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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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. © 2022 Elsevier Inc. All rights reserved. (Am J Cardiol 2022;173:64−72)

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
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
set, and between the COVID-19 and influenza study sets (Supplementary Tables 5, 6, and 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 1

| Variable                                              | Normal sinus rhythm (n = 5522) | New-onset atrial arrhythmias (n = 626) | History of atrial arrhythmias (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%)                            | <0.0001       |
| 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/m²)*                               | 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       |
| 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          |

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).
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 2
Laboratory values and presenting vital signs in 3 groups

| Variable                        | Normal sinus rhythm | New-onset atrial arrhythmias | History of atrial arrhythmias | Kruskal-Wallis p-value |
|---------------------------------|---------------------|------------------------------|-------------------------------|------------------------|
| Lactate dehydrogenase (U/L)    | 317 (232, 444)      | 354 (244, 527)              | 295 (217, 406)               | <0.0001                |
| Ferritin (ng/ml)                | 487 (218, 872)      | 614 (239, 910)              | 398 (167, 861)               | 0.0009                 |
| Troponin I (ng/ml)              | 0.024 (0.01, 0.06)  | 0.05 (0.02, 0.09)           | 0.04 (0.02, 0.08)            | <0.0001                |
| Creatine phosphokinase (U/L)   | 88 (63, 217)        | 88 (61, 262)                | 78 (53, 99)                  | <0.0001                |
| C-reactive protein (mg/dl)      | 7.1 (4.9, 9.2)      | 8.3 (5.6, 9.7)              | 7.6 (4.2, 9.5)               | <0.0001                |
| B-type natriuretic peptide (pg/ml) | 55 (27, 117)   | 189 (82, 475)               | 249 (110, 532)               | <0.0001                |
| Interleukin-6 (pg/ml)           | 25 (9, 65)          | 41.8 (20, 76.9)             | 41 (11.8, 102)               | 0.0034                 |
| Serum creatine (nmol/L)         | 1.1 (0.8, 1.6)      | 1.6 (1.1, 3.4)              | 1.4 (1.2, 2.5)               | <0.0001                |
| Lactate (mmol/L)                | 1.5 (1.2, 2.3)      | 1.9 (1.3, 2.9)              | 1.8 (1.3, 2.7)               | <0.0001                |
| Procalcitonin (ng/ml)           | 0.27 (0.15, 0.79)   | 0.46 (0.22, 1.6)            | 0.34 (0.17, 1)               | <0.0001                |
| D-dimer (ng/ml)b                | 705 (370, 1550)     | 1190 (605, 2500)            | 850 (410, 1720)              | <0.0001                |
| Albumin (g/dL)                  | 3.4 (2.6, 3.4)      | 2.6 (2.1, 3)                | 2.8 (2.3, 3.2)               | <0.0001                |
| Serum potassium (mEq/L)         | 3.6 (3.3, 3.9)      | 3.6 (3.2, 3.9)              | 3.6 (3.2, 3.9)               | 0.42                   |
| Serum magnesium (mg/dl)         | 1.9 (1.7, 2)        | 1.8 (1.6, 1.9)              | 1.8 (1.6, 1.9)               | <0.0001                |
| Lymphocyte count (K/UL)         | 0.6 (0.4, 0.9)      | 0.4 (0.2, 0.7)              | 0.5 (0.3, 0.8)               | <0.0001                |
| Hemoglobin (gm/dl)              | 11.7 (10.4, 12.9)   | 10.7 (10.1, 12.2)           | 11 (10.1, 12.5)              | <0.0001                |
| Presenting clinical signs       |                     |                             |                              |                        |
| Systolic blood pressure (mmHg)* | 132 (118, 148)      | 131 (112,147)               | 132 (115,149)                | 0.0563                 |
| Diastolic blood pressure (mmHg)*| 74 (65, 84)         | 70 (60, 81)                 | 72 (61, 82)                  | <0.0001                |
| Hypoxia*                        | 2222 (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%
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%), 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), 25.1% in group 3 (n = 196), and 11.6% 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
| Variable                                         | Normal sinus rhythm | New-onset atrial arrhythmias | History of atrial arrhythmias | Odds ratio | 95% confidence interval, p-value |
|-------------------------------------------------|---------------------|-----------------------------|-----------------------------|------------|---------------------------------|
| 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                |
| Intensive care unit admission                   | 1089 (19.7%)        | 282 (45%)                   | 206 (26.4%)                 | 1.46       | 1.23-1.74 <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                 |
| Hospital readmission within 90 days             | 444 (8%)            | 43 (6.9%)                   | 99 (12.7%)                  | 1.67       | 1.32-2.10 <0.001                |
| Respiratory failure requiring mechanical ventilation| 569 (10.3%)        | 178 (28.4%)                 | 99 (12.7%)                  | 1.27       | 1.01-1.59 <0.001                |
| Days on ventilator*                             | 8 (4, 14)           | 9 (5, 16)                   | 8 (3, 14)                   | 0.99       | 0.97-1.01 0.309                |
| Vaspressors/inotropes usage                     | 759 (13.8%)         | 228 (36.4%)                 | 195 (25%)                   | 2.10       | 1.75-2.51 <0.001                |
| New-onset congestive heart failure              | 171 (3.1%)          | 71 (11.3%)                  | 49 (6.3%)                   | 2.10       | 1.51-2.91 <0.001                |
| Transient ischemic attack and ischemic stroke   | 100 (1.8%)          | 20 (3.2%)                   | 39 (5%)                     | 2.86       | 1.96-4.17 <0.001                |
| ST-segment elevation myocardial infarction      | 21 (0.4%)           | 4 (0.6%)                    | 0                           | N/A        | 1.68 (0.58-4.92) 0.34           |
| Non−ST-segment elevation myocardial infarction | 303 (5.5%)          | 105 (16.8%)                 | 91 (11.7%)                  | 2.28       | 1.78-2.92 <0.001                |
| Other arterial thromboembolism                  | 94 (1.7%)           | 24 (3.8%)                   | 42 (5.4%)                   | 3.29       | 2.27-4.77 <0.001                |
| Deep vein thrombosis                           | 179 (3.2%)          | 35 (5.6%)                   | 19 (2.4%)                   | 0.75       | 0.46-1.21 0.23                 |
| Pulmonary embolism                              | 233 (4.22%)         | 35 (5.6%)                   | 22 (2.8%)                   | 0.66       | 0.42-1.03 0.066                |
| Acute renal failure                             | 1669 (30.2%)        | 325 (51.9%)                 | 339 (43.5%)                 | 1.78       | 1.53-2.07 <0.001                |
| Renal failure requiring new renal replacement therapy | 128 (2.3%) | 37 (5.9%) | 23 (3.0%) | 1.28 | 0.82-2.01 0.279 |
| Ventricular fibrillation                        | 11 (0.2%)           | 7 (1.1%)                    | 4 (0.5%)                    | 2.59       | 0.82-8.14 0.104                |
| Ventricular tachycardia                         | 90 (1.6%)           | 41 (6.6%)                   | 46 (5.9%)                   | 3.79       | 2.63-5.45 <0.001                |
| Major bleeding                                  | 330 (6%)            | 93 (14.9%)                  | 73 (9.4%)                   | 1.63       | 1.25-2.12 <0.001                |
| Minor bleeding                                  | 517 (9.4%)          | 117 (18.7%)                 | 117 (15%)                   | 1.71       | 1.38-2.12 <0.001                |

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, endothelitis, 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).\(^1,5\) In the United States, the prevalence of AA is reported from 15.8% to 19.6% across different academic centers.\(^1–3,11\) 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\(^7\)). 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.\(^12,14,15\)

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.\(^13\) 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...
corticosteroids, whereas others suggest a preventive effect of steroids.\textsuperscript{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.

1. Colon CM, Barrios JG, Chiles JW, McElwee SK, Russell DW, Madden WR, Kay GN. Atrial arrhythmias in COVID-19 patients. JACC Clin Electrophysiol 2020;6:1189–1190.
2. Pelzter B, Manocha KK, Ying X, Kirzner J, Ip JE, Thomas G, Liu CF, Markowitz SM, Lerman BB, Safiﬁd MM, Goyal P, Cheung JW. Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19. J Cardiovasc Electrophysiol 2020;31:3077–3085.
3. Cho JH, Namazi A, Shelton R, Ramireddy A, Eddaie A, Shehata M, Wang X, Marbán E, Chugh SS, Cingolani E. Cardiac arrhythmias in hospitalized patients with COVID-19: a prospective observational study in the western United States. PLoS One 2020;15:e0244533.
4. Kang Y, Chen T, Mui D, Ferrari V, Jegadusa D, Scherrer-Crosbie M, Chen Y, Han Y. Cardiovascular manifestations and treatment considerations in COVID-19. Heart 2020;106:1132–1141.
5. Ratanawong P, Shen W, El Masry H, Sorajja D, Srivathsan K, Vellel-arde A, Scott LR. Guidance on short-term management of atrial ﬁbrillation in coronavirus disease 2019. J Am Heart Assoc 2020;9:e017529.
6. Katta S, Ahmad D, Spyropoulos AC, Schulman S. Subcommittee on Control of Anticoagulation. Deﬁnition of clinically relevant non-major bleeding in studies of anticoagulants in atrial ﬁbrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119–2126.
7. Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. J Stat Softw 2011;42:1–52.
8. Wang Y, Wang Z, Tse G, Zhang L, Wan EY, Guo Y, Lip GYH, Li G, Lu Z, Liu T. Cardiac arrhythmias in patients with COVID-19. J Arrhythm 2020;36:827–836.
9. Shahrezaei M, Fahhoum R, Akinskeye O, Bhandari S, Dang G, Khouzam RN. Severe sepsis and cardiac arrhythmias. Ann Transl Med 2018;6:6.
10. Bosch NA, Cimmini J, Walkey AJ. Atrial ﬁbrillation in the ICU. Chest 2018;154:1424–1434.
11. Chean CS, McAuley D, Gordon A, Welters ID. Current practice in the management of new-onset atrial ﬁbrillation in critically ill patients: a UK-wide survey. PeerJ 2017;5:e3716.
12. Inciardi RM, Adamo M, Ligi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccoone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorgia E, Lombardi CM, Milese G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. Eur Heart J 2020;41:1821–1829.
13. Mountantonakis SE, Saleh M, Fishbein J, Gandomi A, Lesser M, Chellico J, Gabriels J, Quo M, Epstein LM, Northwell COVID-19 Research Consortium. Atrial ﬁbrillation is an independent predictor for in-hospital mortality in patients admitted with SARS-CoV-2 infection. Heart Rhythm 2021;18:501–507.
14. Lubitz SA, Benjamin EJ, Ellinor PT. Atrial ﬁbrillation in congestive heart failure. Heart Fail Clin 2010;6:187–200.
15. Anter E, Jessup M, Callans DJ. Atrial ﬁbrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009;119:2516–2525.
16. Vardeny O, Solomon SD. Inﬂuenza and heart failure: a catchy comorbidity. JACC Heart Fail 2019;7:118–120.
17. Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd. The hidden burden of inﬂuenza: a review of the extra-pulmonary complications of inﬂuenza infection. Inﬂuenza Other Respir Viruses 2017;11:372–393.
18. Li SS, Cheng CW, Fu CL, Chan YH, Lee MP, Chan JW, Yiu SF. Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. Circulation 2003;108:1798–1803.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–1062.
20. Arentz M, Yim E, Klaﬀ L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323:1612–1614.
21. Shinbani JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997;29:709–715.
22. Horby P, Lim WS, Emberson JR, Mathew M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmaidhi P, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Bailey JK, Haynes R, Landray MJ, RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693–704.
23. Shiroshita-Takeshita A, Brundel BJ, Lavoie J, Nattel S. Prednisone prevents atrial ﬁbrillation promotion by atrial tachycardia remodeling in animal models and clinical studies. J Am Coll Cardiol 2006;48:1639–1645.
24. Vardeny O, Solomon SD. Inﬂuenza and heart failure: a catchy comorbidity. JACC Heart Fail 2019;7:118–120.
25. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–1062.
26. Arenz M, Yim E, Klaﬀ L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323:1612–1614.
27. Shinbani JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997;29:709–715.
28. Schnitzer TA, Takeshita A, Brundel BJ, Lavoie J, Nattel S. Prednisone prevents atrial ﬁbrillation promotion by atrial tachycardia remodeling in dogs. Cardiovasc Res 2006;69:865–875.
29. Dernjulis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial ﬁbrillation. Eur Heart J 2004;25:1100–1107.
30. Liu L, Jing FY, Wang WX, Li LJ, Zhou RQ, Zhang C, Wu QC. Effects of corticosteroids on new-onset atrial ﬁbrillation after cardiac surgery: a meta-analysis of randomized controlled trials. Med (Baltim) 2021;100:e25130.
31. Moreschi G, Heininger J, Brusselle GG, Hofman A, Witteman JC, Kingma JH, Stricker BH. Corticosteroids and the risk of atrial ﬁbrillation. Arch Intern Med 2006;166:1016–1020.
32. Huerta C, Lanes SF, García Rodríguez LA. Respiratory medications and the risk of cardiac arrhythmias. Epidemiology 2005;16:360–366.