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# Mortality and Major Adverse Cardiovascular Events in Hospitalized Patients With Atrial Fibrillation With COVID-19

Lucas Wang, MD[a,*], Lawrence Hoang, MD[a], Kristopher Aten, DO[a], Mujahed Abualfoul, DO[a], Victor Canela, DO[a], Sri Prathivada, MD[c], Michael Vu, DO[a], Yi Zhao, MD[a], and Manavjot Sidhu, MD[b]

**COVID-19 results in increased incidence of cardiac arrhythmias, including atrial fibrillation (AF). However, little is known about the combined effect of AF and COVID-19 on patient outcomes. This study aimed to determine if AF, specifically new-onset AF (NOAF), is associated with increased risk of mortality and major adverse cardiovascular events (MACEs) in hospitalized patients with COVID-19. This multicenter retrospective analysis identified 2,732 patients with COVID-19 admitted between March and December 2020. Data points were manually reviewed in the patients' electronic health records. Multivariate logistic regression was used to assess if AF was associated with death or MACE. Patients with AF (6.4%) had an increased risk of mortality (risk ratio 2.249, 95% confidence interval [CI] 1.766 to 2.864, p <0.001) and MACE (risk ratio 1.753, 95% CI 1.473 to 2.085, p <0.001) compared with those with sinus rhythm. Patients with NOAF had an increased risk of mortality compared with those with existing AF (odds ratio 19.30, 95% CI 5.39 to 69.30, p <0.001); the risk of MACE was comparable between NOAF and patients with existing AF (p = 1). AF during hospitalization with COVID-19 is associated with a higher risk of mortality and MACE. NOAF in patients with COVID-19 is associated with a higher risk of mortality but a similar risk of MACE compared with patients with existing AF.**  **(Am J Cardiol 2023;189:41−48)**

As of September 2022, there have been over 600 million cases of COVID-19, with over 6 million deaths worldwide.[1] COVID-19 is understood to primarily affect the pulmonary system, with the potential to cause severe medical conditions, such as pneumonia and acute respiratory distress syndrome. These medical conditions frequently necessitate mechanical ventilation and often lead to death.[2] As more information is captured on this disease, we began to see that the effects of COVID-19 extend far beyond the lungs.[3−5] Recent studies have shown that COVID-19 increases the incidence of complications in most major organ systems, especially the cardiovascular system.[6] Elevated cardiac markers,[6] prothrombotic states,[7] and newly diagnosed arrhythmias[8] have been observed in some patients with COVID-19. Among the plethora of sequelae of COVID-19, recent studies have reported an increased incidence of atrial fibrillation (AF) associated with COVID-19.[9,10] Both AF and COVID-19 have been shown to be independent predictors of increased incidence of mortality and major adverse cardiovascular events (MACEs).[11−13] Further clarification is needed on the effects of AF and, in particular, new-onset AF (NOAF) induced by COVID-19 on mortality and MACE. Our study aimed to better understand and describe the relations between COVID-19 and AF, namely how AF affects mortality and MACE rates in hospitalized patients with COVID-19. Our objectives were to determine if AF significantly increases the risk of MACE or mortality in hospitalized patients with COVID-19 compared with those presenting with sinus rhythm (SR) and to determine whether patients with a known history of AF ($AF_1$) have increased rates of MACE or all-cause mortality compared with those with NOAF.

## Methods

This multicenter retrospective cohort study included unvaccinated adults (aged ≥18 years) with polymerase chain reaction-confirmed COVID-19, admitted at 4 hospitals within the Methodist Health System from March 2020 to December 2020. Patient data were abstracted from the electronic medical records. All hospitalized patients who tested polymerase chain reaction-positive for COVID-19, regardless of the reason for admission, were included (Figure 1). Patients were excluded if there was no electrocardiogram (ECG) on admission or telemetry during hospitalization, if their initial heart rhythm was not SR or AF, or if their COVID-19 test was positive at an outside hospital. All patient data were deidentified before analysis, and data abstraction was approved by WCG/Aspire Institutional Review Board (institutional review board number 20201424).

Data manually collected from the electronic medical records included baseline demographics, symptoms and

[a]Department of Internal Medicine; [b]Methodist Dallas Cardiovascular Consultants, Methodist Medical Group, Division of Cardiology; and [c]Clinical Research Institute, Methodist Dallas Medical Center, Dallas, Texas. Manuscript received July 8, 2022; revised manuscript received and accepted November 19, 2022.

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*Corresponding author: Tel: 254-716-0273; fax: (214) 947-8181.

*E-mail address:* lucaswang@mhd.com (L. Wang).

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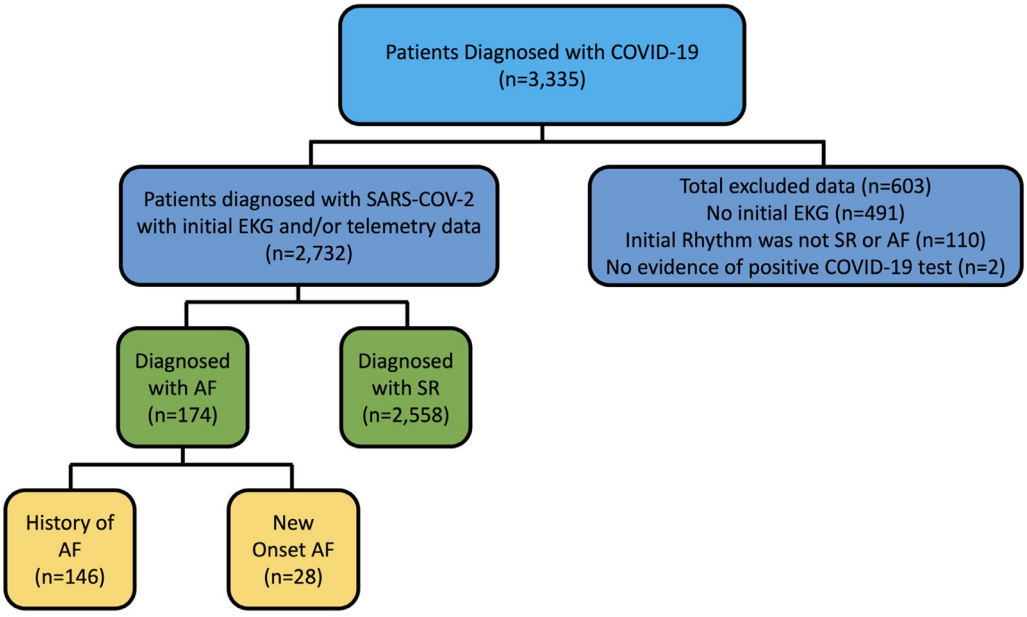


Figure 1. Flowchart of the patients who participated in our study.

vital signs on arrival, co-morbidities (i.e., history of congestive heart failure, stroke, diabetes, hypertension, chronic obstructive pulmonary disease [COPD], asthma, chronic kidney disease [CKD], end-stage renal disease [ESRD], cirrhosis, human immunodeficiency virus, coronary artery bypass graft, and cancer), laboratory measurements, inpatient medications, and outcomes (i.e., mortality and MACE). Our study defined MACE as either heart failure exacerbation, cardiac tamponade, pericardial effusion, myocarditis, pericarditis, myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, or shock. Mortality was defined as either in-hospital death or discharge to hospice. A patient was determined to have AF by either ECG or telemetry findings. ECG and telemetry strips were manually read by 2 or more trained medical physicians. Patients were considered to have NOAF if they presented with SR and developed AF at any point after the initial ECG or telemetry reading and if they did not have $AF_1$.

Continuous variables were characterized by mean and SD or median and interquartile range, depending on whether they were normally distributed. For multiple means or medians, 1-way analysis of variance and/or Kruskal −Wallis test was used based on normality. Bonferroni correction was used to adjust the $\alpha$ when multiple comparisons were performed. A $p \leq 0.05$ was considered significant.

Multivariate logistic regression was used to assess whether AF or NOAF was independently associated with death or MACE. Logistic regression was used to assess if AF was independently associated with MACE events. Regression was constructed to adjust for co-morbidities, demographics, and laboratory values (Supplementary Table 1). The base regression only included variables with data available for >90% of patients. Additional subsets included patients with NOAF versus $AF_1$. We did not perform imputation for missing laboratory values because they were likely nonrandom. C-reactive protein, D-dimer, initial troponin, and peak troponin levels were inputted sequentially as appropriate, in addition to the base regression noted before because of missing data. Statistical analysis was performed in R version 4.1.2, using the EZR package version 1.55.

## Results

In total, 3,335 patients with COVID-19 were admitted at our health system during the study period. Among 2,732 patients with initial ECG and/or telemetry data, 174 were confirmed to have AF (6.4%), including 82 with rapid ventricular rate (RVR; 47.1%) and 28 with NOAF(16%; Figure 1, Table 1). The mean age of patients presenting with SR was significantly lower than patients with AF (61.37 ± 16.3 years vs 76.9 ± 11.3 years, $p < 0.001$). Patients with AF had lower median body mass indexes than those with SR (28.9 [24.8 to 33.3] vs 30.2 [25.6 to 35.7], $p = 0.014$).

In our population, patients with AF had higher rates of hypertension (76.4% vs 63.5%, $p = 0.001$), coronary artery disease (CAD; 35.1% vs 14.3%, $p < 0.001$), CKD/ESRD (24.7% vs 13.8%, $p = 0.01$), COPD/asthma (24.7% vs 15.2%, $p = 0.002$), and congestive heart failure (28.2% vs 12.5%, $p < 0.001$) than patients with SR (Table 1). Our AF patient population also demonstrated higher levels of potassium (4.2 [3.8 to 4.7] vs 4.0 [3.7 to 4.4] milliequivalents/L, $p = 0.005$), D-dimer (1.83 [0.94 to 3.49] vs 1.13 [0.62 to 2.25] ng/ml; $p < 0.001$), initial troponin (0.03 [0.011 to 0.07] vs 0.011 [0.011 to 0.033] ng/ml, $p < 0.001$), and peak troponin (0.030 [0.011 to 0.09] vs 0.011 [0.011 to 0.041] ng/ml, $p < 0.001$) than patients with SR.

The demographics and co-morbidities in patients with AF that presented with RVR were examined (Table 1). Patients with AF and RVR tended to be younger than patients with AF without RVR (75.04 ± 11.77 years vs 79 ± 9.96 years, $p = 0.024$). Otherwise, the "with RVR" and "without RVR" demographics and co-morbidities data were comparable with each other. Overall, these data

Table 1
Demographics of the study cohort

| Factor | Group | SR (n = 2558) | AF (n = 174) | p Value | AF Without RVR (n = 65) | AF With RVR (n = 109) | p Value | $AF_1$ (n = 146) | NOAF (n = 28) | p Value |
|---|---|---|---|---|---|---|---|---|---|---|
| Age, mean (SD) | | 61.37 (16.3) | 76.52 (11.3) | **<0.001** | 79 (9.96) | 75.04 (11.77) | **0.024** | 77.03 (11.30) | 73.86 (10.93) | 0.173 |
| BMI, median [IQR] | | 30.2 [25.6, 35.7] | 28.9 [24.8, 33.3] | **0.014** | 27.70 [25.1, 31.47] | 29.21[24.80, 35.4] | 0.109 | 28.85 [24.83, 33.27] | 28.94 [24.80, 32.90] | 0.873 |
| Gender, n (%) | Female | 1225 (47.9) | 64 (36.8) | **0.005** | 20 (30.8) | 44 (40.4) | 0.256 | 53 (36.3) | 11 (39.3) | 0.832 |
| | Male | 1333 (52.1) | 110 (63.2) | | 45 (69.2) | 65 (59.6) | | 93 (63.7) | 17 (60.7) | |
| Race/Ethnicity, n (%) | White | 764 (29.9) | 104 (59.8) | **<0.001** | 44 (67.7) | 60 (55) | 0.421 | 92 (63.0) | 12 (42.9) | 0.217 |
| | Black | 902 (35.3) | 36 (20.7) | | 9 (13.8) | 27 (24.8) | | 26 (17.8) | 10 (35.7) | |
| | Hispanic | 631 (24.7) | 22 (12.6) | | 7 (10.8) | 15 (13.8) | | 18 (12.3) | 4 (14.3) | |
| | Asian | 81 (3.2) | 4 (2.3) | | 2 (3.1) | 2 (1.8) | | 3 (2.1) | 1 (3.6) | |
| | Native American | 4 (0.2) | 1 (0.6) | | 0 (0) | 1 (0.9) | | 1 (0.7) | 0 (0.0) | |
| | Other | 172 (6.7) | 7 (4.0) | | 3 (4.6) | 4 (3.7) | | 6 (4.1) | 1 (3.6) | |
| $O_2$ Requirements, n (%) | No $O_2$ | 819(32) | 55 (31.6) | 0.079 | 22 (33.8) | 33 (30.3) | 0.588 | 49 (33.6) | 6 (21.4) | 0.501 |
| | 1 − 6L | 1294 (50.6) | 76 (43.7) | | 24 (36.9) | 52 (47.7) | | 63 (43.2) | 13 (46.4) | |
| | 7 − 20 L | 264 (10.3) | 28 (16.1) | | 13 (20) | 15 (13.8) | | 21 (14.4) | 7 (25) | |
| | 21 − 100 L | 74 (2.9) | 4 (2.3) | | 1 (1.5) | 3 (2.8) | | 4 (2.7) | 0 (0) | |
| | Intubated | 107 (4.2) | 11 (6.3) | | 5 (7.7) | 6 (5.5) | | 9 (6.2) | 2 (7.1) | |
| Co-morbidities, median [IQR] | | 2 [1, 3] | 2 [1, 4] | **<0.001** | 2 [1, 4] | 3 [1, 3] | 0.835 | 2.00 [1.00, 4.00] | 3.00 [1.75, 3.25] | 0.669 |
| Co-morbidities, n (%) | Hypertension | 1625 (63.5) | 133 (76.4) | **0.001** | 52 (80) | 81 (74.3) | 0.462 | 112 (76.7) | 21 (75.0) | 0.812 |
| | Diabetes | 1061 (41.5) | 68 (39.1) | 0.578 | 23 (35.4) | 45 (41.3) | 0.521 | 51 (34.9) | 17 (60.7) | **0.019** |
| | CAD | 365 (14.3) | 61 (35.1) | **<0.001** | 28 (43.1) | 33 (30.3) | 0.102 | 54 (37) | 7 (25.0) | 0.282 |
| | Cirrhosis | 61 (2.4) | 6 (3.4) | 0.317 | 3 (4.6) | 3 (2.8) | 0.672 | 5 (3.4) | 1 (3.6) | 1 |
| | CKD/ESRD | 354 (13.8) | 43 (24.7) | **< 0.001** | 18 (27.7) | 25 (22.9) | 0.586 | 34 (23.3) | 9 (32.1) | 0.343 |
| | COPD/Asthma | 390 (15.2) | 43 (24.7) | **0.002** | 14 (21.5) | 29 (26.6) | 0.475 | 38 (26) | 5 (17.9) | 0.475 |
| | Heart Failure | 320 (12.5) | 49 (28.2) | **<0.001** | 19 (29.2) | 30 (27.5) | 0.862 | 43 (29.5) | 6 (21.4) | 0.494 |
| | HIV | 18 (0.7) | 0 (0.0) | 0.624 | 0 (0.0) | 0 (0.0) | N/A | 0 (0.0) | 0 (0.0) | 1 |
| | MAP < 65 mm Hg | 61 (2.4) | 6 (3.4) | 0.317 | 3 (4.6) | 3 (2.8) | 0.672 | 5 (3.4) | 1 (3.6) | 1 |
| | History of Stroke | 229 (9.0) | 25 (14.4) | **0.022** | 5 (7.7) | 20 (18.3) | 0.073 | 45 (30.8) | 6 (21.4) | 0.372 |

(*continued on next page*)

Table 1 (*Continued*)

| Factor | Group | SR (n = 2558) | AF (n = 174) | p Value | AF Without RVR (n = 65) | AF With RVR (n = 109) | p Value | $AF_1$ (n = 146) | NOAF (n = 28) | p Value |
|---|---|---|---|---|---|---|---|---|---|---|
| Laboratory values, median [IQR] | Potassium (mmol/L) | 4 [3.7, 4.4] | 4.2 [3.80, 4.70] | **0.005** | 4.3 [3.8, 4.8] | 4.2 [3.7, 4.6] | 0.315 | 4.20 [3.80, 4.60] | 4.10 [3.80, 4.70] | 0.915 |
| | Creatinine (mg/dL) | 0.90 [0.7, 1.4] | 1.3 [0.9, 2.1] | **<0.001** | 1.34 [0.9, 2.28] | 1.2 [0.88, 1.95] | 0.233 | 1.27[0.90, 2.10] | 1.37 [0.78, 3.37] | 0.77 |
| | CRP (mg/L) | 71 [34, 184.2] | 69 [27, 190] | 0.863 | 69 [22, 191] | 69 [33 186.25] | 0.456 | 64 [24, 173.0] | 128 [48.25, 225.00] | 0.154 |
| | D-Dimer ($\mu$/mL) | 1.13 [0.62, 2.25] | 1.83 [0.94, 3.49] | **<0.001** | 1.88 [1.24, 3.85] | 1.57 [0.75, 2.68] | 0.062 | 1.93 [0.87, 3.58] | 1.82 [1.57, 2.67] | 0.585 |
| | Initial Troponin (ng/mL) | 0.011 [0.01, 0.03] | 0.03 [0.01, 0.07] | **<0.001** | 0.03 [0.01, 0.07] | 0.03 [0.01, 0.08] | 0.92 | 0.03 [0.01, 0.07] | 0.04 [0.02, 0.09] | 0.114 |
| | Peak Troponin (ng/mL) | 0.01 [0.01, 0.04] | 0.03 [0.01, 0.09] | **<0.001** | 0.03 [0.01, 0.08] | 0.03 [0.01, 0.12] | 0.934 | 0.03 [0.01, 0.08] | 0.09 [0.02, 0.21] | **0.02** |

Values are n (%) or median [IQR] with Wilcoxon rank sum test *P*.

AF = atrial fibrillation, $AF_1$ = known history of atrial fibrillation, BMI = body mass index, CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, ESRD = end-stage renal disease, HIV = human immunodeficiency virus, MAP = mean arterial pressure, NOAF = new-onset atrial fibrillation, $O_2$ = oxygen, RVR = rapid ventricular rate.

indicate that RVR was not a contributing factor in the outcomes in our study cohort.

Comparing $AF_1$ and NOAF, the only significant differences between the 2 groups were that patients with NOAF tended to have a higher incidence of diabetes (34.9% vs 60.7%, p = 0.019) and higher peak troponin levels (0.03 [0.01 to 0.08] vs 0.09 [0.02 to 0.21] ng/ml, p = 0.02; Table 1).

The mortality rate of patients with AF was significantly higher than that of patients with SR (31% vs 13.8%, risk ratio [RR] 12.249, 95% confidence interval [CI] 1.766 to 2.864, p <0.001; Figure 2). Of note, patients with AF presenting with RVR did not have an increased risk of mortality compared with patients with AF without RVR (p = 1). The logistic regression model for mortality showed that AF was not independently associated with increased risk of mortality (odds ratio [OR] 1.45, 95% CI 0.97 to 2.17, p = 0.073; Figure 3). The significant factors associated with increased incidence of mortality included male gender (OR 1.41, 95% CI 1.10 to 1.81, p = 0.007), mean arterial pressure <65 mm Hg (OR 2.33, 95% CI 1.24 to 4.38, p = 0.009), age (OR 1.05, 95% CI 1.04 to 1.07, p <0.001), and peak troponin level (OR 1.02, 95% CI 1.01 to 1.04, p = 0.01). Also, patients requiring any level of oxygenation, including 1 to 6 liters (OR 2.33, 95% CI 1.68 to 3.24), 7 to 20 liters (OR 6.59, 95% CI 4.44 to 9.80), 21 to 100 liters (OR 11.6, 95% CI 6.57 to 20.5), and intubated (OR 20.7, 95% CI 12.5 to 34.2) all showed an increased risk of mortality (p <0.001; Supplementary Table 2).

The presence of AF was significantly associated with MACE incidence (46.0% vs 26.2%; RR 1.753, 95% CI 1.473 to 2.085, p <0.001; Figure 4, Table 2). Individual MACE outcomes that were significantly associated with AF included heart failure exacerbation (RR 3.915, 95% CI 2.343 to 6.542, p <0.001), myocardial infarction (RR 1.947, 95% CI 1.602 to 2.367, p <0.001), and shock (RR 1.604, 95% CI 1.061 to 2.425, p = 0.038) (Figure 5). Significant factors associated with increased incidence of MACE were older age (p <0.001), male gender (p = 0.013), African-American race (p <0.001), any amount of $O_2$ requirement on arrival, history of CAD (p <0.001), history of CKD/ESRD (p <0.001), history of heart failure (p <0.001), history of stroke (p = 0.018), mean arterial pressure <65 mm Hg on arrival (p = 0.006), and elevated D-Dimer (p <0.001) (Supplementary Table 3). There was no significant difference in the rates of MACE between the AF and AF with RVR cohorts (p = 1).

Patients with NOAF were, on average, older than patients with SR or $AF_1$ (73.86 ± 10.93 vs 62.2 ± 16.41, p <0.001); had more co-morbidities (3 [1.75 to 3.25] vs 2 [1 −3], p = 0.004); and had higher levels of creatinine (1.37 [0.78 to 3.37] mg/100 ml vs 0.95 [0.70 to 1.46], p = 0.031), D-dimer (1.82 [1.57 to 2.67] vs 1.15 [0.62 to 2.32] $\mu$g/ml, p = 0.013), initial troponin (0.04 [0.02 to 0.09] vs 0.01 [0.01 to 0.04] ng/ml, p <0.001), and peak troponin (0.09 [0.02 to 0.21] vs 0.01 [0.01 to 0.04], p <0.001; Supplementary Table 4).

After accounting for co-morbidities and demographics, NOAF was associated with substantially higher mortality risk than the rest of the patients (OR 7.84, 95% CI 3.27 to 18.80, p <0.001; Figure 3, Supplemental Table 5) and those

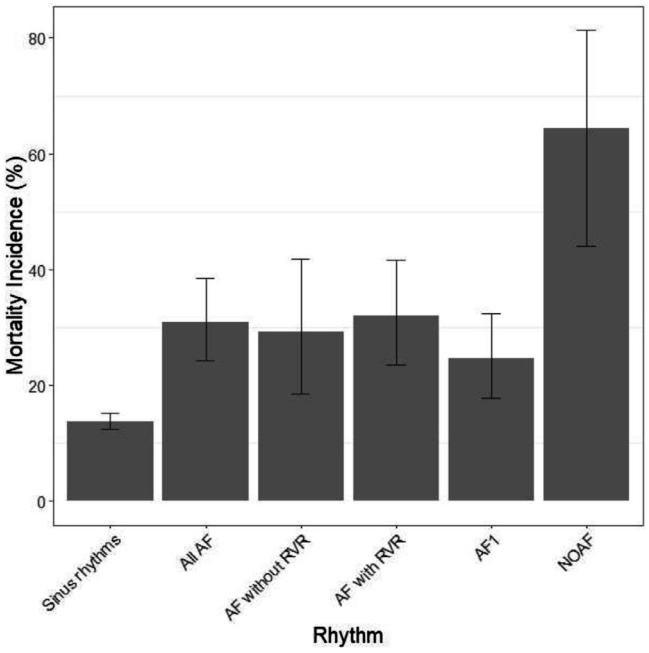


Figure 2. In-hospital mortality rates categorized by heart rhythm. Error bars represent 95% CI.

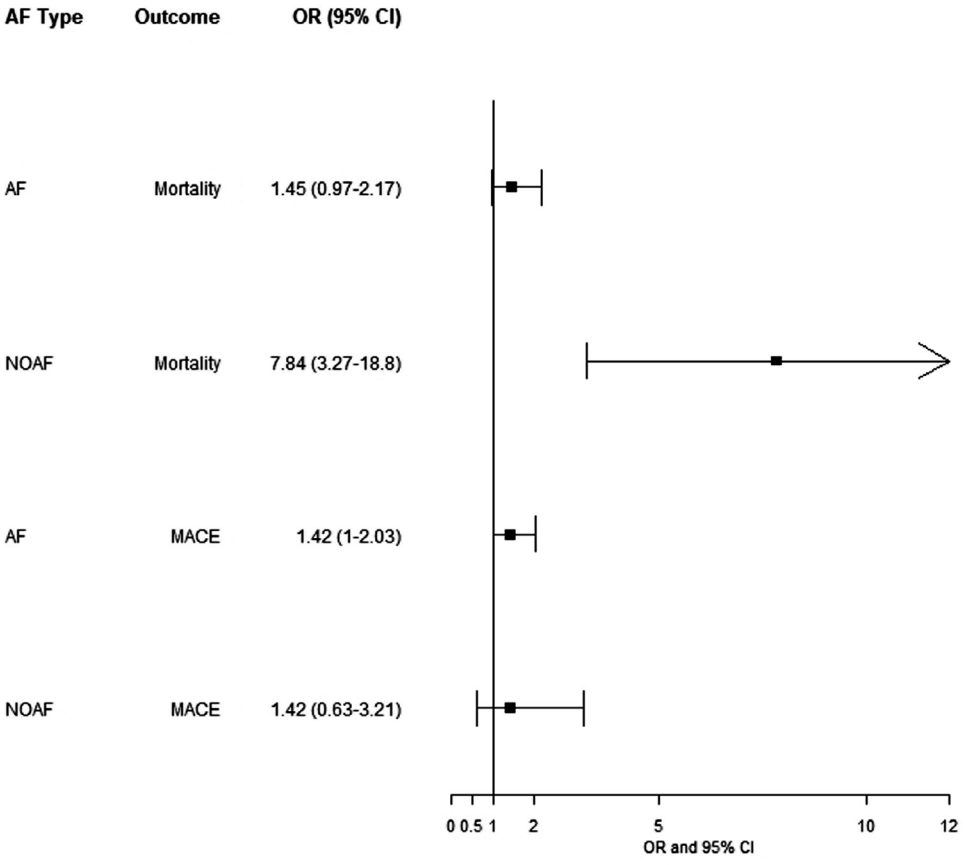


Figure 3. Adjusted ORs of the associations between AF and all-cause mortality and major adverse cardiac events. Boxes indicate ORs, and the lines indicate the 95% CIs.

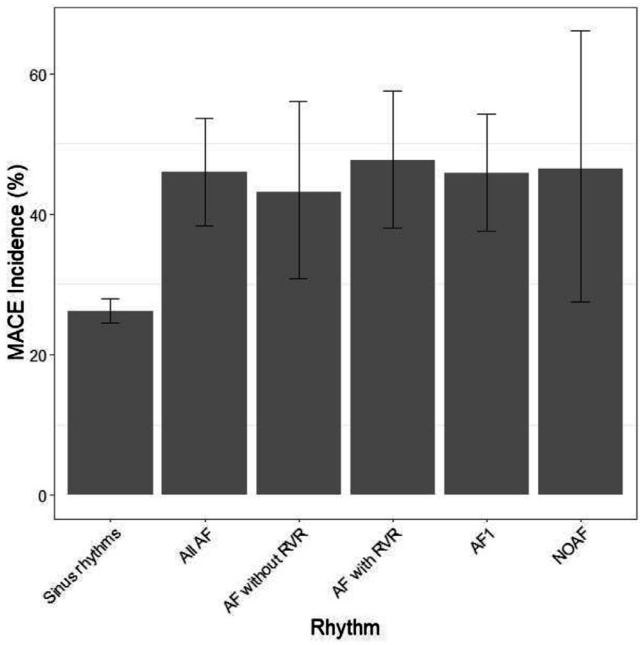


Figure 4. In-hospital major adverse cardiac event rates characterized by heart rhythm. Error bars represent 95% CI.

with $AF_1$ (64.3% vs 24.7%, OR 19.30, 95% CI 5.39 to 69.30, p <0.001; Supplementary Table 6).

NOAF was also associated with increased incidence of MACE (46.4% vs 27.3%, RR 1.701, 95% CI 1.137 to 2.544, p = 0.032), specifically, the incidence of myocardial infarction (42.9% vs 23.9%, RR 1.791, 95% CI 1.162 to 2.762, p = 0.026) and shock (35.7% vs 9.2%, RR 3.894, 95% CI 2.336 to 6.491, p <0.001), compared with SR (Figure 4, Table 3). Compared with $AF_1$, NOAF was associated with increased incidence of shock (35.7% vs 15.1%, RR 2.37, 95% CI 1.26 to 4.44, p = 0.016) but not the MACE total (p = 1) or myocardial infarction (p = 1; Supplementary Table 7).

## Discussion

In this study, we analyzed the outcomes of hospitalized patients with COVID-19 across 4 hospitals in Dallas, Texas. Here, we demonstrated that AF was an individual predictor for mortality, and that patients with NOAF were more susceptible to mortality than patients with $AF_1$. NOAF was associated with significantly higher rates of mortality and MACE. These data suggest that COVID-19 or its sequelae is associated with a higher rate of AF, which can lead to increased incidence of mortality and MACE. The strengths unique to this study include: (1) a large, diverse patient population across 4 different hospitals, with significant numbers of known AF risk factors, (2) a comprehensive validation of data, with a thorough chart review of each individual measurement, (3) a direct comparison of both mortality and MACE in the same patient population, with a focused comparison of patients with NOAF versus $AF_1$, and (4) patient data from a unique point in the history of COVID-19 because patients in this study were all not immunized, given the vaccine was not yet widely distributed.

The data from this study replicate the trend observed in the study by Musikantow et al[14] in that in-hospital AF in patients with COVID-19 occurred more often in those with

Table 2
Major adverse cardiac events associated with atrial fibrillation with and without rapid ventricular rate

| Factor | Group | SR (n = 2558) | AF (n = 174) | p Value | RR | Without RVR (n = 65) | With RVR (n = 109) | p Value | RR |
|---|---|---|---|---|---|---|---|---|---|
| MACE | No | 1887 (73.8) | 94 (54.0) | | | 37 (56.9) | 57 (52.3) | | |
| | Yes | 671 (26.2) | 80 (46.0) | **< 0.001** | 1.753 (1.473−2.085) | 28 (43.1) | 52 (47.7) | 0.638 | |
| Heart failure exacerbation (%) | No | 2484 (97.1) | 158 (90.8) | | | 62 (95.4) | 96 (88.1) | | |
| | Yes | 74 (2.9) | 16 (9.2) | **<0.001** | 3.087 (1.839 − 5.182) | 3 (4.6) | 13 (11.9) | 0.173 | |
| Cardiac tamponade (%) | No | 2589 (100.0) | 174 (100.0) | | | 65 (100.0) | 109 (100.0) | | |
| | Yes | 0 (0) | 0 (0) | | | 0 (0) | 0 (0) | | |
| Pericardial effusion (%) | No | 2544 (99.5) | 171 (98.3) | 0.089 | | 63 (96.9) | 108 (99.1) | | |
| | Yes | 14 (0.5) | 3 (1.7) | | | 2 (3.1) | 1 (0.9) | 0.557 | |
| Myocarditis (%) | No | 2551 (99.7) | 174(100.0) | 1 | | 65 (100.0) | 109(100.0) | | |
| | Yes | 7 (0.3) | 0 (0.0) | | | 0 (0.0) | 0 (0.0) | | |
| Pericarditis (%) | No | 2555 (99.9) | 174 (100.0) | 1 | | 65 (100.0) | 109 (100.0) | | |
| | Yes | 3 (0.1) | 0 (0.0) | | | 0 (0.0) | 0 (0.0) | | |
| Myocardial infarction (%) | No | 1976 (77.2) | 97 (55.7) | | | 36 (55.4) | 61 (56.0) | | |
| | Yes | 582 (22.8) | 77 (44.3) | **<0.001** | 1.945 (1.622−2.332) | 29 (44.6) | 48 (44.0) | 1 | |
| Stroke (%) | No | 2454 (95.9) | 166 (95.4) | 0.692 | | 61 (93.8) | 105 (96.3) | | |
| | Yes | 104 (4.1) | 8 (4.6) | | | 4 (6.2) | 4 (3.7) | 0.474 | |
| PE/DVT (%) | No | 2448 (95.7) | 166 (95.4) | 0.846 | | 63 (96.9) | 103 (94.5) | | |
| | Yes | 110 (4.3) | 8 (4.6) | | | 2 (3.1) | 6 (5.5) | 0.712 | |
| Shock (%) | No | 2332 (91.2) | 142 (81.6) | **< 0.001** | 2.082 (1.486−2.915) | 53 (81.5) | 89 (81.7) | | |
| | Yes | 226 (8.8) | 32 (18.4) | | | 12 (18.5) | 20 (18.3) | 1 | |

Values are n (%) or median [IQR] with Wilcoxon rank sum test *P*.

AF = atrial fibrillation, $AF_1$ = known history of atrial fibrillation, BMI = body mass index, CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, ESRD = end-stage renal disease, HIV = human immunodeficiency virus, MAP = mean arterial pressure, NOAF = new-onset atrial fibrillation, $O_2$ = oxygen, RVR = rapid ventricular rate.

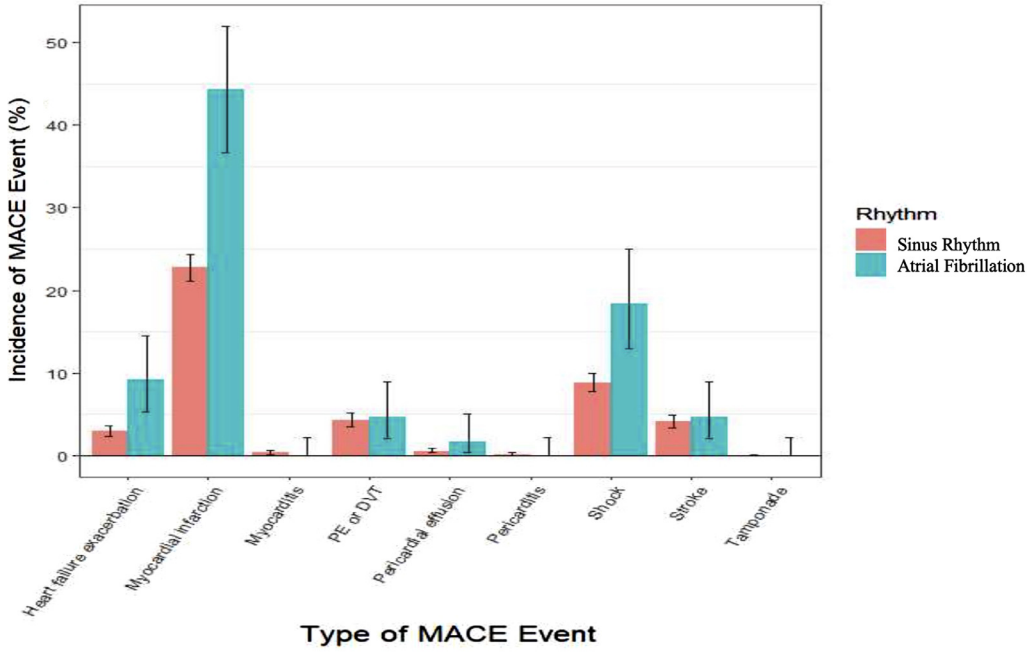


Figure 5. Frequency of major adverse cardiac events in patients with sinus rhythm or atrial fibrillation. PE = pulmonary embolism, DVT = deep venous thrombosis.

Table 3
Major adverse cardiac events associated with new-onset atrial fibrillation

| MACE, n (%) | SR and AF1 (n = 2704) | NOAF (n= 28) | p Value | RR (95% CI) |
|---|---|---|---|---|
| Any MACE | 738 (27.3) | 13 (46.4) | **0.032** | 1.701 (1.137−2.544) |
| Heart failure exacerbation | 90 (3.3) | 0 (0.0) | 1 | |
| Cardiac tamponade | 0 (0.0) | 0 (0.0) | | |
| Pericardial effusion | 17 (0.6) | 0 (0.0) | 1 | |
| Myocarditis | 7 (0.3) | 0 (0.0) | 1 | |
| Pericarditis | 3 (0.1) | 0 (0.0) | 1 | |
| Myocardial infarction | 647 (23.9) | 12 (42.9) | **0.026** | 1.791 (1.162−2.762) |
| Stroke | 110 (4.1) | 2 (7.1) | 0.32 | |
| PE/DVT | 118 (4.4) | 0 (0.0) | 0.631 | |
| Shock | 248 (9.2) | 10 (35.7) | **<0.001** | 3.894 (2.336−6.491) |

Values are n (%). Analysis was done with $X^2$ or Fisher's exact test.

CI = confidence interval, ECG = electrocardiogram, DVT = deep vein thrombosis, MACE = major adverse cardiovascular event, NOAF = new-onset atrial fibrillation, PE = pulmonary embolism, RR = relative risk, SR = sinus rhythm.

pre-existing co-morbidities, in particular CAD, CKD/ESRD, COPD, asthma, and congestive heart failure. Interestingly, for NOAF, the number of co-morbidities likely matters more than the presence of any single factor, except for age and CKD.

To the best our knowledge, this is the first study involving a large cohort of patients to address the effect of in-hospital AF in its various forms in patients with COVID-19 in terms of mortality and MACE. A previous analysis involving a cohort of 1,053 patients in 2 healthcare centers showed atrial arrhythmias were independently associated with increased mortality.[15] Another study analyzed a smaller sample of 160 hospitalized patients with COVID-19 and demonstrated that NOAF is related to worse cardiovascular outcomes and increased mortality.[16] In the studies on critical care, NOAF has been linked to increased mortality in non-COVID-19 acute respiratory distress syndrome.[17]

Here, we demonstrated that patients with COVID-19 diagnosed with AF showed a significantly higher rate of mortality, particularly in those with NOAF. Interestingly, NOAF was not associated with an increase in any category of MACE, except for shock, compared with $AF_1$. Previous studies have demonstrated an association with COVID-19 and a prothrombotic state[18] and increased incidence of heart failure exacerbation[17] or other cardiovascular injury.[19] However, none seemed to observe a significant difference in the mortality rates in patients with NOAF compared with patients with $AF_1$.

This study is limited to a specific time during the height of the Alpha variant, with some crossing over to the rising prominence of the Delta variant. Unfortunately, we do not have data specific to the Omicron variant because of the time of our study and therefore, we cannot speak to the current COVID-19 climate. Given the nature of retrospective

studies based on chart reviews, we cannot say with absolute certainty the exact timing of AF onset and if it was because of COVID-19. Furthermore, this study did not directly compare patients with similar cardiovascular risk profiles. However, we propose that our comprehensive set of values accounted for in our multivariate linear regression model to determine AF and NOAF as independent predictors of mortality and MACE encompasses the cardiac and noncardiac co-morbidities used in previous studies.[20–22] Another limitation to this study is that the analysis of both mortality and MACE was not adjusted for the severity of COVID-19 disease during the hospitalization.

The results of this study will help practitioners better triage and treat patients with COVID-19 with multiple co-morbidities presenting with AF. By understanding the risk factors for major outcomes, such as mortality and MACE, physicians cannot only gain insight over the clinical course of these patients but also prepare better to manage and anticipate complications associated with this process.

## Disclosures

The authors have no conflicts of interest to declare.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.11.040.

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