ORIGINAL ARTICLE

Prevalence of Electrocardiographic Abnormalities of Hospitalized COVID-19 Infected Patients in King Chulalongkorn Memorial Hospital

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Background: Coronavirus disease 2019 (COVID-19) was recognized as an outbreak in December 2019. While the main symptoms and severe complications of COVID-19 involve the respiratory system, this disease can also result in cardiac complications including cardiac dysrhythmias. In the previous studies, several electrocardiographic patterns were associated with poor outcomes. However, there is still sparse data on electrocardiographic abnormalities and their prognostic outcomes in Thailand.

Objective: To describe the prevalence of electrocardiographic abnormalities of hospitalized COVID-19 infected patients in King Chulalongkorn Memorial Hospital and electrocardiographic patterns associated with in-hospital mortality.

Materials and Methods: The present study was a retrospective, single-center, observational study. The medical records of hospitalized symptomatic patients diagnosed with COVID-19 infection confirmed by RT-PCR between January 2020 and December 2021 were reviewed. Data from each electrocardiogram and in-hospital mortality of patients were collected. Patients without electrocardiograms and patients who had pacemakers were excluded. The primary outcome was the prevalence of electrocardiographic abnormalities. The secondary outcome was the abnormal electrocardiographic patterns associated with in-hospital mortality.

Results: There were 180 patients included in the present study with a mean age of 61.01±16.17 years, and 56% were male. From the present study, 154 patients (85.6%) had at least one abnormal electrocardiographic finding during admission. The most common abnormal electrocardiographic patterns were prolonged QT interval at 36.8%, tachycardia at 29.1%, ST depression at 23.4%, and pathologic Q wave at 19.5%. Thiry-three patients (18.3%) died during hospitalization, and electrocardiographic patterns associated with in-hospital mortality were tachycardia (OR 7.86, 95% CI 2.75 to 22.44, p<0.001), premature atrial complexes (OR 5.06, 95% CI 1.29 to 19.78, p=0.02), prolonged QTc interval (OR 4.71, 95% CI 1.6 to 13.9, p=0.005), and ST depression (OR 2.96, 95% CI 1.04 to 8.4, p=0.042). All deaths had at least one electrographic abnormality.

Conclusion: The prevalence of electrocardiographic abnormalities of hospitalized COVID-19 infected patients in King Chulalongkorn Memorial Hospital who had underwent 12-lead electrocardiogram was 85.6%. In addition, some electrocardiographic patterns were associated with in-hospital mortality.

Keywords: Electrocardiogram; ECG; SARS-CoV-2; COVID-19; Mortality

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In December 2019, cases of pneumonia with severe acute respiratory syndrome caused by coronavirus (SARS-CoV-2), called coronavirus disease 2019 (COVID-19), emerged in Wuhan, China, which has been stated as a global pandemic subsequently. While the main symptoms and severe complications of COVID-19 involve the respiratory system especially pneumonia and respiratory distress syndrome[1], this disease can also result in cardiac complications including myocarditis, acute coronary syndromes, and cardiac dysrhythmias[2].

There have been proposed mechanisms that contribute to myocardial injury related to COVID-19, resulting in abnormal electrocardiograms (ECG), including direct cardiomyocyte injury via angiotensin-converting enzyme 2 (ACE2) receptors on the surface of cardiac epithelial cells, inflammatory response and cytokine storm syndrome, hypoxia-induced myocardial injury, and endothelial cell injury[3]. Furthermore, cardiac arrhythmias after COVID-19 vaccination, like atrial arrhythmias, bradyarrhythmias, and ventricular arrhythmias were also reported. The postulated mechanisms

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are S protein production that binds ACE2 receptors and elevates cathecholamines, and auto-antibodies production and involves adrenergic receptors and vasodepressor response resulting in orthostatic tachycardia[4].

There are several types of abnormal ECG among COVID-19 infected patients, including sinus tachycardia, supraventricular tachycardias, ventricular arrhythmias, bradycardias, left and right bundle branch block, axis deviation, and ST segment and T wave changes. From the previous studies, several ECG patterns were associated with poor outcomes, which comprised atrial fibrillation, ST segment and T wave change, prolonged corrected QT (QTc) interval, and ventricular tachycardia and fibrillation[2].

Nguyen et al. evaluated ECG characteristics at the first presentation at the emergency department in 356 patients with possible COVID-19 pneumonia and reported that common ECG abnormalities were atrial fibrillation in 9%, ECG reflecting atrial enlargement with P mitrale, P-wave duration pf of 110 milliseconds or more, premature atrial contractions in 38%, and repolarization abnormalities in 14%. Nonetheless, the patients in the COVID-19 group had no significant differences of ECG abnormalities compared with those in the non-COVID-19 group[5].

A single-center Spanish study reviewed 1,476 COVID-19 patients, new arrhythmic events were found in 76 patients (5.1%), and 66 patients of these (86.8%) died. Most of the arrhythmias were atrial fibrillation at 3.2%, atrial flutter at 1%, and ventricular arrhythmias at 0.6%. Multivariable analysis demonstrated that a history of atrial flutter, heart failure, dyslipidemia, treatment with lopinavir/ritonavir, and combined use of hydroxychloroquine and azithromycin were associated with these new arrhythmic events[6].

Studies have reported an association of ECG types with mortality. Lanza et al. studied 324 admitted patients with diagnosis of COVID-19 infection in Italy, showing that the presence of left bundle branch block (LBBB), QRS duration of 110 milliseconds or more, ST segment and T wave change, and presence of any ECG abnormality were associated with 30-day mortality from the multivariable analysis. Most of the patients (70.5%) in the dead group had at least one ECG abnormality[7]. Vandenberk et al. from Belgium also reported repolarization abnormalities at the admission of COVID-19 patients as a predictor of 30-day mortality[8].

In addition, a Spanish study found that prolonged QTc interval, with QTc interval greater than 480 milliseconds, was associated with all-cause death in SARS-CoV-2 hospitalized patients[9]. ECG analyses in COVID-19 patients from hospitals in New York showed that right ventricular strain, atrial fibrillation and flutter, and ST segment abnormality were associated with death or need for mechanical ventilator within 48 hours of diagnosis[10]. McCullough et al. found that patients with ECG patterns of both left-sided heart disease including atrial premature contractions, intraventricular block, and repolarization abnormalities, and right-sided disease including right bundle branch block were also associated with death[11].

However, there is still sparse data on ECG abnormalities and their prognostic outcomes in Thailand. The present study summarized the prevalence of relevant abnormal electrocardiographic findings in hospitalized COVID-19 infected patients in King Chulalongkorn Memorial Hospital (KCMH) in Thailand and their association with clinical outcomes regarding in-hospital mortality.

Materials and Methods

Study design

The present study was a retrospective, single-center, observational analytic study conducted in KCMH. The protocol of the present study was approved by the Institutional Review Board (IRB no. 1490/2022) of KCMH.

Study population and protocol

The authors enrolled consecutive patients with symptomatic COVID-19 infection who were diagnosed with SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) and admitted at KCMH between January 1, 2020 and December 31, 2021. Patients aged 18 years or older who had standard 12-lead surface ECG during admission were eligible for this study. Patients without ECG and patients who had pacemakers were excluded.

The medical records of the enrolled patients were reviewed from the in-patient database using ICD 10 of COVID-19 infection (U071). The demographic data as age and gender, underlying disease, current medications, clinical data such as weight and height, vital signs, pulse oximetry, and disease severity, ECG characteristics with optional baseline ECG, echocardiogram, laboratory tests, treatment medications, and discharge status such as alive versus dead, were collected.

SARS-CoV-2 RNA detection was based on RT-

PCR. Specimens were retrieved from nasopharyngeal swabs or endotracheal suction. Lower respiratory tract symptoms along with the respiratory rate, peripheral capillary oxygen saturation, chest radiograph, and need for oxygen supplement or mechanical ventilator were the factors used for grading COVID-19 disease severity[12]. Acute respiratory distress syndrome severity (ARDS) was determined according to the Berlin definition of ARDS[13].

ECG analysis

Standard 12-lead ECGs during admission were retrieved from the in-patient medical records division. The ECGs were analyzed by two trained cardiology fellows independently. In cases of discordance, consensus agreements were reached by a third cardiology fellow.

All ECG variables were recorded. In patients who had more than one ECG during admission, the ECGs with different characteristics were all collected. ECG definitions and abnormalities were described according to AHA/ACCF/HRS recommendations for the standardization and interpretation of the ECG and the Minnesota code manual of ECG findings[14-19].

ECG was identified as abnormal type if there was the presence of at least one of the following characteristics, non-sinus rhythm, tachycardia with any rhythm with heart rate greater than 100 bpm, or bradycardia with any rhythm with heart rate of less than 60 bpm, presence of P pulmonale or P mitrale, first-degree or more atrioventricular block, pathologic Q wave, ST elevation or ST depression, T wave abnormality, left or right bundle branch block, QTc greater than 450 milliseconds in male or greater than 460 milliseconds in female, premature atrial or ventricular complexes, and left or right ventricular hypertrophy. Patients who had at least one of the abnormal ECGs were counted in the abnormal type group. Each abnormal ECG characteristic was presented as prevalence per all ECGs.

Clinical outcomes

The primary outcome of the present study was the prevalence of electrocardiographic abnormalities in hospitalized COVID-19 infected patients. The secondary outcome was abnormal electrocardiographic patterns which were associated with in-hospital mortality.

Statistical analysis

According to the prevalence of ECG abnormalities from the previous study of 70.5%[7], the authors estimated that at least 80 patients would need to be enrolled to preserve the two-sided type 1 error at 0.05 and the estimation error at 0.1. Continuous variables were reported as mean and standard deviation (SD) for normal distribution and as the median and interquartile range (IQR) for skewed distribution. Categorical variables were reported as frequencies and percentages.

Differences among groups were compared using the unpaired t-test or Mann-Whitney U test for continuous independent variables and the chi-square test or Fisher's exact test for categorical variables. Univariate and multivariate logistic regression analysis were used to identify variables associated with in-hospital mortality, results were reported as an odds ratio (OR), 95% confidence interval (CI), and p-value. Variables with a p-value less than 0.05 in univariate analysis were all included in multivariate analysis and were also reported as adjusted OR, 95% CI, and p-value. Interobserver variability was assessed using the kappa coefficient. All data were analyzed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Between January 1, 2020 and December 31, 2021, 1,365 consecutive patients with symptomatic COVID-19 infection diagnosed by SARS-CoV-2 RT-PCR were admitted at KCMH using ICD-10 code U071. One thousand one hundred eighty-three hospitalized patients who did not have standard 12-lead surface ECG recorded during admission were excluded, and two patients who had pacemakers were also excluded. There was no patient with defibrillator or cardiac resynchronization therapy in the present study. Therefore, 180 patients hospitalized COVID-19 infected patients with standard 12-lead surface ECG were included (Figure 1).

Among 180 patients, the average age was 61.01±16.17 years, and 56% were male. The average body mass index (BMI) was 26.04±6.01 kg/m^2. There were 28 patients (15.6%) who had prior heart disease, including ischemic heart disease, atrial fibrillation, heart failure, valvular heart disease, and cardiomyopathy. Calcium channel blockers and angiotensin receptor antagonists were the most commonly used medications by 31.1% and 23% of the patients, respectively. The average heart rate was 86.44±19.47 beats per minute (bpm). The average peripheral capillary oxygen saturation was

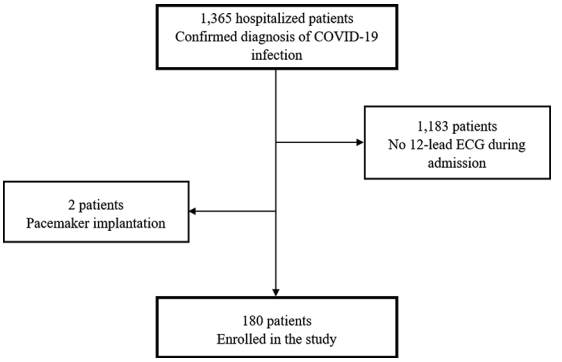

Figure 1. Flow chart of patients' enrolment.

92.76±8.59%. Almost 50% of patients had developed ARDS (Table 1).

For in-hospital mortality, 147 patients (81.7%) were alive and 33 patients (18.3%) died. The average age of the dead group was older than the alive group at 70.21±16.41 versus 58.94±15.43 years (p<0.001). History of atrial fibrillation, diabetes mellitus, and chronic kidney disease tended to have more prevalence in the dead group. The number of patients with ARDS were significantly higher in the dead group at 87.8% versus 36.1% (p<0.001). The data showed lower peripheral capillary oxygen saturation at 89.21±13.12% versus 93.56±7.01% (p=0.008) and higher heart rate at 96.52±17.64 versus 84.18±19.20 bpm (p<0.001) in the dead group. There was no significant difference in current medications between patients in the alive and dead group (Table 1).

Some laboratory tests were significantly higher in the dead group, including high sense troponin I (hs-TropI) at 60.2 (17.7, 1,672.8) versus 8.45 (4.5, 25.1) ng/L (p<0.001), N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 1,152.1 (503.9, 8,101.8) versus 250.8 (101.8, 1,057) pg/mL (p<0.001), and interleukin-6 (IL-6) at 52.43 (26.41, 119) versus 25.92 (9.61, 78.68) pg/mL (p=0.018). The cycle threshold (CT) of virus was lower in the dead group at 17.38±4.55 versus 21.02±6.10 (p=0.001). For treatment medications, remdesivir and corticosteroids were more frequently used in COVID-19 infected patients in the dead group at 69.7% versus 43.5% (p=0.007) and 97% versus 76.9% (p=0.006), respectively.

There were 261 ECGs counted in the present study. Two hundred thirty-four ECGs (89.7%) showed sinus rhythm. Atrial fibrillation and atrial flutter were presented in 6.9% and 2.3%, respectively. There were two ECGs with ventricular tachycardia detected at 0.8%. First-degree atrioventricular block was detected in 6.5%, while there was no second or third-degree atrioventricular block detected. The average heart rate was 88.07±24.93 bpm. LBBB and right bundle branch block were presented in 2.3% and 14.2%. The most common abnormal ECG patterns were prolonged QTc interval at 36.8%, tachycardia at 29.1%, ST depression at 23.4%, and pathologic Q wave at 19.5% (Table 2). The result was still similar among the first ECGs at admission.

From the present study, 154 patients (85.6%) had abnormal ECG during admission. Some ECG characteristics were found to be more prevalent in patients in the dead group, such as ST elevation at 21.2% versus 7.5% (p=0.026), ST depression at 48.5% versus 19.7% (p=0.001), T wave abnormality at 36.4% versus 16.3% (p=0.009), prolonged QTc interval at 66.7% versus 36.1% (p=0.002), and premature atrial complexes at 24.2% versus 5.4% (p=0.002). All patients in the dead group had at least one ECG abnormality (Table 3). The kappa coefficient for interobserver variability was 0.61.

From univariate analysis, clinical and laboratory variables associated with death included age (p=0.001), atrial fibrillation (p=0.03), diabetes mellitus (p=0.03), chronic kidney disease (p=0.024), heart rate (p=0.001), peripheral capillary oxygen saturation (p=0.02), ARDS severity (p<0.001), and CT of the virus (p=0.003). ECG characteristics associated with in-hospital mortality included tachycardia (p<0.001), premature atrial complexes (p=0.002), prolonged QTc interval (p=0.002), ST depression (p=0.001), ST elevation (p=0.023), and T wave abnormality (p=0.011) (Table 4).

From multivariate analysis, the remaining clinical and laboratory variables associated with in-hospital mortality included ARDS severity (p<0.001) and the CT of the virus (p=0.001). For ECG variables, tachycardia (OR 7.86, 95% CI 2.75 to 22.44, p<0.001), premature atrial complexes (OR 5.06, 95% CI 1.29 to 19.78, p=0.02), prolonged QTc interval (OR 4.71, 95% CI 1.6 to 13.9, p=0.005), and ST depression (OR 2.96, 95% CI 1.04 to 8.4, p=0.042) maintained an association with in-hospital mortality (Table 4).

In addition, multivariate analysis in 82 patients that developed ARDS showed similar results that the clinical and laboratory variables were still associated with in-hospital mortality included heart rate (p<0.023) and the CT of the virus (p=0.009). ECG variables included tachycardia (OR 16.03, 95% CI 2.4 to 107.09, p=0.004), prolonged QTc interval (OR 12.5, 95% CI 1.45 to 107.87; p=0.022),

Table 1. Population characteristics

Characteristics	All (n=180)	Alive (n=147)	Dead (n=33)	p-value
Age (years); mean±SD	61.01±16.17	58.94±15.43	70.21±16.41	<0.001
Male; n (%)	100 (55.6)	80 (54.4)	20 (60.6)	0.518
Weight (kg); mean±SD	68.41±18.02	68.89±18.10	62.27±17.75	0.452
Height (cm); mean±SD	161.87±8.90	161.83±8.87	162.06±9.17	0.896
BMI (kg/m^2); mean±SD	26.04±6.01	26.21±5.84	25.31±6.79	0.44
Comorbidities; n (%)				
Prior heart diseases	28 (15.6)	20 (13.6)	8 (24.2)	0.128
Atrial fibrillation	8 (4.4)	4 (2.7)	4 (12.1)	0.039
Hypertension	98 (54.4)	78 (53.1)	20 (60.6)	0.432
Diabetes mellitus	63 (35.0)	46 (31.3)	17 (51.5)	0.028
Dyslipidemia	68 (37.8)	54 (36.7)	14 (42.4)	0.542
History of stroke	18 (10.0)	13 (8.8)	5 (15.2)	0.332
COPD	3 (1.7)	2 (1.4)	1 (3.0)	0.457
Chronic kidney disease	26 (14.4)	17 (11.6)	9 (27.3)	0.029
Obesity	32 (17.8)	25 (17.0)	7 (21.2)	0.568
Malignancy	13 (7.2)	10 (6.8)	3 (9.1)	0.709
Current medications; n (%)				
Beta-blockers	35 (21.7)	25 (18.9)	10 (34.5)	0.066
CCBs	50 (31.1)	41 (31.1)	9 (31.0)	0.998
ACE inhibitors	10 (6.2)	8 (6.1)	2 (6.9)	1.0
ARBs	37 (23)	27 (20.5)	10 (34.5)	0.104
Furosemide	10 (6.2)	7 (5.3)	3 (10.3)	0.388
Aspirin	27 (16.8)	24 (18.2)	3 (10.3)	0.415
Statins	67 (41.6)	52 (39.4)	15 (51.7)	0.223
Vital signs; mean±SD				
SBP (mmHg)	133.3±22.13	133.7±22.08	131.51± 22.60	0.609
DBP (mmHg)	77.27±14.48	78.25±13.39	72.9±18.18	0.055
Heart rate (bpm)	86.44±19.47	84.18±19.20	96.52±17.64	<0.001
SpO_2 (%)	92.76±8.59	93.56±7.01	89.21±13.12	0.008
COVID-19 severity; n (%)				<0.001
Mild	29 (16.1)	29 (19.7)	0 (0.0)	
Moderate	28 (15.6)	26 (17.7)	2 (6.1)	
Severe	41 (22.8)	39 (26.5)	2 (6.1)	
ARDS	82 (45.5)	53 (36.1)	29 (87.8)	
• Mild	20 (11.1)	17 (11.6)	3 (9.1)	
• Moderate	48 (26.7)	33 (22.5)	15 (45.4)	
• Severe	14 (7.8)	3 (2.0)	11 (33.3)	
Laboratory tests				
Hemoglobin (g/dL); mean±SD	12.5±2.10	12.67±1.99	11.76±2.45	0.024
WBC (per uL); median (IQR)	6,440 (4,560, 9,400)	6,110 (4,550, 9,000)	7,360 (5,390, 9,580)	0.189
Creatinine (mg/dL); median (IQR)	0.93 (0.71, 1.38)	0.91 (0.69, 1.29)	1.15 (0.86, 1.87)	0.044
hs-TropI (ng/L); median (IQR)	12.8 (5.4, 46.5)	8.45 (4.5, 25.1)	60.2 (17.7, 1,672.8)	<0.001
NT-proBNP (pg/mL); median (IQR)	444.8 (123.6, 1,712.45)	250.8 (101.8, 1,057)	1,152.1 (503.9, 8,101.8)	<0.001
D-dimer (ng/mL); median (IQR)	1,069.71 (688.87, 2,035.81)	1,008.77 (680.05, 1,782.37)	1,343.82 (831.44, 3,520.46)	0.101
hs-CRP (mg/L); median (IQR)	71.84 (32.02, 126.93)	72.55 (29.65, 124.89)	58.59 (35.07, 132.59)	0.809
IL-6 (pg/mL); median (IQR)	29.81 (11.96, 86.63)	25.92 (9.61, 78.68)	52.43 (26.41, 119)	0.018

BMI=body mass index; COPD=chronic obstructive pulmonary disease; CCBs=calcium channel blockers; ACE=angiotensin-converting enzyme; ARBs=angiotensin II receptor antagonists; SBP=systolic blood pressure; DBP=diastolic blood pressure; SpO_2=peripheral capillary oxygen saturation; ARDS=acute respiratory distress syndrome; WBC=white blood cell; hs-TropI=high sense Troponin I; NT-proBNP=N-terminal pro-B-type natriuretic peptide; hs-CRP=high sense C-reactive protein; IL-6=interleukin-6; SD=standard deviation; IQR=interquartile range

Table 1. (continued)

Characteristics	All (n=180)	Alive (n=147)	Dead (n=33)	p-value
Laboratory tests (continued)				
Cycle threshold (CT); mean±SD	20.32±6.01	21.02±6.10	17.38±4.55	0.001
pH; mean±SD	7.42±0.06	7.43±0.04	7.40±0.10	0.055
Treatment; n (%)				
Favipiravir	151 (83.9)	123 (83.7)	28 (84.9)	0.868
Remdesivir	87 (48.3)	64 (43.5)	23 (69.7)	0.007
Lopinavir/ritonavir	13 (7.2)	13 (8.8)	0 (0.0)	0.13
Tocilizumab	33 (18.3)	24 (16.3)	9 (27.3)	0.142
Corticosteroids	145 (80.6)	113 (76.9)	32 (97.0)	0.006
Azithromycin	22 (12.2)	19 (12.9)	3 (9.1)	0.77
Hydroxychloroquine	18 (10.0)	18 (12.2)	0 (0.0)	0.047
Amiodarone	6 (3.3)	3 (2.0)	3 (9.1)	0.076

BMI=body mass index; COPD=chronic obstructive pulmonary disease; CCBs=calcium channel blockers; ACE=angiotensin-converting enzyme; ARBs=angiotensin II receptor antagonists; SBP=systolic blood pressure; DBP=diastolic blood pressure; SpO_2=peripheral capillary oxygen saturation; ARDS=acute respiratory distress syndrome; WBC=white blood cell; hs-TropI=high sense Troponin I; NT-proBNP=N-terminal pro-B-type natriuretic peptide; hs-CRP=high sense C-reactive protein; IL-6=interleukin-6; SD=standard deviation; IQR=interquartile range

Table 2. Prevalence of electrocardiographic characteristics of hospitalized COVID-19 infected patients per all ECGs

ECG characteristics	n=261
Sinus rhythm; n (%)	234 (89.7)
Normal sinus rhythm	149 (57.1)
Sinus tachycardia	57 (21.9)
Sinus bradycardia	28 (10.7)
Atrial fibrillation; n (%)	18 (6.9)
Atrial flutter; n (%)	6 (2.3)
Heart rate (bpm); mean±SD	88.07±24.93
Left axis deviation; n (%)	17 (6.5)
Right axis deviation; n (%)	14 (5.4)
Tachycardia; n (%)	76 (29.1)
Bradycardia; n (%)	30 (11.5)
P pulmonale; n (%)	2 (0.8)
P mitrale; n (%)	28 (10.7)
First-degree AV block; n (%)	17 (6.5)
Pathologic Q wave; n (%)	51 (19.5)
QRS duration (msec); mean±SD	96.59±18.29
ST elevation; n (%)	26 (10.0)
ST depression; n (%)	61 (23.4)
T wave abnormality; n (%)	50 (19.2)
Left bundle branch block; n (%)	6 (2.3)
Right bundle branch block; n (%)	37 (14.2)
QTc interval (msec); mean±SD	450.76±44.48
Prolonged QTc interval; n (%)	96 (36.8)
Premature atrial complexes; n (%)	16 (6.1)
Premature ventricular complexes; n (%)	13 (5.0)
Left ventricular hypertrophy; n (%)	24 (9.2)
Right ventricular hypertrophy; n (%)	6 (2.3)
Any ECG abnormality; n (%)	224 (85.8)

ECG=electrocardiogram; AV=atrioventricular; SD=standard deviation

Table 3. ECG characteristics of the study population compared between patients in the alive vs. dead group

ECG characteristics	Alive (n=147)	Dead (n=33)	p-value
Sinus rhythm; n (%)	133 (90.5)	26 (78.8)	0.073
Normal sinus rhythm	83 (61.5)	7 (26.9)	0.001
Sinus tachycardia	30 (22.2)	16 (61.5)	<0.001
Sinus bradycardia	22 (16.3)	3 (11.6)	0.451
Atrial fibrillation; n (%)	9 (6.1)	5 (15.2)	0.14
Atrial flutter; n (%)	4 (2.7)	2 (6.1)	0.303
Heart rate (bpm); mean±SD	84.18±19.20	96.52±17.64	<0.001
P pulmonale; n (%)	0 (0.0)	1 (3.0)	0.183
P mitrale; n (%)	15 (10.2)	5 (15.2)	0.375
First-degree AV block; n (%)	11 (7.5)	2 (6.1)	1.0
Pathologic Q wave; n (%)	28 (19.1)	11 (33.3)	0.072
QRS duration (msec); mean±SD	95.05±15.68	97.38±19.56	0.463
ST elevation; n (%)	11 (7.5)	7 (21.2)	0.026
ST depression; n (%)	29 (19.7)	16 (48.5)	0.001
T wave abnormality; n (%)	24 (16.3)	12 (36.4)	0.009
LBBB; n (%)	1 (0.7)	1 (3.0)	0.334
RBBB; n (%)	19 (12.9)	8 (24.2)	0.1
Prolonged QTc interval; n (%)	53 (36.1)	22 (66.7)	0.002
PACs; n (%)	8 (5.4)	8 (24.2)	0.002
PVCs; n (%)	8 (5.4)	3 (9.1)	0.426
LVH; n (%)	17 (11.6)	4 (12.1)	1.0
RVH; n (%)	3 (2.0)	1 (3.0)	0.559
Any ECG abnormality; n (%)	121 (82.3)	33 (100)	0.005

ECG=electrocardiogram; AV=atrioventricular; LBBB=left bundle branch block; RBBB=right bundle branch block; PACs=premature atrial complexes; PVCs=premature ventricular complexes; LVH=left ventricular hypertrophy; RVH=right ventricular hypertrophy; SD=standard deviation

Table 4. Univariate and multivariate logistic regression analysis for clinical and ECG variables which were associated with in-hospital mortality

	Univariable analysis		Multivariable analysis	
	Crude odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Age	1.04 (1.02 to 1.07)	0.001		
Comorbidities				
Atrial fibrillation	4.93 (1.16 to 20.85)	0.03		
Diabetes mellitus	2.33 (1.08 to 5.02)	0.03		
Chronic kidney disease	2.86 (1.14 to 7.18)	0.024		
Vital signs				
Heart rate	1.03 (1.01 to 1.05)	0.001		
SpO_2	0.95 (0.91 to 0.99)	0.02		
ARDS severity	12.86 (4.29 to 38.56)	<0.001	11.64 (3.43 to 39.46)	<0.001
Cycle threshold (CT)	0.89 (0.82 to 0.96)	0.003	0.84 (0.76 to 0.93)	0.001
ECG characteristics				
Tachycardia	6.89 (2.95 to 16.07)	<0.001	7.86 (2.75 to 22.44)	<0.001
PACs	5.56 (1.91 to 16.18)	0.002	5.06 (1.29 to 19.78)	0.02
Prolonged QT interval	3.54 (1.59 to 7.88)	0.002	4.71 (1.6 to 13.9)	0.005
ST depression	3.82 (1.73 to 8.47)	0.001	2.96 (1.04 to 8.4)	0.042
ST elevation	3.32 (1.18 to 9.38)	0.023		
T wave abnormality	2.92 (1.27 to 6.73)	0.011		
Treatment				
Remdesivir	2.98 (1.32 to 6.71)	0.008		
Corticosteroids	9.62 (1.26 to 73.08)	0.029		

SpO_2=peripheral capillary oxygen saturation; ARDS=acute respiratory distress syndrome; ECG=electrocardiogram; PACs=premature atrial complexes; CI=confidence interval

Table 5. Univariate and multivariate logistic regression analysis for clinical and ECG variables which were associated with in-hospital mortality in patients who developed ARDS

	Univariable analysis		Multivariable analysis	
	Crude odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Vital signs				
Heart rate	1.04 (1.01 to 1.07)	0.007	1.06 (1.01 to 1.12)	0.023
Cycle threshold (CT)	0.88 (0.8 to 0.97)	0.01	0.72 (0.57 to 0.92)	0.009
ECG characteristics				
Tachycardia	5.84 (2.04 to 16.75)	0.001	16.03 (2.4 to 107.09)	0.004
Prolonged QT interval	2.9 (1.11 to 7.54)	0.029	12.5 (1.45 to 107.87)	0.022
ST depression	3.79 (1.45 to 9.92)	0.007	10.12 (1.47 to 69.91)	0.019

ECG=electrocardiogram; CI=confidence interval

and ST depression (OR 10.12, 95% CI 1.47 to 69.91, p=0.019) (Table 5).

In subgroup analysis, patients with prior heart diseases tended to have abnormal ECG (p=0.016) (Table 6). The patients with QRS duration of 110 milliseconds or longer or less than 110 milliseconds had no significant difference in in-hospital mortality rate (p=0.271) (Table 7).

For treatment medications, lopinavir/ritonavir were significantly associated with prolonged QTc interval (p=0.007), and amiodarone tended to be associated with prolonged QTc interval (p=0.083). While remdesivir and azithromycin were not associated with prolonged QTc interval in the present study.

Furthermore, there was an upward trend of abnormal ECG in patients with more COVID-19 severity. All patients with severe ARDS symptoms had abnormal ECG, 100% of the patients (Figure 2). There was also a relation between in-hospital mortality and older age. The mortality in patients aged over 80 years was 41.7% (Figure 3).

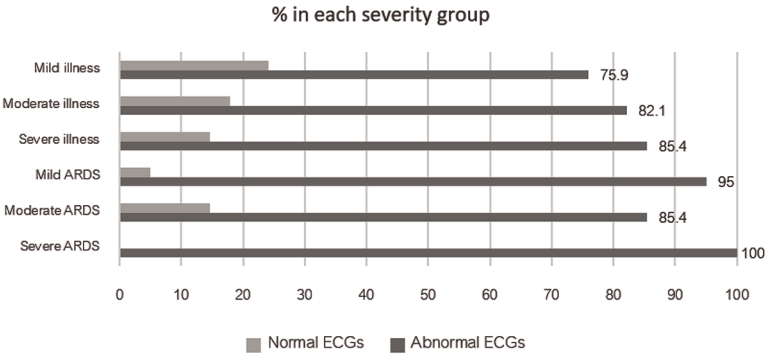

Figure 2. Proportion of abnormal ECGs in each COVID-19 severity group.

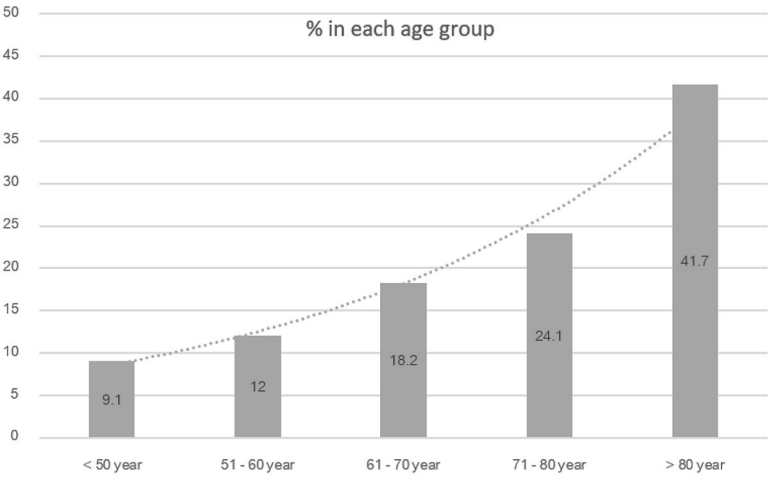

Figure 3. Proportion of in-hospital mortality in each age group.

Table 6. Subgroup analysis of abnormal ECG in patients with prior heart diseases

Characteristics	All (n=180)	Normal ECG (n=26)	Abnormal ECG (n=154)	p-value
Prior heart diseases; n (%)	28 (15.6)	0 (0.0)	28 (18.2)	0.016

ECG=electrocardiogram

Table 7. Subgroup analysis of in-hospital mortality rate in patients with QRS duration ≥110 msec and <110 msec

Characteristics	All (n=180)	Alive (n=147)	Dead (n=33)	p-value
QRS duration; n (%)				0.271
≥110 msec	26 (14.4)	19 (12.9)	7 (21.2)	
<110 msec	154 (85.6)	128 (87.1)	26 (78.8)	

However, the cause of mortality in 33 patients were mostly ARDS and pneumonia at 81.8%. Two patients with superimposed pneumonia had unstable atrial fibrillation with rapid ventricular response. Two patients developed myocarditis and died from ARDS and sepsis, respectively.

Discussion

There are various types of ECG characteristics among COVID-19 disease patients. These ECG changes may occur due to inflammatory process, direct viral endothelial or myocardial damage, hypoxic injury, electrolytes or acid-base imbalance, plaque rupture, microthrombi, and coronary spasm[2]. The present study data showed the prevalence of ECG abnormalities of hospitalized COVID-19 infected patients was up to 85.6% with 154 patients, predominantly patients with critical illness severity or ARDS. However, this prevalence number could be overestimated due to selection bias. From patients' enrolment, there were only about 13.3% of admitted patients who underwent ECGs. Patients with a 12-lead ECG during admission might have a higher probability of abnormal ECG characteristics from preceding clinical signs and symptoms, while

excluded patients did not have cardiac manifestations to avoid unnecessary exposure for healthcare workers. The calculated sample size estimation was 80 patients, but further enrollment was needed because there was a very low rate of in-hospital mortality in the early period of consecutive enrollment, which might be explained by mild COVID-19 disease symptoms. From the present study, 67 patients (37%) had their baseline ECGs, and the prevalence of ECG abnormalities remained at 75% (135 out of 180 patients) when excluded patients with abnormal ECGs that did not differ from their baseline studies.

Prolonged QTc interval was the most common abnormal ECG characteristic in the present study at 36.8%. It was still common even among the first ECGs at admission when there was no effect from the treatment medications. In addition, prolonged QTc interval was significantly associated with in-hospital mortality from multivariate analysis. This data supports the Farré et al. cohort study[9] to determine prolonged QTc interval as a prognostic factor of poor clinical outcome regarding in-hospital mortality due to COVID-19 infection. For medications, lopinavir/ritonavir were associated with prolonged QTc interval. However, azithromycin did not significantly affect QTc prolongation as mentioned in the same study[9], which may be explained by fewer patients' use, with only 12%, than the previous study.

The second most common abnormal ECG variable in the present study was tachycardia at 29.1%, which can be explained by fever, hypoxia, dyspnea, and hypovolemia. Patients who died had significantly higher heart rates, this association of tachycardia with death corresponds to the previous study[7].

Atrial fibrillation prevalence in the present study was 6.9%, which is similar to the previous studies[5,7], while ventricular tachycardia was much less common at 0.8%. This result correlates with the previous study in Spain[6], in which new arrhythmic events involved atrial mechanisms.

In contrast to the previous study[7], the present study showed a higher prevalence of right bundle branch block when compared to LBBB at 14.2% versus 2.3%. The right bundle branch block may be caused by severe disease of COVID-19 pneumonia, coincident pulmonary embolism, myocarditis, and myocardial infarction.

The in-hospital mortality rate in the present study was 18.3%, and all patients in the dead group had at least one ECG abnormality. This mortality rate is similar to the multicenter cohort study in 2022 at 18.2%[20]. However, the prevalence of ECG abnormalities in COVID-19 infected patients with mortality in the present study is higher than in the previous study[7] with 100% versus 70.5%, supposed to be from the smaller size of the population.

Clinical factors that were associated with death from univariate analysis included age, atrial fibrillation, diabetes mellitus, chronic kidney disease, heart rate, peripheral capillary oxygen saturation, ARDS severity, CT of the virus, and remdesivir treatment, all of these factors correlate with disease severity. Elderly patients and those with diabetes mellitus or chronic kidney disease have some degree of immunosuppression, which takes part in disease severity and mortality. Atrial fibrillation may be precipitated by COVID-19 infection or rate-control medication withdrawal due to any cause such as hypotension and shock. Patients with more disease severity tended to receive remdesivir and corticosteroids, which univariate and multivariate analyses did not show the significance of in-hospital mortality in a subgroup of ARDS patients. However, age and these comorbidities were not significantly associated with in-hospital mortality from multivariate analysis.

From multivariate analysis, the remaining factors that were still associated with in-hospital mortality included ARDS severity and the CT of the virus. The CT of the virus was lower in the patients in the dead group, and from ROC analysis, the CT of the virus at lower than 18.14 was associated with in-hospital mortality (OR 5.23). Therefore, the CT of the virus at admission may be used as one of the prognostic factors for this disease.

Some ECG characteristics were associated with in-hospital mortality. First, tachycardia, with a high OR of 7.86, could be explained by non-specific physiologic response according to disease severity. This result also corresponded with the multicenter cohort study that demonstrated an association of sinus tachycardia rate of more than 120 bpm with an increased risk of death[20]. Second, premature atrial complexes were supposed to be found in patients with suspected unknown atrial disease and were apparent during stress illness. Atrial fibrillation also tended to be associated with in-hospital mortality, however, there was limited data on patients' echocardiograms in the present study, which may require further studies. Third, prolonged QTc interval, which might be affected by medications, but the association was still not demonstrated in the present study, or it might result directly from COVID-19 infection. Finally, ST depression, which might be affected by primary

or secondary myocardial ischemia, or patients had unknown prior ischemic heart disease. Nevertheless, the present study still had limited data on patients' coronary angiogram due to COVID-19 situation at that time.

Regarding COVID-19 vaccination, only 20 patients (11%) identified from the medical records had already received the vaccine, which might be according to the early period of COVID-19 pandemic in Thailand. Studies had reported an association of messenger ribonucleic acid (mRNA) COVID-19 vaccine and subsequent myocarditis and pericarditis[21], however, there were four out of twenty patients who died from severe ARDS and pneumonia without myocarditis. As a result, the association of a history of COVID-19 vaccination and in-hospital mortality or disease severity still could not be interpreted.

Overall, the present study is the first study to report the approximate prevalence of ECG abnormalities and their association with death in COVID-19 infected patients in Thailand. The results could be beneficial for the ECG screening in elderly COVID-19 infected patients, or those with disease severity. However, this is a single-center, small size of population study, more data are required to represent the larger populations.

Limitation

The present study has limitations to be acknowledged. First, the study population is confined to the patients who had 12-lead ECG recorded. This could overestimate the overall prevalence if the excluded patients tended to have normal ECGs. However, the present study data may be representative of the patients in the severe or ARDS group according to their baseline characteristics. Second, patients who had abnormal ECG from monitoring temporarily but did not undergo a 12-lead ECG were excluded, which may mask ECG variables' prevalence. Third, ECG characteristics associated with in-hospital mortality were not specific predictors for COVID-19 infection because comparing the risk with the surviving ones, not those with non-COVID-19 infection. Finally, some patients might have pre-existing abnormal ECG but there was no recorded baseline ECG, therefore, detected abnormal ECG characteristics may not be affected by COVID-19 infection.

Conclusion

The prevalence of electrocardiographic abnormalities of hospitalized COVID-19 infected patients in KCMH who underwent 12-lead ECG was 85.6%. The most common abnormal ECG characteristics were prolonged QTc interval, tachycardia, ST depression, and pathologic Q wave, respectively. Some electrocardiographic patterns were associated with in-hospital mortality including tachycardia, premature atrial complexes, prolonged QTc interval, and ST depression.

What is already known on this topic?

From the previous studies, there are various abnormal ECGs among COVID-19 infected patients, including sinus tachycardia, supraventricular tachycardias, ventricular arrhythmias, bradycardias, left and right bundle branch block, axis change, ST segment and T wave change, prolonged QTc interval, and repolarization abnormalities. Several ECG patterns have been associated with poor outcomes regarding death or need for mechanical ventilators.

What does this study add?

There was a high prevalence of electrocardiographic abnormalities of hospitalized COVID-19 infected patients in KCMH who underwent 12-lead ECG, with 85.6%, predominantly patients with critical illness severity or ARDS. This study confirmed an association of some ECG characteristics with in-hospital mortality including prolonged QTc interval, tachycardia, ST depression, and pathologic Q wave. This study provides a benefit of ECG as a screening prognostic marker for in-hospital mortality, especially in patients with more COVID-19 severity. Furthermore, ARDS severity and the CT of the virus were key factors that were associated with death.

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Conflicts of interest

The authors have no conflicts of interest relevant to the content of this article.

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