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Incidence, Mortality, and Imaging Outcomes of Atrial Arrhythmias in COVID-19

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Incidence, Mortality, and Imaging Outcomes of Atrial Arrhythmias in COVID-19

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Atrial arrhythmias (AAs) are common in hospitalized patients with COVID-19; however, it remains uncertain if AAs are a poor prognostic factor in SARS-CoV-2 infection. In this retrospective cohort study from 2014 to 2021, we report in-hospital mortality in patients with new-onset AA and history of AA. The incidence of new-onset congestive heart failure (CHF), hospital length of stay and readmission rate, intensive care unit admission, arterial and venous thromboembolism, and imaging outcomes were also analyzed. We further compared the clinical outcomes with a propensity-matched influenza cohort. Generalized linear regression was performed to identify the association of AA with mortality and other outcomes, relative to those without an AA diagnosis. Predictors of new-onset AA were also modeled. A total of 6,927 patients with COVID-19 were included (626 with new-onset AA, 779 with history of AA). We found that history of AA (adjusted relative risk [aRR] 1.38, confidence interval [CI], 1.11 to 1.71, p = 0.003) and new-onset AA (aRR 2.02, 95% CI 1.68 to 2.43, p <0.001) were independent predictors of in-hospital mortality. The incidence of new-onset CHF was 6.3% in history of AA (odds ratio 1.91, 95% CI 1.30 to 2.79, p <0.001) and 11.3% in new-onset AA (odds ratio 4.01, 95% CI 3.00 to 5.35, p <0.001). New-onset AA was shown to be associated with worse clinical outcomes within the propensity-matched COVID-19 and influenza cohorts. The risk of new-onset AA was higher in patients with COVID-19 than influenza (aRR 2.02, 95% CI 1.76 to 2.32, p <0.0001), but mortality associated with new-onset AA was higher in influenza (aRR 12.58, 95% CI 4.27 to 37.06, p <0.0001) than COVID-19 (aRR 1.86, 95% CI 1.55 to 2.22, p <0.0001). In a subset of the patients with COVID-19 for which echocardiographic data were captured, abnormalities were common, including valvular abnormalities (40.9%), right ventricular dilation (29.6%), and elevated pulmonary artery systolic pressure (16.5%); although there was no evidence of a difference in incidence among the 3 groups. In conclusion, new-onset AAs are associated with poor clinical outcomes in patients with COVID-19. **(Am J Cardiol 2022;00:1−9)**

Introduction

There is a high incidence of cardiac electrophysiologic issues in patients with COVID-19.[1−3] Mechanisms for arrhythmias and cardiac injuries in patients with COVID-19 could be threefold including viral infection-related (endothelial damage, microthrombi formation, and inflammatory cytokine storm); hypoxemia mediated tissue injury; and the administration of arrhythmogenic medications.[4] Common unintended nontherapeutic target effects of COVID−19 treatment include potassium channel blockade, cytochrome P450 isoenzyme inhibition or activation, and drug-drug interactions with anticoagulants; these may also lead to the occurrence of arrhythmias.[5] To further identify the etiology of cardiac injury and arrhythmias in these patients, transthoracic echocardiography (TTE) can be useful in directing treatment; however, because of infection control, TTE examinations are limited. Although more patients with COVID-19 are getting TTE than at the start of the pandemic, the data on TTE findings in patients with COVID-19 and particularly the impact of atrial arrhythmias (AAs) on echocardiographic phenotypes are scarce. Moreover, data on the effect of AA on chest computed tomography (CT) findings are also limited. In this multicenter study, we evaluated the association of new-onset and history of AA with clinical and imaging outcomes in hospitalized patients with COVID-19. The clinical outcomes are also compared with a cohort of hospitalized patients with influenza.

Methods

Data were collected for patients with COVID-19 and influenza from 1 quaternary care and 5 community hospitals at Henry Ford Health and Trinity Health systems. For

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See page 9 for disclosure information.

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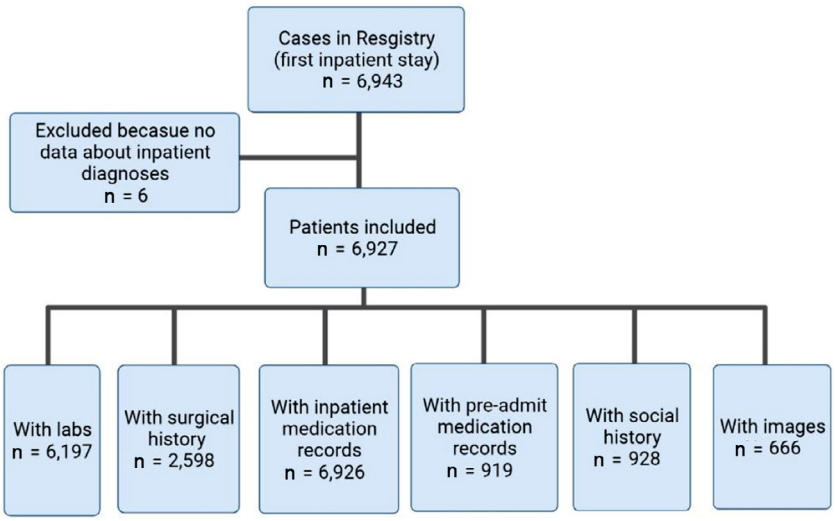

Figure 1. Consort diagram of Southeastern Michigan registry consortium database.

patients with COVID-19, clinical data were derived from electronic health records that were deidentified and stored in the Southeast Michigan COVID-19 Consortium Registry Database (SMCRD) using REDCap. Each institution independently collected data both retrospectively and concurrently from March 1, 2020, to March 31, 2021. Adult patients with positive SARS-CoV-2 polymerase chain reaction tests were included. Of 6,943 patients in the SMCRD registry, 16 patients were excluded because of lack of data on inpatient diagnoses, and 6,927 patients met the inclusion criteria (Figure 1). Data were collected for patients hospitalized with a diagnosis of influenza (identified by International Classification of Diseases, Tenth Revision [ICD-10] codes) at Henry Ford Health System and deidentified (Supplementary Table 1). The study period for patients with influenza was from January 1, 2014 to December 31, 2019. A total of 14,174 patients with influenza were included (Supplementary Table 2). This study was approved by both Trinity and Henry Ford health systems institutional review boards.

Patients with AA (atrial fibrillation [AF] and atrial flutter) were identified using standardized text and ICD-10 codes. Collected data for COVID-19 and influenza populations included baseline demographics, co-morbid conditions, and in-hospital events (electronically abstracted from standardized text variables and ICD-10 codes). For patients with COVID-19, inpatient vital signs, laboratory values, and medications were electronically abstracted from the medical record. Social history, preadmission medications, chest CT, and echocardiographic data were obtained through manual abstraction. We studied the cumulative steroid use including methylprednisolone, dexamethasone, and hydrocortisone. COVID-19 treatments, including azithromycin, hydroxychloroquine, tocilizumab, remdesivir, lopinavir, and ritonavir were also recorded (Supplementary Figure 1). Moreover, we reported inpatient rate control, rhythm control, and anticoagulant therapies in patients with COVID-19 (Supplementary Tables 3 to 4).

The patients in this study were divided into 3 groups: Group 1, defined as the normal sinus rhythm (NSR) group who remained in NSR throughout hospitalization; group 2, defined as new-onset AA group who did not have a history of AA but developed AF or atrial flutter during hospitalization; and group 3, defined as patients with a history of AA and may have stayed in NSR or experienced AA during hospitalization. The primary outcome was in-hospital mortality in 3 groups in patients with COVID-19. Secondary outcomes included the incidence of new-onset congestive heart failure (CHF), ventricular arrhythmias, hospital length of stay (LOS), 90-day readmission rate, intensive care unit (ICU) admission and LOS, rate of intubation and days on ventilation, rate of vasopressor and inotrope use, arterial and venous thromboembolic events, acute renal failure (ARF), requirement for new renal replacement therapy (RRT), bleeding events, and imaging findings including chest CT and TTE. Major bleeding was defined per International Society on Thrombosis and Haemostasis definition.[6] Bleeding (including gastrointestinal bleed, urogenital bleeding, respiratory passages, hemothorax) that did not fit the criteria for the International Society on Thrombosis and Haemostasis definition of major bleeding was classified into minor bleeding.

Summary statistics for patient characteristics were presented as medians with interquartile ranges or means with SDs for continuous data and total numbers and percentages for categoric data. Chi-square tests, Fisher's exact tests, Kruskal−Wallis test, and analysis of variance were used to assess differences between groups. To examine whether AAs were independently associated with the primary end point of in-hospital mortality, multivariable generalized linear regression model using a log link with Poisson distribution (multi-parameter regression [MPR]) model was built using baseline demographic characteristics, co-morbid conditions and presenting labs which were significantly different between the groups, and hypoxia in the emergency room. A similar MPR was built to identify the predictors of new-onset AA.

In the next step, we matched the COVID-19 population to the influenza cohort, a suitable pre-COVID viral pneumonia comparator (Supplementary Figure 2). Propensity scoring was used serially to generate balanced AA groups, within the COVID-19 study set, within the influenza study

Table 1
Baseline characteristics of patients with COVID-19

Variable	Normal sinus rhythm (n = 5522)	New-onset atrial arrhythmias (n = 626)	History of atrial arrythmias (n = 779)	p Value
Age (years)*	62.7 (17)	74.9 (12.4)	77.3 (11.7)	**<0.0001**
Women	2,877 (52%)	275 (44%)	362 (46.5%)	**<0.0001**
Men	2,645 (48%)	351 (56%)	417 (53.5%)	
Black	2,076 (37.6%)	173 (27.7%)	155 (19.9%)	**<0.0001**
White	2,839 (51.4%)	421 (67.4%)	579 (74%)	
Other races	399 (7.3%)	21 (4.7%)	28 (3.6%)	
Body mass index (kg/m^2)*	31.5 (8.6)	30.4 (7.8)	29.5 (7.7)	**<0.0001**
Smoker				**<0.0001**
Never	449 (59.6%)	27 (34.6%)	32 (33%)	
Current	49 (6.5%)	3 (5.1%)	7 (7.2%)	
Former	222 (29.5%)	41 (52.6%)	50 (51.6%)	
Unknown	33 (4.43%)	7 (9%)	8 (8.2%)	
Alcohol user				0.4096
Never	395 (52.5%)	42 (52.9%)	59 (60.8%)	
Current	187 (24.8%)	17 (21.8%)	15 (15.5%)	
Former	62 (8.2%)	5 (6.4%)	6 (6.2%)	
Unknown	109 (14.5%)	14 (18%)	17 (17.5%)	
Marijuana user	32 (4.3%)	1 (1.3%)	5 (5.2%)	0.4001
Diabetes mellitus	1,929 (35%)	241 (38.5%)	310 (39.8%)	0.05
Hypertension	3,462 (62.7%)	477 (76.2%)	665 (85.4%)	**<0.0001**
Congestive heart failure	642 (11.6%)	206 (32.9%)	408 (52.4%)	**<0.0001**
Coronary artery disease	348 (9.8%)	68 (17.9%)	115 (28.7%)	**<0.0001**
	n = 3548	n = 380	n = 401	
Stroke/transient ischemic attack	448 (8.1%)	77 (12.3%)	166 (21.3%)	**<0.0001**
Deep vein thrombosis	269 (4.9%)	40 (6.4%)	68 (8.7%)	**0.0002**
Pulmonary embolism	208 (3.8%)	12 (1.9%)	38 (4.9%)	0.054
CHA_2DS_2-VASc ≥ 2	3,514 (77.2%)	507 (91.7%)	669 (95.4%)	**<0.0001**
CHA_2DS_2-VASc ≥ 4	1,369 (30.1%)	267 (48.3%)	435 (62.1%)	**<0.0001**
Pulmonary disease (COPD, asthma, bronchiectasis, interstitial lung disease)	1,146 (20.8%)	181 (28.9%)	255 (32.7%)	**<0.0001**
Pulmonary hypertension	53 (1%)	8 (1.3%)	38 (4.9%)	**<0.0001**
Liver disease (alcoholic liver disease, cirrhosis, nonalcoholic steatohepatitis, hepatitis B, hepatitis C)	137 (2.5%)	19 (3%)	17 (2.2%)	0.91
Sarcoidosis	43 (0.8%)	5 (0.8%)	5 (0.6%)	0.91
Chronic kidney disease	598 (10.8%)	109 (17.4%)	195 (25%)	**<0.0001**
End-stage renal disease	143 (2.6%)	23 (3.7%)	44 (5.7%)	**0.0001**
Solid cancer and hematological malignancy	767 (13.9%)	133 (21.3%)	190 (24.4%)	**<0.0001**
Autoimmune disease (lupus, rheumatoid arthritis, systemic sclerosis including limited cutaneous and diffuse cutaneous, autoimmune hepatitis, other autoimmune disease)	208 (3.8%)	24 (3.8%)	52 (6.7%)	**0.0036**
Hyperthyroidism	74 (1.3%)	16 (2.6%)	31 (4%)	**<0.0001**
Hypothyroidism	480 (8.7%)	78 (12.5%)	92 (11.8%)	**0.0031**
Transplant (renal, lung, liver, heart)	51 (2.6%)	6 (2.4%)	6 (1.6%)	0.91
	n = 1674	n = 437	n = 339	

One-way ANOVA was used for age and body mass index, and chi-square were tests otherwise.
Social history (smoking, alcohol, and marijuana use) was available for 928 patients.
COPD = chronic obstructive pulmonary disease.
Bold values denote statistical significance at the $p < 0.05$ level
* Mean (standard deviation).

set, and between the COVID-19 and influenza study sets (Supplementary Tables 5, 6, and 7).[7] Statistical analysis was performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 6,927 patients with COVID-19 were included in the study; 5,522 patients (79.7%) remained in NSR (group 1); 626 patients (9%) had new-onset AA (group 2); whereas 779 patients (11.3%) had history of AA (group 3) (Figure 2). The demographic characteristics of 3 groups of patients with COVID-19 are summarized in Table 1. The baseline characteristics of 14,174 patients with influenza are shown in Supplementary Table 2.

Home medications of patients with COVID-19 were reviewed, with findings of statins, β blockers, digoxin, diuretics, and antiplatelets usage more common in groups 2 and 3 (Supplementary Table 8). In multivariable generalized linear regression analysis, age (increments of 10

Table 2
Laboratory values and presenting vital signs in 3 groups

Variable Peak laboratory values, median (Q1, Q3)*	Normal sinus rhythm	New-onset atrial arrhythmias	History of atrial arrhythmias	Kruskal-Wallis p-value
Lactate dehydrogenase (U/L)	317 (232, 444) n = 4,013	354 (244, 527) n = 447	295 (217, 406) n = 487	**<0.0001**
Ferritin (ng/ml)	487 (218, 872) n = 4,045	614 (239, 910) n = 460	398 (167, 861) n = 495	**0.0009**
Troponin I (ng/ml)	0.024 (0.01, 0.06) n = 2,431	0.05 (0.02, 0.09) n = 430	0.04 (0.02, 0.08) n = 449	**<0.0001**
Creatine phosphokinase (U/L)	88 (63, 217) n = 3,930	88 (61, 262) n = 452	78 (53, 99) n = 478	**<0.0001**
C-reactive protein (mg/dl)	7.1 (4, 9.2) n = 4,026	8.3 (5.6, 9.7) n = 460	7,6 (4.2, 9.5) n = 496	**<0.0001**
B-type natriuretic peptide (pg/ml)	55 (27, 117) n = 3,016	189 (82, 475) n = 428	249 (110, 532) n = 482	**<0.0001**
Interleukin-6 (pg/ml)	23 (9, 65) n = 567	41.8 (20, 76.9) n = 107	41 (11.8, 102) n = 81	**0.0034**
Serum creatinine (mg/dl)	1.1 (0.8, 1.6) n = 4,591	1.6 (1.1, 3.4) n = 528	1.4 (1, 2.5) n = 589	**<0.0001**
Lactate (mmol/L)	1.5 (1.2, 2.3) n = 1,226	1.9 (1.3, 2.9) n = 237	1.8 (1.3, 2.7) n = 215	**<0.0001**
Procalcitonin (ng/ml)	0.27 (0.15, 0.79) n = 2,292	0.46 (0.22, 1.6) n = 333	0.34 (0.17, 1) n = 319	**<0.0001**
D-dimer (ng/ml)[b]	705 (370, 1550) n = 3,948	1190 (605, 2500) n = 451	850 (410, 1720) n = 493	**<0.0001**
Alanine aminotransferase (U/L)	34 (20, 60) n = 4,401	34 (21, 66) n = 507	27 (17, 46) n = 563	**<0.0001**
Aspartate aminotransferase (U/L)	41 (28, 65) n = 4,404	49 (31, 75) n = 508	39 (27, 61) n = 563	**<0.0001**
Serum potassium (mEq/L)	4.5 (4.1, 4.9) n = 4,582	4.8 (4.4, 5.6) n = 528	4.7 (4.3, 5.3) n = 589	**<0.0001**
Serum magnesium (mg/dl)	2.2 (2, 2.4) n = 4,450	2.3 (2.1, 2.7) n = 518	2.2 (2, 2.4) n = 576	**<0.0001**
Lowest laboratory values, median (Q1, Q3)*				
Albumin (g/dL)	3 (2.6, 3.4) n = 4,401	2.6 (2.1, 3) n = 508	2.8 (2.3, 3.2) n = 562	**<0.0001**
Serum potassium (mEq/L)	3.6 (3.3, 3.9) n = 4,582	3.6 (3.2, 3.9) n = 528	3.6 (3.2, 3.9) n = 589	0.42
Serum magnesium (mg/dl)	1.9 (1.7, 2) n = 4,450	1.8 (1.6, 1.9) n = 518	1.8 (1.6, 1.9) n = 576	**<0.0001**
Lymphocyte count (K/UL)	0.6 (0.4, 0.9) n = 4,644	0.4 (0.2, 0.7) n = 525	0.5 (0.3, 0.8) n = 588	**<0.0001**
Hemoglobin (gm/dl)	11.7 (10.4, 12.9) n = 4,676	10.7 (10.1, 12.2) n = 528	11 (10.1, 12.5) n = 590	**<0.0001**
Presenting clinical signs				
Systolic blood pressure (mmHg)*	132 (118, 148) n = 4,698	131 (112,147) n = 528	132 (115,149) n = 590	0.0563
Diastolic blood pressure (mmHg)*	74 (65, 84) n = 4,698	70 (60, 81) n = 528	72 (61, 82) n = 590	**<0.0001**
Hypoxia[c]	2221 (43.6%)	321 (56.5%)	313 (46.8%)	**<0.0001**

Bold values denote statistical significance at the $p < 0.05$ level

* Median (interquartile range).

[b] Fibrinogen-equivalent units (FEU)

[c] Oxygen saturation <95%

years), male gender, White race, history of coronary artery disease, CHF, end-stage renal disease, presenting leukocytosis, hypermagnesemia, and hypomagnesemia were independently associated with the occurrence of AA (Supplementary Table 9).

Patients with new-onset AA had higher peaks of myocardial injury marker (troponin I) and inflammatory markers including lactate dehydrogenase, ferritin, C-reactive protein, procalcitonin, D-dimer, interleukin-6, and aspartate aminotransferase and more pronounced lymphopenia, hypoalbuminemia, and hyperkalemia compared with patients with history of AA and NSR (Table 2). Among 123 patients who underwent chest CT, with results abstracted for the SMCRD, 59.4% had ground-glass opacities and multifocal pneumonia (n = 73), 20.3% had pleural effusion (n = 25), and 2.4% had pleural effusions or pulmonary vascular congestion (n = 3) (Supplementary Table 10). The prevalence of pleural effusion was highest in group 3 (group 1 13.8%, group 2 13.3%, group 3 54.6%, p = 0.02) with no significant difference in the prevalence of other

Table 3
Echocardiographic findings in patients with COVID-19

Variable	Normal sinus rhythm (n = 84)	New-onset atrial arrhythmias (n = 20)	History of atrial arrhythmias (n = 11)	Fisher-exact p-value
Right ventricular size				
Normal	54 (64.3%)	13 (65%)	5 (45.5%)	0.68
Mildly enlarged	14 (16.7%)	2 (10%)	4 (36.4%)	
Moderately enlarged	8 (9.5%)	2 (10%)	0	
Severely enlarged	4 (4.8%)	0	0	
Unknown	4 (4.8%)	3 (15%)	2 (18.2%)	
Left ventricular size				
Normal	74 (88.1%)	16 (80%)	9 (81.8%)	0.68
Mildly enlarged	5 (6%)	1 (5%)	0	
Moderately enlarged	0	0	0	
Severely enlarged	0	0	1 (9.1%)	
Unknown	5 (6%)	3 (15%)	1 (9.1%)	
Left ventricular ejection fraction				
Reduced (<40%)	7 (8.3%)	5 (25%)	3 (27.3%)	0.129
Borderline (40 - 49%)	5 (6%)	3 (15%)	0	
Preserved (≥50%)	70 (83.3%)	10 (50%)	8 (72.7%)	
Unknown	2 (2.4%)	2 (10%)	0	
Pericardial effusion				
None	70 (83.3%)	15 (75%)	8 72.7%)	0.68
Small	6 (7.1%)	3 (15%)	1 (9.1%)	
Moderate	1 (1.2%)	0	0	
Large	1 (1.2%)	0	0	
Unknown	6 (7.1%)	2 (10%)	2 18.2%)	
Valvular abnormality				
None	49 (58.3%)	8 (40%)	3 (27.3%)	0.68
Mild	22 (26.2%)	9 (45%)	5 (45.5%)	
Moderate	6 (7.1%)	1 (5%)	1 (9.1%)	
Severe	3 (3.6%)	0	0	
Unknown	4 (4.8%)	2 (10%)	2 (18.2%)	
Pulmonary artery systolic pressure				
Normal (0−40 mm Hg)	38 (45.2%)	13 (65%)	7 (63.6%)	0.68
Mild elevation (41−50 mm Hg)	5 (6%)	2 (25%)	1 (9.1%)	
Moderate elevation (51−60 mm Hg)	4 (4.8%)	1 (5%)	1 (9.1%)	
Severe elevation (>60 mm Hg)	5 (6%)	0	0	
Unknown	32 (38.1%)	4 (20%)	2 (18.2%)	

findings among the 3 groups. The most common TTE abnormalities were valvular abnormalities (40.9%), right ventricular dilation (29.6%), elevated pulmonary artery systolic function (16.5%), reduced left ventricular (LV) ejection fraction (13.9%), pericardial effusion (10.4%), and LV dilation (6.1%) with no significant difference in the prevalence of these echocardiographic abnormalities among the 3 groups (Table 3).

Among all patients, 61.8% (N=1507) received corticosteroids during hospitalization; group 2 (group that developed new-onset AA) received steroids more frequently than the other 2 groups (group 2 vs 3 vs 1, 61.8% vs 49.4% vs 51.8%, p <0.0001) (Supplementary Figure 1). Remdesivir, azithromycin, and hydroxychloroquine usage were more frequent in the NSR group. Rhythm control therapy was used more frequently in patients with new-onset AA than those with a history of AA (Supplementary Table 3). A total of 76.6% of patients with new-onset AA and 76.4% with history of AA received therapeutic doses of anticoagulation (Supplementary Table 4).

We analyzed in-hospital events among 3 groups (Table 4). Group 3 had 6.3% patients with new-onset CHF (n = 49) versus 11.3% in group 2% (n = 71) and 3.1% in group 1 (n = 171) (p <0.001). Ventricular tachycardia (VT) and ventricular fibrillation were more common in group 2 and 3 than group 1. Group 2 had a longer hospital LOS than the other 2 groups. Group 2 had worse outcomes in terms of higher rate of intubation, vasopressor/ionotropic support, and ICU admission and LOS than the other groups. Group 2 also had more complications including non−ST-elevation myocardial infarction, deep vein thrombosis, ARF, and need for new RRT. The incidences of transient ischemic attack, ischemic stroke, arterial thromboembolism, and major and minor bleeding were also higher in group 2 and 3.

The all-cause in-hospital mortality was 39.6% in group 2 (n = 248), 25.16% in group 3 (n = 196), and 11.61% in group 1 (n = 641). In MPR model, history of AA (adjusted relative risk [aRR] 1.38, confidence interval [CI] 1.11 to 1.71, p = 0.003) and newly detected AA (aRR 2.02, 95% CI 1.68 to 2.43, p <0.001) were independently associated with

Table 4
In-hospital events in 3 groups of patients with COVID-19

Variable	Normal sinus rhythm	New-onset atrial arrhythmias	History of atrial arrhythmias	Odds ratio		
				95% confidence interval, p-value		
				Group 3 vs group 1	Group 2 vs group 1	Group 2 vs group 3
Hospital length of stay*	5.1 (3.1, 8.9)	8.1 (4.8, 15.1)	6.4 (4.1, 11.7)	1.02 (1.01-1.03) **<0.001**	1.04 (1.04-1.05) **<0.001**	1.03 (1.02-1.04) **<0.001**
Intensive care unit admission	1089 (19.7%)	282 (45%)	206 (26.4%)	1.46 (1.23-1.74) **<0.001**	3.34 (2.81-3.96) **<0.001**	2.28 (1.82-2.85) **<0.001**
Intensive care unit length of stay*	7 (3, 13)	9 (4, 16)	5 (3, 12)	0.99 (0.97-1.00) 0.14	1.01 (1.00-1.03) **0.02**	1.03 (1.01-1.05) **0.006**
Hospital readmission within 90 days	444 (8%)	43 (6.9%)	99 (12.7%)	1.67 (1.32-2.10) **<0.001**	0.84 (0.61-1.17) 0.304	0.51- (0.35-0.74) **<0.001**
Respiratory failure requiring mechanical ventilation	569 (10.3%)	178 (28.4%)	99 (12.7%)	1.27 (1.01-1.59) **<0.001**	3.46 (2.85-4.20) **<0.001**	2.73 (2.08-3.59) **<0.001**
Days on ventilator*	8 (4, 14)	9 (5, 16)	8 (3, 14)	0.99 (0.97-1.01) 0.309	1.01 (0.99-1.02) 0.275	1.02 (1.00-1.05) 0.11
Vasopressors/inotropes usage	759 (13.8%)	228 (36.4%)	195 (25%)	2.10 (1.75-2.51) **<0.001**	3.59 (3.00-4.30) **<0.001**	1.72 (1.36-2.16) **<0.001**
New-onset congestive heart failure	171 (3.1%)	71 (11.3%)	49 (6.3%)	2.10 (1.51-2.91) **<0.001**	4.01 (3.00-5.35) **<0.001**	1.91 (1.30-2.79) **<0.001**
Transient ischemic attack and ischemic stroke	100 (1.8%)	20 (3.2%)	39 (5%)	2.86 (1.96-4.17) **<0.001**	1.79 (1.10-2.91) **0.019**	0.63 (0.36-1.09) 0.095
ST-segment elevation myocardial infarction	21 (0.4%)	4 (0.6%)	0	N/A	1.68 (0.58-4.92) 0.34	N/A
Non−ST-segment elevation myocardial infarction	303 (5.5%)	105 (16.8%)	91 (11.7%)	2.28 (1.78-2.92) **<0.001**	3.47 (2.73-4.41) **<0.001**	1.52 (1.13-2.06) **0.006**
Other arterial thromboembolism	94 (1.7%)	24 (3.8%)	42 (5.4%)	3.29 (2.27-4.77) **<0.001**	2.30 (1.46-3.63) **<0.001**	0.70 (0.42-1.17) 0.17
Deep vein thrombosis	179 (3.2%)	35 (5.6%)	19 (2.4%)	0.75 (0.46-1.21) 0.23	1.77 (1.22-2.56) **0.003**	2.37 (1.34-4.18) **0.003**
Pulmonary embolism	233 (4.22%)	35 (5.6%)	22 (2.8%)	0.66 (0.42-1.03) 0.066	1.34 (0.93-1.94) 0.11	2.04 (1.18-3.51) **0.01**
Acute renal failure	1669 (30.2%)	325 (51.9%)	339 (43.5%)	1.78 (1.53-2.07) **<0.001**	2.49 (2.11-2.95) **<0.001**	1.40 (1.13-1.73) **0.002**
Renal failure requiring new renal replacement therapy	128 (2.3%)	37 (5.9%)	23 (3.0%)	1.28 (0.82-2.01) 0.279	2.65 (1.82-3.86) **<0.001**	2.06 (1.21-3.51) **0.007**
Ventricular fibrillation	11 (0.2%)	7 (1.1%)	4 (0.5%)	2.59 (0.82-8.14) 0.104	5.67 (2.19-14.67) **<0.001**	2.19 (0.64-7.52) 0.617
Ventricular tachycardia	90 (1.6%)	41 (6.6%)	46, 5.9%	3.79 (2.63-5.45) **<0.001**	4.23 (2.90-6.18) **<0.001**	1.12 (0.72-1.73) 0.212
Major bleeding	330 (6%)	93 (14.9%)	73 (9.4%)	1.63 (1.25-2.12) **<0.001**	2.75 (2.15-3.53) **<0.001**	1.69 (1.22-2.34) **0.002**
Minor bleeding	517 (9.4%)	117 (18.7%)	117 (15%)	1.71 (1.38-2.12) **<0.001**	2.23 (1.79-2.78) **<0.001**	1.30 (0.98-1.72) 0.067

Odds ratios were calculated for each 2-group comparison using univariate logistic regression.
Group 1: normal sinus rhythm; group 2: new-onset atrial arrhythmias; group 3: history of atrial arrhythmias.
* Median (interquartile range).

higher in-hospital mortality (Supplementary Table 11), relative to those with NSR. The 90-day readmission rate in new-onset AA was lower than in patients with history of AA and NSR, which could be possibly explained by the higher mortality in patients with new-onset AA. Among patients with influenza, the in-hospital mortality was 6.3% in group 2 (n = 22), 1.3% in group 3 (n = 20), and 0.7% in group 1 (n = 81).

After propensity matching across the AA groups and 2 study cohorts, the clinical trends in patients with COVID-19 remained similar with new-onset AA associated with higher ICU admission, rate of intubation, usage of vasopressors and inotropes, new-onset CHF, non−ST-elevation myocardial infarction, ARF, and VT. Likewise, in patients with influenza, new-onset AA were associated with higher ICU admission, rate of intubation, usage of vasopressors and inotropes, incidence of new-onset CHF, STEMI, VT, and ventricular fibrillation, and need for new RRT (Supplementary Tables 12 to 13). In a separate analysis, the risk of inpatient mortality for patients with influenza was higher in history of AA than NSR (aRR 12.58, 95% CI 4.27 to 37.06, p <0.0001), which was not the case for patients with COVID-19 (aRR 1.15, 95% CI 0.92 to 1.42, p = 0.2429). The risk of inpatient mortality associated with new-onset AA compared with NSR was higher in both influenza and COVID-19 cohorts, with the risk higher in influenza (aRR 12.58; 95% CI 4.27 to 37.06, p <0.0001) than in COVID-19 (aRR 1.86, 95% CI 1.55 to 2.22, p <0.0001). However, the risk of new-onset AA in hospitalized patients with COVID-19 was higher than patients with influenza (aRR 2.02, 95% CI 1.76 to 2.32, p <0.001).

Discussion

This is a comprehensive study of patients with COVID-19 categorized into 3 groups based on electrophysiologic status with a comparison of the outcomes among the 3 groups. We report a 20.3% prevalence of AA in a large cohort (n = 6,927). The pathophysiology in COVID-19 infection, including cytokine storm, endotheliitis, and systemic infection, causing hemodynamic instability is hypothesized to be associated with a higher incidence of new-onset AA.[4,8] The prevalence of AA was lower in the influenza cohort at 13.1% with a lower incidence of new-onset AA (2.5%) than in COVID-19 (9%); this could be due to the less severe inflammatory response of influenza infection and frequent usage of steroids which are the standard of care for hypoxic patients with COVID-19.

AAs are the most common sustained cardiac rhythm disorder in critically ill patients and those with sepsis.[9−11] AAs are common in patients with COVID-19 with variable incidence. The prevalence of AF was 19% among hospitalized patients with COVID-19 in an Italian study and 36% in patients with cardiac disease, AF was more common in patients who died (42.1% vs 32.5% in survivors).[12] In the United States, the prevalence of AA is reported from 15.8% to 19.6% across different academic centers.[1−3,13] The higher prevalence (20.3%) of AA in our cohort could be explained by the larger size of our study cohort, the larger epidemic surge in Michigan compared with other regions, necessitating stricter admission criteria leading to the admission of patients with advanced COVID-19 disease, and thereby increased usage of steroids.

In hospitalized patients with COVID-19, AAs were independently associated with higher in-hospital mortality (aRR 1.46, 95% CI 1.34 to 1.59 in 1 study[13] and adjusted odds ratio [OR] 1.93, 95% CI 1.20 to 3.11 in the other[2]). In our study, we found that both history of AA and new-onset AA were independently associated with in-hospital mortality. New-onset AAs were associated with a more severe course of the disease and are potentially a marker of severe systemic COVID-19 illness. Likewise, both new-onset AA and history of AA were associated with a higher mortality in patients with influenza. Compared to COVID-19, patients with influenza with new-onset AA had an even higher risk of mortality (aRR 12.58, 95% CI 4.27 to 37.06 vs 1.86, 95% CI 1.55 to 2.22); although because of the low mortality numbers in the influenza cohort, this finding should be explored in future clinical studies.

Our COVID-19 cohort had a high incidence of ICU admission and myocardial infarction. In this analysis, the incidence of new-onset CHF was 4.2% (n = 291). Patients with new-onset AA had the highest odds of new-onset CHF (OR 4.01, 95% CI 3.00 to 5.35, p <0.001), followed by patients with history of AA (OR 1.91, 95% CI 1.30 to 2.79, p <0.001). A similar trend was seen in patients with COVID-19 and influenza after matching between the 2 cohorts. The association of both AA and CHF was appreciated more than a decade ago and AAs may exacerbate the development of decompensated CHF.[14,15]

Respiratory viruses like influenza have the potential to trigger decompensated CHF and lead to increased mortality.[15−17] A study showed a decrease in LV function in patients with severe acute respiratory syndrome coronavirus; the impairment was worse in more critically ill patients.[18] A Chinese study found that the incidence of CHF was higher in COVID-19 nonsurvivors than survivors (52% vs 12%).[19] Another smaller COVID-19 study (n = 21) in the United States reported cardiomyopathy in 1/3 of the critically ill patients.[20] The exact mechanism of tachycardia-induced cardiomyopathy is not well defined.[15] Animal models have suggested that myocardial ischemia, myocardial energy depletion, abnormalities in calcium regulation, and extracellular matrix remodeling could be the underlying mechanisms.[21]

RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial showed lower 28-day mortality in patients with COVID-19 who received dexamethasone, leading to the recommendation of steroid use by COVID-19 treatment guidelines.[22] We defined steroid (including methylprednisolone, dexamethasone, and hydrocortisone) use during hospitalization to reach clinically significant cumulative effect and looked for association with incidence of AA (Supplementary Figure 1). All subtypes of steroids usage were more common in the new-onset AA group, followed by history of AA. This suggests an association between high-dose steroid use and the incidence of new-onset AA, although causality cannot be determined. Some studies have suggested an increased incidence of AF in patients receiving high-dose

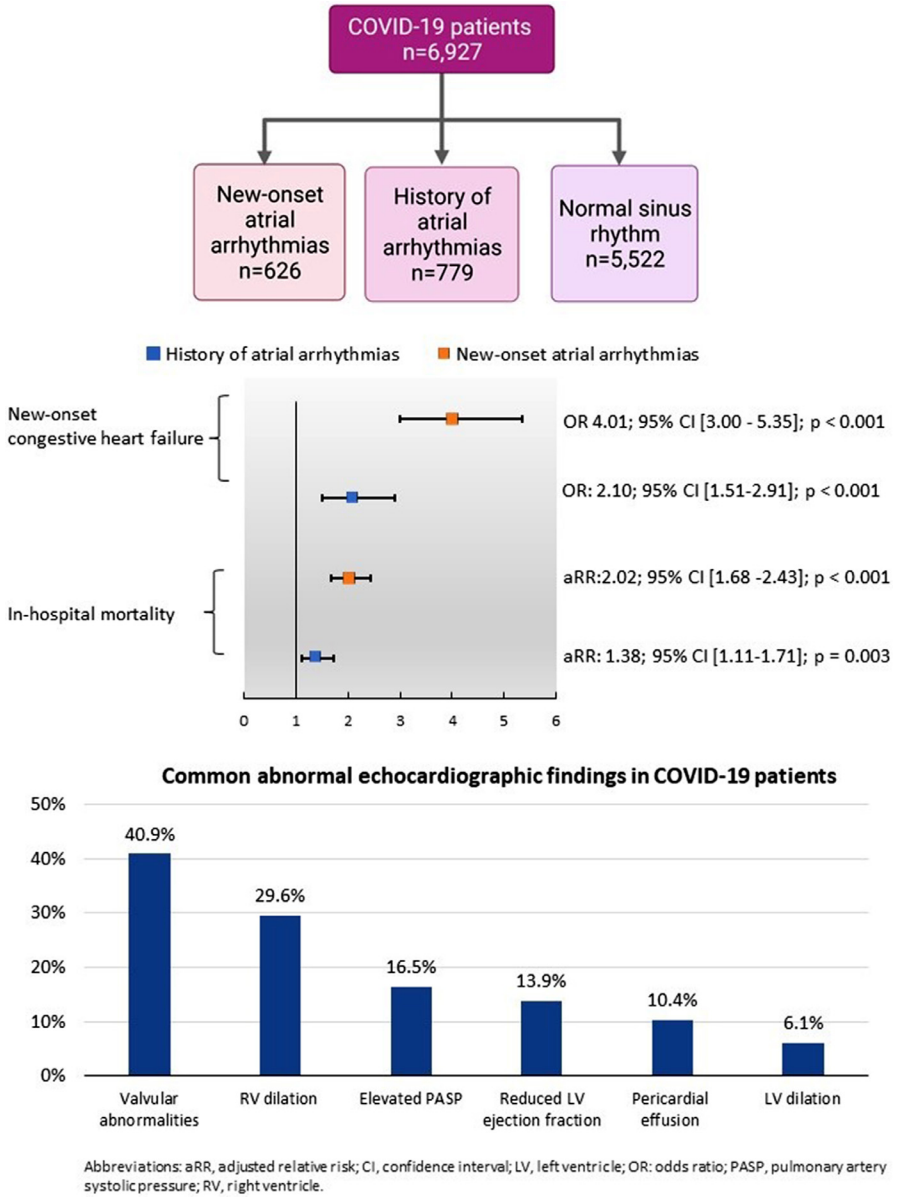

Figure 2. Central illustration. aRR, adjusted relative risk; CI, confidence interval; LV, left ventricle; OR, odds ratio; PASP, pulmonary artery systolic pressure; RV, right ventricle

corticosteroids, whereas others suggest a preventive effect of steroids.[23–27] Although corticosteroids are currently the first-line treatment for hypoxic patients with COVID-19, their use could be associated with an increased risk of developing AA because of their potential arrhythmogenic effect in patients with COVID-19.

Our study has both strengths and limitations. The strengths include a large sample size, multicenter-based data, availability of complete outcome events data, and comparison to a large matched cohort of patients with influenza. Limitations are the observational study design and the inherent risk of bias from unregistered confounders. Since we did not examine the exact onset of AA in our cohort, the temporal relation between arrhythmia onset and in−hospital outcomes was not examined. Because our follow-up only extended to hospital discharge, the occurrence and impact of AA after hospitalization is not known. Also, we did not examine the cause of death in the patients who died.

In conclusion, new-onset AAs are a poor prognostic marker in hospitalized patients with COVID-19. AAs occurred in 20.3% of hospitalized patients with COVID-19 and 13.1% of patients with influenza. Compared with influenza, the risk of new-onset AA was higher in COVID-19; whereas new-onset AA were associated with a higher risk of mortality in influenza. The incidence of new-onset CHF was higher in patients with new-onset AA than patients with NSR in both cohorts. Previous or new-onset atrial AA did not increase the prevalence of echocardiographic abnormalities in patients with COVID-19.

Figure 2

Disclosures

The authors have no conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.02.051.

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