

2021

## Atrial fibrillation is an independent predictor for in-hospital mortality in patients admitted with SARS-CoV-2 infection.

S. E. Mountantonakis

*Zucker School of Medicine at Hofstra/Northwell, smountanto@northwell.edu*

M. Saleh

J. Fishbein

A. Gandomi

M. Lesser

*See next page for additional authors*

Follow this and additional works at: <https://academicworks.medicine.hofstra.edu/articles>

 Part of the [Cardiology Commons](#)

---

### Recommended Citation

Mountantonakis SE, Saleh M, Fishbein J, Gandomi A, Lesser M, Chelico J, Gabriels J, Qiu 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.. . 2021 Jan 01; ():Article 7677 [ p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/7677>. Free full text article.

This Article is brought to you for free and open access by Donald and Barbara Zucker School of Medicine Academic Works. It has been accepted for inclusion in Journal Articles by an authorized administrator of Donald and Barbara Zucker School of Medicine Academic Works. For more information, please contact [academicworks@hofstra.edu](mailto:academicworks@hofstra.edu).

---

**Authors**

S. E. Mountantonakis, M. Saleh, J. Fishbein, A. Gandomi, M. Lesser, J. Chelico, J. Gabriels, M. Qiu, L. M. Epstein, and Northwell COVID-19 Research Consortium



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 fibrillation is an independent predictor for in-hospital mortality in patients admitted with SARS-CoV-2 infection

Stavros E. Mountantonakis, MD, MBA,\* Moussa Saleh, MD,\* Joanna Fishbein, MPH,<sup>†</sup> Amir Gandomi, PhD,<sup>‡</sup> Martin Lesser, PhD,<sup>†</sup> John Chelico, MD,<sup>†</sup> James Gabriels, MD,\* Michael Qiu, MD, PhD,<sup>‡</sup> Laurence M. Epstein, MD,\* and the Northwell COVID-19 Research Consortium

From the \*Department of Cardiology, Northwell Health, New York, New York, <sup>†</sup>The Feinstein Institutes for Medical Research, Northwell Health, New York, New York, and <sup>‡</sup>Frank G. Zarb School of Business, Hofstra University, Hempstead, New York.

**BACKGROUND** Atrial fibrillation (AF) is the most encountered arrhythmia and has been associated with worse in-hospital outcomes.

**OBJECTIVE** This study was to determine the incidence of AF in patients hospitalized with coronavirus disease 2019 (COVID-19) as well as its impact on in-hospital mortality.

**METHODS** Patients hospitalized with a positive COVID-19 polymerase chain reaction test between March 1 and April 27, 2020, were identified from the common medical record system of 13 Northwell Health hospitals. Natural language processing search algorithms were used to identify and classify AF. Patients were classified as having AF or not. AF was further classified as new-onset AF vs history of AF.

**RESULTS** AF occurred in 1687 of 9564 patients (17.6%). Of those, 1109 patients (65.7%) had new-onset AF. Propensity score matching of 1238 pairs of patients with AF and without AF showed higher

in-hospital mortality in the AF group (54.3% vs 37.2%;  $P < .0001$ ). Within the AF group, propensity score matching of 500 pairs showed higher in-hospital mortality in patients with new-onset AF as compared with those with a history of AF (55.2% vs 46.8%;  $P = .009$ ). The risk ratio of in-hospital mortality for new-onset AF in patients with sinus rhythm was 1.56 (95% confidence interval 1.42–1.71;  $P < .0001$ ). The presence of cardiac disease was not associated with a higher risk of in-hospital mortality in patients with AF ( $P = .1$ ).

**CONCLUSION** In patients hospitalized with COVID-19, 17.6% experienced AF. AF, particularly new-onset, was an independent predictor of in-hospital mortality.

**KEYWORDS** Atrial fibrillation; SARS-CoV-2; Pandemic; COVID-19; Mortality

(Heart Rhythm 2021;■:1–7) © 2021 Heart Rhythm Society. All rights reserved.

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia and has been associated with worse outcomes in hospitalized patients.<sup>1,2</sup> Its prevalence and clinical impact are even more prominent in patients with pulmonary disease, critical illness, and systemic inflammatory response syndrome.<sup>3–5</sup>

Coronavirus disease 2019 (COVID-19) in hospitalized patients is often characterized by respiratory involvement with hypoxia, systemic inflammatory response, and cardiac involvement, all of which are known predisposing factors for the development of AF. In addition, the onset of AF has deleterious hemodynamic effects<sup>6</sup> that can further deteriorate

the clinical presentation of a tenuous patient. Finally, the hypercoagulable state during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to influence thromboembolic events related with AF.<sup>7</sup> The objectives of this study were to examine the incidence of AF in patients hospitalized with COVID-19 and to evaluate its impact on in-hospital mortality.

## Methods

### Study design and cohort definition

The study was conducted at 13 hospitals in the Northwell Health system. Patients admitted between March 1 and April 27, 2020, with a positive COVID-19 polymerase chain reaction test were included in the study. Patients were followed through May 31, 2020. Patients with multiple readmissions during the study period were evaluated as a single presentation. Patients with a negative or absent nasopharyngeal

Funding sources: The authors have no funding sources to disclose. Disclosures: The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Stavros E. Mountantonakis, Department of Cardiology, Northwell Health, 100 E 77th St 2 Lachman, New York, NY 10075. E-mail address: [smountanto@northwell.edu](mailto:smountanto@northwell.edu).

swab, patients without progress notes or documented basic laboratory values within the first 96 hours of initial registration, patients who were still in the hospital as of May 31, and those whose outcome could not be determined as of May 31 were excluded.

The Northwell Health Institutional Review Board approved this study. The research reported in this article adhered to Helsinki Declaration as revised in 2013.

## Data collection

For data extraction, a detailed EMR search was performed, which included scanning of all medical notes, diagnoses, medications, orders, and electrocardiogram and telemetry interpretations. First available laboratory results within 96 hours from the initial presentation were used for the analyses. Natural language processing (NLP) techniques were used to detect AF diagnosis for each patient from a total of >24 million progress notes in the data set. To this end, a rule-based text classification algorithm was developed using the word “atrial fibrillation” and all possible variants (eg, “atrial flutter,” “rapid ventricular rate,” and “paroxysmal atrial fibrillation”) and abbreviations (eg, “AF,” “afib,” “RVR,” and “PAF”). The algorithm was designed to include misspellings and hyphenations in acronyms (eg, “a-fib”). It excluded irrelevant acronym matches and false partial matches (eg, “has a fibroid”). Furthermore, a set of explicit language rules were developed to handle negation (eg, “no evidence of AF”), uncertainty (eg, “at risk of AF”), a reference to family history, and other false-positive cases such as “afib[ ]” (where missing an “X” in square brackets indicates the absence). Python’s NLTK library was used to tokenize the text into sentences and regular expressions module was used to develop and implement inclusion/exclusion rules at the sentence level. To evaluate the accuracy of the algorithm in detecting the presence of an AF diagnosis in patients’ charts, a random set of 250 patients (~2.6% of the population) were independently and blindly reviewed by 2 physicians. This revealed an overall accuracy of 99.6% (sensitivity 100%; specificity 98%) for AF detection. The rate of agreement between the 2 clinicians was 100%.

Similarly, a rule-based NLP algorithm was developed to determine whether a patient has new-onset AF or a history of AF. SAS Rule Builder procedure was first used to automatically extract an initial rule set based on 500 sentences labeled by 2 clinicians. Rules were then fine-tuned by iteratively implementing and evaluating the results at the patient level. Satisfactory results were achieved after 11 iterations with a total of 46 inclusion/exclusion rules. The final validation of the algorithm in differentiating between new AF and known AF was performed by 2 clinicians who blindly and independently evaluated a random sample of 400 patients (~4.1% of the population). They had disagreement rates of 4% on “history of AF” and 9% on “new-onset of AF.” Disagreements were settled with deliberation. The final labels showed an overall accuracy of 95.0% for “new-onset of AF” (sensitivity

98.6%; specificity 91.0%) and an overall accuracy of 98.8% for “history of AF” (sensitivity 98.3%; specificity 99.1%).

The AF group was defined as those patients who had AF during hospitalization irrespective of a history of AF. Those with AF were further classified into 2 subgroups: patients with new-onset AF and patients with a history of AF. Moreover, final diagnosis (ICD-9 and ICD-10) codes were also reviewed in the subset of patients who had any prior hospitalization recorded in the EMR to identify preexisting conditions, including AF, not recorded during the patients’ COVID admission.

## Comparison groups and outcome measures

The primary outcome of this study was in-hospital mortality. In-hospital mortality was compared between patients with AF and those without AF, between the 2 AF subgroups, and patients with new-onset AF and those without AF. Finally, to examine the effect of underlying cardiac disease (ie, coronary artery disease, congestive heart failure, and valvular heart disease) on hospital mortality in patients with AF, patients with a history of cardiac disease were compared with those without such a history.

## Statistical analysis

Propensity score matching (PSM) was used to control for potential confounding variables. The efficiency of the PSM procedure in producing comparability of the 2 groups after matching was evaluated using standardized mean differences (SMDs). An absolute SMD of <0.1 was deemed as adequate comparability.<sup>8</sup> Descriptive statistics on the factors used to develop the propensity score in the entire cohort before and after matching are presented in Table 1. Continuous factors are reported as mean ± SD or median (first quartile, third quartile) in their original units, and categorical factors are presented as frequency and proportion.

Exact binomial methods were used to compute the proportion of patients with AF along with the corresponding 95% confidence intervals (CIs).

The McNemar test for matched pairs was used to assess whether the risk of in-hospital mortality differed according to the status of AF and relevant subgroups during the patients’ hospital stay.<sup>9</sup> Risk ratios (RRs) for the matched-pair analyses were computed and corresponding 95% CIs were estimated using 1000 bootstrap resamples with replacement.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

A total of 10,207 patients with COVID-19 were admitted between March 1 and April 27, 2020. Of those patients, 9564 patients met inclusion criteria. Eight thousand fifty-eight patients (84.3%) had 1 hospital admission and 1506 (15.7%) had more than 1 hospital admission. Figure 1 shows the flow diagram of the cohort selection. Out of the total, 4938 patients (51.6%) did not have a prior hospitalization within

**Table 1** Comparability of the groups according to in-hospital AF status

Variable	Before matching			After matching		
	AF (n = 1687)	No AF (n = 7877)	SMD	AF (n = 1238)	No AF (n = 1238)	SMD
Age (y)	74.6 ± 12.9	62.6 ± 16.2	0.816*	73.1 ± 13.5	73.6 ± 13.3	-0.034
Sex: male	1054 (62.5)	4578 (58.1)	0.089	777 (62.8)	774 (62.5)	0.005
Smoking status						
Current	123 (7.3)	411 (5.2)	0.086	90 (7.3)	89 (7.2)	0.003
Former	298 (17.7)	1062 (13.5)	0.116*	208 (16.8)	217 (17.5)	-0.019
Never	1059 (62.8)	5928 (75.3)	-0.272*	783 (63.3)	777 (62.8)	0.010
Unknown	207 (12.3)	476 (6.0)	0.217*	157 (12.7)	155 (12.5)	0.005
Race						
Asian	133 (7.9)	676 (8.6)	-0.025	102 (8.2)	117 (9.5)	-0.043
Black	299 (17.7)	1766 (22.4)	-0.117*	229 (18.5)	227 (18.3)	0.004
White	851 (50.4)	2745 (34.9)	0.319*	585 (47.3)	602 (48.6)	-0.027
Other/multiracial	355 (21.0)	2321 (29.5)	-0.195*	284 (22.9)	247 (20.0)	0.073
Unknown	49 (2.9)	369 (4.7)	-0.093	38 (3.1)	45 (3.6)	-0.031
BMI						
<18.5 kg/m <sup>2</sup>	41 (2.4)	123 (1.6)	0.062	29 (2.3)	38 (3.1)	-0.045
18.5 to <25 kg/m <sup>2</sup>	371 (22.0)	1370 (17.4)	0.116*	250 (20.2)	266 (21.5)	-0.031
25 to <30 kg/m <sup>2</sup>	440 (26.1)	2266 (28.8)	-0.060	333 (26.9)	333 (26.9)	0.000
30 to <40 kg/m <sup>2</sup>	364 (21.6)	1981 (25.2)	-0.085	276 (22.3)	260 (21.0)	0.031
≥40 kg/m <sup>2</sup>	86 (5.1)	479 (6.1)	-0.043	65 (5.3)	65 (5.3)	0.000
Unknown	385 (22.8)	1658 (21.1)	0.043	285 (23.0)	276 (22.3)	0.017
Medical history						
Chronic liver disease	35 (2.1)	210 (2.7)	-0.039	26 (2.1)	23 (1.9)	0.016
Atrial fibrillation	578 (34.3)	109 (1.4)	0.951*	131 (10.6)	109 (8.8)	0.051
Hypertension	1318 (78.1)	4691 (59.6)	0.409*	925 (74.7)	940 (75.9)	-0.027
Coronary artery disease	853 (50.6)	2543 (32.3)	0.378*	584 (47.2)	593 (47.9)	-0.015
Peripheral vascular disease	97 (5.8)	203 (2.6)	0.159*	61 (4.9)	62 (5.0)	-0.004
Chronic obstructive pulmonary disease	229 (13.6)	455 (5.8)	0.266*	149 (12.0)	135 (10.9)	0.039
Asthma	151 (9.0)	742 (9.4)	-0.016	102 (8.2)	98 (7.9)	0.011
End-stage renal disease	165 (9.8)	415 (5.3)	0.172*	101 (8.2)	107 (8.6)	-0.018
Chronic kidney disease	254 (15.1)	541 (6.9)	0.264*	151 (12.2)	152 (12.3)	-0.003
Diabetes	771 (45.7)	3009 (38.2)	0.152*	547 (44.2)	548 (44.3)	-0.002
Congestive heart failure	451 (26.7)	575 (7.3)	0.535*	244 (19.7)	237 (19.1)	0.016
Cancer	306 (18.1)	825 (10.5)	0.220*	208 (16.8)	210 (17.0)	-0.005
Lactate						
Normal, within range	115 (6.8)	637 (8.1)	-0.048	78 (6.3)	79 (6.4)	-0.003
Abnormal/high	1064 (63.1)	4858 (61.7)	0.029	813 (65.7)	807 (65.2)	0.010
Missing	508 (30.1)	2382 (30.2)	-0.003	347 (28.0)	352 (28.4)	-0.009
Magnesium						
Abnormal/low	60 (3.6)	175 (2.2)	0.080	43 (3.5)	40 (3.2)	0.013
Normal, within range	1201 (71.2)	5202 (66.0)	0.111*	873 (70.5)	880 (71.1)	-0.012
Abnormal/high	162 (9.6)	621 (7.9)	0.061	128 (10.3)	124 (10.0)	0.011
Missing	264 (15.7)	1879 (23.9)	-0.21*	194 (15.7)	194 (15.7)	0.000
Procalcitonin						
Normal, within range	260 (15.4)	1592 (20.2)	-0.126*	196 (15.8)	205 (16.6)	-0.020
Abnormal/high	1095 (64.9)	4443 (56.4)	0.175*	810 (65.4)	785 (63.4)	0.042
Missing	332 (19.7)	1842 (23.4)	-0.090	232 (18.7)	248 (20.0)	-0.032
D-dimer						
Normal, within range	184 (10.9)	918 (11.7)	-0.024	118 (9.5)	106 (8.6)	0.034
Abnormal/high	1004 (59.5)	4321 (54.9)	0.094	769 (62.1)	782 (63.2)	-0.022
Missing	499 (29.6)	2638 (33.5)	-0.084	351 (28.4)	350 (28.3)	-0.009
Ferritin						
Normal, within range	320 (19.0)	1540 (19.6)	-0.015	225 (18.2)	201 (16.2)	0.051
Abnormal/high	1072 (63.5)	4819 (61.2)	0.049	818 (66.1)	838 (67.7)	-0.034
Missing	295 (17.5)	1518 (19.3)	-0.046	195 (15.8)	199 (16.1)	-0.009
CRP						
Normal, within range	22 (1.3)	119 (1.5)	-0.018	18 (1.5)	13 (1.1)	0.036
Abnormal/high	1291 (76.5)	5961 (75.7)	0.020	957 (77.3)	973 (78.6)	-0.031
Missing	374 (22.2)	1797 (22.8)	-0.015	263 (21.2)	252 (20.4)	0.022
Creatinine						
Normal, within range	835 (49.5)	5527 (70.2)	-0.431*	646 (52.2)	604 (48.8)	0.068
Abnormal/high	852 (50.5)	2350 (29.8)	0.431*	592 (47.8)	634 (51.2)	-0.068

(Continued)

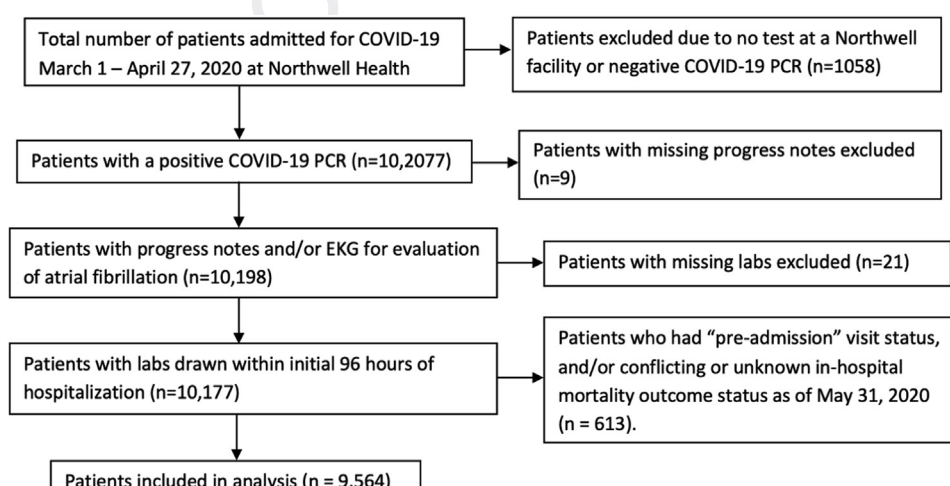


**Table 1** (Continued)

Variable	Before matching			After matching		
	AF (n = 1687)	No AF (n = 7877)	SMD	AF (n = 1238)	No AF (n = 1238)	SMD
<b>BUN</b>						
Normal, within range	719 (42.6)	5433 (69.0)	-0.55*	561 (45.3)	530 (42.8)	0.050
Abnormal/high	968 (57.4)	2444 (31.0)	0.55*	677 (54.7)	708 (57.2)	-0.050
<b>Lymphocyte count</b>						
Abnormal/low	1107 (65.6)	4556 (57.8)	0.161*	814 (65.8)	802 (64.8)	0.020
Normal, within range	554 (32.8)	3226 (41.0)	-0.169*	405 (32.7)	413 (33.4)	-0.014
Abnormal/high	26 (1.5)	95 (1.2)	0.029	19 (1.5)	23 (1.9)	-0.025
<b>AST</b>						
Abnormal/low	4 (0.2)	25 (0.3)	-0.015	1 (0.1)	1 (0.1)	0.000
Normal, within range	665 (39.4)	3241 (41.2)	-0.035	466 (37.6)	492 (39.7)	-0.014
Abnormal/high	1018 (60.3)	4611 (58.5)	0.037	771 (62.3)	745 (60.2)	0.043
<b>ALT</b>						
Abnormal/low	75 (4.5)	210 (2.7)	0.096	42 (3.4)	42 (3.4)	0.000
Normal, within range	1187 (70.4)	4888 (62.1)	0.176*	860 (69.5)	865 (69.9)	-0.009
Abnormal/high	425 (25.2)	2779 (35.3)	-0.221*	336 (27.1)	331 (26.7)	0.009
<b>ALK Phos</b>						
Abnormal/low	50 (3.0)	237 (3.0)	-0.003	33 (2.7)	35 (2.8)	-0.010
Normal, within range	1371 (81.3)	6482 (82.3)	-0.027	1017 (82.2)	1019 (82.3)	-0.004
Abnormal/high	266 (15.8)	1158 (14.7)	0.030	188 (15.2)	184 (14.9)	0.009
<b>Serum glucose</b>						
Abnormal/low	19 (1.1)	80 (1.0)	0.011	14 (1.1)	9 (0.7)	0.042
Normal, within range	225 (13.3)	1076 (13.7)	-0.001	137 (11.1)	150 (12.1)	-0.033
Abnormal/high	1443 (85.5)	6721 (85.3)	0.001	1087 (87.8)	1079 (87.2)	0.020
<b>Potassium</b>						
Abnormal/low	172 (10.2)	949 (12.1)	-0.059	131 (10.6)	121 (9.8)	0.027
Normal, within range	1361 (80.7)	6465 (82.1)	-0.036	989 (79.9)	1009 (81.5)	-0.041
Abnormal/high	154 (9.1)	463 (5.9)	0.124*	118 (9.5)	108 (8.7)	0.028
<b>Sodium</b>						
Abnormal/low	571 (33.9)	2848 (36.2)	-0.048	430 (34.7)	424 (34.3)	0.010
Normal, within range	965 (57.2)	4651 (59.1)	-0.037	706 (57.0)	706 (57.0)	0.000
Abnormal/high	151 (9.0)	378 (4.8)	0.165*	102 (8.2)	108 (8.7)	-0.017
<b>WBC</b>						
Abnormal/low	119 (7.1)	476 (6.0)	0.041	86 (7.0)	81 (6.5)	0.016
Normal, within range	1160 (68.8)	5682 (72.1)	-0.074	849 (68.6)	871 (70.4)	-0.039
Abnormal/high	408 (24.2)	1719 (21.8)	0.056	303 (24.5)	286 (23.1)	0.032

AF = atrial fibrillation; ALK Phos = XXXX; ALT = XXXX; AST = XXXX; BMI = body mass index; BUN = XXXX; CRP = C-reactive protein; SMD = standardized mean difference; WBC = white blood count.

\*Absolute SMD values  $\geq 0.1$  indicate the presence of an imbalance between groups.



**Figure 1** Flow diagram of the cohort selection. COVID-19 = coronavirus disease 2019; EKG = electrocardiogram; PCR = polymerase chain reaction.

the Northwell Health system. This was a sick population, with 1881 (19.7%) receiving mechanical ventilation.

Of the total 9564 patients, 1687 (17.6%; 95% CI 16.9%–18.4%) experienced AF during the course of hospitalization. Of the 1687 patients with AF, 1109 patients (65.7%; 95% CI 63.4%–68.0%) had new-onset AF and 578 (34.3%; 95% CI 32.0%–36.6%) had a medical history of AF, of whom 518 were identified using NLP only and 60 patients were additionally identified using *ICD-9/ICD-10* codes from prior hospitalization records in the EMR. There were 109 patients with a history of AF but no documented AF during hospitalization (1.4%).

### AF status

Before matching, the mean age of the cohort was  $64.8 \pm 16.4$  years and 5632 (58.9%) were men. Comorbidities that were more frequent in patients with AF included a history of hypertension, coronary artery disease, congestive heart failure, peripheral vascular disease, renal disease, chronic obstructive pulmonary disease, cancer, and diabetes (Table 1). As measured by the SMD, BUN and creatinine values were higher in patients with AF than in patients with sinus rhythm. The lymphocyte count was lower in the AF group. There were no differences in inflammatory biomarkers, namely, C-reactive protein (CRP), ferritin, and D-dimer. Patients with in-hospital AF were more likely to receive mechanical ventilation than patients who never experienced AF during their hospitalization (37.5% vs 15.9%;  $P < .0001$ ).

After controlling for possible confounding factors using PSM, 1238 patients with AF were successfully matched with patients without AF for a total of 2476 patients. In-hospital mortality was observed in 672 patients with AF as compared with 460 patients without AF (54.3% vs 37.2%;  $P < .0001$ ). The relative risk (RR) of in-hospital mortality in those with AF compared with those without AF was 1.46 (95% CI 1.34–1.59).

### New-onset AF vs a history of AF

To examine the incremental effect of new-onset AF within the AF group, 500 patients with new-onset AF were again matched with 500 patients with a history of AF. Among those patients, 276 with new-onset AF died in the hospital compared with 234 with a history of AF (55.2% vs 46.8%;  $P = .009$ ) for an RR of in-hospital mortality of 1.18 (95% CI 1.04–1.33).

### New-onset AF vs no AF

The in-hospital mortality in the new-onset AF group was also compared with that in the no AF group. Of 1109 patients with new-onset AF, 1107 patients were matched and compared with patients without AF. In-hospital mortality risk was significantly higher in the new-onset AF group (56.1% vs 36.0%), yielding an RR of 1.56 (95% CI 1.42–1.71;  $P < .0001$ ).

### AF with cardiac disease vs AF with no cardiac disease

The relationship between AF and in-hospital mortality was also examined in patients with cardiac disease. PSM analysis of 568 matched pairs did not suggest a difference in risk of in-hospital mortality between patients with AF with cardiac disease and patients without cardiac disease. Finally, 48.1% of those with a history of cardiac disease and AF died in the hospital compared with 52.6% without cardiac disease history and AF (RR 0.91; 95% CI 0.81–1.03;  $P = .12$ ). The RR of in-hospital mortality for each analysis is shown in Figure 2.

### Discussion

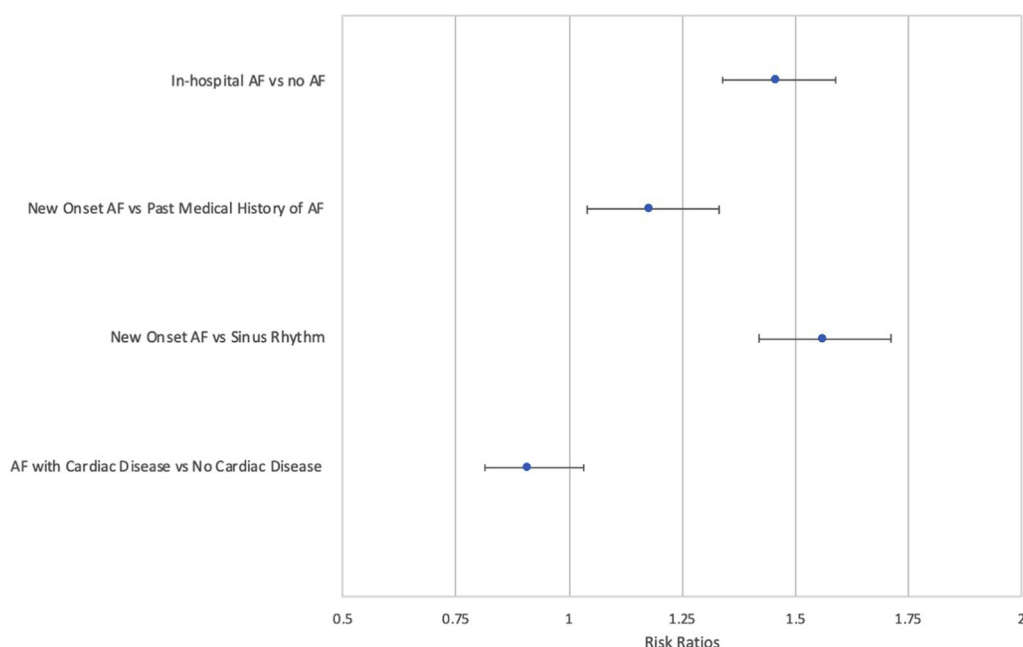
The main findings of this study in a sick cohort of patients hospitalized with COVID-19 were as follows: (1) 17.6% experienced AF, and 12.5% of patients without a history of AF were diagnosed with new-onset AF; (2) the risk of in-hospital mortality was significantly higher in patients who experienced AF (54% vs 37%); and (3) AF, particularly new-onset AF, was independently associated with in-hospital mortality.

It is estimated that 33.5 million people carry a diagnosis of AF worldwide,<sup>1,2</sup> with AF more prevalent in the elderly, men, and patients with hypertension, heart failure, coronary artery disease, valvular disease, obesity, diabetes, and renal disease.<sup>3–5</sup> Patients with the above comorbidities are also more likely to develop a more aggressive course of COVID-19 and be hospitalized.<sup>10</sup> The baseline characteristics of the entire unmatched cohort showed that patients who developed AF had a higher prevalence of the above comorbidities, were more likely to receive mechanical ventilation, and had a significantly higher in-hospital mortality.

### Incidence of AF

The prevalence and incidence of AF during hospitalization for COVID-19 is unclear; however, one should expect similarities with other systemic inflammatory response syndromes and sepsis. In the largest series of 60,209 Medicare beneficiaries with sepsis and a mean age of 80.2 years, AF was present in 25.5% of patients. In the present study, 17.6% of patients experienced AF, which is particularly high, considering that this cohort was much younger and included patients treated in a non-intensive care unit (ICU) setting.<sup>11</sup> In a different series of 49,082 patients (mean age 69 years; 48% women) with severe sepsis, AF was newly diagnosed in 5.9% of patients.<sup>12</sup> Bhatla et al<sup>13</sup> reported a 3.5% incidence of AF in 700 patients (mean age  $50 \pm 18$  years) hospitalized with COVID-19, of whom 79 (11.2%) were in an ICU setting. This is in contrast to the much higher 11.6% of new-onset AF in this study. In addition to the much greater size of the present cohort, differences are most likely due to the stricter admission criteria mandated by the much larger magnitude of the epidemic surge in New York compared with other regions, leading to hospitalization of patients only with advanced or aggressive presentation of COVID-19. The high proportion of patients requiring





**Figure 2** Relative risk ratios of in-hospital mortality. The plot provides risk ratios along with corresponding 95% confidence intervals for 4 separate analyses. Each risk ratio should be interpreted independently and not directly compared across all 4. AF = atrial fibrillation.

mechanical ventilation, the readmission rate of 15.7%, and the high mortality rate are indicative of the effort to preserve hospital beds for the sickest population.

### AF as a marker of in-hospital mortality

AF is previously described as a risk factor for increased all-cause mortality.<sup>14–17</sup> In 3100 patients hospitalized with sepsis, AF was associated with a 1.45 RR increase in mortality.<sup>18</sup> A retrospective study of 3,240,083 patients showed that patients with severe sepsis who experienced AF were more likely to die (odds ratio 1.19; 95% CI 1.14–1.24).<sup>19</sup> In particular, new-onset AF is an independent risk factor for mortality in patients admitted to the ICU with severe sepsis or septic shock.<sup>20</sup> For cardiac patients, AF is an independent mortality predictor for patients presenting with myocardial infarction<sup>21</sup> or heart failure exacerbation.<sup>17</sup> The present cohort supports the notion that AF is a marker of severe systemic illness similarly to the sepsis literature. Nevertheless, the results of the strict PSM that controlled for all previously described demographic, clinical, and laboratory confounders support an independent association between COVID-19 and AF that has not been described previously. The strong association between AF and COVID-19 was most likely driven by the new AF cases, with >50% of patients with newly diagnosed AF dying, again suggesting the strong association between the development of AF and in-hospital mortality.

This study highlights the importance of using AF as a clinical and noninvasive marker of in-hospital mortality in patients hospitalized with COVID-19. To date, laboratory markers on admission, such as CRP and D-dimer, have been used clinically to identify patients with COVID-19 with a poorer prognosis. In a recent report, higher levels of

CRP and D-dimer level > 2.0 mg/L have an RR of 11.97 and 10.17, respectively, for mortality.<sup>22–24</sup> In the present study, both CRP and D-dimer did not differ between the AF and no AF groups. In addition, both biomarkers were controlled for in all PSM analyses. The RR of 1.56 for new-onset AF provides an incremental risk to the 2 inflammatory biomarkers that are currently used as mortality predictors, suggesting that the association between COVID-19 and AF might be due to mechanisms other than systemic inflammatory response.

### Potential pathogenesis of AF in COVID-19

Recently, it has been suggested that the SARS-CoV-2 virus may directly contribute to the pathogenesis of AF through attaching to pericytes, cells responsible for microvascular integrity of cardiac tissue. This results in the release of a number of growth factors, causing cardiac tissue inflammation and altering atrial cellular electrophysiology.<sup>25–27</sup> Similarly, dysregulation of cellular angiotensin-converting enzyme 2 receptors by the SARS-CoV-2 virus results in the release of angiotensin II, further contributing to AF.<sup>38–30</sup>

Understanding how AF contributes to the increased risk of in-hospital mortality is important. The present cohort is reflective of a sick population with COVID-19 admitted to the hospital at the height of the New York pandemic. The health system was flooded with the sickest patients with COVID-19, overwhelming care and rapidly depleting resources. Most patients were treated with a rate-controlled strategy. Transesophageal echocardiograms and cardioversions were discouraged because of exposure risk. The use of anticoagulation across the health system evolved rapidly during the study period. Although most patients admitted during the study period were likely to have received

some form of anticoagulation for COVID-19, the true prevalence and type of anticoagulation in this cohort, especially related to the timing of the development of AF, was not in the scope of this study.

### Limitations

The study is subject to the same limitations as other retrospective studies. Because of the nature of collecting the data from the EMR, and the decreased rigor in documentation during the pandemic, the true incidence of AF may be higher because of reporting bias. However, the NLP algorithm was created after rigorous review of a random sample of medical records by electrophysiologists and enabled a review of >24 million notes. The results are not generalizable to those with that may develop AF in the outpatient setting.

### Conclusion

AF occurred in 17.6% of patients hospitalized with COVID-19. In 12.5% of patients, there was no history of AF (new-onset AF). The occurrence of any AF, and particularly new-onset AF, was independently associated with a significantly higher in-hospital mortality.

### References

- Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; 129:837–847.
- Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013;112:1142–1147.
- Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;6:213–220.
- McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. *Circulation* 2012;126:e143–e146.
- Chiang CE, Naditch-Brule L, Murin J, et al. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol* 2012;5:632–639.
- Clarke DM, Plumb VJ, Epstein AE, et al. Haemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997;30:1039–1045.
- Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. *JAMA* 2020;324:799–801.
- Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;38:1228–1234.
- Austin PC. Comparing paired vs non-paired statistical methods of analyses when making inferences about absolute risk reductions in propensity-score matched samples. *Stat Med* 2011;30:1292–1301.
- Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19 [published online ahead of print June 25, 2020]. *SN Compr Clin Med*. <https://doi.org/10.1007/s42399-020-00363-4>.
- Walkey AJ, Greiner MA, Heckbert SR, et al. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J* 2013;165:949–955.e3.
- Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–2254.
- Bhatla A, Mayer MM, Adusumalli S, et al. COVID-19 and cardiac arrhythmias. *Heart Rhythm* 2020;17:1439–1444.
- Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–952.
- Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359–364.
- Andersson T, Magnuson A, Bryngelsson IL, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013; 34:1061–1067.
- Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez A, Peterson E, Fonarow G. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of Get With The Guidelines-Heart Failure. *Circ Heart Fail* 2012;5:191–201.
- Gandhi S, Litt D, Narula N. New-onset atrial fibrillation in sepsis is associated with increased morbidity and mortality. *Neth Heart J* 2015;23:82–88.
- Kumar GDA, Taneja A, Kumar N. Atrial fibrillation is more frequent in patients with severe sepsis and septic shock predicts a worse outcome. *Chest* 2010; 138:899.
- Wells GL, Morris PE. Incidence and prognosis of atrial fibrillation in patients with sepsis. *Cardiol Res* 2011;2:293–297.
- Lau DH, Huynh LT, Chew DP, Astley CM, Soman A, Sanders P. Prognostic impact of types of atrial fibrillation in acute coronary syndromes. *Am J Cardiol* 2009;104:1317–1323.
- Sahu BR, Kampa RK, Padhi A, Panda AK. C-reactive protein: a promising biomarker for poor prognosis in COVID-19 infection. *Clin Chim Acta* 2020; 509:91–94.
- Yamada T, Wakabayashi M, Yamaji T, et al. Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): a systematic review and meta-analysis. *Clin Chim Acta* 2020;509:235–243.
- Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care* 2020; 8:49.
- Sweeney M, Folders G. It takes two: endothelial-perivascular cell cross-talk in vascular development and disease. *Front Cardiovasc Med* 2018;5:154.
- Stark K, Eckart A, Haidari S, et al. Capillary and arteriolar pericytes attract innate leukocytes exiting through venules and 'instruct' them with pattern-recognition and motility programs. *Nat Immunol* 2013;14:41–51.
- Kennedy-Lydon T. Immune functions and properties of resident cells in the heart and cardiovascular system: pericytes. *Adv Exp Med Biol* 2017; 1003:93–103.
- Granger DN, Rodrigues SF, Yildirim A, Senchenkova EY. Microvascular responses to cardiovascular risk factors. *Microcirculation* 2010; 17:192–205.
- McKinney CA, Fattah C, Loughrey CM, Milligan G, Nicklin SA. Angiotensin-(1-7) and angiotensin-(1-9): function in cardiac and vascular remodeling. *Clin Sci (Lond)* 2014;126:815–827.
- Jansen HJ, Mackasey M, Moghtadaei M, et al. Distinct patterns of atrial electrical and structural remodeling in angiotensin II mediated atrial fibrillation. *J Mol Cell Cardiol* 2018;124:12–25.