




ORIGINAL ARTICLE

ECG characteristics of COVID-19 patient with arrhythmias: Referral hospitals data from Indonesia

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Abstract

Background: Arrhythmia is a significant clinical modifier in COVID-19 patient outcomes. Currently, data on arrhythmia and ECG characteristics in COVID-19 from lower middle-income countries are limited.

Methods: COVID-19 was confirmed by polymerase chain reaction testing of a nasopharyngeal sample. All clinical records were systematically evaluated to obtain demographic characteristics and medical comorbidities. The ECG was recorded on admission, in-hospital, and at discharge.

Results: Total documented arrhythmia events account for 22% of patients, comprising 6% of new-onset arrhythmia and 16% of existing arrhythmia. Atrial fibrillation is the most common arrhythmia. The ECG changes were a decrease in heart rate (91 ± 22 vs. 83 ± 20 , $p < .001$) and an increase in the QT interval (354.7 ± 53.70 vs. 371.4 ± 59.48 msec, $p < .001$) from hospital admission to hospital discharge, respectively. The in-hospital HR of 85 bpm or higher increases the risk of death (OR = 2.69, $p = .019$).

Conclusion: The incidence of arrhythmias in COVID-19 patients at COVID-19 referral hospitals in Indonesia is 22%. Atrial fibrillation is the most common arrhythmia in COVID-19 patients. Prolongation of QRS duration from admission to discharge was related to the occurrence of new-onset arrhythmia. The in-hospital HR of 85 bpm or higher increased the risk of death.

KEYWORDS

arrhythmia, Covid-19, ECG, heart rate

1 | INTRODUCTION

The Covid-19 pandemic lasted for almost 2 years since the first case in December 2019 at Wuhan. Although the main symptoms of Covid-19 are related to the respiratory system, heart involvement, especially

arrhythmias, has been previously identified. Initial work by Wang et al.¹ revealed that arrhythmia occurrence was about 17% among hospitalized Covid-19 patients. Currently, only limited data on arrhythmia characteristics in Covid-19 patients have been published, and most of them come from developed countries equipped with sophisticated medical facilities.

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This study aims to elaborate on arrhythmia and ECG characteristics of Covid-19 patients hospitalized in a lower middle-income country with fewer medical facilities and budgets.

2 | METHODS

2.1 | Study population

A total of 200 confirmed Covid-19 patients by polymerase chain reaction testing of a nasopharyngeal sample participated in this study. A retrospective cohort was done in Covid-19 referral hospitals of Pertamina Jaya Hospital, Fatmawati General Hospital, and National Cardiovascular Center Harapan Kita. The study received approval from the Institutional Review Board at National Cardiovascular Center Harapan Kita, Jakarta.

2.2 | Clinical variables

All clinical records were systematically evaluated to obtain demographic characteristics and medical comorbidities. All the comorbidities were based on the final diagnosis recorded in medical records made by the physicians at discharge. The ECGs were recorded on admission and at discharge. If any arrhythmias occurred during hospitalization, additional ECG was recorded. Subjects with arrhythmia events were divided into new-onset and preexisting arrhythmia groups. Patients with normal sinus rhythm during admission who had arrhythmia events during hospitalization were classified as new-onset arrhythmia group. Meanwhile, patients who had arrhythmias during admission were classified into the preexisting arrhythmia group. The outcomes of this study were mechanical ventilation requirement, ICU admission, hospital length of stay, and mortality. In addition, the outcomes were analyzed in relation to the patient's grouping.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS, version 25. We compared the clinical and ECG characteristics of patients with and without arrhythmias. The proportion of arrhythmias was calculated against the total number of patients who participated during the study period. The ECG characteristics and type of arrhythmia were analyzed using Pearson regression for correlation with clinical outcome. The categorical variables were analyzed using the Chi-square test, while an independent sample *t* test/Mann-Whitney *U* test was used for continuous data. Nominal variables will be displayed as means and standard deviations. Various confounding variables will be tested by bivariate followed by multivariate. Statistical significance was considered significant if the *p* value was $<.05$.

3 | RESULTS

3.1 | Clinical characteristics

The majority of cases are male and relatively young. Hypertension and cerebrovascular disease (CVD) are the predominant comorbidities. Table 1 shows demographic and comorbid proportions. All patients took azithromycin 500 mg QD for the initial 5 days of hospitalization, but none took hydrochloroquine. Other medications were antiviral (favipiravir or remdesivir), additional intravenous antibiotic if needed, 1 g vitamin C injection, oral vitamin D 5000 IU, and oral Zinc sulfate. Actemra was rarely given due to undersupply and high cost.

3.2 | Rhythm characteristics

Total documented arrhythmia events account for 22% of patients, comprising 6% of new-onset arrhythmia and 16% of preexisting arrhythmia. Atrial fibrillation was the commonest arrhythmia encountered in our subjects, but there was no documented ventricular arrhythmia event. During the average hospital length of stay of 17.50 ± 11.02 days proportion of most arrhythmias decreases significantly from admission to discharge (Table 2). Total AV block occurred in 1 patient and persisted until 14 days, warrants permanent pacemaker implantation (Figure 1).

3.3 | ECG parameters

Three cardiology fellows manually calculated basic ECG parameters with intra- and interobserver agreement of 0.80 and 0.89,

TABLE 1 Clinical characteristics

Parameters	Description
Age	52 ± 14
Gender	
Male	134 (67%)
Female	66 (33%)
Comorbidities	
Hypertension	88 (44%)
CAD	5 (2.5%)
DM	68 (34%)
Chronic respiratory disease	19 (9.5%)
CKD	23 (11.5%)
CVD	104 (52%)
Obesity	5 (2.5%)
LOS (days)	17 ± 11

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; LOS, length of stay.

respectively. There was a total of 400 ECGs on admission and discharge. The mean heart rate was decreased, whereas the QT interval was slightly increased from admission to discharge (Table 2). The QRS duration, QT corrected (QTc) interval, and ST-T changes were not statistically different.

Subgroup analysis based on arrhythmia onset showed that in patients with normal sinus rhythm, heart rate was significantly decreased from admission to discharge. On the contrary, the QT interval was increased. Patients in the new-onset arrhythmia group had a significant increase in QRS duration from admission to discharge. The preexisting arrhythmia group showed no significant differences in all measured ECG parameters (Table 3).

The in-hospital and discharge/last recorded heart rate (HR) were significantly higher in patients who required ICU or died (Table 4). The in-hospital and discharge/last ECG HR of >85bpm had an increased risk of death (OR = 2.69, $p = .019$ and OR = 2.47, $p = .035$, respectively) (Table 5).

TABLE 2 The arrhythmia types and ECG parameters during admission and discharge

Rhythm and ECG	Recording time		p value
	Admission (n = 200)	Discharge (n = 200)	
Rhythm types			
Sinus rhythm	171 (85.5%)	176 (88%)	<.001
Atrial fibrillation	21 (10.5%)	18 (9%)	<.001
Atrial flutter	2 (1%)	1 (0.5%)	.01
Junctional rhythm	1 (0.5%)	1 (0.5%)	1.00
Pacing rhythm	1 (0.5%)	2 (1%)	.01
AV block	4 (2%)	2 (1%)	.04
ECG parameters			
Heart rate (bpm)	91 ± 22	83 ± 20	<.001
QRS duration (ms)	88.7 ± 18.5	90.3 ± 21.1	.224
QT interval (ms)	354.7 ± 53.7	371.4 ± 59.5	<.001
QTc interval (ms)	431.4 ± 81.7	430.9 ± 56.5	.229
ST-T changes (%)	35	36	.695

3.4 | Arrhythmia outcomes

In patients with sinus rhythm, 20% required a ventilator, 34.8% required ICU care, and 14.7% died during an average of 18 ± 11 days length of stay. Neither existing nor new-onset arrhythmias changed outcomes in terms of mechanical ventilation requirement, ICU stay, hospital length of stay, and mortality (Table 6).

Atrial fibrillation was not associated with the need for a ventilator, ICU hospitalization, and death. Other documented arrhythmias were not influenced the clinical outcomes as well (Supporting Information Table S1).

3.5 | Inflammation markers

In 60 subjects, who had complete laboratory data, we analyzed the relationship of inflammatory markers to the changes in ECG parameters. The admission CRP level showed a significant and moderate correlation with an increase in QRS duration ($r = .35$, $p = .03$) and QTc intervals ($r = .36$, $p = .03$) at discharge (Table 7). The admission CRP level did not differ between normal rhythm and arrhythmia subjects (33.2 ± 41.4 vs. 28.9 ± 38.1 , $p = .759$, respectively). In addition, the ESR is moderately correlated with discharge QT interval ($r = .36$, $p = .03$). However, there is no significant association between inflammation markers and AF in our subset.

4 | DISCUSSION

Our study found that the prevalence of arrhythmia events in Covid-19 patients was 22% in total. The arrhythmias occurred in 18% of patients during admission and remained found in 15% of patients at discharge. Previous work reported the incidence of cardiac arrhythmias in COVID-19 patients was about 17%.¹ However, we found no difference in clinical outcome between patients who developed arrhythmias during hospitalization and patients who already had arrhythmias on admission compared with patients without arrhythmias. This happened because the Covid-19 mortality in our

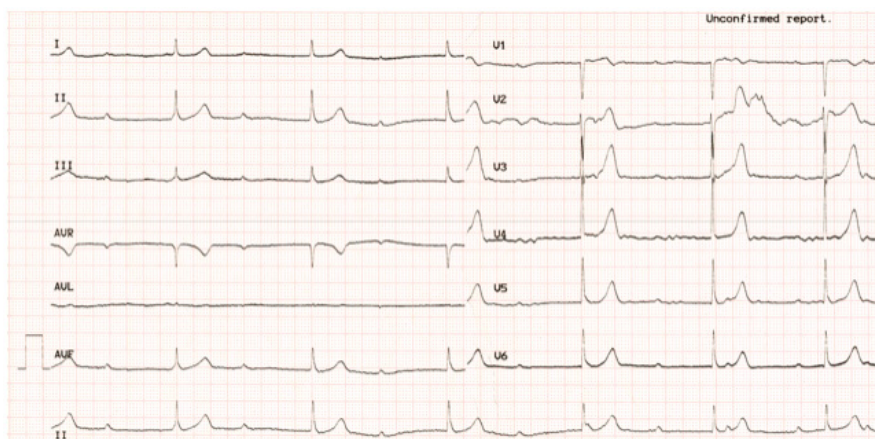


FIGURE 1 Complete heart block happened at ninth days of hospitalization in one patient

TABLE 3 The ECG parameters on normal rhythm and arrhythmia

Variable	Normal rhythm			New-onset arrhythmia			Existing arrhythmia		
	Admission	Discharge	p value	Admission	Discharge	p value	Admission	Discharge	p value
Heart Rate (bpm)	90 ± 19.7	83 ± 17.3	<.001	84 ± 14.02	71 ± 28.09	.080	100 ± 31.9	88 ± 26.1	.072
QRS Duration (msec)	87.5 ± 18.1	88.1 ± 19.4	.583	86.3 ± 16.6	93.5 ± 23.6	.041	95 ± 20.2	99.7 ± 25.7	.181
QT interval (msec)	352.3 ± 46.8	368.7 ± 56.9	.001	375.5 ± 42.8	407.5 ± 70.7	.155	357.7 ± 81.9	371.5 ± 64.9	.372
QTc interval (msec)	426.3 ± 53.8	430.3 ± 52.3	.324	441.4 ± 50.4	422.5 ± 65.9	.318	452.9 ± 163.6	437 ± 72.2	.608
ST-T changes (%)	32.7	35.3	.373	41.7	33.3	.339	43.8	40.6	.662

series was high (15.5%), which was higher than in previous reports.¹ Patients with existing arrhythmias tend to have a higher mortality rate. Wang et al.¹ found more frequent ICU admission in arrhythmia patients than in patients with a normal rhythm.

We found that atrial fibrillation is the most common arrhythmia during Covid-19 hospitalization among documented arrhythmia events. However, there is no correlation between atrial fibrillation and clinical outcomes of Covid-19 patients in our series. As an emerging disease, data on clinical factors associated with Covid-19 are evolving and conflicting. Bhatla et al. found a 25% incidence of atrial fibrillation, the most common arrhythmia in their cohort. Their data showed atrial fibrillation was associated with mortality but was not an independent factor in multivariate analysis.² In recent publications from developed countries, Paris et al. and Mountantonakis et al. reported that AF was found in 15%–17.6% of Covid-19 cases and significantly had higher hospital mortality compared with patients without atrial fibrillation.^{3,4} In-hospital death occurred in 38.7% of the patients with a history for AF vs. 20.8% of those without. The association between AF and mortality remained significant after adjustment for variables associated with COVID-19 severity, such as comorbidities, previous anticoagulant use, oxygen saturation, red blood cells count, hemoglobin, CRP, plasma troponin, and HF history. Of note, the mean age of patients in this study was 67.4 ± 13.2 years old and even older in AF patients (75.8 ± 10.9 and 73.1 ± 13.5 years old, respectively).^{3,4} They did not adjust to the age, even though age is a prominent risk factor of AF. Our patients were younger (51.9 ± 13.7 years old) with lower AF incidence (10.5%). Furthermore, in our study, arrhythmia documentation was based on the 12-lead ECG of patients treated in a regular ward and witnessed ECG monitoring during ICU treatment. This method potentially underestimates actual AF events. However, it generally shows the importance of routine ECG screening to avoid undetectable AF events.

Our study found significant ECG changes in Covid-19 patients: a decrease in heart rate and an increase in the QT interval from hospital admission to hospital discharge. Fever and inflammation due to moderate to severe Covid-19 infection may cause an increase in heart rate at admission, which gradually normalized at discharge.

A recent publication by Thakore et al.⁵ found that the admission QTc interval in 828 Covid-19 patients was prolonged compared with discharged patients (450.1 ± 30.2 ms vs. 423.4 ± 21.7 ms, $p < .0001$). Our study found that the QTc interval did not differ from admission to discharge. On the contrary, the discharge QT interval in our study was longer than its admission value. As the QTc was calculated using Bazett's formula, it depends mainly on changes in RR intervals or HR, affecting the QTc values. In addition, smaller sample size in our study might also influence the results. Furthermore, the QT interval is influenced by several factors. A population-based survey, which was conducted on 11,209 participants over the age of 35 in China, found that older age, abdominal obesity, hypertension, diabetes, hypokalemia, and any medicine used in the past 2 weeks were associated independently with increased risk for prolonged QTc interval (all $p < .05$ in the

TABLE 4 The ECG parameters and clinical outcomes

	Survive (n = 169)	Death (n = 31)	p	Non-ICU (132)	ICU (n = 67)	p
HR 1	90.2 ± 22.4	96.8 ± 19.6	.128	91.4 ± 22.6	91.2 ± 21.3	.958
HR 2	79.9 ± 17.2	88.2 ± 16.3	.028	79.3 ± 17.0	84.9 ± 17.1	.059
HR 3	80.4 ± 16.2	97.5 ± 30.3	.001	80.9 ± 17.0	86.9 ± 24.4	.046
QRS Dur 1	88.9 ± 18.8	87.5 ± 16.7	.709	88.8 ± 19.2	88.5 ± 17.3	.89
QRS Dur 2	90.1 ± 20.7	89.5 ± 18	.897	91.7 ± 22	89 ± 16.1	.175
QRS Dur 3	90.2 ± 21.4	90.1 ± 19.9	.943	91.2 ± 22.3	88.8 ± 18.6	.446
QT 1	356.8 ± 56.1	343.582 ± 36.8	.207	359.3 ± 58.1	345.6 ± 43.3	.09
QT 2	379.2 ± 57.3	364.5 ± 41.6	.217	383.4 ± 59.2	364.8 ± 44.1	.051
QT 3	373.8 ± 59.4	358.3 ± 59	.182	378.8 ± 62.5	357.7 ± 50.7	.017
QTc 1	432.8 ± 86.8	423.9 ± 44.3	.576	437.1 ± 92.4	420.7 ± 54.4	.181
QTc 2	433.0 ± 51.4	432.0 ± 58.5	.932	436.7 ± 53.7	425.6 ± 50.3	.223
QTc 3	429.5 ± 54.2	439 ± 67.9	.389	434.8 ± 55.4	423.4 ± 58.6	.18

Note: 1 = admission, 2 = in-hospital, 3 = discharge or last ECG.

Abbreviations: HR, heart rate; QRS Dur, QRS duration.

TABLE 5 Logistic regression test of heart rate for the outcomes

HR cutoff	HR2				HR3			
	Deathn (%)	Surviven (%)	p	OR	Deathn (%)	Surviven (%)	p	OR
≥ 85	16 (51.6)	48 (28.4)	.013	2.69	19 (61.3)	66 (39.1)	.024	2.47
< 85	15 (48.4)	121 (71.6)			12 (38.7)	103 (60.9)		
Total	31 (100)	169 (100)			31 (100)	169 (100)		

Abbreviations: HR2, in-hospital heart rate; HR3, discharge/last ECG heart rate; OR, odds ratio.

Rhythm at admission	Ventilator requirement		ICU admission		Death	
	Requirement	p value	Admission	p value	Death	p value
Sinus rhythm	Ref		Ref		Ref	
Atrial fibrillation	4 (19%)	1.00	6 (28.6%)	.85	4 (19%)	.53
Atrial flutter	0 (0%)	1.00	2 (100%)	.12	0 (0%)	1.00
Junctional rhythm	0 (0%)	1.00	0 (0%)	1.00	0 (0%)	1.00
Pacing rhythm	1 (100%)	.21	1 (100%)	.34	1 (100%)	.15
AV block	1 (25%)	1.00	1 (25%)	1.00	1 (25%)	.48

TABLE 6 Association of arrhythmia types with clinical outcomes

TABLE 7 Pearson correlation between inflammatory markers and ECG parameters (n = 60)

Inflammatory markers	QRS duration				QT interval				QTc interval			
	Admission		Discharge		Admission		Discharge		Admission		Discharge	
	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value
ESR	.07	.67	.08	.62	-.13	.41	.34	.03	-.16	.29	.20	.21
WBC	.06	.70	-.14	.36	.06	.72	-.06	.72	.02	.91	-.54	.73
CRP	.22	.19	.35	.03	-.22	.19	.31	.06	-.11	.52	.36	.03

fully adjusted logistic regression model).⁶ The younger subjects in our study population might cause a different pattern of QTc interval change.

Our study showed that in-hospital HR of >85 bpm significantly increased the risk of death (OR = 2.47, *p* = .035). Patients with high HR throughout hospitalization might be associated with prolonged

and severe inflammation. In the ICU setting, high HR has been associated with increased mortality.⁷ In the general population, a meta-analysis revealed that higher resting HR was independently associated with increased risks of all-cause and cardiovascular mortality in the general population. This indicates that resting HR is a predictor of all-cause and cardiovascular mortality.⁸ In this study, an increase in the inflammatory marker CRP was significantly associated with lengthening of QRS duration and QTc intervals. Electrocardiographic changes are related to myocardial injury and higher inflammatory biomarkers in Covid-19.⁹ Inflammation has also been recognized as a pivotal factor in QT interval prolongation. Several studies showed that persistent high-grade systemic inflammation of rheumatoid arthritis was associated with QTc prolongation¹⁰⁻¹⁵ and increased arrhythmias incidence.^{16,17} A meta-analysis of population-based studies showed the risk of AF in rheumatoid arthritis patients was significantly increased.¹⁸ Earlier reports of QT interval prolongation in Covid-19 patients were associated with drugs that prolong QT intervals, such as hydroxychloroquine or chloroquine and azithromycin.¹⁹⁻²¹ This should encourage clinicians to always pay attention to the side effects of medications that can prolong QT intervals and not underestimate the inflammatory influence on changes in QT intervals and arrhythmia events.

4.1 | Limitation

This study has some limitations, such as different hospital discharge times resulting in different discharge ECG recording times. The changes in ECG parameters associated with inflammation might differ regarding recovery time. In addition, we only checked limited ECG parameters. Further studies in this younger age group by adding other ECG parameters such as QTd and QRS diminution²² may describe changes in the ECG pattern more completely.

5 | CONCLUSION

The incidence of arrhythmias in Covid-19 patients at Covid-19 referral hospitals in Indonesia is 22%, consisting of 16% at admission and 15% at discharge. Atrial fibrillation is the most common arrhythmia in Covid-19 patients. Prolongation of QRS duration from admission to discharge was related to the occurrence of new-onset arrhythmia. The in-hospital HR of 85 bpm or higher increases the risk of death.

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CONFLICT OF INTEREST

The authors declared that they have NO affiliation with or involvement in any organization or entity with any financial interest or

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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