Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Arrhythmias in patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: Incidences and implications

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) continues to impact populations around the globe. Information regarding the incidences and implications of arrhythmias in COVID-19 is limited.
Methods: A total of 463 patients with COVID-19 and who had at least one electrocardiogram recording from February 1 to March 19, 2020, in Wuhan Union Hospital were enrolled in the study.
Results: Arrhythmias occurred in 85 of 463 (18.4%) patients: atrial arrhythmias in 10.2%, junctional arrhythmias in 0.2%, ventricular arrhythmias in 3.5%, and conduction block in 7.3%. Compared with patients without arrhythmias, those with arrhythmias had higher mortality, both during the time from symptom onset ($p < 0.001$) and from admission to follow-up ($p < 0.001$). The frequencies of severe COVID-19 (44.7% vs. 21.2%; $p < 0.001$) and death (25.9% vs. 10.1%; $p < 0.001$) were higher in patients with arrhythmias than in those without arrhythmias. Atrial arrhythmias and ventricular arrhythmias could predict severity and mortality, their odds ratios (OR) were 4.45 (95% confidence interval [CI] 2.35 to 8.40), 5.80 (95% CI 1.89 to 17.76) respectively for severity, and were 3.51 (95% CI 1.74 to 7.08), 3.41 (95% CI 1.13 to 10.24) respectively for mortality. High levels of interleukin-6 (IL-6) and IL-10 were associated with the occurrence of arrhythmias (all $p < 0.05$).
Conclusion: Arrhythmias were significantly associated with COVID-19 severity and mortality. Atrial arrhythmia was the most frequent arrhythmia type. IL-6 and IL-10 levels can predict the risk of arrhythmias in COVID-19 patients.

Introduction

An outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 [1]. The number of deaths due to COVID-19 far exceeded the death toll of severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) [2–4]. Cardiovascular complications have been identified as common risk factors for disease severity and mortality in patients with COVID-19 [1,5–9]. The most common cardiovascular complications related to SARS-CoV-2 infection include arrhythmias, cardiac injury, myocarditis, and heart failure [1]. Arrhythmias were identified as aggravating factors in patients with COVID-19 and were more frequent among patients in intensive care units (ICU) [8].

However, the prevalence of arrhythmia in patients with COVID-19 and their implications in COVID-19 severity and mortality remain unclear. In this study, we retrospectively investigated the prevalence and clinical relevance of different types of arrhythmias in COVID-19 patients.

Methods

Study design and participants

This retrospective study was performed at Wuhan Union Hospital, West Campus of Huazhong University of Science and Technology, Wuhan, China, a designated hospital for providing COVID-19 diagnosis and treatment. All consecutive patients with confirmed COVID-19 and who had at least one electrocardiogram (ECG) recording from February 1, 2020, to March 19, 2020, were enrolled in the study. COVID-19 was diagnosed according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" criteria released by the National Health Commission & State Administration of Traditional Chinese Medicine on March 3, 2020.

The study complied with the Declaration of Helsinki and was approved by the institutional ethics board of Wuhan Union Hospital of

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Huazhong University of Science and Technology (No.20200254). Written informed consent was waived.

Data collection and definitions

The electronic medical records, including clinical charts, nursing records, laboratory findings, 12-lead ECGs, and ECG monitoring for all patients diagnosed with COVID-19, were reviewed by two trained cardiologists who worked in Wuhan Union Hospital West Campus. Demographic, clinical, laboratory, and ECG data were collected using standardized data collection forms. Cases without available medical records or 12-lead ECG recordings were excluded.

Patients were divided according to disease severity into two groups: non-critical group and critical group. Critically ill patients were considered those with any of the following characteristics: (a) requiring mechanical ventilation due to respiratory failure; (b) displaying shock; (c) having organ failure and requiring ICU monitoring. Arrhythmias were diagnosed by 12-lead electrocardiography as atrial arrhythmias (premature atrial beats, atrial tachycardia, atrial fibrillation, and atrial flutter), junctional arrhythmias (junctional premature beats and paroxysmal supraventricular tachycardia), ventricular arrhythmias (premature ventricular beats, ventricular tachycardia, and ventricular fibrillation), and conduction block. Conduction block cases included incomplete right bundle branch block (RBBB), complete RBBB, complete left bundle branch block, left anterior fascicular block, left posterior fascicular block, first-degree atrial ventricular block (AVB), second-degree AVB, and third-degree AVB. We analyzed patients' clinical laboratory findings throughout the course of the disease. The sampling points were the highest or lowest points of laboratory examination results, and the time point to judge the disease severity is consistent with the sampling point.

Statistical analysis

Categorical variables were expressed as percentages, and continuous variables were given as medians and interquartile range (IQR). Categorical variables were compared using the χ^2 test or Fisher's exact

Table 1
Baseline characteristics and laboratory findings of patients with COVID-19.a§, b*

Characteristics	Total	Arrhythmias		p value[b]
		With	Without	
No. of patients	463 (100.0%)	85 (18.4%)	378 (81.6%)	NA
Age, y	61 (51–69)	70 (63–75)	58.5 (48–67)	<0.001
<65y	283 (61.1%)	29 (34.1%)	254 (67.2%)	<0.001
≥65y	180 (38.9%)	56 (65.9%)	124 (32.8%)	
Male	222 (47.9%)	54 (63.5%)	168 (44.4%)	0.001
Time from symptom, d	42 (31–52)	41 (29–56)	42 (32–51)	0.808
Time from admission, d	22 (15–35)	22 (12–35)	22 (16–35)	0.358
Comorbidities				
Hypertension	170 (36.7%)	43 (50.6%)	127 (33.6%)	0.003
Coronary heart disease	50 (10.8%)	21 (24.7%)	29 (7.7%)	<0.001
Heart failure	5 (1.1%)	3 (3.5%)	2 (0.5%)	0.038
Atrial fibrillation	6 (1.3%)	4 (4.7%)	2 (0.5%)	0.011
Cardiomyopathy	4 (0.9%)	2 (2.4%)	2 (0.5%)	0.150
Valvular heart disease	2 (0.4%)	0 (0.0%)	2 (0.5%)	0.367
Diabetes mellitus	72 (15.6%)	20 (23.5%)	52 (13.8%)	0.025
Laboratory findings				
Increased				
Neutrophil count	210 (45.4%)	46 (54.1%)	164 (43.4%)	0.073
Neutrophil percentage	248 (53.6%)	53 (62.4%)	195 (51.6%)	0.072
C-reactive protein	280 (60.5%)	61 (71.8%)	219 (57.9%)	0.018
Procalcitonin	346 (74.7%)	72 (84.7%)	274 (72.5%)	0.019
D-dimer	302 (65.2%)	61 (71.8%)	241 (63.8%)	0.161
Aspartate aminotransferase	222 (47.9%)	53 (62.4%)	169 (44.7%)	0.003
Alanine aminotransferase	322 (69.5%)	66 (77.6%)	256 (67.7%)	0.072
Lactate dehydrogenase	247 (53.3%)	57 (67.1%)	190 (50.3%)	0.005
Bilirubin	136 (29.4%)	42 (49.4%)	94 (24.9%)	<0.001
Creatinine	166 (35.9%)	47 (55.3%)	119 (31.5%)	<0.001
Blood urea nitrogen	139 (30.0%)	46 (54.1%)	93 (24.6%)	<0.001
Creatine kinase	100 (21.6%)	32 (37.6%)	68 (18.0%)	<0.001
Creatine kinase-MB fraction	109 (23.5%)	34 (40.0%)	75 (19.8%)	<0.001
High-sensitivity troponin I	96 (20.7%)	37 (43.5%)	59 (15.6%)	<0.001
B-type natriuretic peptide	113 (24.4%)	44 (51.8%)	69 (18.3%)	<0.001
Decreased				
White blood cell count[a]	285 (61.6%)	42 (49.4%)	243 (64.3%)	0.011
Lymphocyte count	278 (60.0%)	63 (74.1%)	215 (56.9%)	0.003
Lymphocyte percentage	295 (63.7%)	58 (68.2%)	237 (62.7%)	0.337
Eosinophil count	206 (44.5%)	42 (49.4%)	164 (43.4%)	0.312
Albumin	299 (64.6)	54 (63.5%)	245 (64.8%)	0.823
Disease severity				
Non-critical	345 (74.5%)	47 (55.3%)	298 (78.8%)	<0.001
Critical	118 (25.5%)	38 (44.7%)	80 (21.2%)	
Clinical outcomes				
Died	60 (13.0%)	22 (25.9%)	38 (10.1%)	<0.001
Myocardial infarction	4 (0.86)	2 (2.35)	2 (0.53)	0.321
Heart failure	62 (13.39)	29 (34.12)	33 (8.73)	<0.001

Data are median(IQR) or n (%).
COVID-19, coronavirus disease 2019; NA, not applicable; IQR, interquartile range.
[a] The laboratory indicator of white blood cell count selects COVID-19 patients with normal or decreased results, while the other laboratory indicators under this category select the patients with decreased results.
[b] Comparison of with versus without arrhythmias.

test, as appropriate. Continuous variables were analyzed using the Kolmogorov-Smirnov test for distribution normality; normally distributed data were compared using the *t*-test, and not normally distributed data were analyzed using the Mann-Whitney *U* test. Survival curves were plotted using the Kaplan-Meier method, and differences among groups were determined using the log-rank test. Multivariable analysis was conducted using binary logistic regression with disease severity and clinical outcomes as dependent variables. Statistical analyses were performed using SPSS version 22.0 (IBM), and a two-sided $p < 0.05$ was considered significant. To eliminate type I error, we adjusted *p* values using Bonferroni correction for multiple comparisons.

Results

In total, 470 patients with COVID-19 and who had at least one ECG recording were admitted to Wuhan Union Hospital West Campus between February 1, 2020, and March 19, 2020; seven patients without available medical records or 12-lead ECG data were excluded. Data of 463 patients with confirmed COVID-19 were retrospectively reviewed; among these patients, 85 (18.4%) had arrhythmias and 378 (81.6%) had no arrhythmias. The baseline characteristics and laboratory findings of study participants are summarized in Table 1. The median age of patients was 61 years (IQR, 51–69 years), and 222 (47.9%) patients were men.

Compared with patients without arrhythmias, those with arrhythmias had a higher proportion of men (54 [63.5%] vs. 168 [44.4%]; $p = 0.001$). Patients with arrhythmias appeared to be older than those without arrhythmias (56 [65.9%] vs. 124 [32.8%]; $p < 0.001$). The time between symptom onset or admission and end of follow-up did not differ significantly between the two groups . Several comorbidities were more frequent in patients with arrhythmias than in those without arrhythmias; these comorbidities included hypertension (153 [38.6%] vs. 17 [25.4%]; $p = 0.04$), coronary heart disease (21 [24.7%] vs. 29 [7.7%]; $p < 0.001$), heart failure (3 [3.5%] vs. 2 [0.5%]; $p = 0.038$), atrial fibrillation (4 [4.7%] vs. 2 [0.5%]; $p = 0.011$), and diabetes mellitus (20 [23.5%] vs. 52 [13.8%]; $p = 0.025$). Statistically significant differences were also observed in several clinical laboratory indices. Notably, the proportion of critically ill patients was more frequent among patients with arrhythmias than those without arrhythmias (38 [44.7%] vs. 80 [21.2%]; $p < 0.001$), suggesting an association between arrhythmias and adverse COVID-19 outcomes. Consistently, patients with arrhythmias were more likely to

Table 2
Association of baseline characteristics, laboratory findings and sinus tachycardia.

Type of arrhythmia	No. of patients, n (%)
No. of enrolled patients	463 (100.0)
Total no. of patients with arrhythmias	85 (18.4)
With atrial arrhythmias only	47 (10.2)
Premature atrial beats	29 (6.3)
Atrial tachycardia	1 (0.2)
Atrial fibrillation	17 (3.7)
Atrial flutter	3 (0.6)
With junctional arrhythmias only	1 (0.2)
Junctional premature beats	0 (0.0)
Supraventricular tachycardia	1 (0.2)
With ventricular arrhythmias only	16 (3.5)
Ventricular premature beats	15 (3.2)
Ventricular tachycardia	1 (0.2)
Ventricular fibrillation	0 (0.0)
With conduction block only	34 (7.3)
Incomplete RBBB	14 (3.0)
Complete RBBB	15 (3.2)
Complete LBBB	0 (0.0)
Left anterior fascicular block[t]	5 (1.1)
Left posterior fascicular block	0 (0.0)
First degree AVB	7 (1.5)
Second degree AVB	0 (0.0)
Third degree AVB	0 (0.0)

Data are n (%).
RBBB, right bundle branch block; LBBB, left bundle branch block; AVB, atrial ventricular block.

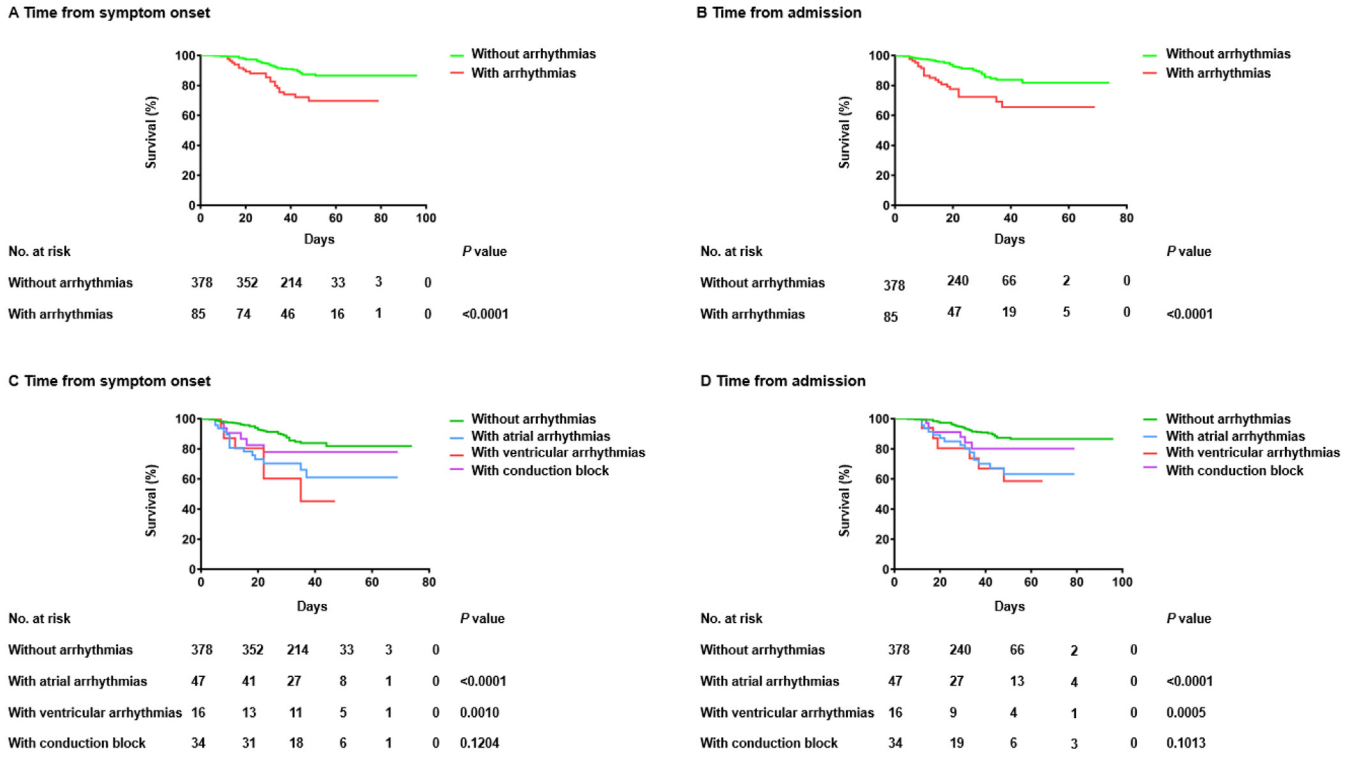

Fig. 1. Survival of patients with COVID-19. Survival analyses in patients with and without arrhythmias from symptom onset (A) and admission (B). Survival analyses in patients with atrial arrhythmias, ventricular arrhythmias, conduction block, and without arrhythmias from symptom onset (C) and admission (D).

develop heart failure during hospitalization than did patients without arrhythmias (29 [34.12%] vs. 33 [8.73%]; $p < 0.001$). Moreover, the all-cause mortality rate was higher in patients with arrhythmias than in those without arrhythmias (22 [25.9%] vs. 38 [10.1%]; $p < 0.001$). Survival analyses showed that arrhythmias were associated with a high mortality rate ($p < 0.001$; Fig. 1A). Furthermore, arrhythmias at admission were associated with an increased risk of death in patients with COVID-19 ($p < 0.001$; Fig. 1B).

The incidence of different types of arrhythmias is shown in Table 2. Arrhythmias occurred in 85 of 463 patients, and some patients had multiple types of arrhythmias. Among the 85 patients with arrhythmias, 47 had only atrial arrhythmias, one had only junctional arrhythmias, 16 had only ventricular arrhythmias, and 34 had only conduction block. The clinical relevance of junctional arrhythmias on COVID-19 severity was not evaluated because of the low incidence of this type of arrhythmias. Patients with atrial arrhythmias and those with ventricular arrhythmias had higher risks of death than patients without arrhythmias, both during the time from symptom onset and from admission (all $p < 0.05$, Figure1C-D).

The relationship between disease severity, clinical outcomes, and arrhythmias was evaluated by binary logistic regression analysis, and the results are presented in Tables 3 and 4. Notably, atrial arrhythmias and ventricular arrhythmias were significantly associated with a high risk of severe COVID-19 and death during hospitalization. Regarding COVID-19 severity, the adjusted odds ratios (ORs) for atrial arrhythmias and ventricular arrhythmias were 4.45 (95% confidence interval [CI], 2.35 to 8.40) and 5.80 (95% CI, 1.89 to 17.76), respectively. As for death during hospitalization, the adjusted OR for atrial arrhythmias was 3.51 (95% CI, 1.74 to 7.08), and that for ventricular arrhythmias was 3.41 (95% CI, 1.13 to 10.24). We also performed binary logistic regression analysis to evaluate the clinical relevance of atrial and ventricular arrhythmia subtypes, including premature atrial beats (PABs), atrial tachycardia/atrial fibrillation/atrial flutter (AT/AF), premature ventricular beats (PVBs), and ventricular tachycardia/ventricular fibrillation (VT/AF). Multivariate logistic regression analyses revealed that PABs (OR, 3.29), AT/AF (OR, 5.23), and PVBs (OR, 3.98) were independent risk factors for critical illness. However, only PABs were independently associated with death (OR, 3.42; 95% CI, 1.47 to 8.00).

Inflammatory cytokine analyses were performed in 328 patients. Patients were divided based on cytokine levels into the following groups: group 1 (normal), group 2 (less than two times elevated compared to the upper limit of normal), group 3 (two to four times elevated compared to the upper limit of normal), group 4 (more than four times elevated compared to the upper limit of normal). The relationship between cytokine levels and different types of arrhythmias is presented in Fig. 2. High levels of IL-10 were significantly associated with the incidence of arrhythmias. Atrial arrhythmias and ventricular arrhythmias were significantly more frequent in patients with elevated IL-10 levels than in those with physiological IL-10 levels (Fig. 2B-C). Additionally, patients with a four times elevated level of IL-6 were more likely to experience atrial arrhythmias when compared with patients with a less than two times elevated level of IL-6 (all $p < 0.05$; Fig. 2B).

Table 3
Association between disease severity and arrhythmias.

Types of different arrhythmias	Patients, No. (%)	Risk of critical condition	
		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Atrial arrhythmias	27/47 (57.4)	4.82 (2.59–8.99)	4.45 (2.35–8.40)
PAB	16/29 (55.2)	4.01 (1.87–8.61)	3.29 (1.48–7.33)
AT/AF	12/21 (57.1)	4.23 (1.73–10.31)	5.23 (1.68–16.21)
Ventricular arrhythmias	11/16 (68.8)	6.99 (2.38–20.57)	5.80 (1.89–17.76)
PVB	10/15 (66.7)	6.30 (2.11–18.82)	3.98 (1.59–9.92)
VT/AF	1/1 (100.0)	NA	NA
Conduction block	10/34 (29.4)	1.24 (0.57–2.67)	NA

OR, odds ratios. 95% CI, 95% confidence interval. PABs, premature atrial beats; AT/AF, atrial tachycardia/atrial fibrillation/atrial flutter; PVBs, premature ventricular beats; VT/AF, ventricular tachycardia/ventricular fibrillation.

Table 4
Association between hospitalized mortality and arrhythmias.

Types of different arrhythmias	Patients, No. (%)	Risk of death	
		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Atrial arrhythmias	15/47 (31.9)	3.87 (1.94–7.68)	3.51 (1.74–7.08)
PABs	10/29 (34.5)	4.04 (1.78–9.18)	3.42 (1.47–8.00)
AT/AF	6/21 (28.6)	2.87 (1.07–7.72)	2.59 (0.94–7.17)
Ventricular arrhythmias	6/16 (37.5)	4.37 (1.53–12.50)	3.41 (1.13–10.24)
PVBs	5/15 (33.3)	3.57 (1.18–10.84)	2.722 (0.85–8.72)
VT/AF	1/1 (100.0)	NA	NA
Conduction block	6/34 (17.6)	1.49 (0.59–3.76)	NA

OR, odds ratios. 95% CI, 95% confidence interval. PABs, premature atrial beats; AT/AF, atrial tachycardia/atrial fibrillation/atrial flutter; PVBs, premature ventricular beats; VT/AF, ventricular tachycardia/ventricular fibrillation.

Discussion

In this retrospective study, we comprehensively analyzed the incidence and clinical relevance of different types of arrhythmias in patients with COVID-19. Previous studies reported that arrhythmias occurred in 4.3% ~ 16.7% of patients infected with SARS-CoV-2 [8,10]. In line with these reports, we found that 18.4% of patients with COVID-19 experienced arrhythmias, with atrial arrhythmias being the most frequent. Previous studies showed that patients with pneumonia developed new-onset AF [11]. It can not be ruled out that pneumonia may affect the function of the adjacent atrium, causing atrial arrhythmias.

Mounting evidence shows a link between cardiac injury, hypoxemia, inflammation, and cardiac arrhythmias. SARS-CoV-1 has been shown to directly damage cardiomyocytes and the cardiac conduction system [12]. Arrhythmias have also been reported in patients diagnosed with SARS. The effects of SARS-CoV-2 and SARS-CoV-1 on the cardiovascular system may be similar because they are highly homologous. Thus, patients with COVID-19 may develop arrhythmias due to damage to the cardiac conduction system. COVID-19 is characterized by dyspnea, and hypoxemia was reported in 36.4% of COVID-19 cases [13,14]. Importantly, hypoxemia dysregulated myocardial electricity [12]. Given that hypoxemia can cause arrhythmias, patients with COVID-19 may develop arrhythmia due to hypoxemia.

We also found that increased levels of IL-6 and IL-10 can predict the risks of atrial and ventricular arrhythmias. Inflammatory cytokines, such as IL-6 and IL-8, have been associated with lung injury and poor outcomes in patients with SARS or MERS [15,16]. A recent study demonstrated that IL-6 and IL-10 were significantly elevated in patients with severe COVID-19 [17]. Xu et al. [18] reported that tocilizumab, a monoclonal antibody targeting the IL-6 receptor, improved clinical symptoms in patients with COVID-19. Of note, it has been found that the release of inflammatory cytokines was correlated with lethal SARS-CoV-1 [[19]]. Hence, inflammation is likely to contribute to deterioration and death in COVID-19 patients.

Our findings suggest that arrhythmias are significantly associated with critical illness and mortality in patients with COVID-19. Consistently, recent studies showed a higher incidence of arrhythmias in critically ill patients with COVID-19 [10,20]. In addition, a meta-analysis demonstrated that patients with COVID-19 experiencing arrhythmias had an increased risk of poor outcomes [21]. Here, we analyzed the effects of different types of arrhythmias and found atrial and ventricular arrhythmias to increase the risk of COVID-19 severity and mortality.

Patients with COVID-19 and who developed life-threatening arrhythmias, such as AT/AF or VT/VF, had unfavorable outcomes. Therefore, patients with COVID-19 should be closely monitored for arrhythmias and treated, if necessary. Many medications used to treat the symptoms caused by SARS-CoV-2 infection have been shown to

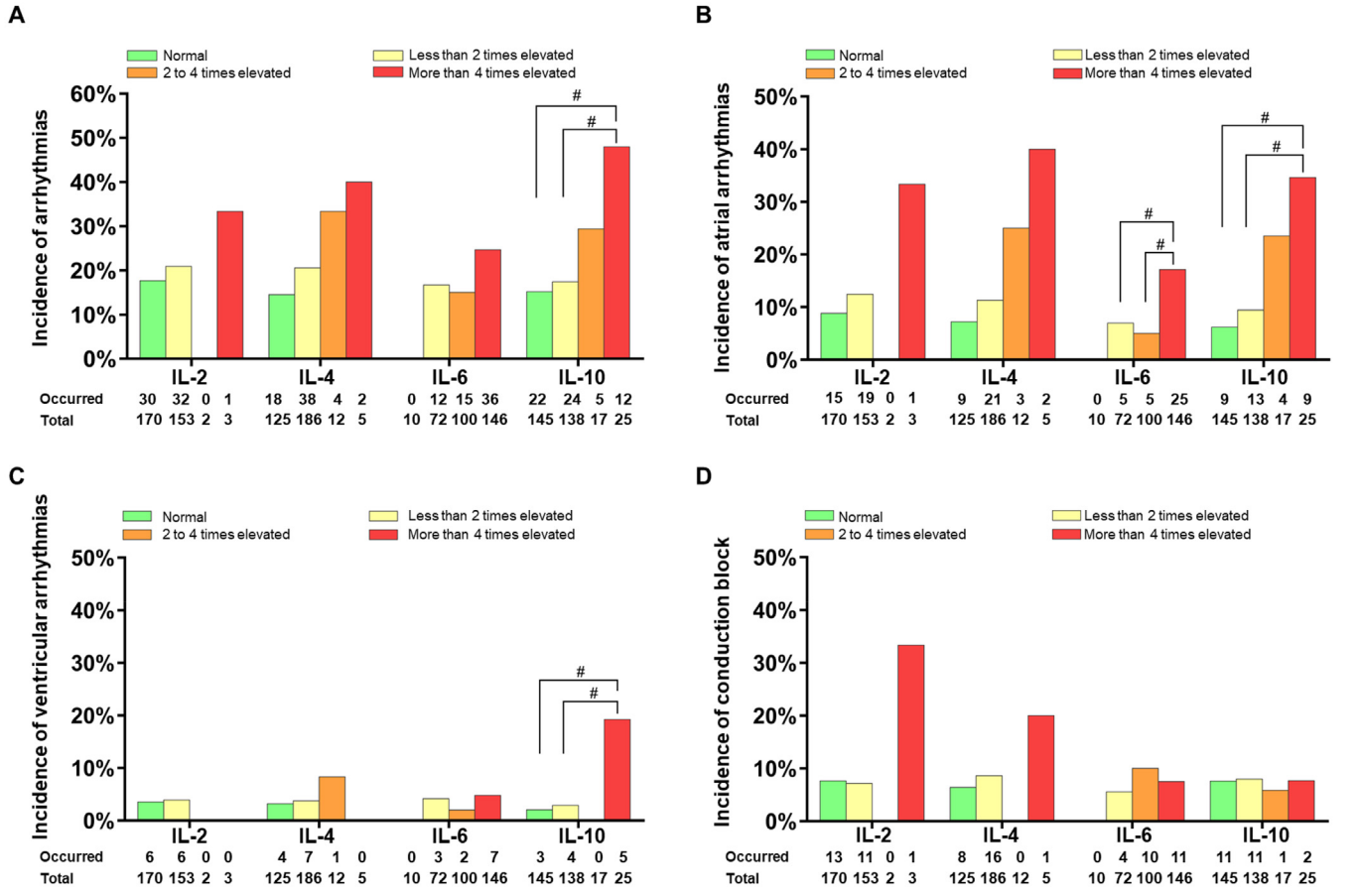

Fig. 2. Relationship between inflammatory cytokines and different types of arrhythmias. Association of inflammatory cytokines and arrhythmias (A), atrial arrhythmias (B), ventricular arrhythmias (C), and conduction block (D). IL, Interleukin. # indicates statistical significance by Bonferroni correction.

affect cardiac electrophysiological activity [22]. Hence, arrhythmias should be taken into account for deciding the appropriate COVID-19 treatment.

Our study has some limitations. First, the case number of severe arrhythmias, such as ventricular arrhythmias, was underestimated because ECGs were not recorded in patients undergoing rescue therapy for cardiac arrest. Additionally, ECGs were not be recorded in patients who died suddenly, even if the cause of death was malignant arrhythmias. Second, as we retrospectively analyzed the follow-up data of hospitalized patients, we could not assess the long-term effects of arrhythmia on COVID-19 outcomes.

Conclusions

Our data suggest that arrhythmias are associated with disease severity and in-hospital mortality in patients with COVID-19. Notably, atrial arrhythmias and ventricular arrhythmias appear to be independent risk factors for critical illness and mortality. Inflammatory cytokines may mediate the occurrence of arrhythmias in patients with COVID-19. Therefore, patients with COVID-19 should be closely monitored for arrhythmias.

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Declaration of Competing Interest

None.

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