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ATRIAL FIBRILLATION

Atrial Fibrillation in Patients Hospitalized With COVID-19

Incidence, Predictors, Outcomes, and Comparison to Influenza

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ABSTRACT

OBJECTIVES The goal of this study is to determine the incidence, predictors, and outcomes of atrial fibrillation (AF) or atrial flutter (AFL) in patients hospitalized with coronavirus disease-2019 (COVID-19).

BACKGROUND COVID-19 results in increased inflammatory markers previously associated with atrial arrhythmias. However, little is known about their incidence or specificity in COVID-19 or their association with outcomes.

METHODS This is a retrospective analysis of 3,970 patients admitted with polymerase chain reaction–positive COVID-19 between February 4 and April 22, 2020, with manual review performed of 1,110. The comparator arm included 1,420 patients with influenza hospitalized between January 1, 2017, and January 1, 2020.

RESULTS Among 3,970 inpatients with COVID-19, the incidence of AF/AFL was 10% (n = 375) and in patients without a history of atrial arrhythmias it was 4% (n = 146). Patients with new-onset AF/AFL were older with increased inflammatory markers including interleukin 6 (93 vs. 68 pg/ml; $p < 0.01$), and more myocardial injury (troponin-I: 0.2 vs. 0.06 ng/ml; $p < 0.01$). AF and AFL were associated with increased mortality (46% vs. 26%; $p < 0.01$). Manual review captured a somewhat higher incidence of AF/AFL (13%, n = 140). Compared to inpatients with COVID-19, patients with influenza (n = 1,420) had similar rates of AF/AFL (12%, n = 163) but lower mortality. The presence of AF/AFL correlated with similarly increased mortality in both COVID-19 (relative risk: 1.77) and influenza (relative risk: 1.78).

CONCLUSIONS AF/AFL occurs in a subset of patients hospitalized with either COVID-19 or influenza and is associated with inflammation and disease severity in both infections. The incidence and associated increase in mortality in both cohorts suggests that AF/AFL is not specific to COVID-19, but is rather a generalized response to the systemic inflammation of severe viral illnesses. (J Am Coll Cardiol EP 2021;7:1120–1130) © 2021 by the American College of Cardiology Foundation.

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As of September 10, 2020, there have been 28 million patients with coronavirus disease-2019 (COVID-19) infections worldwide and more than 900,000 deaths (1). The pathophysiology of the severe acute respiratory syndrome coronavirus 2 viral infection appears driven by an inflammatory immune response with several markers of inflammation, such as C-reactive protein and the cytokine interleukin (IL)-6, correlating with disease severity and mortality (2,3).

Even before the COVID-19 pandemic, atrial fibrillation (AF) and atrial flutter (AFL) had been linked to conditions characterized by elevated inflammatory markers (4,5). Hence, it is not surprising that a high incidence of AF/AFL has been reported with COVID-19 (6–8). However, as available studies have been limited in scope and specificity, the true incidence of AF/AFL in this population is unknown. Also uncertain is whether the inflammatory milieu of COVID-19 is uniquely responsible for AF/AFL, or whether these arrhythmias reflect part of a nonspecific byproduct of severe viral respiratory illness.

Beyond inflammation, COVID-19 has been associated with both an elevated incidence of myocardial injury, and an increased risk of thrombotic events such as venous thromboembolism and ischemic stroke (9–12). Accordingly, it is possible both that AF/AFL may correlate with cardiac injury, and, in the context of a prothrombotic state, contribute to the increased risk of thromboembolic events such as ischemic stroke.

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We performed a retrospective analysis of a large cohort of hospitalized patients afflicted with COVID-19 (n = 3,970) to assess the incidence, predictors, and outcomes of AF/AFL. To address the unusual clinical environment occurring during the New York City COVID-19 pandemic, in a subset of this cohort, we also performed a manual chart review of primary patient data including electrocardiograms (ECGs) and telemetry to assess for under-representation of arrhythmias in clinical coding. Finally, we compared these observations to patients hospitalized with influenza to assess whether these atrial arrhythmias uniquely result from COVID-19, or whether they reflect a response to acute respiratory illness.

METHODS

STUDY POPULATIONS. This multicenter retrospective cohort study included consecutive adult patients (≥18 years of age) with laboratory-confirmed COVID-19 infection, admitted to 5 hospitals within the Mount Sinai Health System. We studied 3 patient cohorts—of which 2 overlapped. 1) The principal automated electronic record abstraction cohort ($\text{COVID-19}_{\text{Primary}}$) included all patients with laboratory-confirmed COVID-19 admitted to the hospitals between February 4 and April 22, 2020. 2) The manually adjudicated patient cohort ($\text{COVID-19}_{\text{Manual}}$) was drawn from the same population of patients, but only included consecutive patients admitted until March 28, 2020, and excluded patients who tested positive for COVID-19 more than 1 week into hospitalization. This exclusion was done because the manual cohort included a disproportionate amount of patients diagnosed at onset of the pandemic including several who had prolonged hospitalizations with unrelated conditions and contracted COVID-19 while an inpatient. 3) The automated electronic record abstraction influenza cohort ($\text{Influenza}_{\text{Primary}}$) included all patients with polymerase chain reaction-positive influenza A or B from January 1, 2017, until January 1, 2020; there was no temporal overlap with the COVID-19 population. All patient data were de-identified before analysis, and data abstraction was approved by the Mount Sinai Institutional Review Board.

DATA COLLECTION. Data were abstracted from the electronic health records including baseline demographics, laboratory measurements, inpatient medications, and outcomes. Using the International Classification of Disease, version 9/10 (ICD 9/10) billing codes, comorbidities were identified; these included congestive heart failure (CHF), hypertension, diabetes, prior stroke/transient ischemic attack (TIA), chronic kidney and liver disease, HIV, chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea. An analysis was then performed using ICD 9/10 codes for the occurrence of in-hospital ischemic stroke or TIA, and AF/AFL.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFL = atrial flutter

COPD = chronic obstructive pulmonary disease

COVID-19 = coronavirus disease-2019

ECG = electrocardiogram

ICD = International Classification of Disease

IL = interleukin

TIA = transient ischemic attack

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Patient Characteristics of the COVID-19$_{Primary}$ Cohort Stratified by In-Hospital AF/AFL and New AF/AFL

				In-Hospital AF/AFL			
	All Patients (N = 3,970)	n	No AF/AFL (n = 3,595)	All AF/AFL (n = 375)	p Value	New-Onset AF/AFL (n = 146)	p Value
Baseline demographics							
Age, yrs	66 (55-77)	3,970	65 (54-76)	77 (68-85)	**<0.01**	74 (68-84)	**<0.01**
Male	2,288 (57.6)	3,970	2,063 (57.4)	225 (60.0)	0.33	90 (61.6)	0.31
Race/ethnicity		3,970			**<0.01**		**<0.01**
Caucasian	946 (23.8)		792 (22.0)	154 (41.1)		55 (37.7)	
African-American	1,107 (27.9)		1,025 (28.5)	82 (21.9)		33 (22.6)	
Asian	208 (5.2)		189 (5.3)	19 (5.1)		9 (6.2)	
Hispanic	1,240 (31.2)		1,154 (32.1)	86 (22.9)		30 (20.6)	
Other or unknown	469 (11.8)		435 (12.1)	34 (9.1)		19 (13.0)	
Obesity	1,312 (33.1)	3,970	1,177 (32.7)	135 (36.0)	0.20	50 (34.3)	0.70
Body mass index, kg/m^2	27.8 (24.2-32.6)	3,580	27.9 (24.3-32.6)	27.4 (23.4-32.9)	0.38	27.4 (23.8-32.4)	0.93
CHF	271 (6.8)	3,970	177 (4.9)	94 (25.1)	**<0.01**	6 (4.11)	**0.66**
Prior atrial arrhythmias		3,970					
Atrial fibrillation or flutter	339 (8.5)		110 (3.1)	229 (61.1)	**<0.01**		
Atrial flutter	57 (1.4)		13 (0.4)	44 (11.7)	**<0.01**		
Atrial fibrillation	326 (8.2)		104 (2.9)	222 (59.2)	**<0.01**		
CAD	410 (10.4)	3,970	320 (9)	90 (24)	**<0.01**	13 (8.9)	0.68
Hypertension	1,367 (34.4)	3,970	1,159 (32.2)	208 (55.5)	**<0.01**	50 (34.3)	0.61
Diabetes	976 (24.6)	3,970	851 (23.7)	125 (33.3)	**<0.01**	36 (24.7)	0.78
Prior stroke/TIA	160 (4.0)	3,970	123 (3.4)	37 (9.9)	**<0.01**	7 (4.8)	0.38
Chronic kidney disease	446 (11.2)	3,970	368 (10.2)	78 (20.8)	**<0.01**	20 (13.7)	0.18
Chronic liver disease	79 (2.1)	3,970	74 (2.1)	5 (1.3)	0.34	0 (0.0)	0.12[a]
HIV	68 (1.7)	3,970	61 (1.7)	7 (1.9)	0.81	1 (0.7)	0.52[a]
COPD	157 (4.0)	3,970	122 (3.4)	35 (9.3)	**<0.01**	3 (2.1)	0.49[a]
Asthma	185 (4.7)	3,970	166 (4.6)	19 (5.1)	0.70	3 (2.1)	0.22[a]
OSA	70 (1.8)	3,970	57 (1.6)	13 (3.5)	**0.01**	1 (0.7)	0.73[a]
Smoking		3,970			**<0.01**		0.35
Current	152 (3.8)		135 (3.8)	17 (4.5)		8 (5.5)	
Past	815 (20.5)		696 (19.4)	119 (31.7)		23 (15.8)	
Never	3,003 (75.6)		2,764 (76.9)	239 (63.7)		115 (78.8)	
Hospitalization vital signs							
Peak heart rate, beats/min	96.0 (84.0-110.0)	3,942	96.0 (84.0-110.0)	96.0 (84.0-110.0)	0.07	99.5 (82.0-117.0)	0.13
Max temperature, °F	101.0 (99.8-102.4)	3,942	101.0 (99.8-102.4)	101.1 (99.8-102.5)	0.87	101.5 (99.9-102.8)	0.11
Laboratory data							
White blood cell count, × 10^9/l	7.6 (5.5-10.6)	3,965	7.6 (5.5-10.5)	7.9 (5.6-11.4)	0.24	8.7 (5.8-12.0)	0.13
Neutrophil count, • 10^9/l	6.3 (4.1-9.7)	2,550	6.2 (4.1-9.6)	6.6 (4.1-10.5)	0.75	7.8 (4.4-11.6)	**0.04**
Lymphocyte count, • 10^9/l	0.90 (0.6-1.2)	2,158	0.9 (0.6-1.2)	0.8 (0.5-1.1)	**0.01**	0.8 (0.5-1.0)	**0.02**
Hemoglobin, g/l	13.4 (11.9-14.6)	2,067	13.4 (12.0-14.6)	13.1 (10.7-14.6)	0.09	13.3 (11.0-14.9)	0.63
Platelet count, • 10^9/l	207.0 (159.0-272.0)	3,963	209.0 (160.0-274.0)	196.0 (150.0-256.0)	**0.02**	195.5 (150.0-259.0)	0.14
Nadir platelet count, • 10^9/l	175.0 (130.0-234.0)	3,963	178.0 (134.0-236.0)	146.0 (110.0-204.0)	**<0.01**	146.5 (112.0-191.0)	**<0.01**
Albumin, g/l	3.2 (2.9-3.6)	3,855	3.2 (2.9-3.6)	3.1 (2.7-3.4)	**<0.01**	3.1 (2.8-3.5)	**<0.01**
ALT, U/l	31.0 (19.0-54.0)	3,835	31.0 (19.0-54.0)	27.0 (17.0-47.0)	**0.02**	29.0 (19.0-57.0)	0.32
AST, U/l	44.0 (30.0-72.0)	3,840	44.0 (30.0-71.0)	41.0 (28.0-74.5)	0.34	47.0 (31.0-80.0)	0.33
Lactate dehydrogenase, U/l	436.0 (331.0-588.0)	3,298	435.0 (332.0-587.0)	440.0 (325.0-605.0)	0.69	481.5 (371.0-648.0)	0.07
Serum creatinine, mg/dl	1.06 (0.80-1.64)	3,925	1.03 (0.80-1.61)	1.27 (0.91-1.99)	**<0.01**	1.2 (0.9-1.9)	**0.05**
D-dimer							
On admission, μg/ml	1.54 (0.86-2.90)	3,046	1.53 (0.85-2.87)	1.61 (0.93-3.04)	0.43	1.9 (1.0-3.3)	**0.02**
Peak level, μg/ml	2.28 (1.22-5.10)	2,653	2.25 (1.20-5.00)	2.65 (1.54-6.24)	**0.01**	3.7 (1.8-8.1)	**0.02**
Troponin-I							
On admission, ng/ml	0.03 (0.02-0.11)	2,588	0.03 (0.02-0.10)	0.06 (0.03-0.17)	**<0.01**	0.1 (0.0-0.2)	**<0.01**
Peak level, ng/ml	0.07 (0.02-0.25)	2,253	0.06 (0.02-0.23)	0.14 (0.05-0.53)	**<0.01**	0.2 (0.1-0.6)	**<0.01**
Brain natriuretic peptide, pg/ml	69.3 (27.2-214.4)	2,321	56.4 (25.4-174.8)	200.1 (86.8-557.5)	**<0.01**	124.8 (48.8-289.9)	**<0.01**
Serum ferritin, μg/ml	767.0 (359.0-1826.5)	3,396	768.0 (360.0-1827.0)	729.0 (340.0-1795.0)	0.63	832.0 (447.0-2012.0)	0.54

Continued on the next page

TABLE 1 Continued

	All Patients (N = 3,970)	n	No AF/AFL (n = 3,595)	In-Hospital AF/AFL: All AF/AFL (n = 375)	p Value	In-Hospital AF/AFL: New-Onset AF/AFL (n = 146)	p Value
C-reactive protein							
On admission, mg/l	117.1 (58.9-198.8)	2,007	118.1 (59.0-198.8)	106.3 (58.2-195.9)	0.24	111.4 (59.3-213.4)	0.43
Peak level, mg/l	176.3 (94.1-271.2)	2,002	175.1 (93.2-270.4)	186.5 (101.9-284.6)	0.34	232.4 (157.9-312.1)	**0.01**
Procalcitonin, ng/ml	0.20 (0.08-0.66)	3,236	0.20 (0.08-0.63)	0.25 (0.09-0.84)	0.06	0.3 (0.1-0.9)	0.09
IL-6, pg/ml	68.5 (34.2-137.0)	2,197	67.8 (33.6-135.2)	83.2 (39.4-154.0)	**0.02**	93.5 (56.2-198.2)	**0.01**
Erythrocyte sedimentation rate, mm/h	62.0 (38.0-88.0)	1,903	63.0 (38.0-88.0)	58.5 (35.0-85.0)	0.09	60.0 (36.0-95.0)	0.43
Nadir $PaCO_2$, mm Hg	33.0 (28.0-38.8)	1,123	33.0 (28.3-39.0)	31.3 (26.0-37.9)	**0.05**	30.4 (28.0-38.7)	**0.01**

Values are median (interquartile range) or n (%). [a]Fisher exact test. Values in **bold** indicate a p value ≤ 0.05.

AF = atrial fibrillation; AFL = atrial flutter; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease-2019; IL = interleukin; OSA = obstructive sleep apnea; $PaCO_2$ = partial pressure of carbon dioxide; TIA = transient ischemic attack.

The COVID-19_{Manual} cohort included laboratory data, baseline demographics, and hospital medications abstracted from the electronic health record and then manually reviewed. Baseline comorbidities, prehospital medications, and in-hospital events (including neurological events) were obtained from available clinical records. All available ECGs were independently reviewed by a cardiologist or electrophysiologist and chart documentation was assessed for atrial arrhythmias.

STATISTICAL ANALYSIS. Continuous variables were summarized as median and interquartile range or means and standard deviations, as appropriate. Categorical variables were summarized as counts or percentages. No imputation was made for missing data. Median/Mann-Whitney U test, Fisher exact test, or chi square test was used to compare data where appropriate. A 2-tailed p value ≤ 0.05 was considered statistically significant. In the comparison of patients with influenza versus COVID-19 with new AF/AFL, we included only variables which were available in at least 75% of patients in both groups. We then plotted Kaplan-Meier curves for in-hospital mortality stratified by the presence of in-hospital AF/AFL. As our follow-up only included the duration of the hospitalization, patients discharged from the hospital were considered to have survived for the purposes of these curves. Separate Kaplan-Meier curves were also created in which discharged patients were censored (Supplemental Figure S1)

A multivariable logistic regression was performed examining predictors of new-onset AF. As not all laboratory values of interest were available for each patient, each value was included in an individual model along with other predictors of new-onset AF (age, race, hypertension, diabetes, and prior history of neurological event). Finally, a sensitivity analysis was performed comparing the relative risk (RR) of developing in-hospital and new-onset AF for patients admitted with COVID-19 versus those admitted with influenza. Models were constructed to adjust for differences in baseline demographics represented by hypertension, diabetes, prior stroke/TIA, chronic kidney disease, and COPD as well as severity of illness as represented by need for mechanical ventilation or vasopressors.

Statistical analysis was performed using SPSS version 25.0 (IBM Corp) as well as STATA version 16.1 (StataCorp LLC).

RESULTS

INCIDENCE AND PREDICTORS OF AF/AFL IN COVID-19 PATIENTS. In the COVID-$19_{Primary}$ cohort, 3,970 patients admitted with polymerase chain reaction-confirmed COVID-19 were identified and incorporated into the analysis. The overall incidence of AF/AFL occurring during hospitalization was 10% (n = 375 patients). As shown in Table 1, patients with AF/AFL were older (median 77 vs. 65 years of age; $p < 0.01$) and with more baseline comorbidities, including hypertension (56% vs. 32%; $p < 0.01$), diabetes (33% vs. 24%; $p < 0.01$), and CHF (25% vs. 5%, $p < 0.01$). Most patients with inpatient AF/AFL (61%) had a history of atrial arrhythmias, and of those with a history of atrial arrhythmias, 71% manifested AF/AFL during hospitalization. The overall incidence of AF/AFL in patients without a history of atrial arrhythmias (new-onset AF/AFL) was 4% (n = 146).

Aside from age (median 74 vs. 66 years; $p < 0.01$) and race, patients with newly detected AF/AFL did not differ significantly in terms of baseline characteristics from those who did not develop AF/AFL. However, there were differences

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TABLE 2 Individual Multivariable Logistic Regression Analyses of Predictors of New-Onset AF/AFL

		95% Confidence Interval		
	Odds Ratio	Lower Limit	Upper limit	p Value
Admission laboratory data				
IL-6, pg/ml	1.000	0.999	1.000	0.66
Serum creatinine, mg/dl	1.054	0.991	1.121	0.09
Brain natriuretic peptide, pg/ml	0.999	0.999	1.000	0.94
Hemoglobin, g/l	1.023	0.920	1.138	0.68
Platelet count, • 10^9/l	0.999	0.997	1.001	0.21
Lymphocyte count, • 10^9/l	0.913	0.669	1.245	0.56
Erythrocyte sedimentation rate, mm/h	0.998	0.991	1.005	0.57
Serum ferritin, μg/ml	1.000	0.999	1.000	0.06
C-reactive protein pg/ml	1.002	0.999	1.005	0.08
D-Dimer, μg/ml	1.025	0.971	1.083	0.37
Hospital course laboratory data				
Platelet nadir, • 10^9 per l	0.996	0.994	0.998	**<0.01**
Peak D-Dimer, μg/ml	1.054	1.011	1.099	0.01
Peak C-reactive protein, pg/ml	1.004	1.002	1.006	**<0.01**
Peak troponin, ng/ml	1.003	0.998	1.001	0.18
Hospitalization treatment and outcomes				
Myocardial injury (peak troponin ≥0.03 ng/ml)	2.489	1.245	4.977	**0.01**
Severe myocardial injury (peak troponin ≥0.09 ng/ml)	3.842	2.083	7.087	**<0.01**
Vasopressors administered	3.456	2.380	5.015	**<0.01**
Steroids	2.350	1.671	3.304	**<0.01**
Intubation	3.687	2.587	5.284	**<0.01**

Each individual laboratory test was compared in a multivariate analysis with several baseline characteristics including: age, hypertension, diabetes, race, and prior stroke. **Bold** indicates p ≤ 0.05.

Abbreviations as in Table 1.

in certain laboratory values, including an increase in peak inflammatory markers: C-reactive protein (median 232 mg/dl vs. 175 mg/dl; p < 0.01) and IL-6 (median 93.5 mg/dl vs. 67.8 mg/dl; p < 0.01). There were also increases in other previously described markers of disease severity, including peak troponin (median 0.2 ng/ml vs. 0.07 ng/ml; p < 0.01), peak D-dimer (median 3.7 μg/ml vs. 2.3 μg/ml; p < 0.01), and B-type-natriuretic peptide (median 125 pg/ml vs. 56 pg/ml; p < 0.01).

A multivariate logistic regression model was constructed including individual laboratory values and in-hospital treatment along with comorbidities found to be predictive of developing new AF (**Table 2**). No admission laboratory value showed significant predictive value in this analysis; however, in-hospital markers of peak inflammation including C-reactive protein and platelet nadir, along with evidence of myocardial injury (troponin ≥0.03 ng/ml) maintained predictive value. Use of steroids and mechanical ventilation were also associated with a higher incidence of new AF in this analysis.

COMPARISON TO MANUALLY ABSTRACTED DATA. To perform a manual review of the COVID-$19_{Primary}$ dataset, a consecutive subset of patients, the COVID-19_{Manual} cohort (n = 1,110) was screened for both baseline and outcome characteristics, including atrial arrhythmias. There were substantially higher rates of certain common comorbidities identified in the COVID-19_{Manual} group compared to the corresponding COVID-$19_{Primary}$ group such as hypertension (63% vs. 35%; p < 0.01) and diabetes (38% vs. 24%; p < 0.01) (Supplemental Table S1). Of those with a pre-existing history of atrial arrhythmias, 43% were considered paroxysmal, 25% persistent, and the remaining could not be determined. Most importantly, including both ECG-confirmed and reported AF/AFL, the overall incidence was higher than the 10% captured in the COVID-$19_{Primary}$ analysis—the AF/AFL in COVID-19_{Manual} was instead 13% (n = 140) with 6.6% of patients showing new AF/AFL.

Similar to the larger COVID-$19_{Primary}$ cohort, AF/AFL in this COVID-19_{Manual} cohort was associated with increases in baseline comorbidities such as HF, hypertension, and age (Supplemental Table S2). In this COVID-19_{Manual} cohort, the pre-admission medications of the AF/AFL patients included more frequent use of anticoagulant, lipid-lowering, and antihypertensive medications, but no significant difference in use of angiotensin-converting enzyme inhibitors (20% vs. 14%; p = 0.07), or angiotensin receptor blockers (16% vs. 17%; p = 0.81).

MANAGEMENT AND OUTCOMES OF AF/AFL. In the COVID-$19_{Primary}$ cohort, patients with AF/AFL were slightly less often treated with hydroxychloroquine (68% vs. 76%; p = 0.03). Use of IL-6 inhibitors was similar compared to those without AF/AFL (**Table 3**). Corticosteroid use differed significantly between groups (40% vs. 28%; p < 0.01), and this association was stronger in patients with new-onset AF/AFL (47% vs. 28%; p < 0.01). In-hospital treatment of AF/AFL frequently included therapeutic anticoagulation with either parenteral heparin or oral anticoagulants (78%). Although there was no significant difference in peak hospitalization heart rates, AF patients frequently received antiarrhythmic drugs (25%), predominately amiodarone (86 of 95 patients, 91%).

Overall, the presence of AF/AFL was associated with worse outcomes, including higher rates of intubation (27% vs. 15%, RR: 1.8; p < 0.01), ischemic stroke (1.6% vs. 0.6%, RR: 2.7; p = 0.05), and mortality (46% vs. 26%, RR: 1.78; p < 0.01).

AF/AFL IN INFLUENZA VERSUS COVID-19. To understand the specificity of observed atrial arrhythmias in COVID-19, we studied a cohort of 1,420

TABLE 3 Treatment and Outcomes Associated With AF/AFL

	All Patients (N = 3,970)	No AF/AFL (n = 3,595)	All AF/AFL (n = 375)	p Value	New-Onset AF/AFL	p Value
Hospital treatments						
Hydroxychloroquine	2,970 (75)	2,714 (76)	256 (68)	**<0.01**	113 (77)	0.60
Azithromycin	2,726 (69)	2,479 (69)	247 (66)	0.22	105 (72)	0.45
Remdesivir	59 (2)	49 (1)	10 (3)	0.07	6 (4)	**0.01**
Interleukin-6 directed drugs	248 (6)	220 (6)	28 (8)	0.32	19 (13)	**<0.01**
Tocilizumab	211 (5)	189 (5)	22 (6)		15 (10)	**0.01**
Sarilumab	37 (1)	31 (1)	6 (2)		4 (3)	**0.02**
Antiarrhythmic drugs	182 (5)	87 (3)	95 (25)	**<0.01**	51 (35)	**<0.01**
Amiodarone	164 (4)	78 (2)	86 (23)	**<0.01**	50 (34)	**<0.01**
Therapeutic anticoagulation	1,587 (40)	1,319 (37)	268 (72)	**<0.01**	114 (78)	**<0.01**
Prophylactic anticoagulation	3,150 (79)	2,948 (82)	202 (54)	**<0.01**	105 (72)	**<0.01**
Steroids	1,173 (30)	1,022 (28)	151 (40)	**<0.01**	68 (47)	**<0.01**
Intubation	650 (16)	550 (15)	100 (27)	**<0.01**	55 (38)	**<0.01**
Number of vasopressors	0.21 ± 0.61	0.20 ± 0.60	0.35 ± 0.78	**<0.01**	0.51 ± 0.85	**<0.01**
Outcomes						
Ischemic stroke or TIA	29 (1)	23 (1)	6 (2)	**0.05**	4 (3)	**<0.01**
Hemorrhagic stroke	5 (0.1)	5 (0.1)	0 (0.0)	0.47	0(0.0)	0.65
Death	1,104 (28)	933 (26)	171 (46)	**<0.01**	80 (55)	**<0.01**
Hospital length of stay, days	7 (4-11)	7 (3-11)	8 (4-13)	**<0.01**	9 (5-17)	0.09

Values are n (%), mean ± SD, or median (interquartile range). **Bold** values indicates p ≤ 0.05.
Abbreviations as in Table 1.

influenza patients ($Influenza_{Primary}$ group). Comorbidities occurred more frequently in patients hospitalized with influenza than COVID-19 (Table 4). The incidence of in-hospital AF/AFL was higher in the $Influenza_{Primary}$ than the $COVID\text{-}19_{Primary}$ cohort (12% vs. 10%, p = 0.03), but the incidence of new-onset AF/AFL was similar (4% vs. 4%; p = 0.93). Not surprisingly, despite more frequent comorbidities, the $Influenza_{Primary}$ cohort had a substantially lower incidence of in-hospital mortality (9% vs. 29%, p < 0.01).

Similar to the COVID-19 patients, influenza patients with in-hospital AF/AFL were older and had higher rates of comorbidities including HF and hypertension (Supplemental Tables S3 and S4). The levels of inflammatory markers were not significantly different in AF/AFL patients in the $Influenza_{Primary}$ cohort; however, they had increased markers of cardiac injury (median 0.08 ng/ml vs. 0.05 ng/ml; p < 0.01). Use of corticosteroids was similar in those with in-hospital AF/AFL (39% vs. 41%, p = 0.73). As in COVID-19 patients, in-hospital AF/AFL in the $Influenza_{Primary}$ cohort was associated with more frequent intubation (14% vs. 7%; p < 0.01) and death (16% vs. 10%; p < 0.01).

We performed sensitivity analyses to address the potential impact of differences in acuity of illness and baseline characteristics in these 2 groups (Supplemental Table S5). After correcting for differences in age, sex, race, and various comorbidities, these analyses revealed similar rates of atrial arrhythmias in both the $COVID\text{-}19_{Primary}$ and $Influenza_{Primary}$ cohorts for both the all in-hospital AF/AFL and the new-onset AF/AFL groups. After adjustment for severity of illness, the $COVID\text{-}19_{Primary}$ cohort showed a lower risk of all in-hospital AF/AFL (odds ratio: 0.79, 95% confidence interval: 0.65 to 0.98). When the analysis focused on new-onset AF/AFL, there was no significant difference between groups (odds ratio: 0.94; 95% confidence interval: 0.67 - 1.32).

Kaplan-Meier analyses (**Figure 1,** Supplemental Figure S1) show an early increase in mortality in patients with in-hospital AF/AFL regardless of whether the arrhythmia was new or preceded by a history of atrial arrhythmias. The association of AF/AFL with mortality was similar with both influenza (RR: 1.78) and COVID-19 (RR: 1.77) (**Central Illustration**).

DISCUSSION

In this study, we examined the incidence, predictors, and outcomes of patients hospitalized with COVID-19 across 5 hospitals during the height of the pandemic in New York City. Our analysis involved an exceptionally ill cohort, as 16% required intubation and mechanical ventilation and 28% died during hospitalization. The incidence of AF/AFL reached 10% to 13%, of which 4% to 6.6% of patients exhibited a new

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TABLE 4 Baseline Demographics of Patients Hospitalized With COVID-19 Versus Influenza

	All Patients	COVID-19 (n = 3,970)	Influenza (n = 1,420)	p Value
Baseline demographics				
Age, yrs	66 (55-78)	66 (55-77)	67 (56-80)	**<0.01**
Male	2,882	2,288 (59)	594 (42)	**<0.01**
Race/ethnicity				**<0.01**
Caucasian	1,347 (25)	946 (24)	401 (28)	
African-American	1,509 (28)	1,107 (28)	402 (28)	
Asian	263 (5)	208 (5)	55 (4)	
Hispanic	1,649 (31)	1,240 (31)	409 (29)	
Other	459 (9)	358 (9)	131 (9)	
Unknown	133 (3)	111 (3)	22 (2)	
Obesity	1,762 (33)	1,312 (33)	450 (32)	0.35
Body mass index, kg/m^2	27.5 (23.9-32.5)	27.8 (24.2-32.6)	26.8 (23.1-31.8)	**<0.01**
CHF	523 (10)	271 (7)	252 (18)	**<0.01**
Atrial arrhythmias	537 (10)	339 (9)	198 (14)	**<0.01**
CAD	686 (13)	410 (10)	276 (19)	**<0.01**
Hypertension	2,000 (37)	1,367 (35)	633 (45)	**<0.01**
Diabetes	1,331 (25)	976 (25)	355 (25)	0.77
Prior stroke/TIA	281 (5)	160 (4)	121 (9)	**<0.01**
Chronic kidney disease	700 (13)	446 (11)	254 (18)	**<0.01**
Chronic liver disease	133 (3)	79 (2)	54 (4)	**<0.01**
HIV	131 (3)	68 (2)	63 (5)	**<0.01**
COPD	343 (6)	157 (4)	186 (13)	**<0.01**
Asthma	425 (8)	185 (5)	240 (17)	**<0.01**
OSA	128 (2)	70 (2)	58 (4)	**<0.01**
Smoking				**<0.01**
Current	327 (6)	152 (4)	175 (12)	
Past	1,267 (24)	815 (21)	452 (32)	
Never	3,796 (71)	3,003 (76)	793 (56)	
Outcomes				
In-hospital AF/AFL	538 (10)	375 (10)	163 (12)	**0.03**
New-onset in-hospital AF/AFL	197 (4)	146 (4)	51 (4)	0.88
Hemorrhagic stroke	9 (0.2)	5 (0.1)	4 (0.3)	0.25
Ischemic stroke or TIA		29 (0.7)	12 (0.8)	**0.67**
Death	1,234 (23)	1,104 (28)	130 (9)	**<0.01**
Hospital length of stay, days	6 (3-11)	7 (4-11)	5 (3-8)	**<0.01**

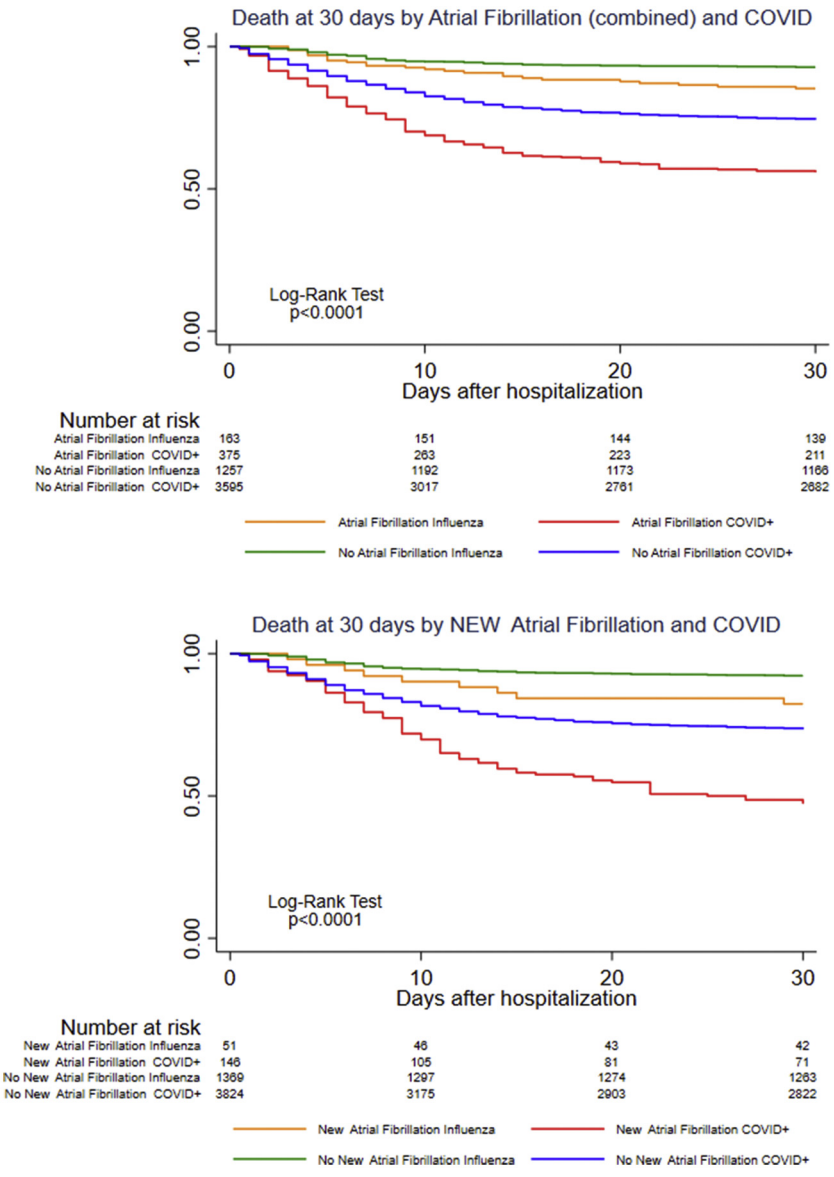
Values are median (interquartile range) or n (%). **Bold** values indicates p ≤ 0.05.
Abbreviations as in Table 1.

diagnosis of atrial arrhythmia. On the other hand, similar rates of in-hospital all and new-onset AF/AFL were found in the influenza group collected from the same New York hospitals suggesting that these atrial arrhythmias occurred as a nonspecific response to severe viral respiratory illness. Several strengths unique to this study include: 1) a large diverse patient dataset across 5 hospitals comprising several potential risk factors for AF/AFL; 2) incorporation of a panel of influenza patients for comparison; and 3) validation of our automated analysis with comprehensive chart review.

Whereas in-hospital AF/AFL in COVID-19 patients occurred more often in those with pre-existing comorbidities, new-onset AF/AFL was largely irrespective of baseline patient characteristics. Rather, new-onset AF/AFL was influenced most by: 1) markers of inflammation such as IL-6 and C-reactive protein, which have previously been associated with AF; 2) laboratory markers such as troponin and D-dimer, which correlate with COVID-19 disease severity; and 3) administration of corticosteroids which, aside from potential drug effect, are frequently targeted toward those manifesting the largest hyper-inflammatory response. Together, these factors suggest a potential mechanistic link between inflammation and new atrial arrhythmias in patients with COVID-19.

This is the first study involving a large cohort of patients to address the incidence of in-hospital AF in COVID-19 patients. A previous analysis involving a manual review of 115 inpatients for various cardiac

FIGURE 1 **Survival Stratified by AF/AFL in COVID-19 Versus Influenza**

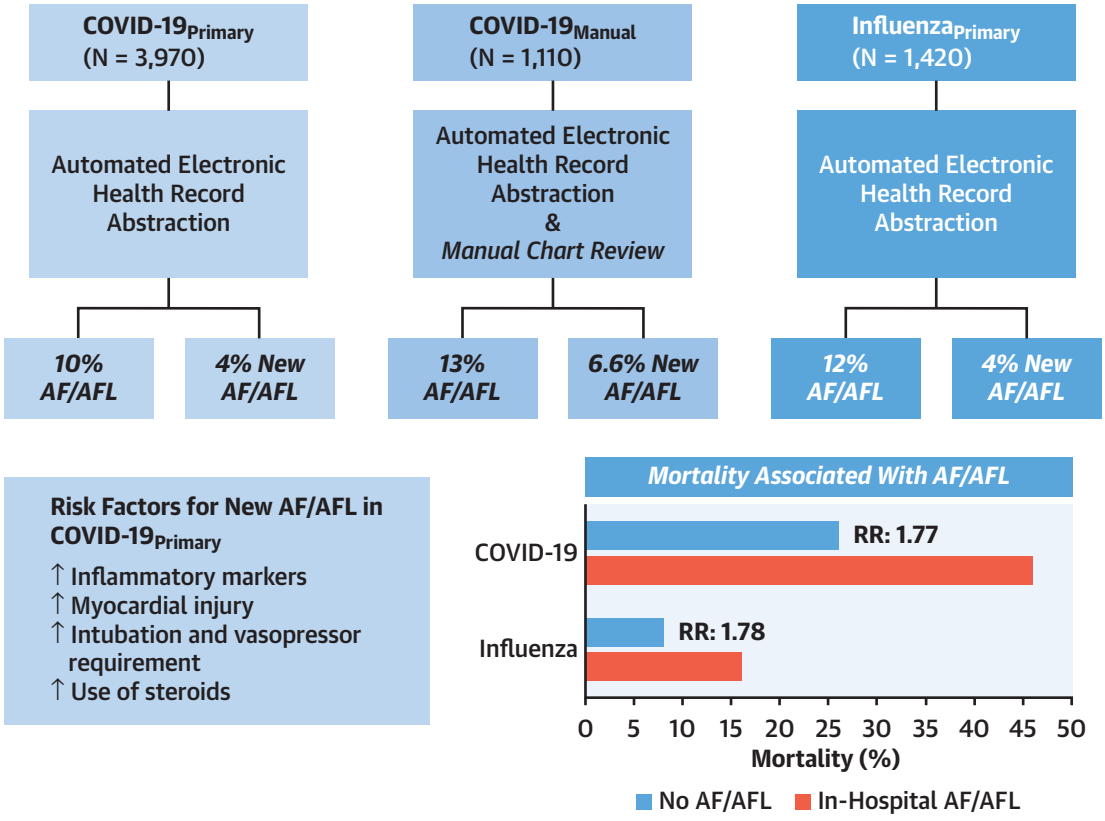


Survival estimates based on the days since hospital admission stratified by COVID-19 versus influenza status as well as the occurrence of in-hospital or new-onset atrial fibrillation. For the purpose of this analysis, patients discharged from the hospital were considered to have survived. AF = atrial fibrillation; COVID = coronavirus disease.

arrhythmias reported an AF incidence of 16.5%, all of which occurred in intensive care units (13). In a nationwide study in Denmark, there was a 47% decrease in the incidence of new-onset AF compared with the corresponding weeks in 2019 (14). Although this most likely resulted from underreporting and lower health care use, it suggests that COVID-19 patients overall do not develop atrial arrhythmias at a greater frequency than other acutely ill hospitalized patients.

Although the incidence of AF/AFL in patients with COVID-19 is not exceedingly high, the occurrence of in-hospital AF/AFL appears impactful to a patient's clinical course, as indicated by the frequent use of antiarrhythmic therapy. Despite the cumulative risk potentially anticipated by combining the

CENTRAL ILLUSTRATION **Incidence, Predictors, and Outcomes of Atrial Arrhythmias in Patients Admitted With COVID-19 Versus Influenza**



Musikantow, D.R. et al. J Am Coll Cardiol EP. 2021;7(9):1120–1130.

AF = atrial fibrillation; AFL = atrial flutter; COVID-19 = coronavirus disease-2019; RR = relative risk.

prothrombotic state of COVID-19 with the stasis of blood flow during AF/AFL, there was only a modest (1%) absolute increase in ischemic stroke in patients with atrial arrhythmias, perhaps due to concurrent use of therapeutic anticoagulation (76%) during hospitalization. Not unexpectedly, as AFL/AFL was associated with comorbidities, markers of inflammation and disease severity, mortality was exceptionally high in this group (46%).

Previous studies have noted new-onset AF in patients with influenza (15). This had been attributed to higher rates of proinflammatory cytokines including IL-6, which is not specific to either influenza or COVID-19 infection (16). The observation that AF occurs in COVID-19 at a frequency similar to that in influenza argues against a unique effect of either virus on atrial rhythm. This similarity may be confounded by a higher rate of baseline comorbidities in the influenza group, more severe systemic illness in COVID-19, and longer duration of hospitalization during the COVID-19 pandemic. Importantly, as many patients with COVID-19 and influenza are managed as outpatients, our study only reflects those patients whose severity of illness warranted hospitalization.

The height of the COVID-19 pandemic imposed a unique stress on the medical system in New York hospitals as providers were called to perform unfamiliar roles. As a result, we believed it important to ascertain whether the automated data abstraction strategy applied to such a large dataset (using ICD 9/10 codes) accurately reflected the incidence of atrial arrhythmias. Manual chart review of a large subset of this population found that 23% of patients with AF/AFL were not identified by the automated analysis—accordingly, the true rate of AF/AFL increased from 10% to 13%. Furthermore, manual review identified

substantially higher rates of common comorbidities that were not discovered by automated indexing of ICD codes. On the other hand, there were minimal differences in laboratory values, treatments, or outcomes between the 2 methods of data abstraction. This highlights the limitations and strengths of "big data" studies which have become commonplace during the COVID-19 pandemic.

STUDY LIMITATIONS. This study was limited by several intrinsic challenges of the COVID-19 pandemic including limited access to telemetry monitoring in the nonintensive care unit setting, a high incidence of sedated and noncommunicative patients, and the potential for underdetection of ischemic stroke due to the difficulty of performing brain imaging tests in infected patients. From a methodological perspective, the comparison between the COVID-19 and influenza patients was performed with a similar automated strategy; however, it remains possible that unlike during the "normal" influenza season, the throes of a pandemic may have resulted in a differentially lower rate of detection of AF/AFL (or potential underreporting using ICD 9/10 codes) in the COVID-19$_{\text{Primary}}$ cohort. However, given the rapid ventricular response common with AF/AFL in the hospitalized COVID-19 pneumonia patient, it seems unlikely that there were many instances of clinically undetected AF/AFL. Additionally, the exact onset of AF/AFL cannot be accurately determined in part because of limitations in the available data and in part because of the potential delays in diagnosis of atrial arrhythmias during the COVID-19 pandemic. As such, it is difficult to discern the temporal relationship between the factors associated with the development of AF/AFL and their occurrence during the hospital course.

It also bears mentioning that these data only pertain to hospitalized patients: it is possible that nonhospitalized COVID-19 patients have different predictors of developing AF/AFL and different outcomes. Also, we cannot rule out the possibly that the decision-making for hospitalizing a COVID-19 patient during a pandemic may differ than for an influenza patient. However, the directionality of any such variance is unclear—perhaps there is a lower threshold for hospitalization with COVID-19 because of the apprehension surrounding a pandemic, or perhaps there is a higher threshold related to scarce resources or apprehension related to hospitalization. On the other hand, because AF/AFL was more likely to occur in the most critically ill patients regardless of the viral etiology, it is likely that the patients most likely to develop AF/AFL were hospitalized. Finally, because our follow-up only extended to hospital discharge, the impact of atrial arrhythmias on the patient's clinical course post-hospitalization was not examined in this analysis.

CONCLUSIONS

In this study, we found that AF/AFL occurred in ~13% of hospitalized patients with COVID-19. However, new-onset AF/AFL occurred in only a small minority (4%), a rate that was similar to that observed in hospitalized influenza patients. In both cohorts, new-onset AF/AFL correlated best with higher degrees of inflammation and disease severity, independent of patient baseline characteristics. These data suggest that these atrial arrhythmias are less likely specific to the COVID-19 viral infection but are rather a generalized response to the systemic inflammatory response of severe viral illness.

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Dr Koruth has received consulting fees from Abbott Laboratories, CardioFocus, Farapulse, and Vytron US, Inc. Dr Dukkipati has received grant support from Biosense Webster; and has equity with Farapulse and Manual Surgical Sciences, LLC. Dr Halperin has received consulting fees from Boehringer Ingelheim, Johnson & Johnson-Janssen Pharmaceuticals, and Medtronic. Dr Reddy is a consultant with Abbott, Ablacon, Acutus Medical, Affera, Apama Medical, Aquaheart, Atacor, Autonomix, Axon, Backbeat, BioSig, Biosense Webster, Biotronik, Boston Scientific, Cardiofocus, Cardionomic, CardioNXT/AFTx, Circa Scientific, Corvia Medical, Dinova-Hangzhou Nuomao Medtech Co., Ltd., East End Medical, EBR, EPD, Epix Therapeutics, EpiEP, Eximo, Fire1, Impulse Dynamics, Javelin, Kardium, Keystone Heart, LuxCath, Manual Surgical Sciences, Medlumics, Medtronic, Middlepeak, Newpace, Nuvera, Philips, Pulse Biosciences, Sirona Medical, Stimda, Surecor, Thermedical, and Valcare; and has equity in Ablacon, Acutus Medical, Affera, Apama, Aquaheart, Atacor, Autonomix, Backbeat, BioSig, Circa Scientific, Corvia Medical, Dinova-Hangzhou Nuomao Medtech Co., Ltd., East End Medical, EPD, Epix Therapeutics, EpiEP, Eximo, Fire 1, Javelin, Kardium, Keystone Heart, LuxCath, Manual Surgical Sciences, Medlumics, Middlepeak, Newpace, Nuvera, Sirona Medical, Surecor, Valcare, and Vizaramed. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study addresses clinical competencies of medical knowledge regarding the incidence, risk factors, and outcomes associated with atrial arrhythmias of hospitalized patients during the ongoing COVID-19 pandemic in contrast with those hospitalized with influenza prior to the pandemic.

TRANSLATIONAL OUTLOOK: It is important to place the incidence and predictors of atrial arrhythmias during the COVID-19 pandemic in context with recent investigations into the importance of inflammation and myocardial injury in patients hospitalized with COVID-19.

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KEY WORDS atrial fibrillation, atrial flutter, coronavirus disease-2019, influenza, ischemic stroke

APPENDIX For a supplemental figure and tables, please see the online version of this paper.