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Cardiac arrhythmia among hospitalized COVID-19 patients at Gunung Jati General Hospital, Indonesia

Arritmia cardiaca entre pacientes hospitalizados con COVID-19 en el Hospital General Gunung Jati, Indonesia

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Palabras clave:
arritmia, coronavirus, COVID-19, hospitalización, resultados adversos, mortalidad.

ABSTRACT

Introduction: arrhythmia is one of the most common extrapulmonary complications of coronavirus 2019 (COVID-19). **Objectives:** this study aimed to assess the outcomes of hospitalized COVID-19 patients with and without arrhythmia from asymptomatic to life-threatening disease severity and the predictors of the in-hospital outcomes. **Material and methods:** a total of 257 patients with confirmed COVID-19 who had at least one electrocardiogram recording from April 01 to December 31, 2021, were enrolled in this cross-sectional study. **Results:** arrhythmia occurred in 36.6% of patients. The mean age of patients with arrhythmia was 52.48 ± 13.936 years, with a male preponderance (57.4%). The most common arrhythmia was sinus tachycardia (69.1%). Pre-existing atrial fibrillation (AF) and new-onset AF occurred in 10.6% and 2.1% of patients, respectively. Total atrioventricular block occurred in 2.1% of patients. Heart failure (20.2%), previous arrhythmia (10.6%), hypertension (46.8%), diabetes mellitus (DM) (42.6%), and chronic kidney disease (55.3%) were more prevalent in patients with arrhythmia. Patients with arrhythmia had a significantly higher need for Intensive Care Unit (ICU) (50%), need for intubation and mechanical ventilation (MV) (7.4%), hypotension requiring vasopressor (16%), and in-hospital mortality (44.7%) compared to patients without arrhythmia. After multivariate analysis, DM was associated with a higher need for ICU, hypotension requiring vasopressor, and in-hospital mortality. History of stroke/transient ischemic attack (TIA) and thrombocytopenia during admission was associated with a higher need for intubation and MV. **Conclusions:** the in-hospital outcomes in patients with COVID-19 and arrhythmia are the worst. In patients with arrhythmia, DM is associated with higher need for ICU, hypotension requiring vasopressor, and in-hospital mortality. A history of stroke/TIA and thrombocytopenia during admission are associated with higher need for intubation and MV.

RESUMEN

Introducción: *las arritmias son una de las complicaciones extrapulmonares más comunes del coronavirus 2019 (COVID-19).* ***Objetivos:*** *este estudio se realizó para evaluar la evolución de los pacientes hospitalizados por COVID-19, desde asintomático hasta grave, que presentaban con y sin arritmias, e investigar los predictores de desenlaces hospitalarios.* ***Material y métodos:*** *se hizo un estudio transversal que incluyó un total de 257 pacientes con COVID-19 confirmado y que contaban con al menos un registro de electrocardiograma entre el 1 de abril y el 31 de diciembre del 2021.* ***Resultados:*** *se observaron arritmias en 36.6% de los pacientes. Su edad promedio fue de 52.48 ± 13.93 y predominaron los de género masculino (57.4%). La arritmia más común fue la taquicardia sinusal (69.1%), seguida por fibrilación auricular (FA) preexistente y la FA de reciente aparición, que ocurrieron, respectivamente, en 10.6% y 2.1% de los pacientes. Hubo bloqueo auriculoventricular completo en 2.1%. Las comorbilidades más frecuentes en el grupo de arritmias fueron: la insuficiencia cardiaca (20.2%), arritmia previa (10.6%), hipertensión arterial (46.8%), diabetes mellitus (DM) 42.6% y enfermedad renal crónica (55.3%). Los pacientes con arritmia tuvieron una mayor necesidad de cuidados intensivos (CI) (50%), intubación y ventilación mecánica (VM) (7.4%), vasopresores (16%) y mayor mortalidad hospitalaria (44.7%). El análisis multivariante asoció la DM con mayor necesidad de CI y necesidad de vasopresores y mortalidad hospitalaria. La historia de accidente cerebrovascular o ataque isquémico transitorio (AIT) y trombocitopenia al momento de la admisión se asoció con mayor necesidad de intubación y VM.* ***Conclusión:*** *los resultados intrahospitalarios en pacientes con COVID-19 y arritmia son los peores. Los pacientes con arritmias y DM requirieron con mayor frecuencia de CI, vasopresores y tuvieron mayor mortalidad hospitalaria, aquellos con historia de accidente cerebrovascular y AIT eran más susceptibles de ser intubados y recibir VM.*

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INTRODUCTION

The coronavirus 2019 (COVID-19), first identified in Wuhan in December 2019, primarily affects the respiratory system.[1,2] However, COVID-19 is also known to affect the other system in the body and can lead to extrapulmonary involvements, including cardiac arrhythmia.[3,4] An early study from Wuhan reported an incidence of arrhythmia in 16.7% of hospitalized COVID-19 patients.[5] In addition, the incidence was higher in patients admitted to the Intensive Care Unit (ICU) and reached 44%.[5] However, the study did not describe the specific type of arrhythmia.[5] The severity of the disease was also found to correlate with the incidence of arrhythmia, with a higher incidence in patients with severe disease compared to mild disease.[6]

In some COVID-19 patients, arrhythmia may be the first infection symptom, preceding the respiratory symptoms.[6] COVID-19-related arrhythmia can manifest as tachyarrhythmia or bradyarrhythmia.[7-11] Atrial fibrillation (AF) was the most commonly reported supraventricular tachyarrhythmia.[12,13] In addition, ventricular tachyarrhythmia such as ventricular tachycardia (VT) was reported in hospitalized COVID-19 patients.[8,14,15] Several studies also reported bradyarrhythmia in the form of sinus bradycardia, total atrioventricular (AV) block, and sinus pause.[8,10,11,14,15]

Despite accumulating evidence, there is still variation in the type and outcomes of arrhythmia associated with COVID-19 in hospitalized patients. Some retrospective studies did not include COVID-19 patients with asymptomatic and mild disease severity. Therefore, this study aims to investigate and to compare the outcomes of hospitalized COVID-19 patients with and without arrhythmia from asymptomatic to life-threatening disease severity and to investigate the predictors that may influence the in-hospital mortality, the need for intensive care (IC), the need for intubation and mechanical ventilation (MV), hypotension requiring vasopressor, thromboembolic event (deep vein thrombosis and pulmonary embolism), major bleeding, and stroke or transient ischemic attack (TIA).

MATERIAL AND METHODS

Inclusion and exclusion criteria. This study included moderate, severe, and critically ill COVID-19 patients ≥ 18 years who were hospitalized with the primary indications of COVID-19 and tested positive with real time-polymerase chain reaction (RT-PCR) between April 1, 2021, and December 31, 2021, at Gunung Jati General Hospital, Cirebon. We also included patients admitted to our hospital due to other medical indications with positive RT-PCR tests. The COVID-19 severity of patients admitted due to other medical indications will be assessed and categorized as asymptomatic, mild, moderate, severe, or critically ill. Patients who were pregnant, discharged, or transferred by their intention before fulfilling treatment were excluded.

Data collection. Data on patients' demographic, clinical characteristics, comorbidities, history of cardiovascular procedures, electrocardiography, management during hospitalization, outcomes were directly collected from hospital medical records. Two cardiologists interpreted the electrocardiography. Any disagreement in the electrocardiography interpretation was resolved through discussion. Continuous telemetry monitoring was performed on all patients admitted to the ICU. We included major arrhythmias (supraventricular tachycardia, new-onset atrial fibrillation, new-onset atrial flutter, pre-existing atrial fibrillation, pre-existing atrial flutter, atrioventricular block, sinus pause, sinus arrest, ventricular tachycardia, ventricular fibrillation) and non-major arrhythmias (sinus tachycardia, sinus bradycardia, premature atrial complex, premature ventricular complex).[7,8] New-onset atrial fibrillation (NOAF) or atrial flutter is defined as electrocardiographic evidence of atrial fibrillation or atrial flutter during admission or hospitalization in patients without a medical history of atrial fibrillation or atrial flutter. Pre-existing atrial fibrillation (PEAF) or atrial flutter is defined as patients with a medical history of atrial fibrillation or atrial flutter. The outcomes were in-hospital mortality, the need for IC, the need for intubation and mechanical ventilation, hypotension requiring vasopressor, thromboembolic event (deep vein thrombosis and pulmonary embolism), major bleeding, and stroke/TIA. Our hospital's ethics committee approved this study with the number No. 087/LAIKETIK/KEPKRSGJ/VI/2021.

Statistical analysis. Descriptive statistics were used to summarize the data. Categorical variables were presented as frequencies and percentages. The Shapiro-Wilk or Kolmogorov-Smirnov normality test was performed as appropriate. Normally distributed data for continuous variables were summarized as mean and standard deviation. Otherwise, the data were presented as the median and interquartile range (25^{th} percentile = P25, 75^{th} percentile = P75). The independent T-test or Mann-Whitney U-test was performed to compare continuous variables between patients with and without arrhythmia. Chi-square (χ^2) and Fisher's exact were used to compare dichotomous variables between patients with and without arrhythmia. Results were considered significant at p-value < 0.05.

Furthermore, the χ^2 test or Fischer's exact test was performed to compare and determine the independent variables according to the outcomes of patients with arrhythmia that will be included in the multivariate logistic regression analysis. Variables with χ^2 or Fisher's exact p-value logistic regression and backward method were applied. The statistical analysis was conducted using SPSS version 22.0.

RESULTS

This cross-sectional studies included 257 patients admitted due to confirmed COVID-19, from April 1 to December 31, 2021, for study analysis. A total of 94 patients (36.6%) had arrhythmia during hospitalization. The patients' demographic data are shown in *Table 1*. Most patients were male (n = 137, 53.3%), and the mean age was 53.49 ± 13.34 years old. The proportion of IHD in patients with arrhythmia was almost twice that of patients without arrhythmia, although the difference did not reach statistical significance.

As seen in *Table 2*, patients with arrhythmia had more severe disease (48.9% vs. 22.7%; p < 0.001) than those without arrhythmia, as reflected in clinical presentation and laboratory results. Compared to patients without arrhythmia, patients with arrhythmia had lower oxygen saturation during initial admission (90.5 vs. 96; p < 0.001). Patients with arrhythmia had a higher level of leukocytes (9,465 vs. 8,070/µL; p = 0.019), neutrophil-to-lymphocyte ratio (NLR) (6.53 vs. 4.62; p < 0.001), creatinine (1.34 vs. 1.14 mg/dL; p = 0.022), and d-dimer level (2,061 vs. 1,167 ng/mL; p < 0.001) compared to patients without arrhythmia, as presented in *Table 3*. The high-flow nasal cannula [23 (24.5%) vs. 15 (9.2%); p = 0.001], anticoagulant [80 (85.1%) vs. 117 (71.8%); p = 0.015], and plasma convalescent [28 (29.8%) vs. 27 (16.6%); p = 0.013] were more commonly prescribed in patients with arrhythmia compared to those without arrhythmia, as seen in *Table 4*.

In this study, 94 patients (36.6%) displayed arrhythmia during hospitalization. The electrocardiographic parameter between patients with and without arrhythmia can be seen in *Table 5*; the arrhythmias are listed in *Table 6*. The patients can present with single or multiple arrhythmias during hospital admission. From patients with single arrhythmia, the most common arrhythmia was sinus tachycardia (69.1%) and followed by pre-existing AF (10.6%). New-onset AF occurred in 2.1% of patients during the hospitalization period. Total AV block also occurred in 2.1% of patients. For patients with multiple arrhythmias, the most common arrhythmia was sinus tachycardia with premature atrial complex (3.2%), followed by sinus tachycardia with premature ventricular complex (1.1%) and sinus bradycardia with first degree AV block and premature ventricular complex (1.1%).

Overall, patients with arrhythmia had significantly worse outcomes than those without during hospitalization, as shown in *Table 7*. The need for intubation and mechanical ventilation [7 (7.4%) vs. 2 (1.2%); p = 0.009] and hypotension requiring vasopressor [15 (16%) vs. 5 (3.1%); p < 0.001] were more commonly observed in patients with arrhythmia compared to patients without arrhythmia. Due to higher disease severity and complications, the need for IC was significantly higher in patients with arrhythmia compared to those without arrhythmia [47 (50%) vs. 38 (23.3%); p < 0.001].

Age ≥ 65 years old (OR 3.203; 95% CI 1.117-9.186; p = 0.026), DM (OR 2.918; 95% CI 1.248-6.824; p = 0.012), leukocytosis during admission (OR 2.616; 95% CI 1.134-6.033; p = 0.023), and NLR > 6.82 during admission (OR 2.641; 95% CI 1.139-6.123; p = 0.017) were associated with the need for IC in univariate analysis. After multivariate analysis, only DM (adjusted OR 2.656; 95% CI 1.114-6.333; p = 0.028) remained associated with the need for IC and can be seen in *Table 8*.

In univariate analysis, history of stroke/TIA (OR 17; 95% CI 1.965-147.046; p = 0.027) and NLR > 6.82 (OR 8.914; 95% CI 1.028-77.292; p = 0.041) were associated with the need for intubation and mechanical ventilation as seen in *Table 8*. After multivariate analysis, history of stroke/TIA (adjusted OR 46.426; 95% CI 1.64-1314.392; p = 0.024), thrombocytopenia during admission (adjusted OR 17.131; 95% CI 1.623-180.777; p = 0.018), and NLR > 6.82 (adjusted OR 0.67; 95% CI 0.005-0.882; p = 0.04) associated with the need for intubation and mechanical ventilation. In univariate analysis, new-onset AF and premature atrial complex (PAC) numerically increased the need for intubation and mechanical ventilation.

In univariate analysis, age ≥ 65 years old (OR 5.802; 95% CI 1.79-18.805; p = 0.004),

Table 1: Basic demographic.

	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
Male sex	137 (53.3)	54 (57.4)	83 (50.9)	0.312
Age (years), mean ± SD	53.49 ± 13.344	52.48 ± 13.936	54.08 ± 12.998	0.355
Duration of hospitalization (days), median [IQR]	12 [9-16]	13 [7-16.5]	11 [9-16]	0.87
BMI (kg/m^2), median [IQR]	23.88 [22.03-26.62]	24.425 [22.108-26.68]	23.74 [21.87-26.57]	0.48
Active smoker	11 (4.3)	5 (5.3)	6 (3.7)	0.537
Ischemic heart disease	22 (8.6)	12 (12.8)	10 (6.1)	0.067
Heart failure	27 (10.5)	19 (20.2)	8 (4.9)	< 0.001
Previous arrhythmia	11 (4.3)	10 (10.6)	1 (0.6)	< 0.001
Hypertension	89 (34.6)	44 (46.8)	45 (27.6)	0.002
Diabetes	85 (33.1)	40 (42.6)	45 (27.6)	0.014
Chronic kidney disease	121 (47.1)	52 (55.3)	69 (42.3)	0.045
Obesity	105 (40.9)	42 (38.4)	63 (66.6)	0.344
COPD	0	0	0	–
Bronchial asthma	3 (1.2)	0	3 (1.8)	0.301
Active cancer	11 (4.3)	1 (1.1)	10 (6.1)	0.06
Stroke or TIA	9 (3.5)	4 (4.3)	5 (3.1)	0.728
Tuberculosis on treatment	7 (2.7)	6 (6.4)	1 (0.6)	0.011
HIV	4 (1.6)	2 (2.1)	2 (1.2)	0.626
Autoimmune disease	2 (0.8)	1 (1.1)	1 (0.6)	1
Valvular heart disease	2 (0.8)	1 (1.1)	1 (0.6)	1
History of PCI	2 (0.8)	0	2 (1.2)	0.534
History of CABG	1 (0.4)	0	1 (0.6)	1

BMI = body mass index. CABG = coronary artery bypass grafting. COPD = chronic obstructive pulmonary disease. IQR = interquartile range. PCI = percutaneous coronary intervention. SD = standard deviation. TIA = transient ischemic attack.

Table 2: Vital signs during admission and COVID-19 symptom severity.

Variable	All patients (N = 257)	Arrhythmia (N = 94)	Non-arrhythmia (N = 163)	p
Vital signs during admission, median [IQR]				
Systolic blood pressure (mmHg)	130 [110-140]	130 [118.75-150]	130 [110-140]	0.075
Diastolic blood pressure (mmHg)	80 [70-90]	80 [70-90]	80 [70-82]	0.106
Heart rate (bpm)	95 [84-104]	103.5 [90.5-117]	89 [83-99]	< 0.001
Respiratory rate	24 [22-28]	27.5 [24-30]	24 [21-26]	< 0.001
Oxygen saturation (%)	95 [88-97.5]	90.5 [82-96]	96 [89-98]	< 0.001
Temperature (ºC)	36.6 [36.35-36.8]	36.7 [36.5-37]	36.6 [36.3-36.8]	0.034
COVID-19 symptom severity, n (%)				
Non severe and critical	174 (67.7)	48 (51.1)	126 (77.3)	< 0.001
Severe and critical	83 (32.3)	46 (48.9)	37 (22.7)	< 0.001

IQR = interquartile range.

Table 3: Laboratory results during admission.

	All patients (N = 257) Median [IQR]	Arrhythmia (N = 94) Median [IQR]	Non-arrhythmia (N = 163) Median [IQR]	p
Hemoglobin (g/dL)	12.8 [11.2-14]	12.9 [11.2-14.125]	12.7 [11.2-13.9]	0.439
White blood cells (µL)	8,590 [6,335-11,970]	9,465 [6,610-13,182.5]	8,070 [6,040-10,750]	0.019
Platelets count (10^3/µL)	240 [176.5-322.5]	228 [169.5-305.5]	251 [179-329]	0.156
Red blood cells (million/µL)	4.5 [3.925-4.945]	4.61 [4.048-5.115]	4.4 [3.8-4.88]	0.033
Neutrophils (%)	77.8 [68.95-86.25]	80.7 [74.075-87.025]	74.6 [65.4-84.5]	0.001
Lymphocytes (%)	15 [8.35-21.5]	12.65 [7.65-17.75]	17.2 [9.9-24.5]	< 0.001
NLR	5.06 [3.17-10.525]	6.53 [4.2-11.25]	4.62 [2.56-8.42]	< 0.001
Ureum (mg/dL)	39 [25.95-68.1]	50.75 [29.15-81.275]	34 [24.5-56.7]	0.003
Creatinine (mg/dL)	1.23 [0.96-1.775]	1.34 [1.04-2.025]	1.14 [0.88-1.56]	0.022
eGFR, mean ± SD	59.297 ± 32.604	57.137 ± 30.415	60.542 ± 33.831	0.421
Sodium (mmol/L)	139.2 [134.375-142.4] N = 233	138.9 [134.2-142.45] N = 89	139.4 [134.325-142.375] N = 144	0.949
Potassium (mmol/L)	4.22 [3.718-4.765] N = 233	4.29 [3.815-4.975] N = 89	4.145 [3.56-4.725] N = 144	0.227
Random blood glucose (mg/dL)	126 [104-191]	135 [109.25-208]	119 [100-178]	0.036
CRP (mg/L)	49.84 [19.12-92.408] N = 178	59.705 [24.42-119.29] N = 66	46.655 [16.8-79.49] N = 112	0.058
D-dimer (ng/mL)	1,384 [675.75-3,568.25] N = 234	2,061 [1,203.25-5,087.75] N = 84	1,167 [592-2,657.25] N = 150	< 0.001

CRP = C-reactive protein. eGFR = estimated glomerular filtration rate. IQR = interquartile range. NLR = neutrophil-to-lymphocyte ratio.

Table 4: Treatments during hospitalization.

	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
Azithromycin	162 (63)	58 (61.7)	104 (63.8)	0.737
High flow nasal cannula	38 (14.8)	23 (24.5)	15 (9.2)	0.001
Vitamin C	233 (90.7)	86 (91.5)	147 (90.2)	0.729
Vitamin D	200 (77.8)	78 (83)	122 (74.8)	0.131
Zinc	80 (31.1)	31 (33)	49 (30.1)	0.627
N-acetylcysteine	150 (58.4)	61 (64.9)	89 (54.6)	0.107
Oseltamivir	40 (15.6)	9 (9.6)	31 (19)	0.044
Remdesivir	154 (59.9)	60 (63.8)	94 (57.7)	0.332
Favipiravir	58 (22.6)	24 (25.5)	34 (20.9)	0.388
Antibiotic	124 (48.2)	51 (54.3)	73 (44.8)	0.143
Anticoagulant	197 (76.7)	80 (85.1)	117 (71.8)	0.015
Unfractionated heparin	137 (53.3)	55 (58.5)	82 (50.3)	0.204
Low molecular weight heparin	53 (20.6)	13 (24.5)	30 (18.4)	0.247
Fondaparinux	7 (2.7)	2 (2.1)	5 (3.1)	1
Corticosteroid	90 (35)	34 (36.2)	56 (34.4)	0.769
Insulin	39 (15.2)	19 (20.2)	20 (12.3)	0.087
Anti IL-6	0	0	0	0
Plasma convalescent	55 (21.4)	28 (29.8)	27 (16.6)	0.013
IVIG	2 (0.8)	2 (2.1)	0	0.062

IL = interleukin. IVIG = intravenous immunoglobulin.

Table 5: Electrocardiography results.

	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
Duration of QRS complex (ms), median [IQR]	80 [80-100]	80 [80-100]	80 [80-100]	0.471
Duration of QT corrected (ms), median [IQR]	401 [373-426]	389.5 [362.5-429.75]	401 [376-423]	0.239
ST-T changes	13 (13.6)	17 (18.1)	18 (11)	0.113
Right bundle branch block	15 (5.8)	4 (4.3)	11 (6.7)	0.412
Left bundle branch block	3 (1.2)	3 (3.2)	0	0.048
Non-specific intraventricular conduction delay	4 (1.6)	0	4 (2.5)	0.3

IQR = interquartile range.

DM (OR 7.286; 95% CI 1.895-28.007; p = 0.001), CKD (OR 3.9; 95% CI 1.021-14.892; p = 0.036), leukocytosis during admission (OR 4.039; 95% CI 1.181-13.810; p = 0.019), and NLR > 6.82 during admission (OR 4.492; 95% CI 1.311-15.387; p = 0.011) were associated with hypotension requiring vasopressor. After multivariate analysis, only DM (adjusted OR 4.850; 95% CI 1.172-20.078; p = 0.029) remained associated with hypotension requiring vasopressor, as shown in *Table 8*.

Regarding in-hospital mortality, age ≥ 65 years old (OR 5.785; 95% CI 1.901-17.598; p = 0.001), DM (OR 8.315; 95% CI 3.270-21.141; p < 0.001), CKD (OR 2.813; 95% CI 1.199-6.6; p = 0.016), leukocytosis during admission (OR 2.778; 95% CI 1.199-6.346; p = 0.016), and NLR > 6.82 during admission (OR 2.745; 95% CI 1.183-6.371; p = 0.017) were associated with in-hospital mortality in univariate analysis. Atrial arrhythmias were also found to increase the risk of in-hospital mortality. After multivariate analysis, only DM (adjusted OR 6.52; 95% CI 2.445-17.387; p < 0.001) remained associated with in-hospital mortality, as shown in *Table 8*.

Table 6: Frequencies and type of arrhythmia in COVID-19 patients.

Arrhythmias	n (%)
Single arrhythmia	
Sinus tachycardia	65 (69.1)
Pre-existing atrial fibrillation	10 (10.6)
PVC	6 (6.4)
Sinus bradycardia	3 (3.2)
New-onset atrial fibrillation	2 (2.1)
Total atrioventricular block	2 (2.1)
First degree atrioventricular block	1 (1.1)
Multiple arrhythmias	
Sinus tachycardia and PAC	3 (3.2)
Sinus bradycardia, PVC, and first degree atrioventricular block	1 (1.1)
Sinus tachycardia and PVC	1 (1.1)

PVC = premature ventricular complex. PAC = premature atrial complex.

DISCUSSION

This study involved 257 patients with confirmed COVID-19. The prevalence of arrhythmia in our study was 36.6%, which was higher than the previously reported prevalence.[5,6,16,17] We found that the most common arrhythmia was sinus tachycardia. This type of arrhythmia was in line with the previous study.[7] No VT or ventricular fibrillation was detected in our study. The need for IC, intubation and MV, hypotension requiring vasopressor, and in-hospital mortality were significantly higher in patients with arrhythmia than those without arrhythmia.

Table 7: Outcomes during hospitalization period.

	All patients (N = 257) n (%)	Arrhythmia (N = 94) n (%)	Non-arrhythmia (N = 163) n (%)	p
The need for ICU	85 (33.1)	47 (50)	38 (23.3)	< 0.001
Intubation and mechanical ventilation	9 (3.5)	7 (7.4)	2 (1.2)	0.009
Hypotension requiring vasopressor	20 (7.8)	15 (16)	5 (3.1)	< 0.001
Thromboembolic event	0	0	0	0
Major Bleeding	5 (1.9)	3 (3.2)	2 (1.2)	0.359
Stroke or TIA	2 (0.8)	1 (1.1)	1 (0.6)	1
Death	70 (27.2)	42 (44.7)	28 (17.2)	< 0.001

ICU = Intensive Care Unit. TIA = transient ischemic attack.

Table 8: Multivariate logistic regression analysis of the need of ICU in patients with arrhythmia.

Univariate			Multivariate		
Variables	Unadjusted odds ratio (95% CI)	p	Variables	Adjusted odds ratio (95% CI)	p
The need for ICU					
Male sex	1.691 (0.741-3.860)	0.211	Diabetes mellitus	2.656 (1.114-6.333)	0.028
Age ≥ 65 years old	3.203 (1.117-9.186)	0.026	Leukocytosis during admission	2.354 (0.996-5.565)	0.051
Any cardiovascular comorbidity	2.074 (0.888-4.843)	0.09			
Diabetes mellitus	2.918 (1.248-6.824)	0.012			
Chronic kidney disease	1.681 (0.740-3.818)	0.213			
Leukocytosis during admission	2.616 (1.134-6.033)	0.023			
Thrombocytopenia during admission	0.393 (0.112-1.379)	0.135			
NLR > 6.82 during admission	2.641 (1.139-6.123)	0.017			
The need for intubation and mechanical ventilation					
History of stroke or TIA	17 (1.965-147.046)	0.027	History of stroke or TIA	46.426 (1.64-1314.392)	0.024
Leukocytosis during admission	3.224 (0.593-17.535)	0.24	Thrombocytopenia during admission	17.131 (1.623-180.777)	0.018
Thrombocytopenia during admission	5.775 (1.125-29.638)	0.053	NLR > 6.82 during admission	0.67 (0.005-0.882)	0.04
NLR > 6.82 during admission	8.914 (1.028-77.292)	0.041	New-onset atrial fibrillation	17.673 (0.777-402.004)	0.072
New-onset atrial fibrillation	14.333 (0.794-258.607)	0.144			
Premature atrial complex	7.083 (0.559-89.744)	0.209			
Hypotension requiring vasopressor					
Age ≥ 65 years old	5.802 (1.79-18.805)	0.004	Age ≥ 65 years old	3.288 (0.911-11.861)	0.069
Obesity	2.091 (0.687-6.444)	0.193	Diabetes mellitus	4.850 (1.172-20.078)	0.029
Tachycardia during admission	2.549 (0.748-8.69)	0.126	Leukocytosis during admission	3.039 (0.814-11.343)	0.098
Any cardiovascular comorbidity	2.87 (0.75-10.979)	0.112			
Diabetes mellitus	7.286 (1.895-28.007)	0.001			
Chronic kidney disease	3.9 (1.021-14.892)	0.036			
Leukocytosis during admission	4.039 (1.181-13.810)	0.019			
NLR > 6.82 during admission	4.492 (1.311-15.387)	0.011			

Continuos Table 8: Multivariate logistic regression analysis of the need of ICU in patients with arrhythmia.

Univariate			Multivariate		
Variables	Unadjusted odds ratio (95% CI)	p	Variables	Adjusted odds ratio (95% CI)	p
In-hospital mortality					
Age ≥ 65 years old	5.785 (1.901-17.598)	0.001	Age ≥ 65 years old	3.404 (0.981-11.818)	0.054
Obesity	1.76 (0.722-4.012)	0.177	Diabetes mellitus	6.52 (2.445-17.387)	< 0.001
Hypoxia during admission	1.937 (0.848-4.422)	0.115	Leukocytosis during admission	2.289 (0.866-6.054)	0.095
Any cardiovascular comorbidity	2.143 (0.904-5.081)	0.081			
Diabetes mellitus	8.315 (3.270-21.141)	< 0.001			
Chronic kidney disease	2.813 (1.199-6.6)	0.016			
Leukocytosis during admission	2.778 (1.199-6.436)	0.016			
NLR > 6.82 during admission	2.745 (1.183-6.371)	0.017			
Atrial arrhythmias (AF & PAC)	2.091 (0.678-6.444)	0.193			

CI = confidence interval. AF = atrial fibrillation. ICU = Intensive Care Unit. NLR = neutrophil-to-lymphocyte ratio. PAC = premature atrial complex. TIA = transient ischemic attack.

The mean age of arrhythmia patients was 52.48 ± 13.94 years old. The mean age from our study was younger compared with earlier studies.[5-7,14] The younger study population may be explained by the admission criteria in our hospital. Our hospital is one of the referral COVID-19 hospitals in West Java. Therefore, we included patients transferred from other hospitals and primary healthcare facilities and traced from communities.

Based on previous studies, arrhythmia was associated with a critical illness.[6,16] From our findings, severe and critical disease severity was more commonly observed in patients with arrhythmia compared to patients without arrhythmia. Higher proportions of severe and critical COVID-19 cases may contribute to elevated in-hospital mortality among hospitalized patients with arrhythmia. Disease severity was reflected in vital signs, comorbidities, and laboratory results in patients with arrhythmia. The oxygen saturation was significantly lower in patients with arrhythmia during initial admission. Low presenting oxygen saturation was associated with severe disease.[18] Previous studies reported that several comorbidities, such as hypertension, DM, HF, and previous arrhythmia, were more prevalent in patients with arrhythmia.[6,16] Indeed, patients with arrhythmia in our study had significantly higher comorbidities (e.g. hypertension, HF, DM, CKD) than those without arrhythmia. The presence of comorbidities, including PEAF, increased the susceptibility to develop a severe COVID-19 disease.[19] Moreover, the neutrophil count, NLR, and D-dimer were significantly elevated compared to patients without arrhythmia. These inflammatory markers were significantly elevated in severe or critical COVID-19 cases.[20] Furthermore, the level of C-reactive protein (CRP), one of the inflammatory markers, was higher in patients with arrhythmia than in patients without, although the difference was not statistically significant.

Based on our cohorts, severe COVID-19 disease was more prevalent in patients with arrhythmia than those without, potentially increasing the risk of poor hospital outcomes for patients with arrhythmia. Theoretically, the combination of low oxygen saturation, high levels of inflammatory markers, and high level of proinflammatory cytokine during severe COVID-19 disease may lead to clinical deterioration during hospitalization.[21-23] In addition, arrhythmia-related changes in heart rate, whether too fast or too slow, may cause clinical instability.[11,24,25] However, our univariate and multivariate analysis did not find arrhythmia to be a predictor of in-hospital outcomes, as shown in *Tables 8 to 12*. Moreover, the most common arrhythmia in this study was sinus tachycardia, a minor arrhythmia with multifactorial aetiologies. Sinus tachycardia may reflect the more severe clinical features of COVID-19 disease but is less likely to cause clinical deterioration. On the other hand, NOAF and AV block may be more significant predictors of in-hospital outcomes than sinus tachycardia. However, neither NOAF nor AV block achieved a p-value < 0.25 and were not included as variables in our multivariate analysis. Thus, it appears that arrhythmia in hospitalized COVID-19 patients may be a marker of the disease's severity rather than a variable that worsens the COVID-19 disease. In addition, univariate analysis was performed to identify the association between atrial fibrillation type and in-hospital outcomes, as presented in *Tables 9 to 12*. Neither NOAF nor PEAF were associated with in-hospital outcomes. However, NOAF is more easily attributable to the COVID-19 infection itself compared to PEAF. Suggesting the NOAF may act as a risk marker of COVID-19 infection, while PEAF may act as a risk factor to worse COVID-19 infection during hospitalization period.

From our study, the need for IC, hypotension requiring vasopressor, and in-hospital mortality were higher in patients with arrhythmia. Our study found an in-hospital mortality rate as high as 44.7%, and this in-hospital mortality rate of patients with arrhythmia was higher than in the previous studies.[6-8,16] Multivariate analysis showed that DM in patients with arrhythmia was associated with the need for ICU, hypotension requiring vasopressor, and in-hospital mortality. Diabetes mellitus can increase disease severity and progression to cardiorespiratory failure by increasing inflammatory cytokines, natural killer cells, reactive oxygen species, interleukin-6, D-dimer, and fibrinogen levels.[26] Diabetes mellitus in COVID-19 was also associated with a two-fold increase in mortality compared to those without DM.[27] Moreover, the presence of DM in our patients with arrhythmia was higher than

Table 9: Type of arrhythmia and the need for Intensive Care Unit.

Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	0.897 (0.359-2.240)	1.000
Pre-existing atrial fibrillation	1.573 (0.414-5.981)	0.740
PVC	1.573 (0.414-2.134)	0.740
Sinus bradycardia	0.319 (0.32-3.182)	0.617
New-onset atrial fibrillation	–	0.495
Total atrioventricular block	–	0.495
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	–	0.056

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

Table 10: Type of arrhythmia and the need for intubation and mechanical ventilation.

Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	2.286 (0.261-19.991)	0.671
Pre-existing atrial fibrillation	–	1.000
PVC	–	1.000
Sinus bradycardia	–	1.000
New-onset atrial fibrillation	14.333 (0.794-258.607)	0.144
Total atrioventricular block	–	1.000
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	3.458 (0.332-36.000)	0.327

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

Table 11: Type of arrhythmia and hypotension requiring vasopressor.

Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	1.544 (0.397-6.000)	0.752
Pre-existing atrial fibrillation	0.556 (0.65-4.742)	1.000
PVC	1.365 (0.260-7.170)	0.659
Sinus bradycardia	–	1.000
New-onset atrial fibrillation	5.571 (0.329-94.371)	0.295
Total atrioventricular block	–	1.000
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	2.897 (0.593-25.629)	0.179

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

in previous studies.[6-8,16] During the period of data collection, the shortage of doctors, nurses, personal protective equipment, ventilators, and COVID-19 drugs occurred in our hospital. Furthermore, Indonesia ranked first with the most COVID-19 cases in Southeast Asia, according to the Center for Strategic and International Studies (CSIS).[28] Combined, this may contribute to higher in-hospital mortality rates compared to previous studies from developed countries and may also explain the higher need for IC and hypotension requiring vasopressor in patients with arrhythmia.

History of stroke, thrombocytopenia during admission, and NLR > 6.82 during admission were associated with the need for intubation and mechanical ventilation. However, the confidence interval was too wide to draw firm conclusions, and NLR > 6.82 during admission reduced the risk for intubation and mechanical ventilation after multivariate analysis. This finding was contrary to the previously reported study.[29] A relatively small number of patients with arrhythmia who required intubation and mechanical ventilation may explain this difference.

From our study, we reported zero incidences of thromboembolic events. At the time of writing this article, our hospital could not perform urgent Doppler ultrasonography for confirming deep vein thrombosis and urgent computed tomography pulmonary angiography or invasive pulmonary angiography for confirming pulmonary embolism. Therefore, the true incidence of either deep vein thrombosis or pulmonary embolism may be missed.

The main limitation of our study was the inability to perform continuous electrocardiographic monitoring on patients outside the ICU ward. Hence, the arrhythmia prevalence in patients with asymptomatic and mild disease may be missed. Second, the study design was cross-sectional, and data were retrospectively collected based on medical records. Changing the study design to a prospective one and contemplating the inclusion of patients with known pre-existing arrhythmia only when they have been diagnosed with COVID-19 could be a valuable consideration. Third, we failed to establish a causal link or a comparative effect between primary arrhythmia and in-hospital outcomes. Fourth, we included patients admitted due to other medical indications that tested positive for COVID-19. Fifth, the relatively small sample size of patients with arrhythmia was included in the multivariate logistic regression analysis resulting in a wide confidence interval. Sixth, some laboratory data, such as electrolyte, CRP, and D-dimer, were not complete and were not included as variables in the multivariate logistic regression analysis. Finally, markers of myocardial injury and pro-inflammatory cytokines were not measured, preventing us from assessing their association with arrhythmia in hospitalized COVID-19 patients.

CONCLUSIONS

According to our data, the in-hospital outcomes in patients with COVID-19 and arrhythmia are the worst. Severe and critical COVID-19 disease was more commonly observed in patients with arrhythmia than in patients without arrhythmia. The arrhythmia may be a marker of severe COVID-19 disease rather than a variable that worsens COVID-19 disease. Diabetes mellitus is associated with a higher need for IC, hypotension requiring vasopressor, and in-hospital mortality in patients with arrhythmia. A history of stroke/TIA and thrombocytopenia during admission are associated with a higher need for intubation and mechanical ventilation. Further prospective trials with a larger sample size are needed to confirm this finding.

Table 12: Type of arrhythmia and in-hospital mortality.

Arrhythmias	Odds ratio (95% CI)	p
Single arrhythmia		
Sinus tachycardia	1.038 (0.413-2.608)	1.000
Pre-existing atrial fibrillation	2.000 (0.525-7.615)	0.334
PVC	0.807 (0.212-3.070)	1.000
Sinus bradycardia	–	0.125
New-onset atrial fibrillation	–	0.500
Total atrioventricular block	–	0.197
First degree atrioventricular block	–	1.000
Multiple arrhythmias (sinus tachycardia and PAC; sinus bradycardia, PVC, and first degree atrioventricular block; sinus tachycardia and PVC)	1.923 (0.306-12.079)	0.653

CI = confidence interval. PVC = premature ventricular complex. PAC = premature atrial complex.

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