Letter to the Editor

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Atrial arrhythmia and its association with COVID-19 outcome: a pooled analysis

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To the Editor,

The current coronavirus disease 2019 (COVID-19) outbreak has escalated rapidly to a global pandemic. While clinical symptoms are primarily linked to the respiratory system, cardiovascular complications have been identified as well. COVID-19 may have a serious effect on cardiac function and cause heart injury along with increased severity of illness and fatal outcomes [1]. Cardiac arrhythmias were found among these documented cardiac manifestations, with varying estimates between studies and according to severity levels [2, 3].

An overall cardiac arrhythmia prevalence of 17% in patients hospitalized for COVID-19 was indicated from China's early reports. Furthermore, in COVID-19 patients admitted to the intensive care unit (ICU), a higher arrhythmia incidence (44%) was observed [2]. Since there is an increasing prevalence of arrhythmia in COVID-19 with atrial fibrillation (AF) being the most common form [4] and its possibility to be associated with COVID-19 prognosis, we aimed to evaluate here whether the incidence of atrial arrhythmia was associated with COVID-19 outcome.

A systematic search was performed in three different databases (PubMed, Scopus, and MedRxiv) using keywords "COVID-19" OR "SARS-CoV-2" AND "atrial arrhythmia" OR "atrial fibrillation" AND "mortality" OR "severity" between

January 1–November 30, 2020. Reference lists of the included studies were also screened to identify additional relevant studies. We included all observational studies or trials involving adult patients with COVID-19 who had any atrial arrhythmia and COVID-19 outcome data. We excluded any study that had missing required data and not in English literature. Titles and abstracts were screened and assessed before full-text retrieval. The full papers that met the eligibility criteria were included in analysis. The primary endpoint of our meta-analysis was the poor outcome of COVID-19. Poor outcome was defined as in-hospital mortality, severity based on WHO criteria, or use of mechanical ventilation during hospitalization in COVID-19 patients. A pooled analysis was performed using STATA v.16. Meta-analysis of proportions was used to pool the incidence of atrial arrhythmia. Mantel-Haenszel formula was used for dichotomous variables to calculate the pooled odds ratios (ORs). Random effect models were used regardless of heterogeneity. Random-effects meta-regression was performed for age and sex.

Search result in 412 records. After duplicate removal, 384 records remained. Title and abstracts were then screened, and a total of 315 records were removed. Sixty-nine full texts were then assessed for eligibility, and 59 articles were excluded due to incorrect patient population (n=9); unavailability of data on atrial arrhythmia (n=23); no outcome of interest (n=27). Finally, we included 10 eligible studies (5,193 patients) for analysis.

All included studies were retrospective observational. Most studies were conducted in USA (Table 1). The prevalence of atrial arrhythmia in patients with COVID-19 was 9.2% (95% CI: 6.5–12.7%; I^2 : 92.66, $p < 0.001$). Atrial arrhythmia occurred in 14.8% (95% CI: 10.0–21.4%; I^2 : 82.99, $p < 0.001$) of patients with poor outcome and 7.0% (95% CI: 4.7–10.5%; I^2 : 91.90, $p < 0.001$) of patients without poor outcome.

Patients with COVID-19 experiencing atrial arrhythmia had an increased risk of poor outcome (OR 2.63 [95% CI: 1.57–4.43], $p < 0.001$; I^2 : 77.64%, $p < 0.001$) (Figure 1). Sensitivity analysis removing the study of Elias et al. showed the statistical robustness with a similar result (OR 2.94 [95% CI: 1.71–5.04], $p < 0.001$; I^2 : 74.03%, $p < 0.001$). The

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Table 1: Characteristics of included studies.

No	Author	Outcome	Study design	Country	Total sample, n ^a	Atrial arrhythmia prevalence, n, %	Type of atrial arrhythmia	Male, %	Age, year
1	Peltzer B, 2020 [14]	Mortality	Retrospective observational	USA	1,053 (184 vs. 869)	166 (15.8)	AF/Aflut	62.3	62 ± 17
2	Mccullough SA, 2020 [15]	Mortality	Retrospective observational	USA	756 (90 vs. 666)	42 (5.6)	AF/Aflut	63.2	63.3 ± 16.0
3	Li L, 2020 [16]	Mortality	Retrospective observational	China	113 (50 vs. 63)	7 (6.2)	NR	60.2	67.3 ± 14.1
4	Quisi A, 2020 [17]	Mortality	Retrospective observational	Turkey	349 (38 vs. 311)	16 (4.6)	AF	43.8	56 (20–80)
5	Russo V, 2020 [18]	Mortality	Retrospective observational	Italy	414 (107 vs. 307)	71 (17.1)	AF	61.1	66.9 ± 15.0
6	Abrams MP, 2020 [19]	Mortality	Retrospective observational	USA	133 (11 vs. 122)	31 (23.3)	AF	55.6	81 (70.5–88)
7	Ghio S, 2020 [20]	Mortality	Retrospective observational	Italy	405 (124 vs. 281)	29 (7.2)	AF	68.6	69.8 (58.6–78.3)
8	Wang Y, 2020 [21]	Severity	Retrospective observational	China	319 (97 vs. 222)	20 (6.6)	AF	47.6	64.97 ± 13.15
9	Elias P, 2020 [22]	MV	Retrospective observational	USA	1,258 (174 vs. 1,101)	108 (13)	AF/Aflut, atrial ectopy	54	61.6 ± 18.4
10	Goyal P, 2020 [23]	MV	Retrospective observational	USA	393 (130 vs. 263)	29 (7.4)	NR	60.6	62.2 (48.6–73.7)

^aData were presented as poor vs. good outcome. AF, atrial fibrillation; Aflut, atrial flutter; NR, not reported; MV, mechanical ventilation.

association between atrial arrhythmia and COVID-19 outcome was not affected by sex ($p=0.855$), but affected by age ($p=0.042$).

Our finding was consistent with the previous meta-analyses showed that arrhythmia was quite prevalent in COVID-19, which was about 19% [3, 5]. This analysis also showed that arrhythmia was associated with poor outcomes. A pooled analysis by Pranata et al. also showed that

arrhythmia incidence was higher in COVID-19 with poor outcomes, which might be a predictor of poor prognosis [5]. However, those previous meta-analyses did not specify the type of arrhythmia in COVID-19.

Arrhythmias and disorder of the conduction system are not an early or typical manifestation of COVID-19. Our understanding of arrhythmic complications is still improving in COVID-19. Several reports have been reported with

Figure 1: Pooled analysis of atrial arrhythmia and COVID-19 outcome.

Atrial arrhythmia was associated with an increased risk of poor outcome.

multiple complications of arrhythmia, and the number is still increasing. The literature, however, lacks studies that explicitly directed at atrial arrhythmias in patients with COVID-19.

Cardiac arrhythmias in COVID-19 may be secondary to side effects of treatment, hypoxia and pulmonary disease, the activity of direct oxidized Ca^{2+} /calmodulin-dependent protein kinase II, activated protein kinase C, and myocarditis. Hypoxemia induced by respiratory failure leads the myocardium to get a relatively hypoxic condition. Hypoxia can facilitate the death of cardiomyocytes and affect ion channels' activity, resulting in alterations in the action prolongation and/or repolarization of the heart, thereby facilitating arrhythmogenesis [6]. Additionally, electrolyte disturbances that may precipitate or worsen heart arrhythmias are often found in these patients [5].

AF was the most frequent cardiac arrhythmia reported in COVID-19 infected patients [4]. Inciardi et al. reported that AF prevalence was 36% in patients with cardiovascular diseases, with more commonly in 42% of patients who did not survive [7]. Similarly, in a study of 115 hospitalized patients (46 admitted to the general ward and 69 ICUs), Colon et al. reported that in 19 patients (16.5%), all of whom were admitted to the ICU (27.5% of ICU patients), new-onset atrial tachyarrhythmia including AF, atrial flutter, and atrial tachycardia were observed [8].

The mechanisms that may induce atrial fibrillation in COVID-19 may be due to systemic infection, direct viral endothelial damage and cardiomyocyte injury, the interaction of CD147 and sialic acid-spike protein, a decrease in the availability of angiotensin-converting enzyme 2 (ACE2) receptors, enhanced inflammatory signaling eventually resulting in an inflammatory cytokine storm, hypoxemia, electrolytes and acid-base balance abnormalities, and patients' vulnerability was owing to old age and their comorbidities, and inevitably, overactivity of the sympathetic nervous system [9, 10]. A case of new-onset atrial fibrillation and flutter in a COVID-19 patient was also documented by Seecheran et al., further indicating the atrial arrhythmogenicity of COVID-19 infection [11].

Whether AF has contribution in increasing the risk of severe COVID-19 is not yet established. But the possible mechanism of AF in increasing risk of severity in COVID-19 was proposed by Sanchis-Gomar et al. In patient with cardiovascular disease, including atrial fibrillation, the level and activity of ACE2 are deranged. SARS-CoV-2 binds with the ACE2 in the cell surface to penetrate the human cell. It has been previously described that plasma ACE2 activity levels are increased in AF and have been suggested as a better marker of disease severity in human AF. Thus,

increasing the risk of developing severe COVID-19 in those population [12].

Notably, the involvement of AF, along with poor rate control, may have a detrimental effect on the prognosis of patients. With a high prevalence of AF in the general population, especially the elderly, and the established correlation between arrhythmic burden and viral disease, AF can affect mortality [13].

In conclusion, our finding showed that atrial arrhythmia was prevalent and associated with poor outcome of COVID-19. Early screening of arrhythmia, especially atrial arrhythmia, may help clinicians differentiate against the arrhythmia's prognostic importance, facilitating more effective risk stratification.

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