Int J Cardiovasc Sci. 2023; 36:e20220181

ORIGINAL ARTICLE

# Frequent Cardiovascular Manifestations Associated With SARS Cov-2 Infection: Experience at a Tertiary Hospital In Cali, Colombia

Duvan Arley Galindes-Casanova,[1,2] Edith Norela Benitez-Escobar,[1,2] Luis Álvaro Melo-Burbano,[1,2] Nelson Eduardo Murillo-Benitez,[1,2] Juan Carlos Avila-Valencia,[2] Jorge Enrique Daza-Arana[1]

*Universidad Santiago de Cali, Facultad de Salud, Especialización en Medicina interna,[1] Cali, Valle del Cauca – Colombia*
*Clínica de Occidente, Departamento de investigación y Medicina interna,[2] Cali, Valle del Cauca – Colombia*

## Abstract

**Background:** Coronavirus disease 2019 (COVID-19) mainly affects the respiratory system, while the most common extrapulmonary complication of COVID-19 is cardiovascular involvement.

**Objective:** To identify the frequency of electrocardiographic changes and cardiac arrhythmias in patients hospitalized with COVID-19 infection.

**Methods:** This was a cross-sectional study, including patients aged >18 years with diagnosis of severe acute respiratory syndrome coronavirus 2 infection in a high-complexity hospital in Santiago de Cali, Colombia, from March to September 2020. A descriptive analysis with an analytical component and multiple logistic regression analysis were performed; all estimates were established with a 95% confidence level (CI) and a 5% significance level.

**Results:** This study included 183 individuals; of whom 160 were considered for electrocardiographic analysis, 63% of which evidenced significant findings, the most frequent being sinus tachycardia (29.4%). The frequency of myocardial injury was 21.9% and was more common among non-survivors than among survivors (41.7% vs. 12.2%, $p < 0.001$). Myocardial injury was also significantly more common in patients who presented electrocardiographic findings than those who did not (26.5% vs. 12.1%, $p = 0.032$) and in those who required intensive care admission (31.8% vs 10.5%, $p < 0.001$). The strongest mortality-associated factor was the need for mechanical ventilation — odds ratio (OR), 9.14; 95% confidence interval, 3.4–24.5.

**Conclusions:** Electrocardiographic findings in patients with COVID 19 are frequent, including newly diagnosed arrhythmias, justifying the use of cost-effective tools for the initial approach and follow-up of this affected population. Worse outcomes depend on factors such as invasive mechanical ventilation, comorbidities, age, and superinfection.

**Keywords:** COVID-19; Arrhythmias, Cardiac; Electrocardiography; Biomarkers; Cardiovascular System.

## Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). To date, more than 700 million confirmed cases and more than 6 million deaths due to secondary complications have been reported. Moreover, it was declared a pandemic in March 2020,[1] thus constituting one of the greatest threats to humanity in recent centuries.

Interaction of the virus with the host occurs through the S protein (spike) of the virus and its entry receptor angiotensin-converting enzyme 2 (ACE 2); however, invasion requires priming of a cellular serine protease called Transmembrane Serine Protease 2 (TMPRSS2).[2] This receptor is present in various cells of the body, mainly in type II pneumocytes, and is also present at the systemic level, including in the heart and blood vessels, which are organs frequently involved in the complications presented during the infection.[3]

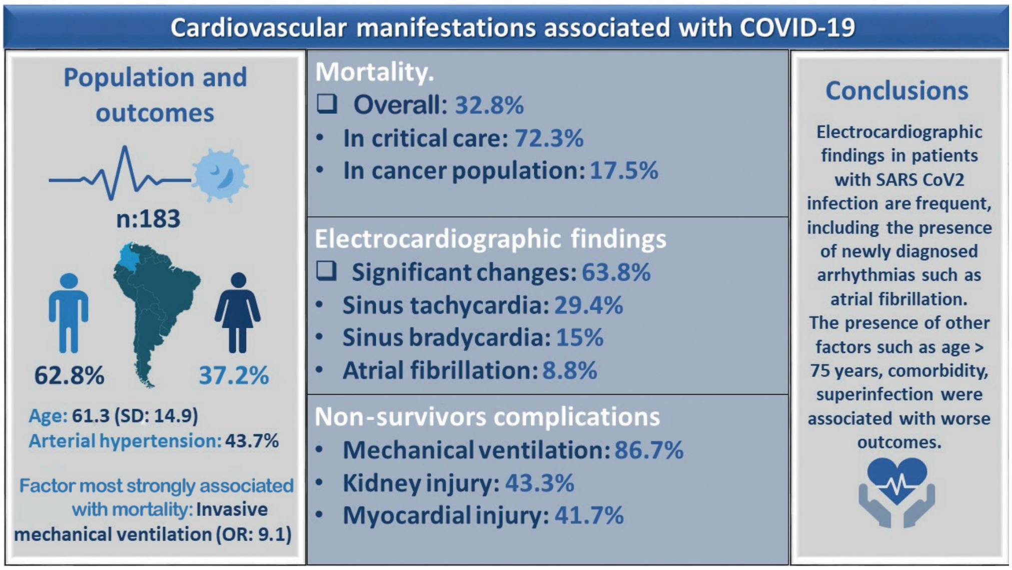
**Mailing Address: Duvan Arley Galindes Casanova**
Universidad Santiago de Cali Facultad de Salud. Facultad de Salud Calle 5ta # 62-00. Postal code: 760035. Pampalinda, Cali – Colombia
E-mail: drdagasc16@gmail.com

DOI: https://doi.org/10.36660/ijcs.20220181

Manuscript received October 25, 2022; revised manuscript August 10, 2023; accepted September 6, 2023.

**Central Illustration:** Frequent Cardiovascular Manifestations Associated With SARS Cov-2 Infection: Experience at a Tertiary Hospital In Cali, Colombia

INTERNATIONAL JOURNAL OF Cardiovascular SCIENCES




Int J Cardiovasc Sci. 2023; 36:e20220181

*SD: standard deviation; OR: odds ratio.*

The mechanisms of cardiovascular complications have been explained by a series of pathophysiological events, which initially occur at the respiratory level but finally occur at the multisystemic level, thereby altering cellular processes, causing modifications in the cardiac excitation and contraction coupling processes, and consequently increasing the potential arrhythmogenic effect.[4,5] This is an event that occurs much more frequently in individuals with cardiovascular risk factors, such as high blood pressure (HBP) and diabetes, and pre-existing arrhythmias and among those aged >55 years. These patients also show an increased need for treatment in the intensive care unit (ICU).[6,7]

Currently, in Colombia and Latin America, knowledge about cardiovascular involvement related to these infections is gaining visibility, in part due to improved understanding of the disease. Early electrocardiographic findings are increasingly described as markers of poor prognosis, such as correlations of QT interval prolongation, higher incidence of recent sustained arrhythmias, and the presence of myocardial injury, all of which are associated with worse outcomes.[8,9] Highlighting these findings, this study aimed to identify the frequency of electrocardiographic changes and cardiac arrhythmias, sociodemographic and clinical characteristics, and factors associated with mortality in patients hospitalized with COVID-19 infection in a tertiary care hospital.

## Methodology

This is an observational, descriptive, cross-sectional, single-center study conducted in a high-complexity hospital in Santiago de Cali, Colombia, from March to September 2020.

### Ethical aspects

The research was conducted in accordance with the international recommendations on clinical research provided in the Declaration of Helsinki and with Colombian Ministry of Health Resolution 8430 of 1993. It has been classified as risk-free research since the data originate from secondary sources, such as clinical records. The project was endorsed by the research and ethics and bioethics committees of the institutions involved in the study.

### Procedure

The study included subjects with a diagnosis of COVID-19 infection confirmed via reverse transcription-polymerase chain reaction (RT-PCR), presence of IgG and IgM type antibodies, or presence of antigens for SARS CoV-2, who also had an electrocardiogram upon admission to the institution. Patients with a known history of cardiac arrhythmia, hospital stay of <24 h, or evidence of cardiorespiratory arrest during their initial care were excluded from the study.

Poor prognosis, comorbidities, and superinfection variables for the disease were defined according to the recommendations of the Colombian consensus on the care, diagnosis, and management of SARS CoV-2/COVID-19 infection in healthcare institutions.[10] The following were used as cutoff points: lymphocyte count < 1000 × $10^3/\mu L$; ferritin > 1000 ng/ml, lactate dehydrogenase (LDH) > 350 IU/L, D-dimer > 1000 mcg/ml, and procalcitonin > 0.5 ng/mL; while a $PaO_2/FiO_2$ ratio <100 indicates severe hypoxemia, 100–200 indicates moderate hypoxemia, 200–300 indicates mild hypoxemia, and a ratio ≥300 indicates no hypoxemia. Presence of hyperkalemia or hypokalemia was defined as values >5.5 mEq/l or <3.5 mEq /l, respectively; transaminitis with increased levels of aminotransferases was defined as levels >3 times the normal upper limit, and a cutoff point of 47.34 ng/l was used for the 99$^{th}$ percentile (99p) of troponin (ADVIA Centaur TNIH) - values above this cutoff are considered indicative of myocardial injury.

During the course of SARS CoV2 infection, any history of illness prior to diagnosis was considered as comorbidity, while any clinical picture suggestive of an infectious process more than 48 hours beyond hospital admission, confirmed by cultures, was defined as superinfection.

Only the first in-hospital electrocardiographic study performed in subjects admitted with a suspected diagnosis of COVID-19 was analyzed, in order to avoid possible confusion with patients admitted for reasons other than COVID-19 infection or cases in which COVID-19 infection was acquired within the hospital.

The electrocardiogram readings were obtained by two medical specialists in clinical cardiology with more than 10 years of experience and who were unaware of the patients' clinical diagnoses. In cases of disagreement regarding identification of the main finding, diagnosis was made by a third physician specialized in clinical cardiology.

Normal tracing was defined as no significant findings after a reading based on the recommendations for standardized electrocardiogram interpretation, including specific considerations such as significant ST-segment elevation when >1 mm in at least two contiguous leads, except v2-v3.[11]

## Data analysis

A descriptive analysis of the variables was conducted for the overall population as well as by survivors and non-survivors. For categorical data, this analysis used frequency distributions and relative and absolute frequencies. For quantitative data, a numerical analysis of measures of central tendency (mean) and dispersion (standard deviation) was conducted, followed by their respective categorizations. The Kolmogorov-Smirnov normality test was used to assess the normality of the data. To evaluate the differences in means, the unpaired Student *t* test and the Chi-square test for difference in proportions were applied, with their respective p values. Statistical significance was established as p values lower than 0.05.

Finally, multivariate analyses were conducted to determine the risk factors associated with mortality in the study population. Explanatory or independent variables were converted to dichotomous categories if necessary. According to statistical criteria, independent variables with $p \leq 0.25$ in the univariate models were introduced into the initial logistic model with crude OR, followed by stepwise-backward elimination with an entry probability of <0.10 and a withdrawal probability of >0.25, which generated the final explanatory model with adjusted OR. All estimates were established with a 95% confidence level (CI) and a 5% significance level. In addition, the Hosmer-Lemeshow goodness-of-fit and verisimilitude tests were performed to validate the model's assumptions. The data analysis was performed using STATA 16® statistical program.

## Results

The selection process and demographic data, clinical characteristics, and severity markers at admission as well as diagnostic aids, therapies, and complications of the subjects who met the inclusion criteria are described in Figure 1 and Table 1, respectively. Overall, the mortality rate was 32.8%, reaching 78.3% in those who required ICU management (53%); the most frequent rhythm of arrest was asystole, which was reported in 96.3% of the non-survivors.

Several characteristics were not statistically significant between survivors and non-survivors. Among non-survivors, age, particularly age >75 years, history of cancer, and cardiovascular disease showed statistically significant relevance. The central figure shows the main results of this study.

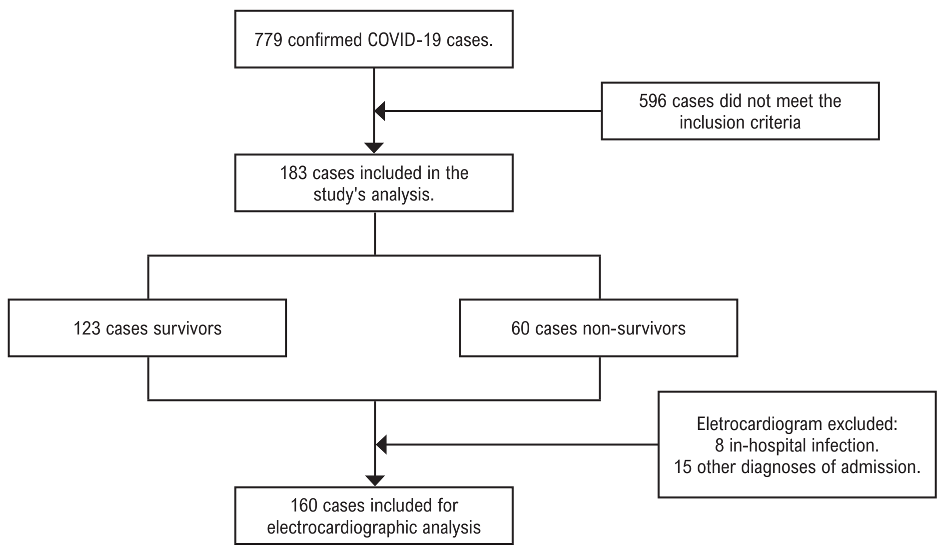



**Figure 1 – Flowchart illustrating patient recruitment and analysis process.**

## Complications and severity markers

Complications occurred more frequently among non-survivors than among survivors, with a greater need for mechanical ventilation, along with higher incidence of acute kidney injury and myocardial injury. Diagnosis of superinfection was also more frequent in this group of patients and was associated with administration of antibiotic regimens lasting more than 5 days.

The most frequently observed severity biomarkers in deceased subjects were lymphocyte count $<1000 \times 10^3/\mu L$, D-dimer level >1000 μg/ml, and elevated troponin levels >99p. Elevated troponin levels were significantly more frequent in subjects admitted to the ICU compared to those not admitted (31.8% vs 10.5%, $p < 0.001$)

## Cardiovascular compromise and myocardial injury

Electrocardiographic findings did not differ between the two groups ($p > 0.05$); 15% of patients presented sinus bradycardia; changes compatible with significant ST-segment elevation occurred in 6.25% of cases; and 30% had troponin values above the 99p, which suggests possible acute myocardial infarction (AMI) with ST-segment elevation. The most frequent rhythm disorder identified was atrial fibrillation. in 8.8%, considered to be the patient's first diagnosis, given the study's exclusion criteria. There was no evidence of QT interval prolongation in this population (Table 2).

These electrocardiographic findings were more frequent and significantly evident when serum potassium and ferritin levels were <3.5 mEq/L and >1000 ng/mL, in 3.5% ($p = 0.037$) and 46.1% ($p = 0.018$) of the subjects, respectively.

The frequency of myocardial injury was significantly higher in patients with abnormal electrocardiographic findings compared to those without (26.5% vs. 12.1%, $p = 0.032$)

Figure 2 illustrates the behavior of the main biomarkers in subjects with abnormal electrocardiographic findings.

Significant ST-segment changes and troponin elevation were present in 7% of the subjects. The multidisciplinary management team considered presence of myocardial injury associated with infection as the first possibility, ruling out AMI or pericarditis and taking into account the absence of symptoms; 33% of these subjects had an echocardiographic study, half of them with LVEF < 40%. However, since they had a history of previous ischemic heart disease, none required specific treatment.

Additional studies such as echocardiography were performed in about a quarter of the patients admitted, while computed tomography (CT) angiography was much less frequent, being positive for pulmonary embolism in 21% of all studies performed.

**Table 1 – Demographic and clinical characteristics and diagnostic aids (Continuation).**

| Variables | Total (n = 183) | Survivors (n = 123) | Non-survivors (n = 60) | p value |
|---|---|---|---|---|
| **Characteristics** | | | | |
| Sex | | | | |
| Male | 115 (62.8%) | 76 (61.8%) | 39 (65%) | 0.673 |
| Mean age (SD) | 61.3 (14.9) | 58.5 (14.2) | 67.1 (14.8) | 0.662 |
| <65 years | 105 (57.4%) | 80 (65.0%) | 25 (41.7%) | 0.003 |
| 65–75 years | 44 (24.0%) | 30 (24.4%) | 14 (23.3%) | 0.875 |
| >75 years | 34 (18.6%) | 13 (10.6%) | 21 (35%) | <0.001 |
| Hospital stay, days, Mean (SD) | 16.557 (14.8) | 16.528 (16.1) | 16.617 (11.7) | 0.966 |
| **Type of diagnostic test** | | | | |
| SARS CoV-2 PCR test | 178 (97.3%) | 120 (65.6%) | 58 (31.7%) | 0.728 |
| SARS CoV-2 Ag test | 3 (1.6%) | 2 (1.6%) | 1 (1.7%) | 0.984 |
| SARS CoV-2 Ab test | 2 (1.1%) | 1 (0.8%) | 1 (1.7%) | 0.602 |
| **Hospitalization service** | | | | |
| Emergency | 6 (3.3%) | 4 (3.2%) | 2 (3.3%) | 0.977 |
| Hospitalization | 80 (43.7%) | 69 (56.1%) | 11 (18.3%) | <0.001 |
| ICU | 97 (53%) | 50 (40.7%) | 47 (78.4%) | <0.001 |
| **Admission diagnosis** | | | | |
| Suspected COVID-19 | 160 (88.9%) | 110 (89.4%) | 50(83.3%) | 0.243 |
| Hospital contact † | 8 (4.4%) | 3 (2.4%) | 5 (8.3%) | 0.067 |
| Other diagnoses | 15 (8.2%) | 10 (8.1%) | 5 (8.3%) | 0.962 |
| **Comorbidities** | | | | |
| Arterial hypertension | 80 (43.7%) | 56 (45.5%) | 24 (40%) | 0.479 |
| Diabetes mellitus | 51 (27.9%) | 33 (26.8%) | 18 (30%) | 0.653 |
| Obesity | 46 (25.1%) | 29 (23.6%) | 17(28.3%) | 0.486 |
| Cancer | 32 ( 17.5% ) | 16 (13.0%) | 16 (26.7%) | 0.022 |
| Chronic kidney disease | 18 (9.8%) | 10 (8.1%) | 8 (13.3%) | 0.267 |
| Hypothyroidism | 18 (9.8%) | 11(8.9%) | 7(11.7%) | 0.561 |
| Cardiovascular disease (Ischemic heart disease, heart failure, cerebrovascular disease) | 25 (13.7%) | 12 (9.8%) | 13 (21.7%) | 0.028 |
| Respiratory diseases (COPD, Asthma) | 16 (8.7%) | 9 (7.3%) | 7 (11.7%) | 0.328 |
| Ex-smoker | 16 (8.7%) | 11(8.9%) | 5 (8.3%) | 0.891 |
| Other | 17 (9.3%) | 11 (8.9%) | 6 (10%) | 0.817 |
| **Complications** | | | | |
| Venous thromboembolism | 10 (5.5%) | 4 (3.3%) | 6 (10%) | 0.059 |
| Stroke | 4 (2.2%) | 1 (0.8%) | 3 (5%) | 0.069 |
| PE | 5 (2.7%) | 3 (2.4%) | 2 (3.3%) | 0.728 |
| Deep vein thrombosis | 1 (0.6%) | 0 | 1 (1.7%) | - |
| Need for invasive mechanical ventilation | 81 (44.3%) | 29 (23.6%) | 52 (86.7%) | <0.001 |
| Myocardial injury | 40 (21.9%) | 15 (12.2%) | 25 (41.7%) | <0.001 |
| Acute kidney injury | 46 (25.1%) | 20 (16.3%) | 26 (43.3%) | <0.001 |
| Need for renal replacement therapy | 32 (17.5%) | 9 (7.3%) | 23 (38.3%) | <0.001 |
| Superinfection | 107 (58.5%) | 55 (44.7%) | 52 (86.7%) | <0.001 |
| Transaminitis | 46 (25.1%) | 34 (27.6%) | 12 (20%) | 0.263 |
| Asystole | 56 (30.6%) | 0 | 56 (96.3%) | - |
| **Pharmacotherapy** | | | | |
| Ivermectin | 141 (77.1%) | 92 (74.8%) | 49 (81.7%) | 0.300 |
| Colchicine | 136 (74.3%) | 92 (74.8%) | 44 (73.3%) | 0.832 |
| Tocilizumab | 2 (1.1%) | 1 (0.8%) | 1 (1.7%) | 0.62 |
| Corticosteroids | 152 (83.1%) | 96 (78.1%) | 56 (93.3%) | 0.010 |
| Anticoagulants | 51 (27.9%) | 29 (23.6%) | 22 (36.7%) | 0.064 |
| Thromboprophylaxis | 129 (70.5%) | 91 (73.9%) | 38 (63.3%) | 0.138 |
| Norepinephrine | 46 (25.1%) | 13 (10.6%) | 33 (55%) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Vasopressin | 14 (7.7%) | 2 (1.6%) | 12 (20%) | <0.001 |
| Hydroxychloroquine | 21 (11.5%) | 12 (9.8%) | 9 (15%) | 0.296 |
| Lopinavir/ Ritonavir | 22 (12.0%) | 13 (10.6%) | 9 (15%) | 0.387 |
| Macrolides | 85 (46.5%) | 46 (37. 5%) | 39 (65%) | <0.001 |
| **Use of other antibiotics** | | | | |
| Total | 119 (65.0%) | 60 (48.8%) | 59 (98.3%) | <0.001 |
| >5 days treatment | 101 (84.9%) | 53 (88.3) | 48 (81.4) | 0.288 |
| Piperacillin Tazobactam | 72 (60.5%) | 39 (65%) | 33 (55.9%) | 0.312 |
| Ampicillin Sulbactam | 15 (12.6%) | 8 (13.3%) | 7 (11.9%) | 0.809 |
| Vancomycin | 11 (9.2%) | 3 (5%) | 8 (13.6%) | 0.107 |
| Meropenem | 9 (7.6%) | 5 (8.3%) | 4 (6.8%) | 0.749 |
| Ceftriaxone | 7 (5.9%) | 5 (8.3%) | 2 (3.4%) | 0.252 |
| Other | 5 (4.2%) | 1 (1.7%) | 4 (6.8%) | 0.165 |
| **Severity markers** | | | | |
| Ferritin (ng/ml) | | | | |
| ≥1000 | 96 (52.5%) | 61 (49.6%) | 25 (41.7%) | 0.313 |
| LDH (IU/L) | | | | |
| ≥350 | 89 (48.6%) | 54 (43.9%) | 35 (58.3%) | 0.067 |
| Lymphocytes | | | | |
| <1000 × $10^3$/µL | 95 (51.9%) | 51 (41.5%) | 44 (73.3%) | <0.001 |
| D-dimer (mcg/ml) | | | | |
| < 1000 | 91(49.7%) | 71(57.7%) | 20 (33.3%) | 0.002 |
| ≥ 1000 | 67(36.6%) | 38 (30.9%) | 29 (48.3%) | 0.022 |
| ≥ 3000 | 25 (13.7%) | 14 (11.4%) | 11(18.3%) | 0.199 |
| Troponin > 99p | 40 (21.9%) | 15 (12.2%) | 25 (41.7%) | <0.001 |
| $PaO_2/FiO_2$ at admission (%) | | | | |
| >100 | 23 (12.6%) | 12 (9.7%) | 11 (18.3%) | 0.1 |
| 100–200 | 35 (19.1%) | 19 (15.5%) | 16 (26.7%) | 0.07 |
| 200–300 | 61 (33.3%) | 41 (33.3%) | 20 (33.3%) | 1 |
| ≥300 | 64 (34.9%) | 51 (41.5%) | 13 (21.7%) | 0.008 |
| Procalcitonin (ng/mL) | | | | |
| ≥0.5 | 25 (13.7%) | 12 (9.8%) | 13 (21.7%) | 0.028 |
| Potassium (mEq/L) | | | | |
| 3.5–5.5 | 152 (83.1%) | 107 (86.9%) | 45 (75%) | 0.042 |
| ≤3.5 | 18 (9.8%) | 9 (7.3%) | 9 (15%) | 0.101 |
| ≥5.5 | 13 (7.1%) | 7 (5.7%) | 6 (10%) | 0.287 |
| Echocardiogram | 50 (27.3%) | 26 (21.1%) | 24 (40%) | 0.007 |
| LVEF < 40% | 3 (6 %) | 1 (3.8 %) | 2 (8.3 %) | 0.504 |
| LVEF: 40%–49% | 7 (14 %) | 3 (11.5 %) | 4 (16.7 %) | 0.602 |
| LVEF ≥ 50% | 40 (80 %) | 20 (76.9 %) | 20 (83.3 %) | 0.571 |
| Probability of pulmonary hypertension* | 9 (18 %) | 6 (23.1 %) | 3 (12.5 %) | 0.331 |
| Mild pericardial effusion | 3 (6 %) | 2 (7.7 %) | 1 (4.2 %) | 0.600 |
| CT angiography | 28 (15.3%) | 20 (16.3%) | 8 (13.3) | 0.606 |
| PE positive | 6 (21.4 %) | 4 (20%) | 2 (25%) | 0.771 |

*SD: standard deviation; PCR: polymerase chain reaction; COPD: chronic obstructive pulmonary disease; 99p: 99th percentile; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; PE: pulmonary embolism; ICU: intensive care unit; CT: computed tomography. † Hospital-acquired infection; * Defined according to tricuspid regurgitation velocity ≤ 2.8 m/s or not measurable, plus other echocardiographic findings.* ***Source:*** *Prepared by the authors.*

## Risk factors associated with mortality

To develop the final logistic model (183 subjects), a saturated model was started, adding variables with statistical significance in the crude associations or bivariate analysis, such as: age, hospitalization service, presence of comorbidity, history of cardiovascular disease and cancer, need for invasive mechanical ventilation and days of ventilation, myocardial injury, acute kidney injury, need for renal replacement therapy, superinfection, need for corticosteroids, vasopressin, norepinephrine, macrolides, use of other antibiotics, and severity markers.

Analysis of the results of the multiple logistic regression model enabled identification of individuals aged >75 years, those with a history of comorbidities (at least one), complications such as superinfection, and need for mechanical ventilation in days (> 2 days) as risk factors with statistical significance for a mortality event. The variability in hospital mortality events can be explained by these variables included in the final model in 33.4% of cases (Pseudo$R^2$) (Table 3).

**Table 2 – Electrocardiographic findings in patients hospitalized with COVID-19**

| Variables | Total (n = 160) | Survivors (n = 110) | Non-survivors (n = 50) | p value |
|---|---|---|---|---|
| **Electrocardiographic findings (%)** | | | | |
| Normal | 58 (36.3%) | 40 (36.4%) | 18 (36%) | 0.965 |
| Sinus tachycardia | 47 (29.4%) | 33 (30%) | 14 (28%) | 0.797 |
| Sinus bradycardia | 24 (15%) | 17 (15.5%) | 7 (14%) | 0.811 |
| Atrial fibrillation | 14 (8.8%) | 8 (7.3%) | 6 (12%) | 0.327 |
| First-degree AV block | 2 (1.3%) | 2 (1.8%) | 0 | |
| Right bundle branch block | 1 (0.6%) | 1 (0.9%) | 0 | |
| Repolarization abnormalities | 2 (1.3%) | 1 (0.9%) | 1 (2%) | 0.565 |
| ST-segment depression > 1 mm | 2 (1.3%) | 1 (0.9%) | 1 (2%) | 0.565 |
| Significant ST-segment elevation | 10 (6.3%) | 7 (6.4%) | 3 (6%) | 0.930 |
| **Heart rate, mean. (SD)** | **86.24 (21.49 )** | **85.71 (20.69)** | **87.4 (23.35)** | **0.662** |
| **PR interval (%)** | | | | |
| Normal | 124 (77.5%) | 85 (77.2%) | 39 (78%) | 0.919 |
| Short | 15 (9.4%) | 11 (10%) | 4 (8%) | 0.687 |
| Prolonged | 7 (4.36%) | 6 (5.5%) | 1 (2%) | 0.322 |
| Not applicable | 14 (8.8%) | 8 (7.3%) | 6 (12%) | 0.327 |
| **QRS complex (%)** | | | | |
| Normal | 125 (78.1%) | 86 (78.2%) | 39 (78%) | 0.979 |
| Narrow | 32 (20%) | 22 (20%) | 10 (20%) | 1 |
| Wide | 3 (1.9%) | 2 (1.8%) | 1 (2%) | 0.937 |

*AV: Atrioventricular; SD: standard deviation. Normal PR interval: 0.12 and 0.20 seconds, normal QRS complex: 0.08 to 0.12 seconds.*
***Source:*** *Prepared by the authors.*

Assessment of the final logistic regression model revealed a good fit to the data (Hosmer–Lemeshow) with a 5.5 (p = 0.86) Chi$^2$ (Degrees of freedom = 5). Differences between the expected and observed frequencies within the risk quantiles could not be confirmed; in other words, the observed and expected values were similar. Classification of the model indicated that it has a high ability to rule out patients who have no probability of mortality, with sensitivity and specificity of 74% and 83.6%, respectively. The probability of identifying a non-survivor among those predicted by the model was 67.27%. The probability of identifying a survivor among the patients who would not die according to the model was 87.6%.

## Discussion

The impact on the cardiovascular system generated by COVID-19 infection has been evident since the beginning of the pandemic and is currently considered one of the main extrapulmonary manifestations, increasing the risk of arrhythmias and myocardial injury associated with worse clinical outcomes.[12]

Among these outcomes, hospital mortality has varied over time according to the epidemiological behavior of the pandemic, which is associated with the scant knowledge of a new disease and the changes in the incidence of cases that are still observed. In addition, mortality is associated with confirmed myocardial injury, which has been reported to be up to 10 times higher.[13,14] In this regard, our study found a mortality rate that is 3.4 times higher than the general mortality of 32.8%, slightly exceeding the frequency of deaths reported in the literature (16%–30%).[15,16] On the other hand, the post-vaccination era has generated significant changes in the behavior of the disease, mentioning complications such as myocarditis, for which a sevenfold higher risk is described in unvaccinated subjects.[17]

The need for ICU management was strongly associated with worse outcomes; however, these can vary if risk factors, such as age, comorbidities, and the presence of complications are considered.[18] In this study, the proportion of patients who required an ICU stay was 53%. Among these, mortality related to myocardial injury was two times higher, which is statistically significant (p = 0.01). These results were demonstrated by the logistic regression model, in which variables such as age and the need for mechanical ventilation are significantly associated with a higher risk of mortality (OR > 1).

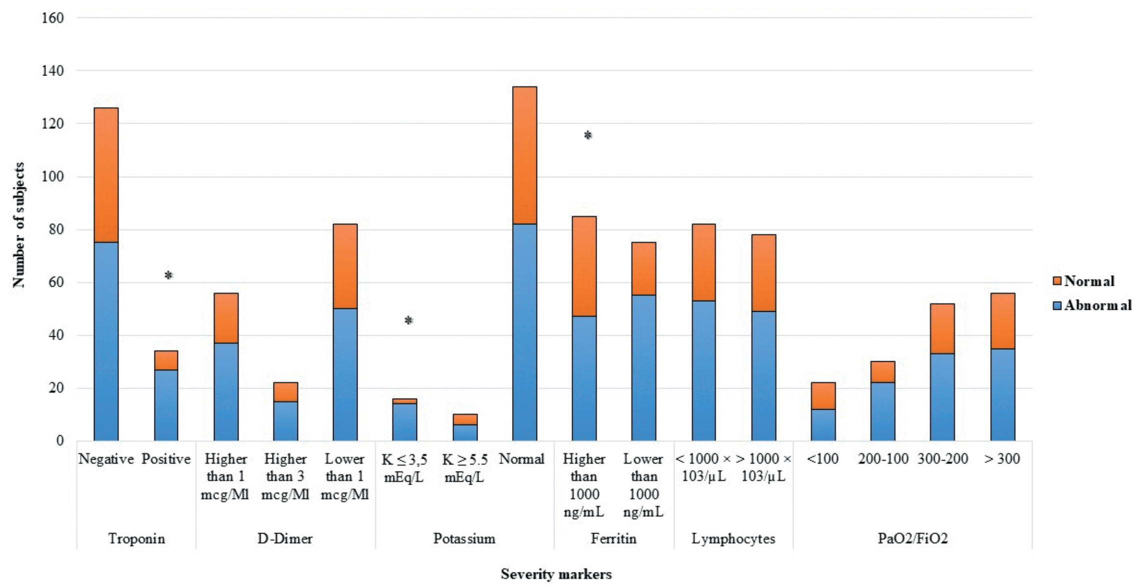



**Figure 2 – Behavior of the main biomakers in relation with electrocardiographic findings.**
**p value < 0.05.* ***Source:*** *Prepared by the autors.*

Notably, both myocardial injury and electrocardiographic changes have gained significant clinical importance, owing to their increasing association with hospital mortality, with a reported prevalence of up to 22% in this type of population.[19]

Male sex is one of the factors reported as having the highest risk of mortality among subjects with COVID-19 infection.[20,21] In our study, the number of men was 2 times higher than that of women, with no significant difference found in this regard.

Furthermore, age has been considered an incremental risk factor for mortality. A recent investigation found a higher frequency of deaths in subjects aged >75 years, which is possibly due to presence of comorbidities of cardiovascular origin, including cardiac arrhythmias.[22-24] This finding is consistent with that reported in our study, where a higher frequency of arterial hypertension was found among the deceased, followed by other cardiovascular antecedents and cancer.

Severe COVID-19 has been reported in up to 23% of cases[25] and is determined by multiorgan involvement. Kidney injury also represents an important factor; kidney involvement may be associated with greater cardiovascular dysfunction and the need for additional therapies. Acute kidney injury can vary and has been reported in 7%–30%[26,27] of cases. Our study found a high frequency, at 25%, with the need for renal replacement therapy in 17% of individuals.

Among the electrolyte changes, those related to potassium represent a prevalent factor during COVID-19 and are associated with greater severity; these are mediated by multiple pathophysiological mechanisms, with known repercussions for the cardiac conduction system.[28,29] Our study evidenced significant electrocardiographic changes with serum potassium levels of <3.5 mEq/L in 3.5% of cases (p = 0.037).

**Table 3 – Adjusted OR of the logistic regression model for mortality**

| Variable | Adjusted OR | 95% CI | p value |
|---|---|---|---|
| Age >75 years | 4.29 | 1.5-12.5 | 0.007 |
| Comorbidity | 5.09 | 1.5-17.6 | 0.010 |
| Invasive mechanical ventilation (>2 days) | 9.14 | 3.4-24.5 | <0.001 |
| Superinfection | 3.53 | 1.2-10.4 | 0.022 |

*CI: confidence interval; OR: odds ratio.* ***Source:*** *Prepared by the authors.*

Knowledge of cardiovascular involvement is increasing every day, including information recently described in Latin America and Colombia on the identification of arrhythmias or electrocardiographic findings as risk predictors,[30] such as identification of prolonged QT interval in up to 10% of patients at hospital admission, associated with almost double the risk of mortality.[8] In this sense, a 12-lead electrocardiogram enables early detection of findings, which are representative of cardiovascular system dysfunction. Besides, it constitutes an accessible, rapid, and cost-effective test for the care of patients with COVID-19.[31] Although these findings have not been fully established and may be variable, their presence represents the possibility of various complications, whether transient or permanent, including lethal arrhythmias.[32]

Within the literature, reports of these manifestations have been changing from a 94% frequency of normal electrocardiographic findings in cases at the beginning of the pandemic,[33] to abnormal findings in 26%–37% of cases over the course of the pandemic, given the greater knowledge regarding cardiovascular system compromise.[34,35] These were found mainly in critically ill subjects, among whom rates reached 90%.[36] Our study found the frequency of these abnormalities to be 64%, with sinus tachycardia and bradycardia being the disorders with the highest rates.

The incidence of arrhythmias detected only using electrocardiography has been reported as approximately 16%–20% of cases and the vast majority of them were of supraventricular origin,[37,38] with atrial fibrillation present in 3%–18% of the cases. Our study identified arrhythmias in 8.8% of the cases, with a higher risk of incidence in the presence of concurrent multiple comorbidities, thus increasing the risk of mortality;[39,40] findings that are very similar to contemporary Latin American studies.[9]

Current studies confirm the presence of these findings using telemetry devices, identifying at least one episode of arrhythmia in 73% of cases analyzed, with a possible increase during the evolution of the disease.[41]

Other findings, such as changes in the ST segment, have also been reported during COVID-19, either mimicking an acute coronary syndrome or as a manifestation of other cardiovascular complications, including myocarditis or pericarditis.[42]

Another important aspect is use of pharmacological therapies with effects on the cardiovascular system, such as macrolides and hydroxychloroquine, which have been reported in our study in 46.5% and 11.5% of cases, respectively, compared with the results of other studies that reported frequency of use of up to 80%.[43,44] These therapies are currently not recommended, as their benefit on the course of the disease[45] has not been proven; however, they do increase the prolongation of the QT interval produced by the infection itself, which has been reported in approximately 20% of the cases,[46,47] a finding that has not been evidenced in our study.

Regarding use of antibiotics, which has been reported in approximately 50% of cases,[48] mainly associated with respiratory system compromise due to the COVID-19 infection, this investigation observed a higher frequency (65%) and the most common indication was suspected bacterial superinfection, significantly affecting survival. Despite this, the coinfection rate reported in the literature is variable, ranging from 5% to 10%,[49] which could increase the risk in the local bacterial epidemiological profile.

### Limitations

This study has some limitations: First, it was conducted retrospectively, which is the reason why performing electrocardiogram at admission was not parameterized; in addition, the high risk of infection at the beginning of the pandemic should be taken into account and therefore the number of patients was lower than the total number of subjects with COVID-19 infections. Second, the electrocardiographic analysis presented corresponds to hospital admission, so it is not possible to confirm persistence of the initial findings reported, which could even be exacerbated in the context of other factors including pharmacological therapies used. However, we describe the acute electrocardiographic changes, including presence of arrhythmias such as atrial fibrillation which had not been previously diagnosed, although it is true that these could constitute existing asymptomatic arrhythmia. Third, exclusion of patients with known arrhythmia limits the description of the behavior of the event in this population.

## Conclusions

Patients with SARS CoV2 infection may present a heterogeneous group of complications, with cardiovascular complications being a frequent finding. This study describes presence of initial electrocardiographic changes in this population, including newly diagnosed arrhythmias such as atrial fibrillation and the presence of myocardial injury. Moreover, need for invasive mechanical ventilation for more than 48 hours, presence of comorbidities, superinfection, and age greater than 75 years were associated with mortality. Further studies are required to evaluate the behavior of these events over the medium and long terms, but they justify the use of cost-effective tools such as electrocardiograms as part of the initial approach and follow-up of patients with COVID 19.

## Author Contributions

Conception and design of the research: Galindes-Casanova DA, Benitez-Escobar EN, Melo-Burbano LA, Murillo-Benitez NE, Avila-Valencia JC; acquisition of data: Benitez-Escobar EN, Melo-Burbano LA; analysis and interpretation of the data: Galindes-Casanova DA, Benitez-Escobar EN, Melo-Burbano LA, Murillo-Benitez NE, Daza-Arana JE; statistical analysis: Galindes-Casanova DA, Benitez-Escobar EN, Melo-Burbano LA, Daza-Arana JE; obtaining financing: Daza-Arana JE; writing of the manuscript: Galindes-Casanova DA, Benitez-Escobar EN, Melo-Burbano LA, Avila-Valencia JC, Daza-Arana JE; critical revision of the manuscript for intellectual content: Galindes-Casanova DA, Benitez-Escobar EN, Melo-Burbano LA, Murillo-Benitez NE, Avila-Valencia JC, Daza-Arana JE.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

This study was funded by General Directorate of Research of Universidad Santiago de Cali under call No. 01-2022.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee on Animal Experiments of the Clinica de Occidente y Universidad Santiago de Cali under the protocol number IYECDO- 1369 del 22/02/2021 y Acta Nro 02 del 2 de febrero/2022.

## References

1. WHO Coronavirus (COVID-19) Dashboard. WHO Coronavirus (COVID-19) Dashboard with Vaccination Data [Internet]. Geneva: WHO; 2023 [cited 2023 May 15]. Available from: https://covid19.who.int/.
2. Yamamoto N, Nishida N, Yamamoto R, Gojobori T, Shimotohno K, Mizokami M, et al. Angiotensin-Converting Enzyme (ACE) 1 Gene Polymorphism and Phenotypic Expression of COVID-19 Symptoms. Genes (Basel). 2021;12(10):1572. doi: 10.3390/genes12101572.
3. Elrobaa IH, New KJ. COVID-19: Pulmonary and Extra Pulmonary Manifestations. Front Public Health. 2021;9:711616. doi: 10.3389/fpubh.2021.711616.
4. Hamouche W, Bisserier M, Brojakowska A, Eskandari A, Fish K, Goukassian DA, et al. Pathophysiology and Pharmacological Management of Pulmonary and Cardiovascular Features of COVID-19. J Mol Cell Cardiol. 2021;153:72-85. doi: 10.1016/j.yjmcc.2020.12.009.
5. Sato K, Sinclair JE, Sadeghirad H, Fraser JF, Short KR, Kulasinghe A. Cardiovascular Disease in SARS-CoV-2 Infection. Clin Transl Immunology. 2021;10(9):e1343. doi: 10.1002/cti2.1343.
6. Manolis AS, Manolis AA, Manolis TA, Apostolopoulos EJ, Papatheou D, Melita H. COVID-19 Infection and Cardiac Arrhythmias. Trends Cardiovasc Med. 2020;30(8):451-60. doi: 10.1016/j.tcm.2020.08.002.
7. Wetterslev M, Jacobsen PK, Hassager C, Jøns C, Risum N, Pehrson S, et al. Cardiac Arrhythmias in Critically Ill Patients with Coronavirus Disease 2019: A retrospective Population-Based Cohort Study. Acta Anaesthesiol Scand. 2021;65(6):770-7. doi: 10.1111/aas.13806.
8. Barbosa S, Muñoz OM, Cañas A, Garcia AA. Prolongation of the QTc Interval at Admission is Associated with Increased Mortality in Patients with SARS-COV-2 During Hospitalization. Arq Bras Cardiol. 2023;120(1):e20220155. doi: 10.36660/abc.20220155.
9. Pimentel M, Magalhães APA, Novak CV, May BM, Rosa LGBD, Zimerman LI. Cardiac Arrhythmias in Patients with COVID-19. Arq Bras Cardiol. 2021;117(5):1010-5. doi: 10.36660/abc.20200963.
10. Gutiérrez AB, Rodriguez-Morales AJ, Mejia AJN, Peña AAG, Montoya AAG, Muñoz AJC, et al. Consenso Colombiano de Atención, Diagnóstico y Manejo de la Infección por SARS-CoV2/COVID 19 en Establecimiento de Atención de la Salud. Infectio. 2021;25(4):1-102 doi: 10.22354/IN.V25I4.973.
11. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram: Part IV: The ST Segment, T and U Waves, and the QT Interval: A Scientific Statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53(11):982-91. doi: 10.1016/j.jacc.2008.12.014.
12. Saha SA, Russo AM, Chung MK, Deering TF, Lakkireddy D, Gopinathannair R. COVID-19 and Cardiac Arrhythmias: a Contemporary Review. Curr Treat Options Cardiovasc Med. 2022;24(6):87-107. doi: 10.1007/s11936-022-00964-3.
13. Si D, Du B, Ni L, Yang B, Sun H, Jiang N, et al. Death, Discharge and Arrhythmias among Patients with COVID-19 and Cardiac Injury. CMAJ. 2020;192(28):E791-E798. doi: 10.1503/cmaj.200879.
14. Ghio S, Baldi E, Vicentini A, Lenti MV, Di Sabatino A, Di Matteo A, et al. Cardiac Involvement at Presentation in Patients Hospitalized with COVID-19 and their Outcome in a Tertiary Referral Hospital in Northern Italy. Intern Emerg Med. 2020;15(8):1457-65. doi: 10.1007/s11739-020-02493-y.

15. Dagher L, Shi H, Zhao Y, Wetherbie A, Johnsen E, Sangani D, et al. New-Onset Atrial Arrhythmias Associated with Mortality in Black and White Patients Hospitalized with COVID-19. Pacing Clin Electrophysiol. 2021;44(5):856-64. doi: 10.1111/pace.14226.

16. Peltzer B, Manocha KK, Ying X, Kirzner J, Ip JE, Thomas G, et al. Outcomes and Mortality Associated with Atrial Arrhythmias among Patients Hospitalized with COVID-19. J Cardiovasc Electrophysiol. 2020;31(12):3077-85. doi: 10.1111/jce.14770.

17. Voleti N, Reddy SP, Ssentongo P. Myocarditis in SARS-CoV-2 Infection vs. COVID-19 Vaccination: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2022;9:951314. doi: 10.3389/fcvm.2022.951314.

18. Gray WK, Navaratnam AV, Day J, Babu P, Mackinnon S, Adelaja I, et al. Variability in COVID-19 In-Hospital Mortality Rates between National Health Service Trusts and Regions in England: A National Observational Study for the Getting It Right First Time Programme. EClinicalMedicine. 2021;35:100859. doi: 10.1016/j.eclinm.2021.100859.

19. Sato K, Sinclair JE, Sadeghirad H, Fraser JF, Short KR, Kulasinghe A. Cardiovascular Disease in SARS-CoV-2 Infection. Clin Transl Immunology. 2021;10(9):e1343. doi: 10.1002/cti2.1343.

20. Ya'qoub L, Elgendy IY, Pepine CJ. Sex and Gender Differences in COVID-19: More to be Learned! Am Heart J Plus. 2021;3:100011. doi: 10.1016/j.ahjo.2021.100011.

21. Marik PE, DePerrior SE, Ahmad Q, Dodani S. Gender-Based Disparities in COVID-19 Patient Outcomes. J Investig Med. 2021;jim-2020-001641. doi: 10.1136/jim-2020-001641.

22. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10. doi: 10.1001/jamacardio.2020.0950.

23. Roth GA, Emmons-Bell S, Alger HM, Bradley SM, Das SR, de Lemos JA, et al. Trends in Patient Characteristics and COVID-19 In-Hospital Mortality in the United States During the COVID-19 Pandemic. JAMA Netw Open. 2021;4(5):e218828. doi: 10.1001/jamanetworkopen.2021.8828.

24. Nogueira PJ, de Araújo Nobre M, Elias C, Feteira-Santos R, Martinho AC, Camarinha C, et al. Multimorbidity Profile of COVID-19 Deaths in Portugal During 2020. J Clin Med. 2022;11(7):1898. doi: 10.3390/jcm11071898.

25. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: A Systematic Review and Meta-Analysis of Clinical Characteristics, Risk Factors, and Outcomes. J Med Virol. 2021;93(3):1449-58. doi: 10.1002/jmv.26424.

26. Zheng KI, Feng G, Liu WY, Targher G, Byrne CD, Zheng MH. Extrapulmonary Complications of COVID-19: A Multisystem Disease? J Med Virol. 2021;93(1):323-35. doi: 10.1002/jmv.26294.

27. Sabaghian T, Kharazmi AB, Ansari A, Omidi F, Kazemi SN, Hajikhani B, et al. COVID-19 and Acute Kidney Injury: A Systematic Review. Front Med (Lausanne). 2022;9:705908. doi: 10.3389/fmed.2022.705908.

28. Chen D, Li X, Song Q, Hu C, Su F, Dai J, et al. Assessment of Hypokalemia and Clinical Characteristics in Patients with Coronavirus Disease 2019 in Wenzhou, China. JAMA Netw Open. 2020;3(6):e2011122. doi: 10.1001/jamanetworkopen.2020.11122.

29. Noori M, Nejadghaderi SA, Sullman MJM, Carson-Chahhoud K, Kolahi AA, Safiri S. Epidemiology, Prognosis and Management of Potassium Disorders in Covid-19. Rev Med Virol. 2022;32(1):e2262. doi: 10.1002/rmv.2262.

30. Mora G. COVID-19 y Arritmias: Relación y Riesgo. Rev Colomb Cardiol. 2020; 27(3):153-9. doi:10.1016/j.rccar.2020.05.004.

31. Mele M, Tricarico L, Vitale E, Favia A, Croella F, Alfieri S, et al. Electrocardiographic Findings and Mortality in Covid-19 Patients Hospitalized in Different Clinical Settings. Heart Lung. 2022;53:99-103. doi: 10.1016/j.hrtlng.2022.02.007.

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

33. 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(7):626-32. doi: 10.1016/j.cardfail.2020.06.005.

34. Angeli F, Spanevello A, De Ponti R, Visca D, Marazzato J, Palmiotto G, et al. Electrocardiographic Features of Patients with COVID-19 Pneumonia. Eur J Intern Med. 2020;78:101-6. doi: 10.1016/j.ejim.2020.06.015.

35. Lanza GA, De Vita A, Ravenna SE, D'Aiello A, Covino M, Franceschi F, et al. Electrocardiographic Findings at Presentation and Clinical Outcome in Patients with SARS-CoV-2 Infection. Europace. 2021;23(1):123-9. doi: 10.1093/europace/euaa245.

36. Long B, Brady WJ, Bridwell RE, Ramzy M, Montrief T, Singh M, et al. Electrocardiographic Manifestations of COVID-19. Am J Emerg Med. 2021;41:96-103. doi: 10.1016/j.ajem.2020.12.060.

37. Patel NH, Rutland J, Tecson KM. Arrhythmias and Intraventricular Conduction Disturbances in Patients Hospitalized with Coronavirus Disease 2019. Am J Cardiol. 2022;162:111-5. doi: 10.1016/j.amjcard.2021.08.052.

38. Denegri A, Sola M, Morelli M, Farioli F, Alberto T, D'Arienzo M, et al. Arrhythmias in COVID-19/SARS-CoV-2 Pneumonia Infection: Prevalence and Implication for Outcomes. J Clin Med. 2022;11(5):1463. doi: 10.3390/jcm11051463.

39. Kaliyaperumal D, Bhargavi K, Ramaraju K, Nair KS, Ramalingam S, Alagesan M. Electrocardiographic Changes in COVID-19 Patients: A Hospital-Based Descriptive Study. Indian J Crit Care Med. 2022;26(1):43-8. doi: 10.5005/jp-journals-10071-24045.

40. Mountantonakis SE, Saleh M, Fishbein J, Gandomi A, Lesser M, Chelico J, et al. Atrial Fibrillation is an Independent Predictor for In-Hospital Mortality in Patients Admitted with SARS-CoV-2 Infection. Heart Rhythm. 2021;18(4):501-7. doi: 10.1016/j.hrthm.2021.01.018.

41. Reynbakh O, Braunstein ED, Hsu M, Ellis J, Crosson L, Lenane J, et al. Arrhythmia Patterns During and After Hospitalization for COVID-19 Infection Detected Via Patch-Based Mobile Cardiac Telemetry. Am Heart J Plus. 2022;13:100084. doi: 10.1016/j.ahjo.2022.100084.

42. Diaz-Arocutipa C, Torres-Valencia J, Saucedo-Chinchay J, Cuevas C. ST-Segment Elevation in Patients with COVID-19: A Systematic Review. J Thromb Thrombolysis. 2021;52(3):738-45. doi: 10.1007/s11239-021-02411-9.

43. Pothen L, Yildiz H, De Greef J, Penaloza A, Beauloye C, Belkhir L, et al. Safe use of Hydroxychloroquine and its Combination with Azithromycin in the Context of Sars-CoV-2 Outbreak: Clinical Experience in a Belgian Tertiary Center. Travel Med Infect Dis. 2020;36:101788. doi: 10.1016/j.tmaid.2020.101788.

44. Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 Patients Treated with Hydroxychloroquine/Azithromycin and Other Regimens in Marseille, France: A Retrospective Analysis. Travel Med Infect Dis. 2020;36:101791. doi: 10.1016/j.tmaid.2020.101791.

45. Sivapalan P, Ulrik CS, Lapperre TS, Bojesen RD, Eklöf J, Browatzki A, et al. Azithromycin and Hydroxychloroquine in Hospitalised Patients with Confirmed COVID-19: A Randomised Double-Blinded Placebo-Controlled Trial. Eur Respir J. 2022;59(1):2100752. doi: 10.1183/13993003.00752-2021.

46. Rubin GA, Desai AD, Chai Z, Wang A, Chen Q, Wang AS, et al. Cardiac Corrected QT Interval Changes among Patients Treated for COVID-19 Infection During the Early Phase of the Pandemic. JAMA Netw Open. 2021;4(4):e216842. doi: 10.1001/jamanetworkopen.2021.6842.

47. Eftekhar SP, Kazemi S, Barary M, Javanian M, Ebrahimpour S, Ziaei N. Effect of Hydroxychloroquine and Azithromycin on QT Interval Prolongation and Other Cardiac Arrhythmias in COVID-19 Confirmed Patients. Cardiovasc Ther. 2021;2021:6683098. doi: 10.1155/2021/6683098.

48. Giannella M, Rinaldi M, Tesini G, Gallo M, Cipriani V, Vatamanu O, et al. Predictive Model for Bacterial Co-Infection in Patients Hospitalized for COVID-19: A Multicenter Observational Cohort Study. Infection. 2022;50(5):1243-53. doi: 10.1007/s15010-022-01801-2.

49. Omoush SA, Alzyoud JAM. The Prevalence and Impact of Coinfection and Superinfection on the Severity and Outcome of COVID-19 Infection: An Updated Literature Review. Pathogens. 2022;11(4):445. doi: 10.3390/pathogens11040445.