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New-onset atrial fibrillation in critically ill patients with coronavirus disease 2019 (COVID-19)

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Abstract

Background: Mortality in critically ill patients with coronavirus disease 2019 (COVID-19) is high, therefore, it is essential to evaluate the independent effect of new-onset atrial fibrillation (NOAF) on mortality in patients with COVID-19. We aimed to determine the incidence, risk factors, and outcomes of NOAF in a cohort of critically ill patients with COVID-19.

Methods: We conducted a retrospective study on patients admitted to the intensive care unit (ICU) with a diagnosis of COVID-19. NOAF was defined as atrial fibrillation that was detected after diagnosis of COVID-19 without a prior history. The primary outcome of the study was the effect of NOAF on mortality in critically ill COVID-19 patients.

Results: NOAF incidence was 14.9% (n = 37), and 78% of patients (n = 29) were men in NOAF positive group. Median age of the NOAF group was 79.0 (interquartile range, 71.5-84.0). Hospital mortality was higher in the NOAF group (87% vs 67%, respectively, $P = .019$). However, in multivariate analysis, NOAF was not an independent risk factor for hospital mortality (OR 1.42, 95% CI 0.40-5.09, $P = .582$).

Conclusions: The incidence of NOAF was 14.9% in critically ill COVID-19 patients. Hospital mortality was higher in the NOAF group. However, NOAF was not an independent risk factor for hospital mortality in patients with COVID-19.

KEYWORDS

atrial fibrillation, COVID-19, critical care, hospital mortality, intensive care unit

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pneumonia outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and began in December 2019.[1] Although the main involvement is in the respiratory system, there are also many other systemic manifestations including cardiac problems. Acute cardiac injury, which is defined by troponin I elevation has recently been reported with increased hospital mortality in patients with COVID-19.[2-4]

The incidence of cardiac arrhythmia was reported at a rate of 16.7% in patients with COVID-19 and the incidence increases up to 44.4% in the intensive care unit (ICU) setting.[5] Similarly, in another study, cardiac arrhythmia was reported in 18.5% of 130 patients who had mechanical ventilation requirements.[6]

It was shown that hospitalized patients with COVID-19 with atrial fibrillation (AF) and atrial flutter history had a higher mortality rate than those without AF.[7] However, the data for the incidence of new-onset AF (NOAF) in patients with COVID-19 are limited. The most common type of new arrhythmia in COVID-19 infection was AF, and AF was mostly detected in the ICU setting.[8,9] In a study, NOAF incidence was 7.5% in patients hospitalized for COVID-19.[10]

The ICU mortality in COVID-19 is 35.5%,[11] and the rate increases up to 45% in patients who require invasive mechanical ventilation.[12] Several other risk factors for mortality were defined such as older age, male sex, higher body mass index (BMI), elevated levels of D-dimer, lactate, and presence of active cancer, coronary artery disease, liver, and kidney dysfunction in patients admitted to ICU.[13,14] This study aimed to determine the incidence of NOAF development in critically ill COVID-19 patients, identify possible risk factors for NOAF development, and evaluate its effect on mortality.

2 | MATERIAL AND METHODS

2.1 | Study population

After approvals from the local ethics committee (with date 01.02.2021 and number 2021/04-27) and the Turkish Ministry of Health, the retrospective cohort study was conducted in adult ICUs of our center. All adult patients (age ≥18 years) diagnosed with COVID-19 infection were included in the study between March 2020 and January 2021. SARS-CoV-2 infection was confirmed by either using reverse transcriptase polymerase chain reaction (RT-PCR) testing on respiratory samples and/or with clinical characteristics, laboratory, and computed tomography findings. The exclusion criteria of the study were having chronic AF diagnosis before COVID-19 diagnosis, presence of cardiac pacemaker/implantable cardioverter-defibrillator, atrial flutter, and NOAF development immediately after cardiopulmonary resuscitation.

2.2 | Definition for NOAF

The NOAF group consisted of patients who had their first AF attack after hospitalization for COVID-19. NOAF was defined as either (1) AF ≥1 h in duration, as noted by bedside telemetry; (2) AF <1 h in duration, but captured on the electrocardiogram, or (3) AF initiating pharmacologic therapy or electrical cardioversion according to literature.[15] 12-derivation electrocardiography (ECG) record is routinely obtained from all patients at the time of admission to the ICU in our center (number of beds = 30). All beds are monitored in the ICU, and nurse to bed ratio was 1/2. When there was either monitor image/alarm or examination findings that are compatible with AF, an immediate 12-derivation ECG was recorded and the intensivist and/or cardiologist confirmed the definite NOAF diagnosis. Medical and/or electrical cardioversion, if required, was decided based on the clinical condition of the patients.

2.3 | Other definitions

The cardiac injury was defined as an increase in high-sensitive (HS) troponin I levels above the 99th-percentile upper reference limit.[2] Acute kidney injury (AKI) was identified according to the Kidney Disease: Improving Global Outcomes definition.[16] Ventilator-associated pneumonia (VAP) was defined as pneumonia occurring more than 48 h after patients have been intubated and received mechanical ventilation. VAP was identified using a combination of positive culture results from the respiratory specimen, clinical, laboratory, and radiological findings.[17] Acute myocardial infarction was defined according to the fourth universal definition of myocardial infarction,[18] and cardiologist confirmation.

2.4 | Variables

The demographic data (age, gender, BMI, smoking history, comorbidities), Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure Assessment (SOFA) Scores, were recorded. Disease characteristics for COVID-19 including the date for symptom onset, RT-PCR results, radiological, and blood tests were collected. Major events during ICU stay (presence of septic shock, presence of cardiac injury, ICU acquired infections including VAP, mechanical ventilation support, AKI, and renal replacement therapy [RRT]) were recorded. The durations from symptom onset of the disease to the development of NOAF were recorded. Lengths of ICU, and hospital stays, and mortality were recorded.

2.5 | Statistical analysis

The primary outcome of the study was whether the presence of NOAF is a risk factor for mortality in COVID-19. Secondary outcomes were the risk factors associated with the development of NOAF. All categorical variables are expressed as numbers and percentages, and continuous variables were expressed as the median and interquartile range (IQR). Categorical variables between groups were compared with chi-square or Fisher's exact test, continuous variables were compared with Mann–Whitney *U*-test. The independent effect of NOAF on hospital mortality was assessed with multivariate logistic regression analysis. To build the model, a purposeful selection method was used to select a subset of covariates that were considered clinically important, adjusting for confounders and statistical significance. An adjusted odds ratio (OR) and a 95% confidence interval (CI) were reported for each independent factor. A two-tailed *P*-value of <.05 was considered statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences Version 24, IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | General characteristics

A total of 248 of 301 patients who were admitted to ICU with suspicion of COVID-19 infection were included in the study. Of them, 37 (14.9%) had NOAF (Figure 1). NOAF positive group was older than the NOAF negative group (79.0 [71.5-84.0] vs 70.0 [60.0-78.0] years, $P < .001$; Table 1).

The median duration from the onset of the COVID-19 infection symptoms to NOAF development was 10.0 (5.0-17.0) days. The median duration from hospitalization to NOAF development was 7.0 (2.0-12.5) days, and the median duration from ICU admission to NOAF development was 3.0 (0.0-10.0) days.

Chronic obstructive pulmonary disease (COPD) (24.3% vs 10.9%, respectively; $P = .03$), and chronic kidney disease (CKD) (27.0%, vs 13.3%, respectively; $P = .046$) were more common in the NOAF positive group than the NOAF negative group. CCI median score was higher in the NOAF positive group than the NOAF negative group as well (6.0 [5.0-7.0] vs 4.0 [2.0-6.0], respectively, $P = .003$). NOAF positive group had higher blood urea nitrogen (BUN) than the NOAF negative group median values (37.1 [28.4-75.0] vs 30.0 [21.0-50.0] mg/dL, respectively, $P = .003$). Although it did not reach statistical significance, PaO2/FiO2 ratio was lower in patients with NOAF than in patients without NOAF (106.0 [91.5-122.5] vs 113.0 [96.0-146.0], respectively, $P = .14$).

3.2 | Cardiopulmonary complications

It was found that the median B-type natriuretic peptide (BNP) level was higher in the NOAF positive group compared to the NOAF negative group (366 [112-850] vs 96 [41-277] pg/mL, respectively, $P = .001$). The BNP levels of 114 (46.0%) patients were >100 pg/mL, which is the upper limit of the normal range, and the proportion of NOAF positives was higher than the rate of NOAF negatives (64.9%, vs 42.7%, respectively; $P = .003$). The median level for HS troponin I was higher in the NOAF positive group than the NOAF negative group (78.0 [17.9-325.0] vs 27.0 [9.7-118.0] ng/L respectively, $P = .02$).

The cardiac injury was detected in 159 (64.1%) patients. Although the rate for cardiac injury was higher in the NOAF positive group than the NOAF negative group it did not reach a statistical significance (75.7%, vs 62.1%, respectively; $P = .13$). Acute myocardial infarction was detected in 10 patients (4.0%) after the COVID-19 diagnosis. None of these patients had NOAF. Pulmonary embolism (PE) was detected in 6 patients (2.4%) after the COVID-19 diagnosis. It was shown that the incidental PE rate was higher in the NOAF positive group than the NOAF negative group (8.1% vs 1.4%, respectively; $P = .045$). All the PE attacks were diagnosed before the NOAF attack.

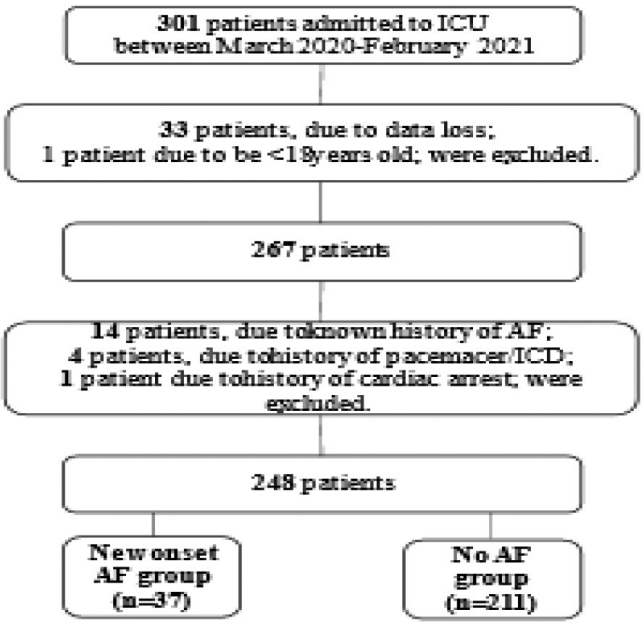

FIGURE 1 Flowchart of the study population

3.3 | Major events during ICU stay

AKI and VAP were more frequent in the NOAF positive group than the NOAF negative group (for AKI 70.3%, vs 51.7%, respectively; $P = .048$ and for VAP 54.1%, vs 35.5%, respectively; $P = .04$). The percentage of patients with secondary bacterial infection was significantly higher in the NOAF positive group than the NOAF negative group (75.7% vs 51.7%, respectively; $P = .007$).

3.4 | Length of stays and mortality

No differences were detected in terms of the median length of ICU stay (for NOAF positive group 9.0 [4.5-15.0] vs for NOAF negative group 7.0 [4.0-14.0] days, $P = .21$) and median length of hospital stay (for NOAF positive group 15.0 [9.5-20.5] vs for NOAF negative group: 14.0 [9.0-20.0] days, $P = .55$). Although ICU mortality of patients was higher in the NOAF positive group compared to the NOAF negative group, no statistically significant difference was detected (83.8% vs 67.3%, respectively, $P = .052$). Hospital mortality was higher in the NOAF positive group than the NOAF negative group (86.5%, vs 67.3%, respectively, $P = .019$).

In this study, hospital mortality was 70.1% (n = 174). Statistically significant variables for hospital mortality are reported in Table 2.

3.5 | Logistic regression analysis for hospital mortality

Multivariable analysis (Table 3) showed vasopressor requirement (OR 12.20, 95%CI 5.12-29.05, $P < .001$), AKI (OR 5.53,

TABLE 1 Demographic and clinical characteristics in patients with and without new-onset atrial fibrillation (univariate analysis)

Characteristics	All Cases (N: 248)	New-onset AF (n: 37)	No AF (n: 211)	*P* value
Age, years	71.0 (61.0-80.0)	79.0 (71.5-84.0)	70.0 (60.0-78.0)	**<.001**
Gender				
Female	72 (29.0)	8 (21.6)	64 (30.3)	.33
Male	176 (71.0)	29 (78.4)	147 (69.7)	
Smoking history	54 (21.8)	11 (29.7)	43 (20.4)	.20
Body mass index, kg/m^2	26.0 (22.5-29.2)	24.6 (20.6-27.7)	26.1 (22.5-29.3)	.07
RT-PCR positivity	226 (91.1)	36 (97.3)	190 (90.0)	.21
Comorbidities				
Hypertension	175 (70.6)	31 (83.8)	144 (68.2)	.07
Diabetes mellitus	91 (36.7)	14 (37.8)	77 (36.5)	.85
Coronary artery disease	65 (26.2)	11 (29.7)	54 (25.6)	.68
Congestive heart failure	39 (15.7)	9 (24.3)	30 (14.2)	.14
Valvular heart disease[a]	7 (2.8)	2 (5.4)	5 (2.4)	.28
Neurological disease[b]	47 (19.0)	11 (29.7)	36 (17.1)	.10
Chronic kidney disease	38 (15.3)	10 (27.0)	28 (13.3)	**.046**
COPD	32 (12.9)	9 (24.3)	23 (10.9)	**.03**
Malignancy[c]	30 (12.1)	4 (10.8)	26 (12.3)	1.00
Hyperlipidemia	15 (6.0)	2 (5.4)	13 (6.2)	1.00
Chronic liver disease	2 (0.8)	0 (0.0)	2 (0.9)	1.00
APACHE II	22.0 (12.0-28.0)	24.0 (16.5-27.0)	20.0 (11.0-28.0)	.15
SOFA[d]	5.0 (3.0-7.0)	6.0 (4.0-7.5)	5.0 (3.0-7.0)	.14
CCI	5.0 (2.0-7.0)	6.0 (5.0-7.0)	4.0 (2.0-6.0)	**.003**
Laboratory data[e]				
BUN, mg/dL	31.0 (23.0-51.0)	37.1 (28.4-75.0)	30.0 (21.0-50.0)	**.003**
Creatinine, mg/dL	1.03 (0.79-1.64)	1.03 (0.87-2.17)	1.03 (0.79-1.56)	.09
Total bilirubin,mg/dL	0.83 (0.62-1.14)	0.96 (0.63-1.22)	0.81 (0.62-1.12)	.27
ALT, U/L	37.0 (24.0-63.7)	34.0 (24.0-58.5)	37.0 (24.0-65.0)	.60
AST, U/L	52.0 (38.0-90.7)	57.0 (38.5-10.5)	52.0 (38.0-91.0)	.69
LDH, U/L	554 (415-705)	521 (357-654)	555 (422-726)	.18
Ferritin ng/mL	622 (338-1130)	627 (298-1562)	617 (340-1121)	.79
HS-troponin I, ng/L	29.0 (11.0-126.2)	78.0 (17.9-325.0)	27.0 (9.7-118.0)	**.02**
D-dimer, μg/mL	1.60 (1.00-3.87)	1.90 (1.20-10.75)	1.60 (0.90-3.60)	.10
BNP (plasma), pg/mL[*]	118 (46-324)	366 (112-850)	96 (41-277)	**.001**
CRP, mg/L	155.0 (84.7-228.2)	158.0 (104.0-219.5)	154.0 (83.0-228.7)	.83
Procalcitonin, ng/mL	0.33 (0.13-1.14)	0.41 (0.18-1.80)	0.32 (0.11-1.13)	.15
WBC, x $10^3/\mu L$	11.1 (7.9-15.1)	11.0 (7.5-16.7)	11.2 (7.9-15.0)	.96
Neutrophil, x $10^3/\mu L$	9.6 (6.8-13.9)	9.5 (6.4-14.1)	9.6 (6.8-14.0)	.87
Lymphocyte, x $10^3/\mu L$	0.5 (0.3-0.9)	0.5 (0.4-0.9)	0.5 (0.3-0.9)	.83
Lymphocyte percentages, %	5.7 (3.2-9.4)	5.4 (3.1-8.0)	5.8 (3.3-9.8)	.45
Hemoglobin, g/dL	12.5 (10.8-13.8)	12.3 (10.2-13.3)	12.5 (11.0-13.9)	.18
Platelet, x $10^3/\mu L$	258 (172-337)	226 (167-317)	260 (173-343)	.21
BNP>100 pg/mL[f]	114 (46.0)	24 (64.9)	90 (42.7)	**.003**
HS-Troponin I > 42.9 ng/L[g]	107 (43.1)	21 (56.8)	86 (40.8)	.07
Arterial blood gas analysis[e]				
pH	7.41 (7.32-7.47)	7.38 (7.27-7.46)	7.42 (7.33-7.47)	.26
PaO_2, mmHg	63.0 (53.0-76.0)	58.2 (46.0-69.0)	64.0 (54.0-78.0)	**.003**
$PaCO_2$, mmHg	34.0 (30.0-42.0)	33 0.0 (27.5-44.5)	35.0 (30.0-41.6)	.46
HCO_3, mmol/L	22.2 (19.6-25.0)	21.0 (16.9-24.5)	22.8 (20.0-25.0)	**.03**
Lactate, mmol/L	2.00 (1.40-3.00)	2.10 (1.50-3,10)	2.00 (1.40-3.00)	.49

(Continues)

TABLE 1 (Continued)

Characteristics	All Cases (N: 248)	New-onset AF (n: 37)	No AF (n: 211)	*P* value
SO_2, %	91.0 (86.0-94.0)	86.0 (80.5-92.5)	91.6 (88.0-94.0)	**.002**
PaO_2/FiO_2	113.0 (95.2-142.5)	106.0 (91.5-122.5)	113.0 (96.0-146.0)	.14
PaO_2/FiO_2 <150, n (%)	193 (77.8)	32 (86.5)	161 (76.3)	.20
Events/therapies during ICU stay				
IMV	198 (79.8)	33 (89.2)	165 (78.2)	.18
Successfully weaning	19 (7.7)	2 (5.4)	17 (8.1)	.53
Vasopressor requirement[h]	166 (66.9)	29 (78.4)	137 (64.9)	.13
VAP	95 (38.3)	20 (54.1)	75 (35.5)	**.04**
Secondary bacterial infections	137 (55.2)	28 (75.7)	109 (51.7)	**.007**
Acute kidney injury	135 (54.4)	26 (70.3)	109 (51.7)	**.048**
Renal replacement therapy	66 (26.6)	14 (37.8)	52 (24.6)	.10
Acute myocardial infarction	10 (4.0)	0 (0.0)	10 (4.7)	.36
Cardiac injury	159 (64.1)	28 (75.7)	131 (62.1)	.13
Acute pulmonary embolism	6 (2.4)	3 (8.1)	3 (1.4)	**.045**
CPR	9 (3.6)	1 (2.7)**	8 (3.8)	1.00
Treatment for COVID-19				
Favipravir	235 (94.8)	36 (97.3)	199 (94.3)	.69
LMWH	235 (94.8)	35 (94.6)	200 (94.8)	1.00
ASA	190 (76.6)	27 (73.0)	163 (77.3)	.50
Dipyridamole	147 (59.3)	22 (59.5)	125 (59.2)	1.00
Corticosteroids	190 (76.6)	28 (75.7)	162 (76.8)	.83
Pulse corticosteroid	101 (40.7)	17 (45.9)	84 (39.8)	.58
Hydroxychloroquine	56 (22.6)	6 (16.2)	50 (23.7)	.39
Azithromycin	9 (3.6)	0 (0.0)	9 (4.3)	.36
Treatment for NOAF				
Amiodarone	N/A	34 (91.9)	N/A	N/A
Electrical cardioversion	N/A	5 (13.5)	N/A	N/A
Conversion to normal sinus rhythm	N/A	11 (29.7)	N/A	N/A
Length of ICU stay, days	7.0 (4.0-14.0)	9.0 (4.5-15.0)	7.0 (4.0-14.0)	.21
Length of hospital stay, days	14.0 (9.0-20.0)	15.0 (9.5-20.5)	14.0 (9.0-20.0)	.55
ICU mortality	173 (69.8)	31 (83.8)	142 (67.3)	**.052**
Hospital mortality	174 (70.2)	32 (86.5)	142 (67.3)	**.019**

Note: All values are expressed as numbers (percentages) or median (interquartile range).

Statistically significant values are expressed in bold.

Abbreviations: AF, atrial fibrillation;ALT, alanine transaminase; APACHE II, Acute Physiology and Chronic Health Evaluation II; ASA, acetylsalicylic acid; AST, aspartate transaminase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; FiO_2, fraction of Inspired oxygen; HS Troponin I, high-sensitive troponin I; ICU, intensive care unit IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; N/A, not applicable; NIV, noninvasive ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; RT-PCR, reverse transcription-polymerase chain reaction; SO_2, arterial oxygen saturation; SOFA Score, The Sequential Organ Failure Assessment Score; VAP, ventilator associated pneumonia; WBC, white blood cell count.

[a]Any valvular disease.

[b]History of cerebrovascular disease or dementia.

[c]Includes hematological and solid organ malignancies.

[d]Calculated on the day of ICU admission.

[e]Tested on the day of ICU admission.

[f]Laboratory upper limit of BNP (100 pg/mL).

[g]Laboratory upper limit of HS-Troponin (42.9 ng/L).

[h]Use of any dose of vasopressor.

*N = 215.; **Detected before CPR.

TABLE 2 Statistically significant variables for hospital mortality (univariate analysis)

Characteristics	All Cases (N: 248)	Dead group (n: 174)	Alive group (n: 74)	*P value*
Age, years	71.0 (61.0-80.0)	75.0 (66.0-81.2)	61.0 (52.0-70.2)	<.001
Body mass index, kg/m^2	26.0 (22.5-29.2)	25.8 (22.0-28.0)	27.0 (23.5-30.5)	.027
Comorbidities				
Neurological disease	47 (19.0)	45 (25.9)	2 (2.7)	<.001
Chronic kidney disease	38 (15.3)	33 (19.0)	5 (6.8)	.020
Malignancy	30 (12.1)	27 (15.5)	3 (4.1)	.010
APACHE II	22.0 (12.0-28.0)	24.0 (15.0-29.2)	12.0 (9.0-22.0)	<.001
SOFA	5.0 (3.0-7.0)	6.0 (4.0-8.0)	3.0 (2.0-4.0)	<.001
CCI	5.0 (2.0-7.0)	5.5 (4.0-7.0)	2.0 (1.0-4.0)	<.001
Laboratory data				
BUN, mg/dL	31.0 (23.0-51.0)	35.0 (26.0-56.2)	24.5 (18.0-31.9)	<.001
Creatinine, mg/dL	1.03 (0.79-1.64)	1.20 (0.81-1.92)	0.95 (0.72-1.10)	<.001
ALT, U/L	37.0 (24.0-63.7)	36.0 (22.0-62.0)	42.5 (26.7-68.5)	.035
Ferritin ng/mL	622 (338-1130)	648 (368-1217)	479 (249-1009)	.011
HS-troponin I, ng/L	29.0 (11.0-126.2)	49.5 (17.0-226.0)	27.1 (11.0-174.0)	<.001
D-dimer, μg/mL	1.60 (1.00-3.87)	2.00 (1.20-5.80)	1.05 (0.50-1.85)	<.001
BNP (plasma), pg/mL*	118 (46-324)	139 (61-415)	72 (21-172)	.001
CRP, mg/L	155.0 (84.7-228.2)	169.0 (91.3-243.5)	124.0 (74.0-191.3)	.009
Procalcitonin, ng/mL	0.33 (0.13-1.14)	0.46 (0.19-1.88)	0.14 (0.07-0.28)	<.001
WBC, x 10^3/μL	11.1 (7.9-15.1)	12.2 (8.3-16.8)	9.4 (7.3-11.9)	.001
Neutrophil, x 10^3/μL	9.6 (6.8-13.9)	10.4 (7.0-14.8)	8.3 (5.9-10.8)	.002
Hemoglobin, g/dL	12.5 (10.8-13.8)	12.2 (10.3-13.6)	12.9 (11.7-14.0)	.007
Arterial blood gas analysis				
pH	7.41 (7.32-7.47)	7.38 (7.29-7.46)	7.44 (7.39-7.48)	.001
HCO_3, mmol/L	22.2 (19.6-25.0)	22.0 (18.0-24.6)	24.2 (21.7-26.0)	<.001
Lactate, mmol/L	2.00 (1.40-3.00)	2.10 (1.47-3.20)	1.80 (1.20-2.40)	.002
Events/therapies during ICU stay				
IMV	198 (79.8)	173 (99.4)	25 (33.8)	<.001
Vasopressor requirement	166 (66.9)	151 (86.8)	15 (20.3)	<.001
VAP	95 (38.3)	87 (50.0)	8 (10.8)	<.001
Secondary bacterial infections	137 (55.2)	117 (67.2)	20 (27.0)	<.001
Acute kidney injury	135 (54.4)	123 (70.7)	12 (16.2)	<.001
Renal replacement therapy	66 (26.6)	62 (35.6)	4 (5.4)	<.001
Cardiac injury	159 (64.1)	131 (75.3)	28 (37.8)	<.001
NOAF	37 (14.9)	32 (18.4)	5 (6.8)	.019

Note: All values are expressed as numbers (percentages) or median (interquartile range).

Abbreviations: ALT, alanine transaminase; APACHE II, Acute Physiology and Chronic Health Evaluation II; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HS Troponin I, high-sensitive troponin I; IMV, invasive mechanical ventilation; SOFA Score, The Sequential Organ Failure Assessment Score; VAP, ventilator associated pneumonia; WBC, white blood cell count.

*N = 215

95%CI 1.87-10.92, *P* = .001), and high CCI (OR 1.36, 95%CI 1.10-1.66, *P* = .003), as factors independently associated with an increased risk of hospital mortality. However, NOAF was not an independent risk factor for hospital mortality (OR 1.42, 95%CI 0.40-5.09, *P* = .582).

4 | DISCUSSION

This retrospective cohort study has two important results. First, NOAF incidence in critically ill COVİD-19 patients is 14.9%. NOAF risk was associated with older age and the presence of comorbidities.

Second, hospital mortality increases in critically ill COVID-19 patients with NOAF.

The incidence of NOAF in surgical and medical mixed ICUs varied between 1.7% and 29.5% in the literature.[19] However, the occurrence of NOAF in critically ill COVID-19 patients has not been well described. Some studies have reported atrial arrhythmia and AF episodes in patients with COVID-19,[8,9,20] and NOAF has mainly occurred in critically ill patients.[8,9] However, in these studies, data of NOAF are limited. NOAF rate was separately reported in one study and incidence of NOAF was 7.5% (n = 12) of 160 patients who were hospitalized for COVID-19 infection.[10] We have found that the incidence of NOAF in critically ill patients is 14.9%; hence the risk of developing NOAF in critically ill patients with severe covid-19 infection is relatively high.

Cardiac involvement, such as myocardial injury, myocardial ischemia, myocarditis, cardiogenic shock, acute cor pulmonale, thrombotic complications, and arrhythmia were previously reported in patients with COVID-19.[3,21] It is considered that myocarditis is caused by inflammatory infiltrates damaging the myocardium and myocardial injury without acute ischemic event.[22] It has been reported that serious infection, severe tissue inflammation, hypoxia, and electrolyte abnormalities may trigger atrial and ventricular arrhythmia.[23] However, the etiology of cardiac arrhythmias in COVID-19 has not yet been fully clarified. The most proposed mechanisms are hypoxemia because of acute respiratory distress, increased inflammatory response, and myocardial damage caused by cytokine crisis, increase in catecholamine, direct viral endothelial damage, acid-base, and electrolyte abnormalities.[24,25] In this study, the PaO2/FiO2 ratio was lower in patients with NOAF than in patients without NOAF, but there was no statistically significant difference. More comprehensive studies are required to investigate the effect of hypoxemia on NOAF development in patients with COVID-19.

The incubation period for COVID-19 is median 5-6 days; however, it can be up to 14 days.[26,27] This relatively short period is not sufficient for developing fibrosis-related conditions; therefore, it is expected that this short incubation period does not increase the risk of AF.[25] Since patients with COVID-19 who developed AF were older and had comorbidities, such as hypertension,[10,28] it was considered that COVID-19 infection triggers NOAF in the presence of a previously predisposing factor.[25] Our findings are also consistent with these reports as patients who had NOAF in this study were older and had higher CCI as well. It was observed that NOAF was developed during the first days of acute illness (median day 3.0 [0.0-10.0]) which is similar to previously reported.[29,30]

To date, the acute cardiac injury was observed between 12.0% and 29.8% in patients with COVID-19.[2-4,31,32] The frequency of cardiac injury was 64.1% in our study and this rate was higher than previously reported. We believe that the higher rate of cardiac injury was probably due to the population studied. Previous reports included a heterogeneous group of patients from both ICU and non-ICU settings, however, this study included only critically ill patients with severe illness.

Our results suggest that patients with COPD are more vulnerable to NOAF development. Previously reported risk factors in ICU patients were advanced age, male sex, accompanying cardiovascular diseases, acute renal failure, acute respiratory failure, shock, sepsis, pulmonary artery catheter use, vasopressor use, need for mechanical ventilation, increased fluid load, and organ failure.[33,34] A study reported that incidental AF frequency was approximately 4 times higher in patients with severe COPD than in non-COPD patients.[35] NOAF prevalence was between 4.7% and 15% in stable patients with COPD,[36] and around 20%–30% in severe patients with COPD.[37] Impaired gas exchange and oxidative stress were considered the possible causes triggering NOAF in COPD.[38] Respiratory failure and hypoxemia because of COVID-19 may have increased the risk of NOAF in this specific group of patients.

In our study, it was also found that NOAF was mostly detected in patients who developed secondary bacterial infections in ICU follow-ups. AF was reported to be the most common arrhythmia in patients with sepsis[39] and was also associated with increased mortality in this group of patients.[40] The use of vasopressor also contributes to NOAF development in septic shock patients.[34]

It was observed that PE rate was higher in the NOAF positive group than the NOAF negative group in this cohort. We believe that the coexistence of NOAF and PE deserves specific attention in COVID-19. A meta-analysis reported that the PE prevalence was 16.5% in COVID-19 infection, which is relatively high.[41] PE-induced ventricular dysfunction and increased atrial tension may be a factor for triggering AF.[42]

New AF attacks have deleterious effects, such as increasing heart rate, causing irregular rhythm and losses in atrial systole, and neurohormonal activation. For this reason, NOAF development can further complicate critical disease or may limit response to therapy.[43] Cardiac output may decrease because of loss of atrial systole and tachycardia, and acute heart failure may develop.[43,44] It was found in some studies that NOAF development correlate with the severity of critical illness.[45]

Although no independent relations were detected in some previous studies between NOAF and hospital mortality,[46-48] some studies

TABLE 3 Logistic regression analysis for risk factors of hospital mortality

	OR (95% CI)	*P* value
Vasopressor requirement	12.20 (5.12-29.05)	**<.001**
AKI	4.53 (1.87-10.92)	**.001**
Charlson comorbidity index	1.36 (1.10-1.66)	**.003**
APACHE II	0.99 (0.92-1.06)	.822
SOFA*	1.22 (0.95-1.58)	.108
New-onset atrial fibrillation	1.42 (0.40-5.09)	.582

Statistically significant values are expressed in bold.

Abbreviations: AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; OR, odds ratio; SOFA, The Sequential Organ Failure Assessment Score.

*Calculated on the day of ICU admission.

found that NOAF was associated with increased hospital mortality regardless of the severity of the critical disease.[29,49] However, in this study, NOAF was not an independent risk factor for hospital mortality in multivariate analysis.

5 | LIMITATIONS AND STRENGTHS OF THE STUDY

This study has several limitations. First, the results are from a single center and could not be generalized. Second, it is impossible to differentiate whether NOAF developed due to COVID-19 related cardiac involvement or due to critical illness itself. Third, we could not analyze long-term consequences of NOAF. However, the study has some strengths. We think that our findings are valuable as NOAF development in critical COVID-19 studied to a lesser extent. Second, the diagnostic accuracy for NOAF was high as the diagnosis was confirmed by an intensivist/cardiologist in all cases.

6 | CONCLUSION

Older patients with comorbidities have a high risk of developing NOAF in severe COVID-19 infection. The prognostic significance of NOAF on ICU and hospital mortality in these patients merits further research.

CONFLICT OF INTEREST

The Authors declare no Conflict of Interests for this article.

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