Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Cardiothoracic and Vascular Anesthesia 36 (2022) 2927–2934

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Electrocardiographic Features and Outcome: Correlations in 124 Hospitalized Patients With COVID-19 and Cardiovascular Events

Pavani Nathala, MBBS[*], Vidyulata Salunkhe, MBBS, MPH[*], Harideep Samanapally, MBBS[*], Qian Xu, MS[†], Stephen Furmanek, MS[*], Omar H. Fahmy, MD[*], Fnu Deepti, BDS, MPH[*], Alex Glynn, MA[*], Trevor McGuffin, BSN[‡], Dylan C. Goldsmith[§], Jessica Petrey, MLS[‖], Tshura Ali, PhD, MPH[*], Derek Titus, DO[¶], Ruth Carrico, PhD[*], Julio Ramirez, MD[*], Demetra Antimisiaris, PharmD[**], Sean P. Clifford, MD[¶], Siddharth Pahwa, MD[††], Lynn Roser, PhD[§], Maiying Kong, PhD[†], Jiapeng Huang, MD, PhD[*,¶,**,††,‡‡,1], Center of Excellence for Research in Infectious Diseases (CERID) Coronavirus Study Group on behalf of the COVID-19 Cardiovascular Research Group (COVID-CVRG)

[*]*Division of Infectious Diseases, Center of Excellence for Research in Infectious Diseases, University of Louisville, Louisville, KY*
[†]*Department of Bioinformatics and Biostatistics, School of Public Health and Information Sciences, University of Louisville, Louisville, KY*
[‡]*School of Nursing, University of Louisville, Louisville, KY*
[§]*School of Medicine, University of Louisville, Louisville, KY*
[‖]*Kornhauser Health Sciences Library, University of Louisville, Louisville, KY*
[¶]*Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY*
[**]*Department of Pharmacology & Toxicology, University of Louisville, Louisville, KY*
[††]*Department of Cardiovascular & Thoracic Surgery, University of Louisville, Louisville, KY*
[‡‡]*Center for Integrative Environmental Health Sciences, University of Louisville, Louisville, KY*

Objectives: Electrocardiographic (ECG) changes have been associated with coronavirus disease 2019 (COVID-19) severity. However, the progression of ECG findings in patients with COVID-19 has not been studied. The purpose of this study was to describe ECG features at different stages of COVID-19 cardiovascular (CV) events and to examine the effects of specific ECG parameters and cardiac-related biomarkers on clinical outcomes in COVID-19.

Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number U18TR003787, NIH P30 (P30ES030283) grant, and Gilead Sciences COMMIT COVID-19 RFP Program grant (Gilead IN-US-983-6063). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Gilead Sciences.

P. Nathala, V. Salunkhe, H. Samanapally, and Q. Xu contributed equally to this article. L. Roser, M. Kong, and J. Huang contributed equally to this article.

[1]Address correspondence to Jiapeng Huang, MD, PhD, Department of Anesthesiology and Perioperative Medicine, University of Louisville, 530 South Jackson Street, Louisville, KY 40202.

E-mail address: jiapeng.huang@louisville.edu (J. Huang).

https://doi.org/10.1053/j.jvca.2022.01.011

Design: Retrospective, cohort study.
Setting: Major tertiary-care medical centers and community hospitals in Louisville, KY.
Participants: A total of 124 patients with COVID-19 and CV events during hospitalization.
Interventions: None.
Measurements and Main Results: Twelve-lead ECG parameters, biomarkers of cardiac injuries, and clinical outcomes were analyzed with Spearman correlation coefficients and Kruskal-Wallis 1-way analysis of variance. Atrial fibrillation/atrial flutter was more frequent on the ECG obtained at the time of the CV event when compared with admission ECG (9.5% *v* 26.9%; p = 0.007). Sinus tachycardia was higher in the last available hospital ECG than the CV event ECG (37.5% *v* 20.4%; p = 0.031). Admission ECG-corrected QT interval was significantly associated with admission troponin levels (R = 0.52; p < 0.001). The last available hospital ECG showed nonsurvivors had longer QRS duration than survivors (114.6 *v* 91.2 ms; p = 0.026), and higher heart rate was associated with longer intensive care unit length of stay (Spearman ρ = 0.339; p = 0.032).
Conclusions: In hospitalized patients with COVID-19 and CV events, ECGs at various stages of COVID-19 hospitalization showed significantly different features with dissimilar clinical outcome correlations.

Key Words: COVID-19; SARS-CoV-2; cardiovascular events; mortality; electrocardiogram; ECG

THE CORONAVIRUS disease 2019 (COVID-19) pandemic continues to be the leading cause of mortality and morbidity throughout the world, with more than 229 million infections and 4.7 million deaths as of September 21, 2021.[1] In the United States alone, more than 40 million people have been infected, and more than 670,000 people have died.[2] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel strain of coronavirus that causes COVID-19, most notably is known to cause severe respiratory disease.[3] However, COVID-19 also is known to cause multiorgan dysfunction, with the cardiovascular system being a significant target.[4-7] Emerging data suggest that cardiac complications occur in as many as 40% of hospitalized patients.[6] Those hospitalized with severe COVID-19 who develop cardiovascular complications have higher mortality, longer length of stay (LOS), and worse prognosis than those who do not experience cardiac complications.[8,9]

A multitude of heart pathologies have been described in association with SARS-CoV-2 infections. Implicated mechanisms of cardiac involvement include: myocardial ischemia secondary to hypoxic state, COVID-19–associated hypercoagulability and resultant microvascular thrombotic complications, cytokine storm, direct viral inflammatory effect, and drug-induced cardiac damage.[10-12] Electrocardiographic (ECG) changes have been correlated with infection severity.[7,13-15] Clinical outcome measures, including admission to intensive care,[14] mechanical ventilation requirement,[14] acute respiratory distress syndrome,[7,15-17] acute renal failure requiring renal replacement therapy,[7,14] and all-cause mortality,[14,16,17] were higher in patients with abnormal ECGs.

The Center of Excellence for Research in Infectious Diseases (CERID) recently analyzed 702 adult patients with COVID-19 hospitalized between March 2020 and June 2020, in a U.S. metropolitan area, and identified 124 patients with cardiovascular (CV) events.[18] Patients with CV events had a much higher mortality rate at 45.2% than those without CV events at 8.7%.[18] The null hypothesis for this project was there are no significant differences among ECGs at admission, CV events, and discharge (death or out of hospital). The purpose of this study was to investigate the ECG features in patients with COVID-19 and CV events at 3 distinct phases of hospitalization: at admission, during the acute CV event, and approaching discharge or death.

Methods

Study Design and Setting

The clinical data used in this study were from the Burden of COVID-19 study, an observational retrospective cohort database maintained by CERID at the University of Louisville.[18-20] The Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies was followed, and the checklist is attached in supplemental material. The primary aim was to describe ECG features at different stages of hospitalization during COVID-19 CV events. The secondary aim was to examine the effects of specific ECG parameters and cardiac-related biomarkers on clinical outcomes in COVID-19.

Human Subjects Protection

The Burden of COVID-19 study, including subsequent research using the database, was approved by the University of Louisville Institutional Review Board (#20-0257). Information from the patients' electronic health records (EHR) was entered into a secure database (REDCap) and is compliant with the Health Insurance Portability and Accountability Act. Patient data were secure through the use of standard data security measures and approved by the institutional review boards of all participating hospitals to protect and safeguard the private healthcare information of all patients.

Patient Cohort and Study Setting

Data from 702 adult inpatients hospitalized with COVID-19 from March 9, 2020, to June 20, 2020, at all 9 adult hospitals in the Louisville metro area, were reviewed. All hospitalized

patients with a diagnosis of COVID-19—as defined by a positive reverse transcriptase-polymerase chain reaction on the first or the repeat test and/or ground glass opacities on a chest computerized tomography—met the inclusion criteria for the study. Patients with COVID-19 seen in the emergency department who were not admitted as a hospital inpatient were excluded from this study.

Data Collection

Data were abstracted from the EHRs of hospitalized patients diagnosed with COVID-19. A comprehensive data abstraction instrument was developed by physicians, nurses, epidemiologists, biostatisticians, public health professionals, and research assistants who were members of the CERID study group. Trained researchers (P.N., V.S., and H.S.) collected information from the patients' EHRs on COVID-19 test results, past medical history, social history, symptoms of current illness, medications, physical examination, management and therapies, radiologic and laboratory data, clinical course of hospitalization, complications, and outcomes. Only CV events occurring after admission to the hospital were considered in the analysis. CV events included heart failure, cardiogenic shock, acute myocardial infarction, cardiomyopathy, myocarditis, cardiac arrhythmias (including tachycardia, bradycardia, supraventricular tachycardia, atrial tachycardia, and bundle-branch blocks), cerebrovascular events, pulmonary embolism, pulmonary edema, deep vein thrombosis, and cardiac arrest. Clinical diagnoses of CV events were made independently by individual physicians at each site. The authors planned to use sensitive cardiac injury/function biomarkers (troponin and B-type natriuretic peptide [BNP]) as short-term outcome measures; and mortality, hospital LOS, and intensive care unit (ICU) LOS as long-term outcome measures.

ECG data assumed normal calibration of ECG paper at 25 mm/s and 1 mV equivalent to 10 mm. Results from ECGs were collected from EHRs through abstraction of confirmed 12-lead ECG results by experienced researchers. First ECG was defined as the earliest available ECG in a patient's EHRs at admission, CV event−triggered ECG was defined as the ECG within 24 hours of a clinically diagnosed CV event, and final ECG was defined as the last recorded ECG before discharge or death.

ECG abnormality was defined as any irregularity in rhythm, left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH), atrioventricular (AV) block, or ST changes. Rhythm information from ECGs included sinus rhythm, sinus tachycardia, atrial fibrillation, atrial flutter, AV blocks (none, first-degree block, second-degree type I heart block, second-degree type II heart block, third-degree heart block), left bundle-branch block, and right bundle-branch block. Collected ECG parameters included P-R segment duration (normal range, 120-200 ms), QRS duration (normal range, 80-100 ms), corrected QTinterval (QTc), presence of pathologic Q-wave (>40 ms wide, >2 mm deep, or >25% of QRS depth), ST-segment elevation, and depression indicative of ischemia (voltage >0.1 mV greater than or less than baseline). Other measurements for analysis included evidence of LVH using Sokolov-Lyon criteria (S wave depth in precordial lead V1 plus tallest R wave height in precordial leads V5-V6 >35 mm) and evidence of RVH (right axis deviation >90° or 110° with larger R and smaller S waves in leads V1 and V2).[21]

Laboratory data included the first and highest (peak) levels of troponin, as well as BNP and N-terminal pro BNP (NT-pro BNP) levels. Measurements of BNP and NT-pro BNP were converted to 1 standard unit of measurement for comparison because hospitals used either BNP or NT-pro BNP, not both. BNP measurement of 1 pg/mL is equivalent to 0.289 pmol/L, and NT-pro BNP measurement of 1 pg/mL is equivalent to 0.118 pmol/L.[22]

Clinical Outcome Variables

Clinical outcome variables included mortality (date of death and number of days from hospital admission to mortality), hospital LOS, and ICU LOS.

Data Analysis

Descriptive statistics were reported; continuous variables were summarized as mean and standard deviation (SD), and categorical variables were summarized as counts and percentages. To examine the association between ECG parameters and troponin/BNP values, Spearman correlation coefficients were used to evaluate the association between 2 continuous variables, and Kruskal−Wallis 1-way analysis of variance was conducted to examine the association between a categorical variable and a continuous outcome variable.[23] To examine whether ECG parameters were associated with mortality (eg, patients discharged alive or not), Mann-Whitney U tests were used for continuous ECG parameters and chi-square tests or Fisher exact tests for categorical ECG parameters. Generalized mixed-effect models were used to examine whether ECG parameters changed over time. In particular, logistic mixed-effect models were used to examine the time effect for categorical ECG parameters, and linear mixed-effect models were used to examine time effect for continuous ECG parameters.[24] In the generalized linear mixed-effect models, each subject was considered as a random effect. The intraindividual variations were captured by the random effects, and the interindividual variations were captured by the individual-level covariates; p Values <0.05 were considered statistically significant. Statistical analyses were conducted using R version 4.0.2 software (R Foundation for Statistical Computing). This complex data analysis was carried out by a PhD student in biostatistics (Q.X.) under the supervision of Maiying Kong, professor in bioinformatics and biostatistics at the University of Louisville.

Results

The sample population consisted of 702 hospitalized patients with COVID-19, 124 of whom had a CV event. Among the 124 patients with a CV event, 22 patients (17.7%)

had heart failure, 19 (15.3%) had cardiac arrest, 14 (11.3%) had cardiogenic shock, 15 (12.1%) had acute myocardial infarction, 12 (9.7%) had pulmonary edema, 54 (43.5%) had new serious arrhythmias, 19 (15.3%) had acute worsening of long-term arrhythmia, 7 (5.6%) had cerebrovascular accidents, 8 (6.5%) had pulmonary embolism, 2 (1.6%) had myocarditis, and 6 (4.8%) had deep venous thrombosis. Preexisting cardiac comorbidities in hospitalized patients with COVID-19 and CV events and in hospitalized patients with COVID-19 without CV events are summarized in Supplementary Table 1. The group with CV events showed significantly higher incidences of all preexisting cardiac comorbidities than the group without CV events except deep venous thrombosis. Among the 124 patients, 86 required ICU care. Fifteen patients received noninvasive mechanical ventilation, and 69 patients needed invasive mechanical ventilation.

Table 1 summarizes the ECG parameters in first, CV event–triggered, and final ECGs. Normal sinus rhythm was significantly more common in the first ECG compared with the CV event–triggered ECG (59.5% *v* 42.6%; p = 0.023). Atrial fibrillation or atrial flutter was more frequent in the CV event–triggered ECG compared with the first ECG (9.5% *v* 26.9%; p = 0.007). Sinus tachycardia was significantly more frequent in the final ECG than in the CV event–triggered ECG (37.5% *v* 20.4%; p = 0.031). Interestingly, the authors found that QRS duration was significantly longer in the CV event–triggered ECG than in the final ECG (107.364 ± 30.2 ms *v* 105.59 ± 30.3 ms; p = 0.047), and the rate of AV block was significantly higher in the CV event–triggered ECG than in the final ECG (31.5% *v* 17.5%; p = 0.018).

Table 2, Supplemental Table 2, and Supplemental Table 3 show the associations among the ECG parameters of first, event-triggered, and final ECG and mortality, ICU LOS, and hospital LOS. For the first ECG, hospital and ICU LOS were significantly longer for patients with normal sinus rhythm than in those with atrial fibrillation or atrial flutter (11.45 *v* 7.61 days for hospital LOS and 6.75 *v* 0.62 days for ICU LOS, respectively; Table 3). For the final ECG, nonsurvivors had much longer QRS duration than survivors (114.6 *v* 91.2 ms; p = 0.026; Supplemental Table 2), and a higher heart rate was significantly associated with longer ICU LOS with a Spearman correlation coefficient of 0.339 (p = 0.032, Supplemental Table 3).

First troponin values were compared between patients with and without an ECG abnormality in the first ECG. There was no significant difference in first troponin level among those with and without an ECG abnormality (Table 4). Supplemental Table 4 showed the correlation coefficients for continuous ECG parameters of the first ECG. QTc was significantly associated with the first troponin levels (R value = 0.52, p < 0.001).

Table 3 showed a comparison of peak troponin values between patients with and without ECG abnormality in rhythm, LVH, RVH, AV block, or ST changes. Peak troponin levels of patients with atrial fibrillation or atrial flutter were significantly lower than those with normal sinus rhythm (0.073 ± 0.1 *v* 0.681 ± 1.3; p = 0.043) (Table 3). There were no significant correlations between peak troponin levels and CV event–triggered ECG parameters (heart rate, P-R interval, QTc, and QRS duration; Supplemental Table 5).

The effects of the first troponin, peak troponin, and BNP levels on mortality, ICU LOS, and hospital LOS for all 702 patients are summarized in Table 5. Levels of first troponin (1.256 ± 11 *v* 0.116 ± 0.6 ng/mL; p < 0.001), peak troponin (0.389 ± 1 *v* 0.311 ± 0.8 ng/mL; p < 0.001), and BNP (1733.718 ± 4536.2 *v* 565.063 ± 2909 pmol/L; p = 0.011) were higher in patients who died in the hospital. First troponin levels were significantly correlated with both hospital LOS (R = 0.165; p < 0.001) and ICU LOS (R = 0.172; p < 0.001). Peak troponin levels were significantly correlated with ICU LOS (R = 0.301; p = 0.001). BNP was significantly correlated with both hospital LOS (R = 0.204; p < 0.001) and ICU LOS (R = 0.212; p < 0.001).

Table 1
Summarized ECG Parameters in the First ECGs, Event-Triggered ECGs, and Final ECGs

Sample sizes	First ECG n = 74	ET ECG n = 108	Final ECG n = 40	p Value for First versus ET	p Value for Final versus ET
Rhythm, n (%)					
Normal sinus	44 (59.5%)	46 (42.6%)	17 (42.5%)	0.023*	0.919
Atrial Fibrillation/flutter	7 (9.5%)	29 (26.9%)	5 (12.5%)	0.007*	0.167
Sinus tachycardia	20 (27.0%)	22 (20.4%)	15 (37.5%)	0.285	0.031*
Other	3 (4.1%)	11(10.2%)	3 (7.5%)	0.155	0.056
Heart rate, mean (SD), bpm	94 (22.7)	100.31(30.3)	95.9 (24)	0.081	0.530
P-R interval, mean (SD), ms	169.3 (73.3)	156.9 (35.5)	144.9 (38)	0.096	0.268
QTc, mean (SD), ms	457.7 (38.6)	469.4 (40.7)	463.8 (46.7)	0.080	0.317
QRS duration, mean (SD), ms	104.0 (26.7)	107.4 (30.2)	105.6 (30.3)	0.898	0.047*
Q-wave, n (%)	0 (0%)	1 (0.9%)	0 (0%)	0.991	0.996
LVH, n (%)	8 (10.8%)	9 (8.3%)	3 (7.5%)	0.103	0.695
RVH, n (%)	1 (1.4%)	0 (0%)	0 (0%)	0.999	0.995
AV block, n (%)	21 (28.4%)	34 (31.5%)	7 (17.5%)	0.441	0.018*
ST changes, n (%)	3 (4.1%)	10 (9.3%)	6 (15%)	0.259	0.252

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; ET, event-triggered; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.
* p Value <0.05.

Table 2
Summary of Statistics Among ECG Parameters at Each Time Point (First, Event-Triggered, and Final ECG) and Outcome Variables in Terms of ICU Length of Stay and Hospital Length of Stay

	First ECG			Event-Triggered ECG			Final ECG		
	n	Hospital LOS, median (IQR)	p Value	n	Hospital LOS, median (IQR)	p Value	n	Hospital LOS, median (IQR)	p Value
All rhythms	74	11.29* (7.42, 18.18)		108	9.02* (5.87, 15.24)		40	10.29* (6.16, 17.95)	
Normal sinus	44	11.45 (7.13, 18.09)	0.004†,‡	46	8.63 (4.79, 14.51)	0.668†	17	8.90 (5.17, 17.86)	0.7868†
Atrial fibrillation /flutter	7	7.61 (5.97, 7.70)	0.012‡,§	29	10.94 (7.35, 16.45)	0.336§	5	11.33 (8.92, 12.02)	0.7616§
Sinus tachycardia	20	14.87 (9.34, 23.51)	0.159§	22	7.98 (5.34, 14.66)	0.964§	15	10.25 (7.53, 34.43)	0.331§
Other	3	5.65 (5.36, 7.42)	0.088§	11	9.18 (6.10, 18.91)	0.407§	3	10.32 (7.26, 17.19)	0.999§
	n	ICU LOS, median (IQR)	p Value	n	ICU LOS, median (IQR)	p Value	n	ICU LOS, median (IQR)	p Value
All rhythms	74	6.10§ (1.91, 12.33)		108	4.60§ (0, 11.11)		40	8.11§ (3.54, 13.22)	
Normal sinus	44	6.75 (1.82, 12.94)	0.008†,‡	46	4.74 (0,11.12)	0.917†	17	4.43 (0.72, 11.05)	0.261†
Atrial fibrillation /flutter	7	0.62 (0, 2.64)	0.014‡,§	29	2.80 (0,9.82)	0.573§	5	11.14 (7.08, 11.90)	0.271§
Sinus tachycardia	20	10.28 (5.98, 16.27)	0.161§	22	5.31 (0, 11.51)	0.857§	15	9.13 (5.92, 32.17)	0.059§
Other	3	2.5 (1.25, 3.71)	0.190§	11	4.91 (0.58, 8.52)	0.918§	3	10.09 (5.62, 16.92)	0.524§

Abbreviations: ECG, electrocardiogram; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.
* Overall median (IQR).
† Overall p value comparing 4 different rhythms.
‡ p Value <0.05.
§ p Value compared with normal sinus rhythm.

Associations of first troponin, peak troponin, and BNP with mortality, ICU LOS, and hospital LOS among the 124 patients with CV events are summarized in Supplemental Table 6. However, no significant correlations with any of these 3 main clinical outcomes were observed.

Discussion

Comprehensive analysis of ECGs in 124 patients with CV events demonstrated distinct features of the first ECG (on admission), CV event–triggered ECG (within 24 hours of CV event), and final ECG (last ECG before discharge or death). Atrial fibrillation/flutter was the most common arrhythmia during CV events, and sinus tachycardia was the most common rhythm in the final ECG. QRS duration was longer, and AV block was more commonly present in the CV event–triggered ECGs.

Two systematic reviews of ECG findings in patients with COVID-19 recently have been published.[25,26] Mehraeen et al.[26] included 20 articles and found ST-T abnormalities—notably ST elevation—were the most observed ECG findings, but the relationship with myocardial injuries is debatable. Garcia-Zamora et al.[25] performed a meta-analysis of 28 studies, with 12,499 participants, and found that the overall prevalence of cardiac arrhythmias was 10.3%, with the most common arrhythmias documented during hospitalization being supraventricular arrhythmias (6.2%), followed by ventricular arrhythmias (2.5%). The incidence of cardiac arrhythmias was higher among critically ill patients (relative risk, 12.1; 95% confidence interval [CI], 8.5-17.3) and among nonsurvivors (relative risk, 3.8; 95% CI, 1.7-8.7). However, neither of these studies analyzed ECG parameters based on the timing of ECG or how ECGs change during hospitalization in patients with COVID-19. This information is critical to understand how cardiac injuries evolve in hospitalized patients with COVID-19. Therefore, this study separated ECGs into 3 important phases—admission, within 24 hours of CV events, and near discharge/death—to study distinct ECG features and their progression. Because troponin level reflects and quantifies acute myocardial damage, the authors decided to correlate the first ECG parameters with the first troponin level and CV

Table 3
Comparisons of the Peak Troponin Level Between Patients With Abnormality and Those Without Abnormality Based on the Event-Triggered ECG Abnormality

Event-Triggered ECG Abnormality	n (%)	Peak Troponin With Abnormality, ng/mL(mean ± SD)	Peak Troponin Without Abnormality, ng/mL(mean ± SD)	p Value
Rhythm: AF/flutter	29 (26.9%)	0.073 ± 0.1	0.681 ± 1.3	0.0430*
Rhythm: sinus tachycardia	22 (20.4%)	0.614 ± 1.4	0.681 ± 1.3	0.7121
Rhythm: others	11 (10.2%)	0.157 ± 0.2	0.681 ± 1.3	0.1654
LVH	9 (8.3%)	0.05 ± NA	0.506 ± 1.1	0.4102
AV block	34 (31.5%)	0.365 ± 0.7	0.556 ± 1.2	0.6647
ST changes	10 (9.3%)	0.922 ± 1.9	0.433 ± 1	0.8219

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; LVH, left ventricular hypertrophy; NA, not available owing to only 1 observation under the conditions; SD, standard deviation.
* p Value <0.05.

Table 4
Comparisons of the First Troponin Level Between Patients With Abnormality and Patients Without Abnormality Based on the First ECG Abnormality

First ECG Abnormality	n (%)	First Troponin Level With Abnormality, ng/mL (mean ± SD)	First Troponin Level Without Abnormality, ng/mL(mean ± SD)	p Value
Rhythm: AF/flutter	7 (9.5%)	0.109 ± 0.1	0.234 ± 0.8	0.2374
Rhythm: sinus tachycardia	20 (27.0%)	0.096 ± 0.1	0.234 ± 0.8	0.3221
Rhythm: others	3 (4.1%)	0.03 ± 0	0.234 ± 0.8	0.1855
LVH	8 (10.8%)	0.082 ± 0.1	0.187 ± 0.7	0.6769
RVH	1 (1.4%)	0.03 ± NA	0.177 ± 0.7	0.7558
AV block	21 (28.4%)	0.164 ± 0.2	0.179 ± 0.8	0.0788
ST changes	3 (4.1%)	0.033 ± 0	0.181 ± 0.7	0.3309

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LVH, left ventricular hypertrophy; NA, not available; RVH, right ventricular hypertrophy; SD, standard deviation.

event–triggered ECG parameters with peak troponin, indicative of the most severe cardiac injuries during hospitalization. This analysis might provide insights into how cardiovascular injuries occur and develop during hospitalization in patients with COVID-19.

ECG abnormalities commonly seen in cardiac injury are arrhythmia, ST elevation, P-R depression, new-onset bundle-branch block, QT prolongation, pseudoinfarct pattern, premature ventricular complexes, bradyarrhythmias, and ventricular tachycardia. Consistent with previous studies,[25,26] this study found atrial fibrillation or flutter to be the most common arrhythmia during CV event–triggered ECG (26.9%). However, atrial fibrillation or flutter was much lower on first ECG (9.5%) and final ECG (12.5%). A recent COVID-19 study found atrial fibrillation in 7.0% of the 201 patients at admission, and atrial fibrillation was associated with increased mortality (odds ratio, 12.74; 95% CI, 3.65-44.48; $p < 0.001$).[27] Other studies have shown that atrial fibrillation or flutter was the most frequently reported serious arrhythmia,[14,17] was associated with higher troponin values, and carried a higher mortality rate than other rhythms.[17] In the present study, AV block was also significantly higher in CV event–triggered ECG (31.5%) compared with admission or discharge ECGs. Both atrial arrhythmia and AV block could represent direct viral infection of the conduction system, myocardial ischemia/edema, diastolic dysfunction, LV dysfunction, pulmonary hypertension from acute respiratory distress syndrome, or pulmonary embolism. For the first ECG, atrial arrhythmia was found to be correlated with shorter hospital and ICU LOS. However, no correlation was found between CV event–triggered or final ECG and either hospital or ICU LOS. One possible explanation could be early mortality with atrial arrhythmia.

QRS duration longer than 120 ms was associated with worse clinical outcomes and higher levels of myocardial injury biomarkers in COVID-19.[28] Prolonged QRS could reflect active myocardial injury during CV events caused by the direct impact of SARS-CoV-2 on the cells.[29] A wide QRS complex previously has been associated with increased mortality risk in patients without COVID-19.[30-32] The authors' findings further confirmed the importance of QRS duration in predicting mortality in patients with COVID-19. CV event–triggered ECG demonstrated significantly longer QRS duration than that on the first or final ECGs. Furthermore, this study found that QRS duration on final ECG was significantly longer in nonsurvivors than in survivors among hospitalized patients with COVID-19 and CV events.

Among all the parameters reviewed on the first ECGs, only QTc showed a significant correlation with the first troponin level. A recent meta-analysis found that the prevalence of QTc > 500 ms was 12.3% in patients with COVID-19.[25] QTc interval prolongation was found to be associated with increased COVID-19 severity and mortality.[33-37] However, the risk of torsades de pointes was not increased in hospitalized patients with COVID-19 who showed a marked prolongation of QTc interval.[38,39] In this study, the authors did not find any correlation between ECG parameters and peak troponin levels among CV event–triggered ECGs. This might suggest that the CV event–triggered ECG parameters are not useful predictors of further outcomes.

Table 5
Association Study Between Each Biomarker (ie, First Troponin Level, Peak Troponin Level, BNP) and Each Outcome Variable (ie, Mortality, ICU Length of Stay, and Hospital Length of Stay) in 702 Patients

	Dead(Mean ± SD)	Alive(Mean ± SD)	p Value	Spearman Correlation(LOS)	p Value(LOS)	Spearman Correlation (ICU LOS)	p Value(ICU LOS)
First troponin level, ng/mL	1.256 ± 11	0.116 ± 0.6	<0.001*	0.165	<0.001*	0.172	<0.001*
Peak troponin, ng/mL	0.389 ± 1	0.311 ± 0.8	0.011*	0.17	0.072*	0.301	0.001*
BNP, pmol/L	1733.718 ± 4536.2	565.063± 2909	<0.001*	0.204	<0.001*	0.212	<0.001*

Abbreviations: BNP, B-type natriuretic peptide; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.
* p Value <0.05.

It has been demonstrated that ECG ST-T segment alterations are the most commonly reported ECG anomaly in patients with COVID-19,[23,24] and are more frequent among patients with severe COVID-19.[13,40,41] Barman et al. showed that ST-T changes on admission ECG were closely associated with the severity of COVID-19 infection.[13] The present study found ST changes on the first ECGs in 4.1% of patients with CV events, and on CV event–triggered ECGs in 9.3%. However, there was no significant correlation with either first or peak troponin level.

Sinus tachycardia was reported to be the most common arrhythmia in patients with COVID-19,[13,14,17,33] and was more frequent in nonsurvivors. This study found that heart rate on the final ECG was significantly correlated with ICU LOS. This could indicate higher levels of stress due to sepsis, hypovolemia, pulmonary embolism, anxiety, or mechanical ventilation.

Research on ECG alterations and hospital LOS is limited. Abrams et al. compared the characteristics of patients with COVID-19 who died of arrhythmias with those who died of other causes, and there was no statistically significant difference in LOS between the 2 groups (median 5 *v* 4 days; $p = 0.76$).[42]

In addition to ECG findings, cardiac involvement can be detected by multiple laboratory markers, including troponin and BNP. Higher BNP values have been associated with abnormal ECG[14] and higher in-hospital mortality.[17] Troponin levels were higher in nonsurvivors than in survivors,[33] as well as in patients with severe illness compared with those with nonsevere COVID-19.[40] For the entire patient cohort (patients with and without CV events), the present study found that the first troponin level, peak troponin level, and BNP were all significantly associated with mortality and ICU LOS. First troponin level and BNP were also significantly associated with hospital LOS. However, the authors did not find any significant correlations among first troponin level, peak troponin level, or BNP and mortality, ICU LOS, or hospital LOS among patients with CV events. These results were surprising yet explicable. If cardiac injury has been ongoing, additional troponin and BNP values could not help further prediction of clinical outcomes. Another explanation could be patients with CV events shared common risk factors that are more dominant to determine the clinical outcomes. It also could be possible that SARS-CoV-2 virus induces myocardial injury through a different mechanism that is not dependent on the level of cardiac biomarkers. This might imply that clinicians should reconsider ordering additional troponin and BNP tests, as they did not effectively predict outcomes in patients with COVID-19 and CV events.

There were limitations to this retrospective study. The results may not be generalizable to all patients with COVID-19, as they may have significantly different characteristics compared with patients hospitalized with COVID-19; hence, the external validity of the study is limited to hospitalized patients. Studies with retrospective design may bias the true incidence and influence of ECG abnormalities, as well as their prognostic value as predictors of clinical outcomes. To reduce these confounders and risk of bias in future research, large-scale prospective studies are needed to determine whether ECG abnormalities play an important role in predicting adverse clinical COVID-19 outcomes.

Conclusion

The simplicity and availability of the 12-lead ECG make it a potentially valuable predictive tool in the risk stratification and management of patients with COVID-19. This study shed light on the importance of ECG findings in hospitalized patients with CV events. The authors found that ECGs at various stages of COVID-19 hospitalization showed significantly different features with dissimilar clinical outcome correlations.

Declaration of Competing Interest

None.

Acknowledgments

The authors acknowledge the excellent efforts of the University of Louisville CERID group and Kornhauser Health Sciences Library to assist with this project.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.01.011.

References

1 Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). COVID-19 dashboard. https://coronavirus.jhu.edu/map.html. Accessed 21 September 2021.
2 Centers for Disease Control and Prevention. United States COVID-19 cases, deaths, and laboratory testing (NAATs) by state, territory, and jurisdiction. https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days. Accessed 11 September 2021, 2021.
3 Wu L, O'Kane AM, Peng H, et al. SARS-CoV-2 and cardiovascular complications: From molecular mechanisms to pharmaceutical management. Biochem Pharmacol 2020;178:114114.
4 Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:819–24.
5 Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol 2020;76:533–46.
6 Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol 2020;5:831–40.
7 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;5:802–10.
8 Karbalai Saleh S, Oraii A, Soleimani A, et al. The association between cardiac injury and outcomes in hospitalized patients with COVID-19. Intern Emerg Med 2020;15;1415-4.
9 Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J 2021;42:1866–78.
10 Bavishi C, Bonow RO, Trivedi V, et al. Special article - Acute myocardial injury in patients hospitalized with COVID-19 infection: A review. Prog Cardiovasc Dis 2020;63:682–9.

11 Li L, Zhou Q, Xu J. Changes of laboratory cardiac markers and mechanisms of cardiac injury in coronavirus disease 2019. Biomed Res Int 2020;2020:7413673.
12 Lippi G, Lavie CJ. Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis 2020;63:390–1.
13 Barman HA, Atici A, Alici G, et al. The effect of the severity COVID-19 infection on electrocardiography. Am J Emerg Med 2021;46:317–22.
14 Bergamaschi L, D'Angelo EC, Paolisso P, et al. The value of ECG changes in risk stratification of COVID-19 patients. Ann Noninvasive Electrocardiol 2021;26:e12815.
15 Giustino G, Croft LB, Stefanini GG, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol 2020;76:2043–55.
16 McCullough SA, Goyal P, Krishnan U, et al. Electrocardiographic findings in coronavirus disease-19: Insights on mortality and underlying myocardial processes. J Card Fail 2020;26;626-2.
17 Poterucha TJ, Elias P, Jain SS, et al. Admission cardiac diagnostic testing with electrocardiography and troponin measurement prognosticates increased 30-day mortality in COVID-19. J Am Heart Assoc 2021;10:e018476.
18 Xu Q, Samanapally H, Nathala P, et al. Outcomes and risk factors for cardiovascular events in hospitalized COVID-19 patients. J Cardiothorac Vasc Anesth 2021;35:3581–93.
19 Carrico R, Ali TS, Hill M, et al. Healthcare workers hospitalized with COVID-19: Outcomes from the Burden of COVID-19 study at the University of Louisville Center of Excellence for Research in Infectious Diseases [CERID]. University of Louisville Journal of Respiratory Infections 2020;4.
20 Carrico R, Balcom D, Johnson W, et al. Implementation of the Louisville COVID-19 Surveillance Protocol: Experiences from the University of Louisville Center of Excellence for Research in Infectious Diseases [CERID]. University of Louisville Journal of Respiratory Infections 2020;4.
21 Surawicz B, Knilans T. Chou's electrocardiography in clinical practice: Adult and pediatric. 6th ed. Philadelphia, PA: Saunders; 2008.
22 Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006;92:843–9.
23 Altman DG. Practical statistics for medical research. Boca Raton, FL: Chapman & Hall/CRC; 1999.
24 Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: Wiley; 2012.
25 Garcia-Zamora S, Lee S, Haseeb S, et al. Arrhythmias and electrocardiographic findings in coronavirus disease 2019: A systematic review and meta-analysis. Pacing Clin Electrophysiol 2021;44:1062–74.
26 Mehraeen E, Seyed Alinaghi SA, et al. A systematic review of ECG findings in patients with COVID-19. Indian Heart J 2020;72:500–7.
27 Denegri A, Pezzuto G, D'Arienzo M, et al. Clinical and electrocardiographic characteristics at admission of COVID-19/SARS-CoV2 pneumonia infection. Intern Emerg Med 2021;16:1451–6.
28 Sonsoz MR, Oncul A, Cevik E, et al. Wide QRS complex and lateral ST-T segment abnormality are associated with worse clinical outcomes in COVID-19 Patients. Am J Med Sci 2021;361:591–7.
29 Centurión OA. Wide QRS complex and left ventricular lateral repolarization abnormality: The importance of ECG markers on outcome prediction in patients with COVID-19. Am J Med Sci 2021;362:1–2.
30 Ukena C, Mahfoud F, Kindermann I, et al. Prognostic electrocardiographic parameters in patients with suspected myocarditis. Eur J Heart Fail 2011;13:398–405.
31 Kalra PR, Sharma R, Shamim W, et al. Clinical characteristics and survival of patients with chronic heart failure and prolonged QRS duration. Int J Cardiol 2002;86:225–31.
32 Horwich T, Lee SJ, Saxon L. Usefulness of QRS prolongation in predicting risk of inducible monomorphic ventricular tachycardia in patients referred for electrophysiologic studies. Am J Cardiol 2003;92:804–9.
33 Kunal S, Sharma SM, Sharma SK, et al. Cardiovascular complications and its impact on outcomes in COVID-19. Indian Heart J 2020;72:593–8.
34 Alareedh M, Nafakhi H, Shaghee F, Nafakhi A. Electrocardiographic markers of increased risk of sudden cardiac death in patients with COVID-19 pneumonia. Ann Noninvasive Electrocardiol 2021;26:e12824.
35 Ding J, Liu W, Guan H, et al. Corrected QT interval in hospitalized patients with coronavirus disease 2019: Focus on drugs therapy. Medicine (Baltimore) 2021;100:e26538.
36 Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. JAMA Cardiol 2020;5:1067–9.
37 Farré N, Mojón D, Llagostera M, et al. Prolonged QT interval in SARS-CoV-2 infection: Prevalence and prognosis. J Clin Med 2020;9:2712.
38 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;5:1036–41.
39 Jankelson L, Karam G, Becker ML, et al. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. Heart Rhythm 2020;17:1472–9.
40 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;311:116–21.
41 Antwi-Amoabeng D, Beutler BD, Singh S, et al. Association between electrocardiographic features and mortality in COVID-19 patients. Ann Noninvasive Electrocardiol 2021;26:e12833.
42 Abrams MP, Wan EY, Waase MP, et al. Clinical and cardiac characteristics of COVID-19 mortalities in a diverse New York City cohort. J Cardiovasc Electrophysiol 2020;31:3086–96.