brady, tachycardia-bradycardia syndrome; TdP, torsade de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.
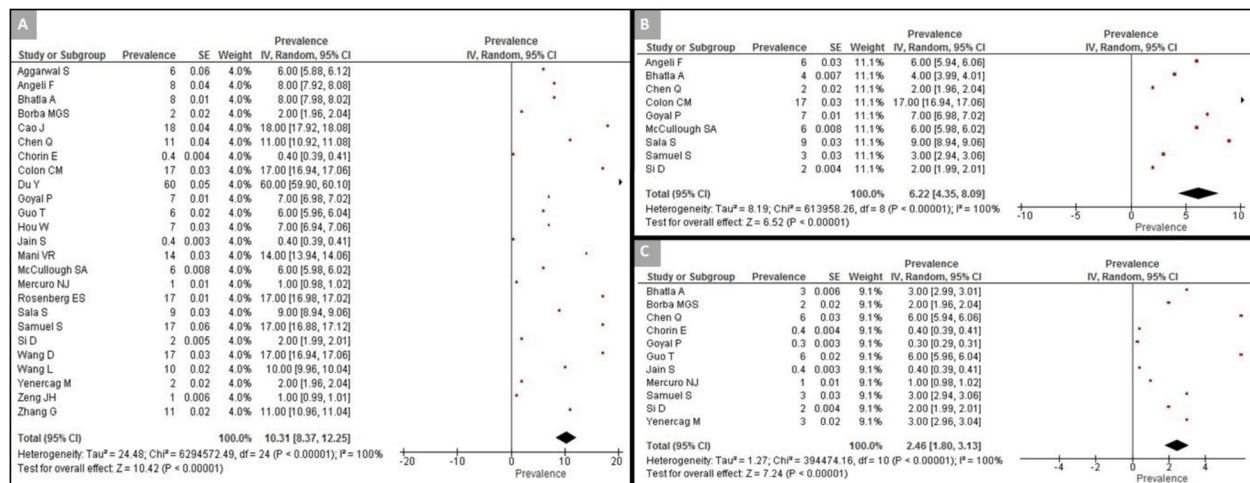*Declared as "Atrial arrhythmia".

FIGURE 2 Forest plot of the prevalence of arrhythmias in hospitalized patients with COVID-19. (A) Prevalence of arrhythmias in analyzed studies; (B) prevalence of supraventricular arrhythmias; (C) prevalence of ventricular arrhythmias [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Relationship between cardiac arrhythmias and adverse outcomes

Eight studies reported the relationship between new-onset cardiac arrhythmias and adverse outcomes in patients with COVID-19 ($n = 2112$, 56.1 ± 17.8 years, 46.4% female).[19,21,23,25,36,44,46,47] Regarding the definition of disease severity, Bhatla et al.,[19] Colon et al.,[23] Yenercag et al.,[36] Wang et al.,[44] and Zeng et al.[46] classified disease severity based on ICU admission, whereas Goyal et al.[25] classified it based on the need for mechanical ventilation. Chen et al.[21] and Zhang et al.[47] classified disease severity based on ICU admission and/or other clinical parameters, including oxygen saturation ≤93%, respiratory rate ≥30 times per minute, or severe respiratory distress (Figure 3).

Critically ill patients showed a higher risk of developing cardiac arrhythmias compared to those who were not critically ill (risk ratio [RR]: 12.1, 95% CI: 8.5–17.3; $I^2 = 0\%$) (Figure 2C), both for ventricular arrhythmias (RR: 10.5, 95% CI: 3.9–27.9; $I^2 = 0\%$) (Figure S3) and

TABLE 4 QTc information in the included studies

Author	Baseline QTc (ms)	SD (+/-)	Comments
AngeliF[18]	428	26 ms	1 patient with QTc > 500 ms
BorbaMGS[20]	424.7	27.4	15.1% QTc > 500 ms
ChorinE[22]	439	29	23% QTc > 500 ms
Jain S[27]	22.4% patients with QT prolongation[£]. No episodes of torsades de pointes. 2 episodes of VT.		
Mani VR[41]	Isolated QT prolongation in 3.8% of the patients and sinus tachycardia with QT prolongation in 1.9% of the patients		
McCullough SA[28]	449	144 ms	No differences in QTc between survivors and non-survivors of COVID-19.
MercuroNJ[29]	455	430–474	20% QTc > 500 ms
ÖztürkF[30]	410.4	24.5 ms	3 patients died, all with QTc < 430 ms
RamireddyA[31]	448	29	Prolonged QTc in 12% of the patients post-treatment (QTc > 500 ms if QRS < 120 ms, and QTc > 550 ms if QRS ≥120 ms OR QTc > 60 ms from baseline)
Rath D[32]	445	33 ms	No differences in QTc between survivors and non-survivors of COVID-19
Richardson S[42]	6.1% of patients with QTc > 500 ms over 4250 patients (from automated ECG reading)		
Rosenberg ES[43]	11% of QTc prolongation with HCQ+AZN; 14.4% QTc prolongation with HCQ alone; 7.1% QTc prolongation with AZN alone & 5.9% QTc prolongation with neither drug ($p = .006$)		
Sala S[33]	No patients with QTc interval > 450 ms, despite drugs administered for COVID-19 treatment		
Samuel S[34]	412	19 ms	Use of HCQ with or without AZN was associated with QTc prolongation (411 ± 19 ms vs. 426 ± 15 ms, $p < .0001$). QTc was not different in patients with and without arrhythmias (425 ± 15 ms vs. 425 ± 15 ms, $p = 1.0$)
Si D[35]	QTc interval was measured in 35 patients and was prolonged by an average of 45 ms in those treated with QT-prolonging medications (455 ms [423–480] vs. 410 ms [364–430], $p = .01$). Fatal VT/VF occurred in6 patients, but only 2 had ECGs recorded before death (1 with QTc prolongation and the other with normal QTc)		
Yenercag M[36]	411.1	23.9 ms	Patients using QT-prolonging medications were excluded

Abbreviations: AZN, Azithromycin; HCQ, Hydroxychloroquine; ms, milliseconds; QTc, corrected QT interval; SD, standard deviation; VF, ventricular fibrillation.; VT, ventricular tachycardia.
[£]QTc interval > 470 ms for QRS duration ≤120 ms or QTc interval > 500 ms for QRS duration > 120 ms.
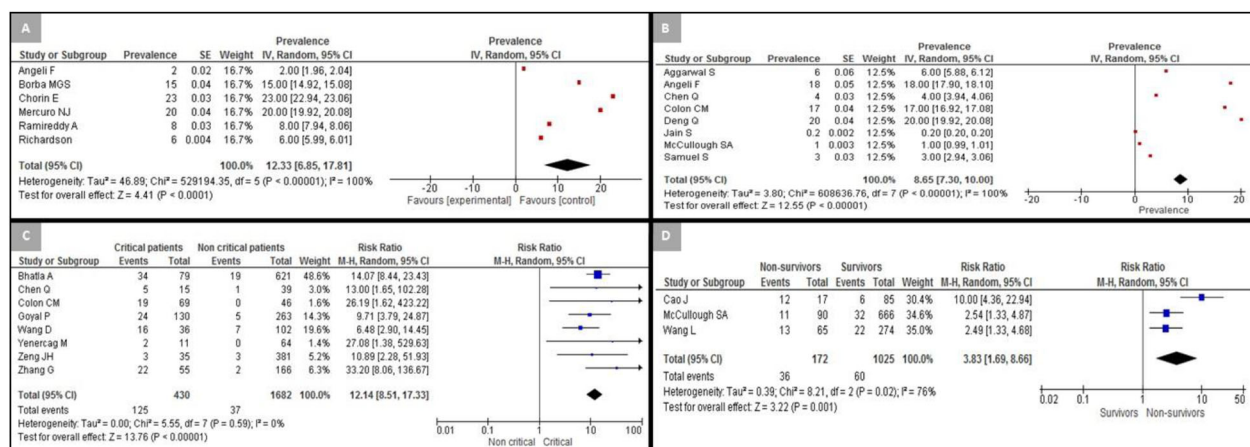

FIGURE 3 Forest plot for QT prolongation, ST prevalence, and arrhythmias among hospitalized patients with COVID-19. (A) Prevalence of corrected QT > 500 ms; (B) prevalence of ST-segment deviation; (C) prevalence of arrhythmias in critical and non-critical patients; (D) prevalence of arrhythmias in survivors and non-survivors of COVID-19 [Color figure can be viewed at wileyonlinelibrary.com]
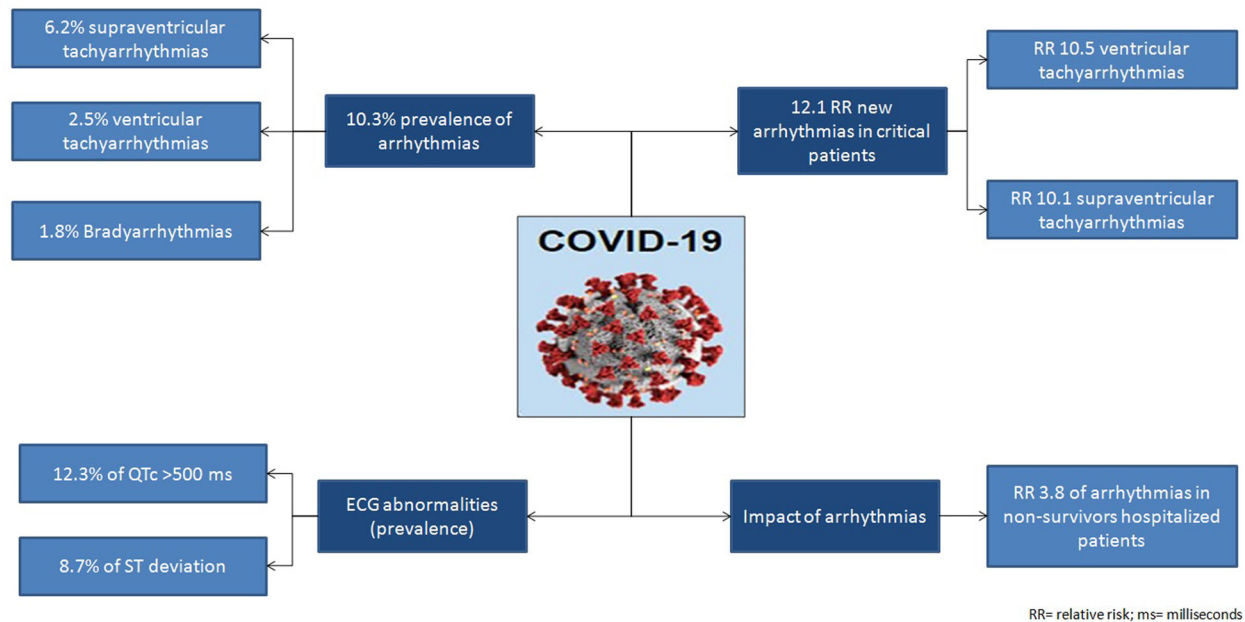
FIGURE 4 Cardiac arrhythmias and electrocardiographic abnormalities in hospitalized patients with COVID-19 [Color figure can be viewed at wileyonlinelibrary.com]

supraventricular arrhythmias (RR: 10.1, 95% CI: 5.7–17.2; $I^2 = 0$%) (Figure S4).

The relationship between cardiac arrhythmias and inpatient mortality was only reported by three studies ($n = 1197$, 62 ± 16 years old, 45.0% female).[28,36,45] Non-survivors were more likely to develop cardiac arrhythmias compared to survivors during their inpatient stay (RR: 3.8, 95% CI: 1.7–8.7; $I^2 = 76$%) (Figure 2D). Of these three studies, only one reported the specific type of arrhythmias observed, which was supraventricular arrhythmias observed in all patients.[28] In this study, non-survivors were also found to be at a higher risk of developing supraventricular arrhythmias (RR: 2.3, 95% CI: 1.2–4.5) (Figure S5).

In Figure 4, we have summarized the main findings our study relating to cardiac arrhythmias and ECG abnormalities among hospitalized COVID-19.

Regarding potential publication bias between analyzed studies, a visual inspection of funnel plots suggested an asymmetric distribution of the occurrence of cardiac arrhythmias in hospitalized COVID-19 patients (Figure S6). The Begg's test suggested no significant publication bias ($z = 1.38$; $p = .17$). The Egger test demonstrated significant asymmetry (t-value -3.0; $p = .006$) (Figure S7). Sensitivity analysis, excluding one study at a time (leave-one-out method), did not reduce the heterogeneity of the results.

4 | DISCUSSION

The main findings of this systematic review and meta-analysis are: (i) cardiac arrhythmias are a common complication among hospitalized COVID-19 patients, and (ii) cardiac arrhythmias can be considered a marker of worsening prognosis.

To the best of our knowledge, this is the largest meta-analysis reporting on the prevalence of ECG findings in hospitalized COVID-19 patients. We found that the frequency of cardiac arrhythmias showed a wide range across the studies, which could be attributable to the differences in the patients' comorbidities and variations seen across disease severity and treatments offered. In our study, premature beats were excluded in order to avoid an overestimation of the clinically significant arrhythmias. Among specific arrhythmias reported across the studies, supraventricular arrhythmias were the most frequent, followed by ventricular arrhythmias. In contrast, bradyarrhythmias were the least observed arrhythmias. Furthermore, the risk of cardiac arrhythmias was higher among non-survivors and critically ill patients hospitalized with COVID-19.

ST-segment changes were the most frequently reported ECG finding. This is a significant ECG abnormality caused by different pathologies such as pericarditis, Takotsubo cardiomyopathy, and acute coronary syndrome. Additionally, QTc prolongation is a significant concern during COVID-19 infection and could be largely attributable to drugs that cause delayed repolarization.[3] However, we were unable to fully evaluate the prognostic implications of ST-segment changes and QT prolongation due to the significant disparities in the reported data across the studies.

Cardiac involvement in COVID-19 has a wide spectrum, and contemporary high sensitivity troponin tests might be elevated in critically ill patients even without apparent myocardial involvement.[48,49] Nevertheless, previous studies have linked cardiac involvement with a worse prognosis in COVID-19.[50] ECG abnormalities are intrinsically related to cardiac pathology, and our findings are in agreement with these observations.

4.1 | Limitations

Our study has important limitations. Firstly, about half of the included articles did not report the types of arrhythmias observed. We were, therefore, unable to accurately estimate the incidence and prevalence of electrocardiographic abnormalities in hospitalized patients with COVID-19. Secondly, we could not investigate the relationship between specific types of arrhythmias and the severity of COVID-19 infection. This information was not consistently reported across the included studies, likely because most studies did not examine cardiac arrhythmias as a specific risk factor for adverse outcomes. Finally, we found high heterogeneity for most comparisons except for the occurrence of arrhythmias in critically ill patients. Nevertheless, such heterogeneity could have a clinical origin due to the differences in the study cohorts amongst the included studies.

5 | CONCLUSION

Our systematic review and meta-analysis showed that QTc prolongation, ST-segment deviation, and other forms of cardiac arrhythmias were observed in patients hospitalized with COVID-19. The presence of cardiac arrhythmias was associated with a worse prognosis. Future studies are needed to explore the possible role of arrhythmias in relation to patient outcomes.

CONFLICT OF INTEREST

Nothing to declare.

ETHICAL APPROVAL

Our meta-analysis was based on published data and did not require approval from an Ethical committee.

AUTHOR CONTRIBUTIONS

Conception and design of the project:

Gary Tse, Sebastian Garcia-Zamora, George Bazoukis, Adrian Baranchuk.

Data collection:

Sebastian Garcia-Zamora, Sharen Lee, Sohaib Haseeb, George Bazoukis, Gary Tse, Jesus Alvarez-Garcia, Enes Elvin Gul, Göksel Çinier, Bryce Alexander, Marcelo Martins Pinto-Filho.

Data analysis and interpretation:

Sebastian Garcia-Zamora, Sharen Lee, Gary Tse, George Bazoukis, Jesus Alvarez-Garcia, Göksel Çinier, Tong Liu, Adrian Baranchuk.

Drafting the article:

Sebastian Garcia-Zamora, Sharen Lee, Sohaib Haseeb, George Bazoukis, Gary Tse, Jesus Alvarez-Garcia, Enes Elvin Gul, Göksel Çinier, Bryce Alexander, Marcelo Martins Pinto-Filho.

Critical revision of the article:

Gary Tse, George Bazoukis, Tong Liu, Adrian Baranchuk.

Final approval of the version to be published:

Sebastian Garcia-Zamora, Sharen Lee, Sohaib Haseeb, George Bazoukis, Gary Tse, Jesus Alvarez-Garcia, Enes Elvin Gul, Göksel Çinier, Bryce Alexander, Marcelo Martins Pinto-Filho, Tong Liu, Adrian Baranchuk

Responsibles for the overall content as guarantors:

Sebastian Garcia-Zamora, George Bazoukis, Gary Tse, Adrian Baranchuk.

DATA AVAILABILITY STATEMENT

The data that support the findings of this systematic review and meta-analysis are available in the studies listed in references.

ORCID

Sebastian Garcia-Zamora MD https://orcid.org/0000-0001-6846-0247

Sharen Lee MD https://orcid.org/0000-0002-2401-2837

Sohaib Haseeb Bsc https://orcid.org/0000-0003-2799-5135

George Bazoukis MD https://orcid.org/0000-0003-1009-9772

Gary Tse MD https://orcid.org/0000-0001-5510-1253

Jesus Alvarez-Garcia MD https://orcid.org/0000-0002-2015-6446

Enes Elvin Gul MD https://orcid.org/0000-0003-1285-0638

Göksel Çinier MD https://orcid.org/0000-0001-5064-1816

Bryce Alexander MD https://orcid.org/0000-0002-6126-1752

Marcelo Martins Pinto-Filho MD https://orcid.org/0000-0002-6646-1163

Tong Liu MD https://orcid.org/0000-0003-0482-0738

Adrian Baranchuk MD https://orcid.org/0000-0002-3042-6569

REFERENCES

1. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846-848.
2. Li X, Guan B, Su T, Wei L, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. *Heart*. 2020;106:1142-1147.
3. Haseeb S, Gul EE, Çinier G, et al. Value of electrocardiography in coronavirus disease 2019 (COVID-19). *J Electrocardiol*. 2020;62:39-45.
4. Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. *Circulation*. 2020;141:1930-1936.
5. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of Coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5:831-840.
6. Wang Y, Roever L, Tse G, Liu T. 2019-Novel Coronavirus-related acute cardiac injury cannot be ignored. *Curr Atheroscler Rep*. 2020;22:14.
7. Jain V, Yuan J-M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. *Int J Public Health*. 2020;65:533-546.
8. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
9. Wells A, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.aspn.d

10. Wang X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.

11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.

12. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.

13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.

14. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011. www.cochrane-handbook.orgn.d. Updated March 2011.

15. Pavri BB, Kloo J, Farzad D, Riley JM. Behavior of the PR interval with increasing heart rate in patients with COVID-19. *Heart Rhythm*. 2020;17:1434-1438.

16. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5:802–810.

17. Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine*. 2020;21:100331.

18. Angeli F, Spanevello A, De Ponti R, et al. Electrocardiographic features of patients with COVID-19 pneumonia. *Eur J Intern Med*. 2020;78:101-106.

19. Bhatla A, Mayer MM, Adusumalli S, et al. COVID-19 and cardiac arrhythmias. *Heart Rhythm*. 2020;17:1439-1444.

20. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e208857.

21. Chen Q, Xu L, Dai Y, et al. Cardiovascular manifestations in severe and critical patients with COVID-19. *Clin Cardiol*. 2020;43:796-802.

22. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. *Heart Rhythm*. 2020;17:1425-1433.

23. Colon CM, Barrios JG, Chiles JW, et al. Atrial Arrhythmias in COVID-19 Patients. *JACC Clin Electrophysiol*. 2020;6:1189-1190.

24. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol*. 2020;311:116-1121.

25. Goyal P, Choi JJ, Pinheiro LC. Clinical Characteristics of COVID-19 in New York City. *N Engl J Med*. 2020;382:2372-2374.

26. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1-8.

27. Jain S, Workman V, Ganeshan R, et al. Enhanced electrocardiographic monitoring of patients with Coronavirus Disease. *Heart Rhythm*. 2019;17:1417-1422.

28. McCullough SA, Goyal P, Krishnan U, Choi JJ, Safford MM, Okin PM. Electrocardiographic findings in coronavirus disease-19: insights on mortality and underlying myocardial processes. *J Card Fail*. 2020;26:626-632.

29. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1036-1041.

30. Öztürk F, Karaduman M, Çoldur R, İncecik Ş, Güneş Y, Tuncer M. Interpretation of arrhythmogenic effects of COVID-19 disease through ECG. *Aging Male*. 2020:1-4. https://doi.org/10.1080/13685538.2020.1769058.

31. Ramireddy A, Chugh H, Reinier K, et al. Experience with hydroxychloroquine and azithromycin in the Coronavirus Disease 2019 Pandemic: implications for QT interval monitoring. *J Am Heart Assoc*. 2020;9:e017144.

32. Rath D, Petersen-Uribe Á, Avdiu A, et al. Impaired cardiac function is associated with mortality in patients with acute COVID-19 infection. *Clin Res Cardiol*. 2020:1-9. https://doi.org/10.1007/s00392-020-01683-0.

33. Sala S, Peretto G, De Luca G. Low prevalence of arrhythmias in clinically stable COVID-19 patients. *Pacing Clin Electrophysiol*. 2020;43(8):891-893. https://doi.org/10.1111/pace.13987.

34. Samuel S, Friedman RA, Sharma C, et al. Incidence of arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with PCR-positive SARS-CoV-2 infection, including drug-induced changes in the corrected QT interval. *Heart Rhythm*. 2020;17:1960-1966.

35. Si D, Du B, Ni L, et al. Death, discharge and arrhythmias among patients with COVID-19 and cardiac injury. *CMAJ*. 2020;192:E791-E798.

36. Yenerçağ M, Arslan U, Doğduş M, et al. Evaluation of electrocardiographic ventricular repolarization variables in patients with newly diagnosed COVID-19. *J Electrocardiol*. 2020;62:5-9.

37. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. *Diagnosis (Berl)*. 2020;7:91-96.

38. Cao J, Tu W-J, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with Coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71:748-755.

39. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan. a retrospective observational study. *Am J Respir Crit Care Med*. 2020;201:1372-1379.

40. Hou W, Zhang W, Jin R, Liang L, Xu B, Hu Z. Risk factors for disease progression in hospitalized patients with COVID-19: a retrospective cohort study. *Infect Dis (Lond)*. 2020;52:498-505.

41. Mani VR, Kalabin A, Valdivieso SC, Murray-Ramcharan M, Donaldson B. At the epicenter of the American Coronavirus outbreak - New York inner city hospital COVID-19 experience and current data: a retrospective analysis. *J Med Internet Res*. 2020;22:e20548.

42. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city Area. *JAMA*. 2020;323:2052-2059.

43. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323:2493-2502.

44. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-1069.

45. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80:639-645.

46. Zeng JH, Wu W-B, Qu JX, et al. Cardiac manifestations of COVID-19 in Shenzhen, China. *Infection*. 2020;48(6):861-870.

47. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol*. 2020;127:104364.

48. Momtazmanesh S, Shobeiri P, Hanaei S, Mahmoud-Elsayed H, Dalvi B. Malakan Rad E. Cardiovascular disease in COVID-19: a systematic review and meta-analysis of 10,898 patients and proposal of a triage risk stratification tool. *Egypt Heart J*. 2020;72:41.

49. Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2012;60:2427-2463.

50. Li JW, Han TW, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: a systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2020;63:518-524.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Garcia-Zamora S, Lee S, Haseeb S. Arrhythmias and Electrocardiographic findings in Coronavirus disease 2019: a systematic review and meta-analysis. *Pacing Clin Electrophysiol*. 2021;44:1062–1074. https://doi.org/10.1111/pace.14247