New-Onset Atrial Fibrillation in Patients With Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease

— Insights From the CLAVIS-COVID Registry —

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Background: Both pre-existing atrial fibrillation (AF) and new-onset AF (NOAF) are observed in patients with coronavirus disease 2019 (COVID-19); however, the effect of AF on clinical outcomes is unclear. This study aimed to investigate the effect of AF, especially NOAF, on the outcomes of hospitalized patients with COVID-19.

Methods and Results: This study analyzed 673 COVID-19 patients with cardiovascular diseases and risk factors (CVDRF). Patients were divided into 3 groups; pre-existing AF (n=55), NOAF (n=28), and sinus rhythm (SR) (n=590). The baseline characteristics and in-hospital outcomes were evaluated. The mean age of the patients was 68 years, 65.4% were male, and the in-hospital mortality rate was 15.6%. The NOAF group demonstrated a higher in-hospital mortality rate (42.9%) than the pre-existing AF (30.9%) and SR (11.2%) groups ($P<0.001$). Patients with NOAF had a higher incidence of acute respiratory syndrome, multiple organ disease, hemorrhage, and stroke than those with pre-existing AF and NOAF. NOAF was independently associated with in-hospital mortality after adjusting for pre-existing AF and 4C mortality score (odds ratio [95% confidence interval]: 4.71 [1.63–13.6], $P<0.001$).

Conclusions: Patients with NOAF had significantly worse outcomes as compared to patients with pre-existing AF and SR. The incidence of NOAF would be a useful predictor of clinical outcomes during hospitalization.

Key Words: Atrial fibrillation; Cardiovascular diseases; COVID-19; Japan; Mortality

Pre-existing cardiovascular diseases and risk factors (CVDRF), including atrial fibrillation (AF), are commonly observed and associated with higher mortality rates after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of coronavirus disease 2019 (COVID-19).^{1,2} SARS-CoV-2 specifically impairs the cardiovascular system and causes myocardial injury, which is related to worse clinical outcomes during hospitalization, particularly in those with underlying cardiovascular disease (CVD).^{3–5} These facts highlight the need to focus on underlying and new-onset CVDs during the clinical course of SARS-CoV-2 infection

as a remarkable and independent predictor of outcomes, which can add clinical value to existing prediction models of COVID-19. Given that the prediction of the clinical course in patients with COVID-19 is difficult due to their heterogeneity, the 4C mortality score,^{6,7} which is another useful predictor independent from the pre-existing prediction model developed and validated specifically in patients with COVID-19, is warranted.

AF is a common arrhythmia that increases the risk of morbidity and mortality in patients with CVD.^{8,9} The incidence of new-onset atrial fibrillation (NOAF) in patients with COVID-19 is common, and is related to worse out-

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comes after SARS-CoV-2 infection.^{10,11} Previous reports have suggested that mechanisms of SARS-CoV-2 infection are related to the occurrence of myocardial injury,^{12,13} acute myocardial infarction,¹² heart failure,^{12,14,15} arrhythmia,^{10,12,16} and thrombotic events;^{12,17,18} hence, the incidence of AF after SARS-CoV-2 infection is assumed to be observed in the general population. Indeed, recent studies have suggested that patients with COVID-19 have a considerable risk of NOAF during the clinical course.^{19,20} Considering severe inflammation status is closely associated with the incidence of AF, the relationship between COVID-19 infection and NOAF may result from the severity of systemic inflammation subsequent to the infection. Thus, we hypothesized that NOAF is a promising independent predictor of clinical outcomes in patients with COVID-19, which adds value to existing prediction models. However, most studies evaluating the effect of NOAF on clinical outcomes of COVID-19 have had small sample sizes and, therefore, could not analyze the independency toward other established prediction models; thus, the generalizability of these results remains controversial.

The clinical outcomes of SARS-CoV-2 infection in hospitalized patients with cardiovascular diseases and/or risk factors (CLAVIS-COVID) registry, a Japanese nationwide study sponsored by the Japanese Circulation Society, was designed to evaluate outcomes in patients with COVID-19 and CVDRF as a specific subtype of COVID-19 associated with poor outcomes after infection.^{21–23} In this post-hoc analysis of CLAVIS-COVID registry, we aimed to investigate the effect of AF, especially NOAF, on the clinical

outcomes of hospitalized patients with COVID-19.

Methods

Study Design and Population

The CLAVIS-COVID registry was designed to evaluate the clinical features and outcomes of patients with pre-existing CVDRF and COVID-19 hospitalized between 1 January and 31 May 2020 in 49 acute care hospitals, and was sponsored by the Japanese Circulation Society.²⁴ SARS-CoV-2 infection was diagnosed on the basis of a positive polymerase chain reaction (PCR) test of a nasal or pharyngeal swab specimen. Patients aged <20 years at the time of admission were excluded from this study. CVDRF involves CVDs and cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia. Cardiovascular diseases were defined as heart failure, coronary artery disease, myocardial infarction, peripheral artery disease, valvular heart disease, cardiac arrhythmia, pericarditis, myocarditis, congenital heart disease, pulmonary hypertension, deep vein thrombosis, pulmonary embolism, aortic dissection, aortic aneurysm, cerebral infarction/transient ischemic attack, use of cardiac devices (e.g., a pacemaker, implantable cardioverter defibrillation, cardiac resynchronization therapy, left ventricular assist device), heart transplantation, and cardiac arrest.

In the present study, 693 patients had COVID-19 and an underlying CVDRF. To compare patients with AF and sinus rhythm (SR), those with a history of cardiac arrhythmia without AF, such as sick sinus syndrome, atrial-ventricular

Table 1. At the Time of Admission (n=673)

Variables	Number of data	Pre-existing AF (n=55)	NOAF (n=28)	SR (n=590)	P value
Age (years)**	673	77.3±10.1	75.8±12.8	66.9±14.8	<0.001
Male	673	36 (65.5)	17 (60.1)	387 (65.6)	0.89
BMI (kg/m ²)	560	23.5±5.6	23.5±4.6	24.4±5.0	0.33
Smoker/ex-smoker	637	19 (36.5)	15 (55.6)	231 (41.4)	0.27
Hypertension**	673	31 (56.4)	22 (84.6)	450 (76.3)	0.007
Diabetes mellitus	673	17 (30.9)	8 (28.6)	235 (39.8)	0.25
Dyslipidemia	673	18 (32.7)	9 (32.1)	236 (40)	0.46
Heart failure**	673	20 (36.4)	1 (3.6)	32 (5.4)	<0.001
Ischemic heart disease**	673	13 (23.6)	6 (21.4)	61 (10.3)	0.0047
CI/TIA***	673	13 (23.6)	1 (3.6)	37 (6.3)	<0.001
Chronic lung disease	673	6 (10.9)	3 (10.7)	55 (9.3)	0.78
CKD****	673	10 (18.1)	1 (3.6)	34 (5.8)	0.005
Cancer	673	7 (12.7)	5 (17.9)	53 (9.0)	0.17
CHA ₂ DS ₂ -VASC****	673	3.82 (3–5)	3.11 (2–4)	2.66 (2–4)	<0.001
Baseline medication					
ACE-I/ARB***	673	14 (25.5)	15 (53.6)	227 (38.5)	0.036
β-blocker**	673	20 (36.4)	8 (28.6)	74 (12.5)	<0.001
CCB	673	14 (25.5)	10 (35.7)	233 (39.5)	0.12
Diuretics**	673	15 (27.3)	3 (10.7)	39 (6.6)	<0.001
Statin	673	14 (25.5)	10 (35.7)	183 (31.0)	0.62
DOAC or Warfarin****	673	33 (60)	1 (3.6)	12 (2.0)	<0.001
Vital signs					
Glasgow coma scale	606	15 (15–15)	15 (15–15)	15 (15–15)	0.294
Heart rate (beats/min)	667	87.2±20.7	84.1±19.7	86.7±17.4	0.74
Systolic BP (mmHg)**	669	126.6±21	127±20.5	134.1±21.7	0.015
Diastolic BP (mmHg)**	668	74.9±14.9	73.1±15.2	79.3±15.4	0.02
Respiratory rate	523	20.2±5.4	19.2±5.2	21.1±6.2	0.27
SpO ₂ (%)	669	95.6±3.2	93.2±7.9	94.4±4.7	0.09
Symptoms					
Cough	673	20 (36.4)	15 (53.6)	289 (49.0)	0.17
Sore throat	673	2 (3.6)	1 (3.6)	69 (11.7)	0.10
Fatigue	673	19 (36.5)	10 (35.8)	196 (33.2)	0.93
Panting/Dyspnea	673	19 (36.5)	12 (42.9)	188 (31.9)	0.42
Dysgeusia	673	3 (5.5)	0 (0)	42 (7.1)	0.46
Asymptomatic	673	4 (7.3)	3 (10.7)	37 (6.3)	0.52
HF edema**	673	7 (12.7)	2 (7.1)	8 (1.4)	<0.001
HF congestion**	673	10 (18.2)	3 (10.7)	23 (3.9)	<0.001

Values are expressed as n (%) or mean±standard deviation, median (interquartile range). *Significant difference in the comparison of the 2 groups, NOAF and SR. **Significant difference in the comparison of the 2 groups, pre-existing AF and SR. ***Significant difference in the comparison of the 2 groups, pre-existing AF and NOAF. ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin 2 receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CI, cerebral infarction; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulants; HF, heart failure; NOAF, new-onset atrial fibrillation; SpO₂, peripheral oxygen saturation; SR, sinus rhythm; TIA, transient ischemic attack.

block, ventricular tachycardia, and other arrhythmias, and those with a history of pacemaker implantation were excluded. Finally, 673 patients were enrolled and divided into 3 groups: pre-existing AF, NOAF, and SR (**Figure 1**). NOAF was defined as new-onset AF after admission, which was sustained for >24h in patients without pre-existing AF. Pre-existing AF involved a history of AF, including paroxysmal, persistent, and permanent AF, and manifestations of AF on admission. The differences in characteristics and in-hospital outcomes among the 3 groups were analyzed. The primary endpoint was in-hospital mortality.

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol, including

the use of an opt-out consent method, was approved by the ethics committee of Toho University Omori Medical Center (No. M20253, 20089, 20040, 20017) and the local ethics committees of all participating institutions. This clinical study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-ID: UMIN000040598) before the first patient was enrolled, in accordance with the International Committee of Medical Journal Editors.

Data Collection

Our dataset referred to the case report form proposed by the International Severe Acute Respiratory and Emerging

Table 2. Examination Findings at the Time of Admission and Treatment During Hospital Course (n=673)

	Number of data	Pre-existing AF (n=55)	NOAF (n=28)	SR (n=590)	P value
Laboratory data					
CRP (mg/L)*	647	5.8 (3.8–11.4)	9.2 (5.8–15.1)	5.8 (1.8–11.5)	0.017
WBC count	658	5,790 (1,700–7,450)	6,050 (4,505–7,932)	5,700 (4,400–7,560)	0.81
Neutrophil count (%)*	583	75.8 (66.5–83.7)	79.8 (73.6–83.8)	74.6 (64.4–82.3)	0.08
Hemoglobin level (g/dL)**	659	12.2 (10.9–13.9)	13 (11.8–13.9)	13.6 (11.9–14.8)	0.001
Hematocrit (%)*	647	37.1 (33.3–41.5)	37.8 (35.7–41.3)	40 (35.5–43.4)	0.008
PLT (10 ⁴ /μL)*	656	16.8 (12.4–25.1)	16.1 (11.6–22.4)	19.1 (15.1–24.8)	0.03
Albumin (g/dL)**	620	2.9 (2.5–3.5)	3.1 (2.9–3.4)	3.3 (2.9–3.8)	<0.001
Na (mEq/L)	659	137 (135–139)	137 (135–140)	138 (135–141)	0.77
K (mEq/L)	659	4.1 (3.7–4.4)	3.8 (3.6–4.2)	4 (3.7–4.3)	0.25
eGFR (mL/min/1.73 m ²)**	660	73.7 (55.8–94.7)	73.6 (45.9–103.3)	88.5 (67.0–106.7)	0.002
Blood urea nitrogen (mmol/L)	660	6.2 (5.4–9.7)	5.7 (5.0–8.9)	5.9 (4.3–8.6)	0.90
LDH (IU/L)	598	290 (211–409)	364 (261–433)	291 (227–413)	0.20
D-dimer (ng/mL)	448	1.53 (0.78–2.62)	1.5 (1.10–1.97)	1.4 (0.71–3.02)	0.98
Troponin positive	138	10 (55.6)	6 (75)	54 (48.2)	0.34
BNP (pg/mL)**	211	375.2 (164.0–749.5)	94.6 (43.5–216.5)	26.3 (10.1–83.9)	<0.001
Chest X-ray					
GGO/consolidation/alveolar opacity***	611	41 (50.9)	27 (96.4)	386 (65.4)	0.008
Congestion***	611	15 (23.3)	6 (21.4)	29 (5.5)	<0.001
Pleural effusion***	611	10 (18.9)	5 (17.9)	28 (4.7)	<0.001
Chest CT					
GGO/consolidation	526	39 (84.8)	21 (87.5)	347 (76.1)	0.24
Pleural effusion***	526	12 (26.1)	10 (41.7)	50 (11.0)	<0.001
Treatment					
Heparin***	673	14 (25.5)	15 (53.6)	111 (18.8)	<0.001
Catecholamine	673	10 (18.2)	8 (28.6)	80 (13.6)	0.071
Inotropic drugs	673	3 (5.5)	2 (7.1)	24 (4.1)	0.42
Vasopressor*	673	7 (12.7)	8 (28.6)	64 (10.8)	0.03
O ₂ demand***	670	41 (74.5)	27 (96.4)	365 (62.2)	<0.001
ICU entry***	673	18 (32.7)	17 (60.7)	162 (27.5)	0.001
Intubation/respiration***	673	13 (23.6)	14 (50)	124 (21)	0.004
Renal replacement therapy	673	2 (3.6)	3 (10.7)	39 (6.6)	0.49
New introduction of renal replacement therapy	673	1 (1.8)	2 (7.1)	22 (3.7)	0.41
V-A ECMO	673	0 (0)	1 (3.6)	2 (0.34)	0.14
V-V ECMO	673	0 (0)	2 (7.1)	21 (3.6)	0.14

Values are expressed as n (%) or mean±standard deviation, median (interquartile range). *Significant difference in the comparison of the 2 groups, NOAF and SR. **Significant difference in the comparison of the 2 groups, pre-existing AF and SR. ***Significant difference in the comparison of the 2 groups, pre-existing AF and NOAF. BNP, B-type natriuretic peptide; CRP, C-reactive protein; CT, computed tomography; eGFR, estimated glomerular filtration rate; GGO, ground-glass opacity; ICU, intensive care unit; LDH, lactate dehydrogenase; PLT, platelet; V-A ECMO, vena-arterial extracorporeal membrane oxygenation; V-V ECMO, veno-venous extracorporeal membrane oxygenation; WBC, white blood cell. Other abbreviations as in Table 1.

Infection Consortium.²⁵

Clinical characteristics, including symptoms, demographics, medical history, home medications, baseline comorbidities, physical findings, laboratory test results, radiography and chest computed tomography (CT) findings, electrocardiography and cardiac echocardiography results, treatment information, and outcomes, were obtained from the patients' electronic medical records using data collection forms. All baseline laboratory and imaging data were obtained at the time of admission. In the analysis of cardiac troponin (cTn), a positive result was defined as an elevation above the 99th percentile of the upper reference limit value in each assay. The date of COVID-19 onset was

defined as the first day of symptom onset; otherwise, if the patients had no symptoms on admission, the day of the first positive PCR test for SARS-CoV-2 was considered.

During the period of patient enrollment, the Japanese government mandated the hospitalization of all patients diagnosed with COVID-19 based on the result of the PCR test, regardless of severity. The participating hospitals fundamentally followed this recommendation. The discharge threshold of all patients with COVID-19 was also determined by the Japanese government guidelines for COVID-19 management.²⁶ The guidelines recommend that patients remain in hospital until: (1) their systemic conditions and respiratory symptoms are improved and stable;

Figure 2. In-hospital outcomes in patients with coronavirus disease 2019 (COVID-19; pre-existing AF, NOAF, and SR groups). *P<0.001. AF, atrial fibrillation; ARDS, acute respiratory syndrome; MOF, multiple organ failure; NOAF, new-onset atrial fibrillation; SR, sinus rhythm.

(2) their body temperature is consistently <37.5°C, for at least 24h; and (3) negative results are confirmed twice, at least 12h apart.

Statistical Analysis

All data are described as presenting frequency, percentages (%) for categorical variables, and the mean value (±standard deviation) or median value with interquartile range (quartiles 1–3) for continuous variables. Fisher's exact test was used to evaluate categorical variables, and the Kruskal-Wallis test was used to assess continuous variables. Univariate and multivariate logistic regression analysis models were used to estimate the effect of pre-existing AF and NOAF on in-hospital outcomes. We used the 4C mortality score, developed and validated in patients with COVID-19, for the adjustment in the multivariable logistic model.^{6,7} The model validation in our cohort has already been described and performed elsewhere.²⁷ All analyses in the present study were performed using Stata software version 15 (StataCorp) and R (version 4.0.3).

Results

Patient Characteristics

Among the 673 patients, the mean age was 68 years, and 65.4% were men. They were categorized into pre-existing AF (55 patients), NOAF (28 patients), and SR (590 patients) groups (Figure 1).

Table 1 presents the baseline characteristics of patients stratified by AF status. Patients with pre-existing AF and NOAF were significantly older than those with SR. History of heart failure, cerebral vascular diseases, and chronic renal disease were more common in patients with pre-existing AF than in the other groups. In addition, the pre-existing

AF group was associated with a higher CHA₂DS₂-VASc score.

The use of β -blockers and diuretics as well as history of heart failure were significantly more common in the pre-existing AF group than in the NOAF and SR groups. In contrast, treatment with an angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker was significantly more frequent in patients with NOAF compared with that for other groups. New oral anticoagulants or warfarin are frequently used in patients with preexisting AF.

Symptoms and Vital Signs

Overall, the most common symptoms at the time of admission were cough (48.1%), fatigue (33.4%), and dyspnea (32.5%). There was no significant difference in the symptoms according to AF status. The pre-existing AF group had a higher incidence of heart failure symptoms, such as edema and congestion, than the NOAF and SR groups. The SR group had significantly higher systolic and diastolic blood pressure at the time of admission than the other groups. However, the heart rate, respiratory rate, and peripheral oxygen saturation on admission were not significantly different between the 3 groups.

Laboratory and Imaging Findings

The baseline laboratory and imaging findings are shown in Table 2. Although there were no significant differences in the number of white blood cells and neutrophils among the 3 groups, the levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) were significantly higher in patients with NOAF than in those of the other groups. Moreover, baseline hemoglobin, hematocrit, platelet, and albumin levels were significantly higher in patients with SR than in those with pre-existing AF and NOAF. The estimated

Table 3. 4C Mortality Scores at the Time of Admission (n=461)

Variable	Overall (n=461)	Pre-existing AF (n=38)	NOAF (n=21)	SR (n=402)	P value
4C mortality score	8.4±3.8	10.1±2.9	10.0±3.7	8.2±3.8	0.001

Values are expressed as mean±standard deviation. Abbreviations as in Table 1.

Table 4. Multivariate Analysis Model Evaluating the Effect of NOAF on In-Hospital Mortality Adjusting for 4C Mortality Score (n=461; 71 In-Hospital Deaths)

Variable	OR	95% CI	P value
NOAF	4.71	1.63–13.6	0.004
Pre-existing AF	2.09	0.90–4.82	0.09
4C mortality score	1.44	1.31–1.59	<0.001

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 1.

glomerular filtration rate was also significantly higher in patients with SR. Moreover, the B-type natriuretic peptide level in the NOAF group was significantly higher than that in the SR group, but less than that in the pre-existing AF group. The D-dimer level and proportion of positive cTn (i.e., >99 percentile upper reference limit) were not statistically different among the 3 groups.

Regarding chest X-ray on admission, findings of ground glass opacity/consolidation/alveolar opacity and congestion were more frequently observed in the NOAF group than in the other groups. Patients with NOAF and pre-existing AF had a higher incidence of congestion on chest radiography and pleural effusion on chest radiography and CT, with a significant difference compared to those with SR.

Treatment During Hospital Course

The use of antibiotics, heparin, and vasopressors was significantly more frequent in patients with NOAF than in the other groups (Table 2). Furthermore, the rates of oxygenation and respiratory ventilator use were significantly higher in patients with NOAF.

In-Hospital Outcomes

In-hospital adverse events, including the incidence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, stroke, acute kidney injury, liver disorder, multiple organ failure, and hemorrhage, were more common in patients with NOAF than in those with pre-existing AF and SR. The number of patients treated in the intensive care unit after admission was also significantly higher in the NOAF group than in the other groups (Figure 2).

The overall in-hospital mortality was 15.6%, and the in-hospital all-cause mortality was significantly different according to the AF status. Patients with NOAF had significantly higher mortality than those with pre-existing AF or SR (pre-existing AF vs. NOAF vs. SR groups: 30.9% vs. 46.4% vs. 12.7%, $P<0.001$) (Figure 2). Furthermore, NOAF was independently associated with in-hospital mortality even after adjustment for pre-existing AF and the 4C mortality score (odds ratio [95% confidence interval]: 4.71 [1.63–13.6], $P=0.004$) (Tables 3,4).

Discussion

In the current study, the presence of both NOAF and pre-existing AF led to higher in-hospital mortality than SR

after SARS-CoV-2 infection. In addition, we found that patients with NOAF had worse in-hospital adverse events, such as multiple organ disease, hemorrhage, stroke, and in-hospital death; this was even in comparison to those with pre-existing AF, despite a higher rate of underlying heart failure and chronic kidney disease (representative predictors of worse outcomes in COVID-19) in patients with pre-existing AF. Patients with NOAF were characterized by a worse inflammatory status during the hospital course than the patients in the other groups. The NOAF group had higher levels of CRP and LDH at the time of admission, and the incidence of ARDS and sepsis was more common in patients with NOAF than in those with pre-existing AF and SR. These findings may support the hypothesis that the incidence of NOAF in patients with COVID-19 is mainly based on cardiac injury due to systemic inflammation, and stimulated sympathetic nervous system due to unstable hemodynamics.^{28–30} Our results also support that severe inflammation is responsible for new-onset CVD after SARS-CoV-2 infection, especially NOAF.

In general, higher levels of CRP, reflecting critically ill conditions in infected patients, are related to the incidence of cardiac arrhythmia, which is represented by AF.³¹ The development of cardiac arrhythmia is caused by several factors, including baseline arrhythmogenic substrate, stimulated autonomic nervous system, and inflammation;²⁸ thus, the occurrence of cardiac arrhythmia is associated with worse clinical outcomes in a critically ill population.^{31,32} In particular, unstable activity of the autonomic nervous system resulting from systemic inflammation has a significant role in the development of cardiac arrhythmia.^{29,30} These relationships between inflammation status and the incidence of NOAF may be explained by increased oxidative damage to the fibrous atrium.^{33,34} Our results showed that the NOAF group had higher levels of CRP and LDH at the time of admission, as well as a higher rate of ARDS, highlighting the relationship between inflammatory status and NOAF incidence. It has been debated and reported that SARS-CoV-2 infection would cause new-onset cardiovascular diseases,³⁵ although a recent report demonstrated that the incidence rate of NOAF is not specifically higher in patients with COVID-19, and that the total rate of NOAF is comparable to that of influenza.²⁰ This fact may support the hypothesis that the occurrence of AF during COVID-19 infection is a generalized response

to systemic inflammation as a result of severe viral illness.

Previous studies have reported that COVID-19 is a risk factor for both arterial and venous thrombotic events.³⁶⁻³⁸ In addition, the incidence of AF is a cause of embolic events, including stroke, as a result of left atrial thrombosis.³⁹ Based on these facts, pre-existing AF and NOAF in patients with COVID-19 is presumed to be a notable predictor of thrombotic events, whereas a recent report suggested that NOAF in patients with COVID-19 was an independent predictor of embolic events.⁴⁰ Consistently, we found that the NOAF group had a higher prevalence of stroke events than the pre-existing AF and SR groups. This is despite the fact that the pre-existing AF group had more comorbidities such as heart failure and chronic kidney disease, which is a classical risk factor for thrombotic events and higher CHADS₂-VASc scores. The mechanism underlying the higher rate of stroke in patients with NOAF remains unclear, and there is a close relationship between the severity of COVID-19 and thrombotic events.³⁶⁻³⁸ Thus, the development of stroke in NOAF may result mainly from thrombotic tendencies in patients severe COVID-19.^{41,42} It is also noteworthy that the proportion of prior oral anticoagulation was lower in patients with NOAF than in those with pre-existing AF (pre-existing AF vs. NOAF: 60.0% vs. 3.6%, $P < 0.001$). The relationship between prior oral anticoagulation therapy and the incidence of stroke after admission is unclear; hence, this possibility should be investigated in future studies.

After hospitalization, NOAF was associated with a higher incidence of ARDS, sepsis, septic shock, acute kidney injury, and multiple organ diseases in patients with CVDRF. Additionally, we found that patients with NOAF after SARS-CoV-2 infection had higher mortality rates. The effect of NOAF on the occurrence of these adverse events was unclear, although our data support that the incidence of NOAF is a beneficial predictor of in-hospital outcomes of patients with COVID-19. Furthermore, a recent report suggested that the incidence of NOAF in the general population hospitalized with COVID-19 is strongly associated with higher in-hospital mortality.²⁰ Therefore, the incidence of NOAF may be a useful predictor of clinical outcomes regardless of the presence of CVDRF. In some cases, detecting accurate severity is difficult according to "silent hypoxemia";^{43,44} thus, the incidence of NOAF, which is an easily accessible predictor, would be useful in the management of COVID-19.

Study Limitations

With regard to limitations, this was a retrospective study with missing baseline characteristics. In addition, the incidence of NOAF was also collected retrospectively from medical records; thus, it is possible to overlook its incidence during hospitalization. The missing data may lead to varying results regarding the effect of NOAF and pre-existing AF on outcomes. Moreover, the date of onset of NOAF was not collected in the CLAVIS-COVID registry, the duration between the occurrence of NOAF and in-hospital events could not be assessed, and the information about systemic condition at the time of the incidence of NOAF was unclear. Therefore, the duration and relationships between the incidence of NOAF and other in-hospital events were not analyzed. Further studies are needed to address these concerns. As we retrospectively analyzed the effect of NOAF, there may be an immortal time bias regarding the association between the incidence of NOAF

and the outcomes. The study population of the CLAVIS-COVID registry was enrolled from January 2020 to May 2020, which was the first wave of the COVID-19 pandemic in Japan, thus our cohort did not include the specific individuals with COVID-19 that have a mutation of virus strains. In addition, given several treatment options established as of 2021, it is unclear whether the effect of NOAF on outcomes is comparable in the population after 2021. Further research is needed to focus on these limitations.

Conclusions

In patients with COVID-19 and CVDRF, the NOAF group was independently associated with worse clinical outcomes than the pre-existing AF and SR groups. These patients are at a high risk of adverse events during hospitalization; hence, intensive monitoring and treatment strategies are needed.

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Disclosures

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IRB Information

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study protocol, including the use of an opt-out consent method, was approved by the ethics committee of Toho University Omori Medical Center (No. M20253) and the local ethics committees of all participating institutions. Furthermore, this clinical study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-ID: UMIN000040598) before the first patient was enrolled, in accordance with the International Committee of Medical Journal Editors.

Data Availability

Due to the nature of this research, the participants of this study did not agree for their data to be shared publicly or upon request. Hence, the data are not available.

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