Frequency of Atrial Arrhythmia in Hospitalized Patients With COVID-19

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There is growing evidence that COVID-19 can cause cardiovascular complications. However, there are limited data on the characteristics and importance of atrial arrhythmia (AA) in patients hospitalized with COVID-19. Data from 1,029 patients diagnosed with of COVID-19 and admitted to Columbia University Medical Center between March 1, 2020 and April 15, 2020 were analyzed. The diagnosis of AA was confirmed by 12 lead electrocardiographic recordings, 24-hour telemetry recordings and implantable device interrogations. Patients' history, biomarkers and hospital course were reviewed. Outcomes that were assessed were intubation, discharge and mortality. Of 1,029 patients reviewed, 82 (8%) were diagnosed with AA in whom 46 (56%) were new-onset AA 16 (20%) recurrent paroxysmal and 20 (24%) were chronic persistent AA. Sixty-five percent of the patients diagnosed with AA (n=53) died. Patients diagnosed with AA had significantly higher mortality compared with those without AA (65% vs 21%; p < 0.001). Predictors of mortality were older age (Odds Ratio (OR)=1.12, [95% Confidence Interval (CI), 1.04 to 1.22]); male gender (OR=6.4 [95% CI, 1.3 to 32]); azithromycin use (OR=13.4 [95% CI, 2.14 to 84]); and higher D-dimer levels (OR=2.8 [95% CI, 1.1 to 7.3]). In conclusion, patients diagnosed with AA had 3.1 times significant increase in mortality rate versus patients without diagnosis of AA in COVID-19 patients. Older age, male gender, azithromycin use and higher baseline D-dimer levels were predictors of mortality. **(Am J Cardiol 2021;147:52−57)**

The Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2) has affected millions across different ethnicities and countries in the past few months since its emergence from Wuhan, China.[1] COVID-19 mostly presents as a respiratory tract infection with different levels of severity. The more severe form of acute respiratory distress requires hospital admission and advanced treatments.[2] There is increasing evidence of associated cardiovascular complications from mild myocardial injuries to more severe forms of myocarditis.[3-5] However, there is limited data on arrhythmic presentations including atrial arrhythmias (AA) in COVID-19. In this study, the incidence, characteristics and outcomes in patients with AA admitted to hospital with COVID-19 were investigated.

Methods

The study included 1029 COVID-19 patients who were 18 years of age or older admitted to the Columbia University's 3 affiliated hospitals between March 1, 2020 and April 15, 2020. All baseline data including patients' demographics, co-morbidities, laboratory results, electrocardiographic (ECG) recordings and hospital course were extracted from the electronic medical records. The initial laboratory results for inflammatory markers, coagulation values, myocardial stretch and injury were collected at the time or near the time of admission.

Medication history prior to admission as well as during hospital course were obtained. Hydroxychloroquine and azithromycin usage during admission for treatment of COVID-19 were also included. Hydroxychloroquine dosing regimen at our institution was an initial loading dose of 600 mg x 2 for 1 day, followed by 400 mg daily for 4 more days. Azithromycin was given with an initial dose of 500 mg for one day, followed by 250 mg daily for 4 additional days.

Patients with atrial fibrillation (AF) or flutter (new or pre-existing) were anticoagulated with intravenous heparin (53%) or direct oral anticoagulants (34%) or low molecular weight heparin (7%) or warfarin (6%). This study was approved by the Columbia University Irving Medical Center Institutional Review Board. All patients included in the

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study had a positive result for SARS-CoV-2 on real time polymerase -chain- reaction testing on pharyngeal or nasal cavity swabs.

AA and its subtype of AF, atrial flutter and supraventricular tachycardia (long or short RP) were diagnosed using three sources: 12 lead ECGs, 24-hour telemetry recordings or implantable device interrogations. The diagnosis of AA was confirmed and verified by two board certified cardiac electrophysiologists who reviewed all ECGs, telemetry recordings and device interrogation reports. The AA patterns of presentation were divided into 3 patterns: new-onset, recurrent paroxysmal AA and chronic persistent AA.[6] New-onset AA including AF was defined as newly diagnosed AA at the time of hospital admission or during the hospital course. The onset of arrhythmia and history of prior AA were verified by reviewing the patient history, ECGs, telemetry recording and device interrogation reports. Recurrent paroxysmal AA was defined as patients with prior history of AA with recurrence at the time of admission. Patients who were chronically in AA before and during the current admission were classified as chronic persistent AA. In patients with new-onset AA, the exact time to the onset of AA was established by reviewing the ECGs, progress reports as well as daily vital sign recordings. All AA lasted longer than 6 minutes.

Hospitalization outcomes were assessed by reviewing the patient's electronic health records. The outcomes were divided into four groups: (1) died by any cause, (2) still admitted and intubated, (3) still admitted but not intubated, (4) discharged from hospital. The cause of death was divided into arrhythmic and non-arrhythmic based on the review of death notes and telemonitoring recordings. Follow-up continued through April 23, 2020.

Continuous variables are presented as mean ± SD. Categorical variables are reported as frequencies and percentages. Shapiro-Wilk test was performed to assess the normality of distribution for continuous variables. Skewed continuous variables were log-transformed for greater symmetry of distribution. Linear regression was used for determining statistically significant differences across continuous variables. Pearson's or Fisher's exact chi square testing were used for analysis of categorical variables. Predictors of mortality in patients with AA were determined using multivariable logistic regression models. In the first model, the association between the clinical risk factors and the outcome of death was examined. The second model examined the relationship between the biomarkers and outcome of death. A 2-sided p value of < 0.05 was considered statistically significant. Statistical analyses were performed using STATA version 11 (College Station, Texas).

Results

Among the 1029 patients who were admitted with COVID-19, 82 (8%) patients were diagnosed with AA, including 46 (4.5%) patients without prior history of AA (new-onset) (Figure 1). The mean age of the 1,029 patients was 63.6 ± 17.4. The mean age of patients with AA was 76 ± 13 and was significantly higher than the mean age of patients without AA (62.4 ± 17.3; $p < 0.001$). The male to female ratio was similar between the two groups (43% female in AA vs 42% female in non AA, $p = 0.9$). Hispanic and/or Latino patients constituted nearly 50% of patients with no significant differences across different patterns of AA ($p = 0.8$).

Of 82 patients with AA, arrhythmia was present at the time of admission in 44 (54%) patients. The rest of the patients were diagnosed on average 3 to 4 days after hospital admission date. Of the 82 patients, 62 (76%) were diagnosed with AF, 13 (16%) patients were diagnosed with atrial flutter (typical flutter based on ECG) and 7 (8%) were found to have supraventricular tachycardia (5 with long RP and 2 with short RP tachycardia) (Table 1). ECGs of the 5 patients with long RP tachycardia showed different p wave morphology than sinus with positive polarity in inferior leads, strongly favoring focal atrial tachycardia. New-onset AA was seen in 46 (56%) of the patients. Recurrent paroxysmal and chronic persistent were diagnosed in 16 (20%) and 20 (24%) patients, respectively (Table 1). New-onset AA patients were significantly younger than the two other patterns, and also had higher BMIs ($p < 0.05$). Patients with new-onset AA less often had a history of heart failure and coronary artery disease compared with recurrent and chronic persistent AA patients ($p < 0.05$). Thirteen (16%) patients had a history of pacemaker and defibrillator implanted among whom a significant number (86%) had a history of AA prior to admission ($p < 0.05$). One patient had

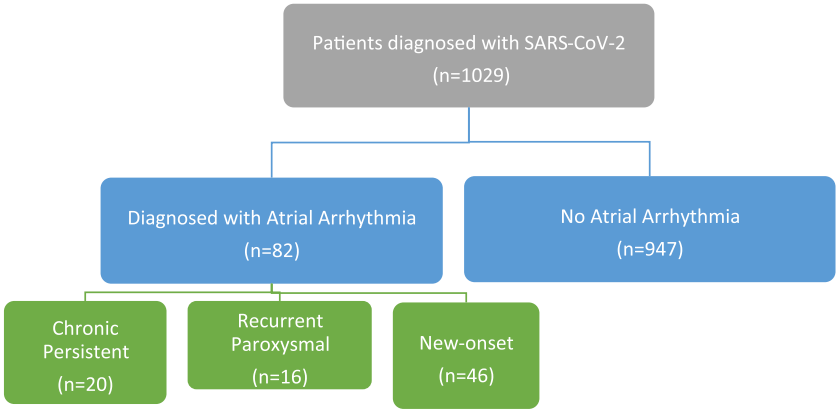

Figure 1. Flowchart of the patients who participated in our study.

Table 1
Characteristics of COVID-19 patients with atrial arrhythmia

Variables	All AA (n = 82)	New-onset AA (n = 46)	Recurrent Paroxysmal AA (n = 16)	Chronic Persistent AA (n = 20)	p value for subtypes
Age (years)	76±13	71±13	82±8	81±13	0.002
Men	47 (57%)	27 (58%)	7 (44%)	13 (65%)	0.8
Hispanic	39 (48%)	21 (46%)	10 (63%)	8 (40%)	0.8
White	32 (39%)	18 (39%)	6 (37%)	8 (40%)	
Black	7 (8%)	3 (6%)		4 (20%)	
Asian	4 (5%)	4 (9%)			
Body mass index (kg/m^2)	29±7	31±8	30±5	26±4	0.011
Diabetes mellitus	42 (51%)	25 (55%)	10 (63%)	7 (35%)	0.23
Hypertension	69 (84%)	36 (78%)	16 (100%)	17 (85%)	0.1
Heart failure	23 (28%)	8 (17%)	8 (50%)	7 (35%)	0.03
Coronary artery disease	29 (35%)	11 (23%)	8 (50%)	10 (50%)	0.04
CKD/ESRD	17 (20%)	10 (22%)	3 (19%)	4 (20%)	1
Prior asthma/COPD	13 (16%)	8 (17%)	4 (25%)	1 (5%)	0.22
Prior PPM/ICD	13 (16%)	2 (4%)	6 (37%)	5 (25%)	0.002
Atrial arrhythmia Type					
Atrial fibrillation	62 (76%)	0 (65%)	13 (81%)	19 (95%)	0.03
Typical Atrial flutter	13 (16%)	9 (20%)	3 (19%)	1 (5%)	0.3
SVT	7 (8%)	7 (15%)	0	0	
Medications					
Hydroxychloroquine	47 (58%)	34 (74%)	7 (44%)	6 (30%)	0.002
Azithromycin	36 (44%)	24 (52%)	9 (56%)	3 (15%)	0.009
Amiodarone use	29 (41%)	26 (56%)	2 (12.5%)	1 (5%)	< 0.001

Atrial arrhythmia=AA; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; ESRD: end stage renal disease; ICD= implantable cardioverter-defibrillator; PPM=permanent pacemaker; SVT= supraventricular tachycardia.

a history of MAZE surgery and another patient had history of pulmonary vein isolation.

Only ESR was found to be significantly elevated in patient with new-onset AA when it was compared with other patterns (p =0.01). The rest of the biomarkers showed no significant differences across the different AA patterns (p > 0.05; Table 2). The hemoglobin level was found to be similar across AA patterns (p = 0.08). Hydroxychloroquine and azithromycin were taken in 58% and 44% of the patients, respectively and predominantly in patients with new-onset AA. In 38% of patients, both medications were taken at the same time. Only two patients were on antiarrhythmics prior to hospital admission. For rate and rhythm control, 29 (37%) patients were started on amiodarone and 7 (8.5%) patients underwent electrical cardioversion. Atrial flutter was terminated in one individual using its pacemaker atrial tachycardia pacing feature.

Of the 82 patients, 53 (65%) died and 9 (11%) remained on ventilators by the end of follow up period. The AA patterns demonstrated no significant differences in the outcomes (p = 0.08) (Figure 2). The mortality rate of patients with AA (65%) was significantly higher than patients without AA (n = 185, 21%; p <0.0001). Type and patterns of AA showed no significant association with mortality in univariate as well as multivariable analysis (p=0.2). There was only one verified arrhythmic death (taking both azithromycin and hydroxychloroquine). After adjusting for all potential clinical risk factors, older age, male gender and azithromycin use were found to be the predictors of mortality in patients with COVID-19 and AA (Table 3). Patients diagnosed with AA demonstrated a 12% increase in odds of death for any one-year increase in age. Men had 6.4 times [95% CI, 1.3 to 32] higher odds of mortality compared with women.

Table 2
Biomarkers and atrial arrhythmia

Variable	All AA (n = 82)	New-onset AA (n = 46)	Recurrent Paroxysmal AA (n = 16)	Chronic Persistent AA (n = 20)	p value for AA patterns
IL-6 > 300 (pg/mL)	29 (35%)	13 (28%)	6 (37%)	10 (50%)	0.25
CRP (mg/L)	187± 113	205±113	163±103	154±115	0.1
ESR (mm/hr)	79±34	87±32	67±26	63±37	0.01
Log D-dimer (μg/mL)	1.08± 1.13	1.32± 1.16	0.52± 0.98	0.9± 1.03	0.1
Log Troponin-T HS (ng/L)	4.42±1.44	4.41±1.6	4.43±1.03	4.41±1.31	0.9
Log BNP (pg/mL)	8.07±1.76	7.81±1.99	8.34±1.27	8.51±1.46	0.1

AA=atrial arrhythmia; IL-6= Interleukin-6; CRP= C reactive protein; ESR= erythrocyte sedimentation rate.
Troponin-T HS= troponin-T High sensitivity; B-NP= B- Type natriuretic peptide.
Normal values for D-dimer is 0.0-0.8 ug/mL; Troponin-T high sensitivity ≤ 14 ng/L; BNP: Age < 50 years: < 450 pg/mL, Age 50 - 75 years: < 1,800 pg/mL.

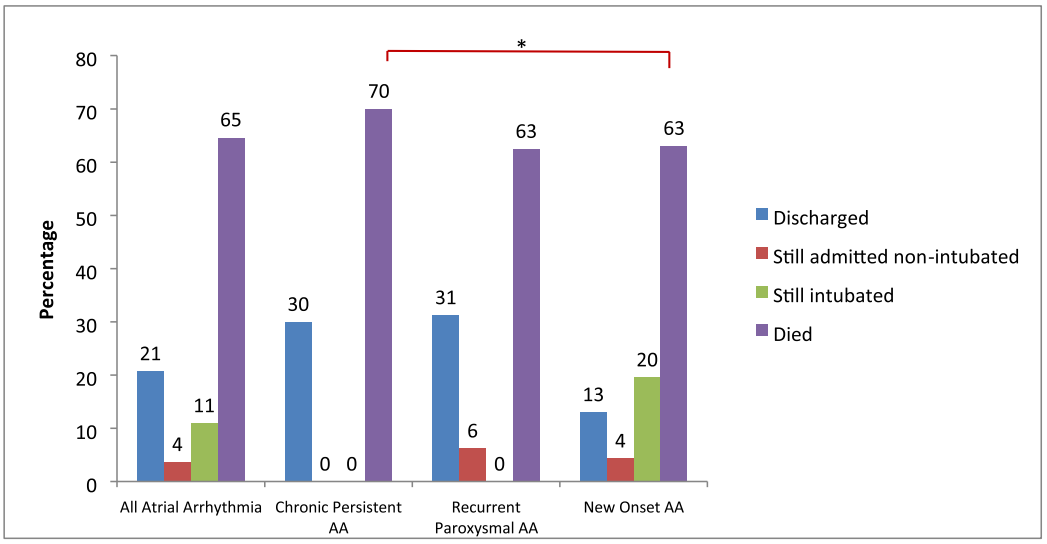

Figure 2. Distribution of outcomes in atrial arrhythmia and its different patterns of presentation. * (p=0.08).

Table 3
Predictors of mortality in patients with atrial arrhythmia and COVID-19

		95% Confidence interval risk factors odds ratio	
		Lower	Upper
Age*	1.12	1.04	1.22
Gender - Male*	6.4	1.3	32
Azithromycin use*	13.4	2.14	84
Log D-dimer†	2.8	1.1	7.3

*Model 1: Multivariable logistic regression model for mortality and clinical risk factors: age, gender, ethnicity, pattern of atrial arrhythmia, BMI, history of diabetes mellitus, history of hypertension, history of heart failure, history of coronary artery disease, history of chronic kidney disease, hydroxychloroquine use, azithromycin use and amiodarone use.

†Model 2: Multivariable logistic regression model for mortality and biomarkers: IL-6>300, Log D-dimer, C-reactive protein, erythrocyte sedimentation rate, Log highly sensitive troponin and Log brain natriuretic peptide.

Finally, azithromycin use increased the odds of mortality by 13.4 folds [95% CI, 2.14 to 84]. Among the biomarkers, D-dimer (Log D-dimer) was the only marker that showed significant association with mortality (Table 3).

Discussion

The current study demonstrates that a significant number of patients (8%) admitted for COVID-19 were diagnosed with some type of atrial arrhythmia, over half (56%) of which were new-onset AA. The incidence of new-onset AF in patients admitted for infectious etiologies was reported as 1.1%, which is significantly lower than what was detected in the current study. The rate of new-onset AA and/or AF in our study was similar to the incidence of new-onset AF in patients admitted due to severe sepsis [7]. Higher incidence of AA and/or AF has also been reported in other viral respiratory tract infections such as influenza, with an 18% increased risk.[8]

There are limited reports on the incidence of AA in patients with COVID-19. In a recent study of 700 hospitalized patients, 25 (3.6%) patients were diagnosed with new onset AF.[9] In a larger population of patients from New York City, AA was also detected in 15.8% of the patients, 9.6% of which were newly diagnosed.[10] This rate is higher than the current study and it is possibly due to the higher percentage of white patients in their cohort. In another study, Goyal *et al* noted that the prevalence of AA was much higher in patients requiring mechanical ventilation (17.7%) compared with those who were not intubated (1.9%).[11]

The increased incidence of AA and AF in the setting of viral infections such as COVID19 is believed to be secondary to the close interplay between AF and an inflammatory process.[12] However, it is possible that SARS-CoV-2 uniquely induces AA via its effect on angiotensin- converting enzyme 2 (ACE2) and renin-angiotensin-aldosterone system (RAAS). SARS-CoV-2 enters the host cell using ACE2 as its cellular receptor.[13] ACE2 plays a major role in angiotensin II regulation and protects against the detrimental effect of RAAS on the cardiovascular system.[14] There is compelling evidence that RAAS plays a major role in the development and perpetuation of AF including new-onset AF.[15] RAAS modulates the atrial electrical and mechanical properties of the atrium. RAAS activation shortens the action potential duration and negatively impacts the intracellular calcium handling to facilitate the initiation of AF.[16-17] We also observed that the mortality in patients with AA was remarkably high. The mortality rate was similarly high between patients with chronic persistent and new-onset AA despite their possible different pathogenesis. The high mortality rate in patients with chronic persistent AA and recurrent paroxysmal AA is less surprising given their old age and high prevalence of pre-existing comorbidities signaling lower baseline reserve, frailty and poor stamina. On the other hand, new-onset AA might be an indicator of the severity of the COVID19 infection. We noticed that baseline ESR level was significantly higher and

CRP trended higher in new-onset AA pattern. This might suggest an elevated inflammatory state and possibly more severe disease. Among inflammatory markers, ESR might be a better indicator of overall inflammation status compared with CRP and interleukin-6, which have shorter half-lives and more fluctuations.[18,19]

Similarly, other studies revealed that older age and male gender were noted to be predictors of mortality in all COVID-19 patients.[20-21] Older age is associated with more comorbidities, less reserve and higher susceptibility to hemodynamic collapse when in the setting of physical stress.[22] It is also known that females have better innate immunity to pathogens as well as antibody- and cell- mediated immune response. The end result is a lower viral load and a prevalence of viral infections in females.[23,24]

The most intriguing observation was the association of azithromycin use with death in patients with AA. Azithromycin has been widely used as an antibiotic in clinical practice and has been subjected to multiple studies regarding its cardiovascular safety.[25,26] In the 2012 study, azithromycin therapy was associated with a small absolute increase in cardiovascular death. The authors suggested that azithromycin can be proarrhythmic via QT prolongation and might contribute to the increase in cardiac death. They also noticed the highest risk of death in patients with higher baseline cardiovascular disease.[27] However, the incidence of cardiac arrhythmia especially *torsades de pointes* is extremely rare in patients taking this medication.[28] Yet it is not established whether azithromycin directly increases mortality in patients with pre-existing cardiovascular disease or its use is simply a marker of severe disease. In our cohort, 38% of the patients were taking hydroxychloroquine and azithromycin simultaneously. However, there was no association between hydroxychloroquine and increased mortality. In addition, there was only one verified arrhythmic death. Overall, it seems that azithromycin should be used with caution in patients with AA and COVID-19 until more data are available on its safety.

Finally, higher baseline D-dimer levels were associated with a higher odds of death in our cohort of patients with AA. The association between higher D-dimer levels and higher mortality was reported in several studies of patients with COVID-19.[20 21] A higher level of D-dimer is also a significant marker of death in patients with other infections or sepsis.[29] D-dimer and other markers of the coagulation cascade increase significantly as part of the inflammatory response to infections especially in severe reaction of disseminated intravascular coagulation.[30] There is mounting evidence that patients with COVID-19 may suffer from a hypercoagulable state resulting in thromboembolic complications and death.[31,32] D-dimer might simply be an indicator of the hypercoagulable state and its associated poor prognosis.

Similar to other observational and retrospective studies, residual confounding could contribute to the relationship observed. We included only the patients that were admitted to the hospital who usually have severe manifestations of COVID-19; hence, AA in milder form and in the outpatient setting might have different characteristics. Data was collected from medical records with all its limitations. It is possible that some of the patients who were labeled as newonset AA had episodes prior to their current admission that went unnoticed or were not documented. In conclusion, patients diagnosed with AA had 3.1 times significant increase in mortality rate versus patients without diagnosis of AA in COVID-19. In COVID-19 patients with AA, older age, male gender, azithromycin use and higher baseline D-dimer levels were predictors of mortality.

Disclosures

The authors have no conflicts of interest to disclose.

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