Implications of atrial fibrillation on the clinical course and outcomes of hospitalized COVID-19 patients: results of the Cardio-COVID-Italy multicentre study

Sara Paris[1,†], Riccardo M. Inciardi [1,†], Carlo Mario Lombardi[1], Daniela Tomasoni [1], Pietro Ameri[2], Valentina Carubelli[1], Piergiuseppe Agostoni [3], Claudia Canale[2], Stefano Carugo [4], Giambattista Danzi[5], Mattia Di Pasquale[1], Filippo Sarullo[6], Maria Teresa La Rovere[7], Andrea Mortara[8], Massimo Piepoli[9,10], Italo Porto[2], Gianfranco Sinagra[11], Maurizio Volterrani[12], Massimiliano Gnecchi [13], Sergio Leonardi [13], Marco Merlo[11], Annamaria Iorio[14], Stefano Giovinazzo[2], Antonio Bellasi[15], Gregorio Zaccone[1], Rita Camporotondo[13], Francesco Catagnano[8,13], Laura Dalla Vecchia[16], Gloria Maccagni[5], Massimo Mapelli[3], Davide Margonato[8,16], Luca Monzo[17], Vincenzo Nuzzi[1], Andrea Pozzi[14], Giovanni Provenzale[4], Claudia Specchia[1], Chiara Tedino[1], Marco Guazzi[18], Michele Senni[14], and Marco Metra [1,*]

[1]Cardiology; ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Piazzale Spedali Civili, 125123 Brescia, Italy; [2]Department of Internal Medicine, IRCCS Ospedale Policlinico San Martino—IRCCS Italian Cardiovascular Network, University of Genova, Genova, Italy; [3]Division of Cardiology, Department of Clinical Sciences and Community Health, Centro Cardiologico Monzino, University of Milan, Milan, Italy; [4]Division of Cardiology, Ospedale San Paolo, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy; [5]Division of Cardiology, Ospedale Maggiore di Cremona, Cremona, Italy; [6]Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital, Palermo, Italy; [7]Istituti Clinici Scientifici Maugeri, IRCCS, Dipartimento di Cardiologia, Istituto Scientifico di Pavia, Pavia, Italy; [8]Cardiology Department, Policlinico di Monza, Monza, Italy; [9]Heart Failure Unit, G da Saliceto Hospital, AUSL Piacenza, Piacenza, Italy; [10]Institute of Life Sciences, Sant'Anna School of Advanced Studies, Pisa, Italy; [11]Department of Cardiology, Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, Trieste, Italy; [12]Department of Medical Sciences, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Pisana Rome, Rome, Italy; [13]Division of Cardiology, Dipartimento Scienze mediche e malattie infettive, Fondazione IRCCS Policlinico S. Matteo, University of Pavia, Pavia, Italy; [14]Cardiovascular Department, Cardiology Unit, Papa Giovanni XXIII Hospital-Bergamo, Piazza OMS, 1, 24127 Bergamo, Italy; [15]Innovation and Brand Reputation Unit, Papa Giovanni XXIII Hospital, Bergamo Research, Bergamo, Italy; [16]Istituti Clinici Scientifici Maugeri, IRCCS, Dipartimento di Cardiologia, Istituto Scientifico di Milan, Milan, Italy; [17]Department of Cardiology, Istituto Clinico Casal Palocco, Policlinico Casilino, Rome, Italy; and [18]Heart Failure Unit, Cardiology Department, University of Milan, IRCCS San Donato Hospital, Milan, Italy

Aims	To assess the clinical relevance of a history of atrial fibrillation (AF) in hospitalized patients with coronavirus disease 2019 (COVID-19).
Methods and results	We enrolled 696 consecutive patients (mean age 67.4 ± 13.2 years, 69.7% males) admitted for COVID-19 in 13 Italian cardiology centres between 1 March and 9 April 2020. One hundred and six patients (15%) had a history of AF and the median hospitalization length was 14 days (interquartile range 9–24). Patients with a history of AF were older and with a higher burden of cardiovascular risk factors. Compared to patients without AF, they showed a higher rate of in-hospital death (38.7% vs. 20.8%; *P* < 0.001). History of AF was associated with an increased risk of death after adjustment for clinical confounders related to COVID-19 severity and cardiovascular comorbidities,

* Corresponding author. Tel: +39 335 646 0581. *E-mail address:* metramarco@libero.it

† The first two authors contributed equally to the study.

including history of heart failure (HF) and increased plasma troponin [adjusted hazard ratio (HR): 1.73; 95% confidence interval (CI) 1.06–2.84; $P = 0.029$]. Patients with a history of AF also had more in-hospital clinical events including new-onset AF (36.8% vs. 7.9%; $P < 0.001$), acute HF (25.3% vs. 6.3%; $P < 0.001$), and multiorgan failure (13.9% vs. 5.8%; $P = 0.010$). The association between AF and worse outcome was not modified by previous or concomitant use of anticoagulants or steroid therapy (P for interaction >0.05 for both) and was not related to stroke or bleeding events.

Conclusion   Among hospitalized patients with COVID-19, a history of AF contributes to worse clinical course with a higher mortality and in-hospital events including new-onset AF, acute HF, and multiorgan failure. The mortality risk remains significant after adjustment for variables associated with COVID-19 severity and comorbidities.

What's new?

- This is the first large study assessing the clinical and prognostic meaning of pre-existing atrial fibrillation (AF) and the incidence of new-onset AF in critically ill coronavirus disease 2019 (COVID-19) patients.
- History of AF is associated with a higher rate of death and increased risk of complications during hospital stay.
- Along with other known comorbidities and COVID-19 severity parameters, AF may represent a marker of increased mortality risk, not related to stroke or bleeding events.

Introduction

The novel coronavirus disease (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is deeply influencing worldwide healthcare systems with more than 120 million affected people as of March 2021.[1]

Interstitial pneumonia and acute respiratory distress syndrome represent the most common clinical manifestations.[1] It has been also shown that the cardiovascular (CV) system is often involved and subjects with previous CV disease are at a higher risk of worse events.[2] Atrial fibrillation (AF) represents a well-known CV risk factor and cause of mortality in the general population. Nevertheless, its prevalence and clinical meaning have been less described in COVID-19 patients. Few studies showed that atrial arrhythmias may be a sign of cardiac involvement in COVID-19 disease,[3] and sinus rhythm at admission in COVID-19 patients has been shown to be associated with better prognosis compared with AF rhythm.[4] Also, new-onset AF can occur as a relevant clinical event during the in-hospital course of patients with COVID-19, but its incidence has not been well explored in large cohorts of affected patients.

The aim of our report is to evaluate the clinical and prognostic meaning of pre-existing AF and to assess the incidence of new-onset AF during the clinical course of COVID-19 in patients enrolled in the Cardio-COVID-Italy study, a multicentre retrospective, observational study.[5]

Methods

Study population

The Cardio-COVID study is a retrospective, multicentre, observational study that included consecutive patients with laboratory-confirmed COVID-19 admitted to 13 Cardiology Units in Italy from 1 March to 9 April 2020. All patients underwent diagnosis of COVID-19 by the amplification of SARS-CoV-2 RNA by real-time reverse transcriptase–polymerase chain reaction of pharyngeal swabs or lower respiratory tract aspirates. The study complied with the Declaration of Helsinki and was approved by the ethical committee of Spedali Civili di Brescia, Brescia, Italy (no. NP 4105) and of each recruiting centre. Informed consent was obtained from all patients who could give it. Patients were deidentified (anonymized) for data analysis.

Data collection

Patients' data included demographics, medical history, in-hospital clinical course, treatment, and in-hospital outcomes and were extracted from the hospital medical records. History of AF was assessed through the collection of anamnestic data. Atrial fibrillation subtypes (paroxysmal, persistent, and permanent) were defined according to the recent AF guidelines.[6] Electrocardiogram (ECG) was recorded at admission during the in-hospital stay and at discharge. Electrocardiogram analysis was performed by experienced cardiologists according to standard definitions and diagnostic criteria. New-onset AF was defined by the occurrence of AF at ECG during the in-hospital stay and not present at admission. Laboratory exams were collected at the time of hospitalization and during the hospital stay upon clinical indications. The Chronic Kidney Disease-Epidemiology Collaboration equation was used to estimate glomerular filtration rate (eGFR). Chest X-ray and echocardiography were performed when clinically indicated.

Statistical analysis

Patients were stratified based on their history of AF. Differences according to the new-onset AF are analysed in Supplementary material online. Normally distributed continuous variables were reported as means and standard deviations, skewed variables as medians and interquartile ranges, and dichotomous variables as counts and percentages.

Comparisons between groups were made using Student's *t*-test for means, Wilcoxon test for medians, and χ^2 test for proportions. Survival curves were obtained using the Kaplan–Meier analysis and compared among patients with vs. without history of AF using the log-rank test. Cox regression analysis was performed to identify the variables that were

significantly associated with an increased risk of death (Supplementary material online, Table S1). The number of variables entered into the Cox regression model was limited according to the number of events, based on the principle of not having more than 1 variable every 10 events. The variables selected for the final model had to be clinically significant and associated with an increased risk of death at univariate analysis (P-value ≤ 0.01). The variables entered into the Cox regression model were demographic and clinical variables, including age, sex, HF, coronary artery disease, AF, hypertension, previous treatment with oral anticoagulant, and variables measured at the time of admission, including creatinine clearance, oxygen saturation, serum troponin, C-reactive protein, red blood count, and haemoglobin.

A two-tailed P-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA statistical software version 9.4 (StataCorp LLC, College Station, TX, USA).

Results

Clinical characteristics

The study included 696 consecutive patients, mean age was 67.4 ± 13.2 years, 69.7% were males. One hundred and six patients (15%) had a history of AF. Demographic and clinical characteristics of the patients stratified by history of AF are shown in *Table 1*. Of these, 36 (36%) suffered from paroxysmal AF, 14 (14%) from persistent AF, and 49 (49%) from permanent AF. Compared with controls, patients with a history of AF were older, with a higher prevalence of heart failure (HF) and CV risk factors (such as hypertension, dyslipidaemia, diabetes) and ischaemic heart disease. Also, other comorbidities, including chronic kidney disease and chronic obstructive pulmonary disease, were more frequent in those with a history of AF. As expected, patients with a history of AF were more likely to receive oral anticoagulant treatment (both warfarin and direct oral anticoagulants, DOACs) and treatment with ACEi/ARBs, mineralocorticoid receptor antagonists, beta-blockers, and statins. At admission, patients with a history of AF showed higher body temperature and slightly lower systolic and diastolic blood pressure.

Laboratory findings are summarized in *Table 1*. Patients with AF had lower haemoglobin levels, worse renal function and higher NT-proBNP plasma levels [3094 (1298–6276) vs. 211 (87.5–660) pg/mL, P < 0.001]. Serum troponin levels were more likely to be elevated among AF patients (67.0% vs. 41.1%, P < 0.001).

Patients with a history of AF also showed lower left ventricle ejection fraction (LVEF) (46.1 ± 12.6% vs. 54.2 ± 10.3%; P < 0.001), although in-hospital echocardiographic measurements were only available for 262 patients, of whom 56 in the AF group.

Data about in-hospital management and outcome are shown in *Table 2*. Patients without a history of AF were less likely to be treated with hydroxychloroquine, anti-interleukin agents (e.g. tocilizumab), and corticosteroids. Oxygen saturation was similar across the two groups. Patients with a history of AF showed higher PaO$_2$/FiO$_2$ and were less likely to be treated with non-invasive ventilation and intubation compared with the others (26.9% vs. 46.4% and 3.8% vs. 17.5%, P < 0.001 for both). Patients 'too sick' for invasive ventilatory support were more frequent in the AF group (34.3% vs. 20.2%, P = 0.002) (*Table 2*).

In-hospital mortality

Median hospitalization length of stay was 14 days (interquartile range 9–24). In-hospital death occurred in 164 patients (23.6%). Patients with a history of AF had higher mortality (38.7% vs. 20.8%, P < 0.001) (*Table 1*). Kaplan–Meier survival curves are shown in *Figure 1*. History of AF was associated with an increased risk of death at both univariate [hazard ratio (HR) 2.47, 95% confidence interval (CI) 1.73–3.53; P < 0.001] (*Table 3*) and multivariable analysis including demographic and clinical variables (adjusted HR 1.73, 95% CI 1.06–2.84; P = 0.029) (*Table 3*). The higher rate of death was not related to stroke or bleeding events (2.3% vs. 2.8%, P = 0.84 and 1.0% vs. 0.3%, P = 0.39, respectively). Similar results were observed when adding potential confounders to the main model (Supplementary material online, Table S1). The role of in-hospital treatment was evaluated in exploratory analyses. The association between history of AF and mortality was not modified by the previous or in-hospital use of anticoagulants (P for interaction = 0.91) and in-hospital steroid treatment (P for interaction = 0.98). The rate of mortality did not differ across AF subtype (36% for paroxysmal AF vs. 35% for persistent AF vs. 40% for permanent AF, P = 0.65).

In-hospital events

Patients with a history of AF were at higher risk of clinical events during hospitalization, such as new-onset AF (36.8% vs. 7.9%; P < 0.001), acute HF (25.3% vs. 6.3%; P < 0.001), multiorgan failure (13.9% vs. 5.8%; P = 0.010), and acute renal failure (21.5% vs. 13.4%; P = 0.06) (*Table 2* and *Figure 2*). New-onset AF occurred during hospitalization in 68 (12.5%) of the 542 patients in whom these data were available. Of these, 30 patients (44%) had a history of paroxysmal AF. Thirty-six (52.9%) of these events were new-onset AF in patients with no history of AF. Eighteen (26.4%) patients underwent cardioversion for haemodynamic instability. Of these, 14 were pharmacological and 4 electrical. There was no difference in terms of in-hospital systemic embolic events among patients with and without history of AF. Nevertheless, pulmonary embolism was slightly more common in patients without a history of AF (2.9% vs. 8.5%, P = 0.046) as well as for acute respiratory distress syndrome (6.7% vs. 19.2%, P = 0.004). Clinical characteristics, laboratory findings, in-hospital management, and outcome of patients who developed in-hospital AF are shown in Supplementary material online, Table S3.

Discussion

Our results show that 15% of the patients hospitalized for COVID-19 had a history of AF and this was associated with an increased risk of death and more in-hospital clinical events including new-onset AF, acute HF, and multiorgan failure. In-hospital death occurred in 38.7% of the patients with AF history vs. 20.8% of those without AF history. The association between AF and mortality remained significant after adjustment for variables associated with COVID-19 severity, such as comorbidities, previous use of anticoagulant, oxygen saturation, red blood cells count, haemoglobin, CRP, plasma troponin, and HF history. Our results highlight the prognostic relevance of a history of AF as a marker of increased risk, along with other common concomitant factors associated with an unfavourable prognostic impact.[5,7] We

Table 1 Clinical characteristics, laboratory and echocardiographic findings, in-hospital management, and outcome of the study population stratified by history of atrial fibrillation

Variables	Total (N = 696)	No history of atrial fibrillation (N = 590)	History of atrial fibrillation (N = 106)	P-value
Clinical characteristics				
Age (years)	67.4 ± 13.2	65.8 ± 13.0	75.8 ± 10.9	<0.001
Sex (male)	485 (69.7)	414 (70.2)	71 (67.0)	0.51
Body mass index (kg/m^2)	27.3 ± 5.3	27.4 ± 5.2	26.6 ± 5.8	0.21
Smoker, n (%)	160 (27.2)	133 (26.2)	27 (33.3)	0.18
Hypertension, n (%)	398 (57.2)	315 (53.4)	83 (78.3)	<0.001
Hyperdyslipidaemia, n (%)	193 (27.8)	140 (23.8)	53 (50.0)	<0.001
Diabetes, n (%)	162 (23.3)	125 (21.2)	37 (34.9)	0.002
Heart failure	93 (13.4)	51 (8.6)	42 (39.6)	<0.001
AF, n (%)	106 (15.2)	0 (0)	106 (100)	<0.001
Paroxysmal AF	–	–	36 (36)	
Persistent AF	–	–	14 (14)	
Permanent AF	–	–	49 (49)	
Coronary artery disease, n (%)	148 (21.3)	104 (17.6)	44 (41.5)	<0.001
Previous percutaneous valve implantation, n (%)	23 (3.3)	15 (2.5)	8 (7.5)	0.008
Heart transplant/LVAD, n (%)	4 (0.6)	4 (0.7)	0 0	0.40
COPD, n (%)	68 (9.8)	45 (7.6)	23 (21.7)	<0.001
CKD, n (%)	128 (18.4)	80 (13.6)	48 (45.3)	<0.001
Treatment before hospitalization				
ACE-i/ARBs/ARNI, n (%)	250 (38.2)	201 (36.3)	49 (49.0)	0.016
Mineralocorticoids, n (%)	43 (8.0)	27 (5.9)	16 (20.8)	<0.001
Beta-blockers, n (%)	249 (38.0)	185 (33.3)	64 (64.6)	<0.001
Direct oral anticoagulants, n (%)	48 (7.4)	11 (2.0)	37 (37.0)	<0.001
Warfarin, n (%)	49 (7.5)	24 (4.4)	25 (24.8)	<0.001
Statins, n (%)	181 (27.5)	131 (23.5)	50 (50.0)	<0.001
Baseline findings				
Temperature (°C)	37.3 ± 1.0	37.3 ± 1.0	36.9 ± 1.0	<0.001
Fever, n (%)	447 (64.4)	396 (67.2)	51 (48.6)	<0.001
Systolic blood pressure (mmHg)	129.7 ± 21.7	130.5 ± 21.3	126.0 ± 21.6	<0.001
Heart rate (b.p.m.)	86.7 ± 18.1	87 ± 16.7	81.6 ± 14.3	0.30
Respiratory rate ≥22, n (%)	279 (52.1)	246 (53.5)	33 (43.4)	0.10
Oxygen saturation (%)	90.4 ± 7.7	90.3 ± 7.7	91.4 ± 7.8	0.15
SOFA score ≥3, n (%)	197 (43.3)	161 (41.4)	36 (54.5)	0.046
Laboratory measurements				
PaO$_2$/FiO$_2$ (mmHg/%)	235.2 ± 131.7	228.9 ± 133.9	270.0 ± 113.5	0.007
Red blood cell count (×10^6/μL)	4.5 (4.0–4.9)	4.5 (4.1–4.9)	4.3 (3.7–4.7)	<0.001
Haemoglobin (g/dL)	13.4 (11.8–14.4)	13.5 (12.1–14.6)	12.2 (10.2–13.9)	<0.001
Haematocrit (%)	39.1 (35.5–42.8)	39.5 (36.1–42.9)	36.5 (30.9–41.3)	<0.001
White blood cell count (per μL)	6815 (5000–9330)	6730 (5000–9100)	7460 (5100–10020)	0.17
Lymphocytes count (per μL)	930 (621–1300)	944 (621–1300)	900 (670–1250)	0.58
Platelets count (×10^3/μL)	204 (156–270)	207 (155–274)	194.5 (159–251)	0.42
Creatinine (mg/dL)	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.3 (0.9–1.9)	<0.001
eGFR (CKD-EPI) (mL/min)	74 (50.1–90.4)	78.6 (57.2–92.3)	49.9 (31–64.7)	<0.001
Sodium (mEq/L)	138 (135–140)	137 (135–140)	138 (136–141)	0.022
Potassium (mEq/L)	3.9 (3.6–4.3)	3.9 (3.6–4.3)	4.0 (3.7–4.6)	0.10
CRP on admission (mg/dL)	23.7 (11.0–36.0)	24.2 (11.2–36.1)	20.9 (92.0–34.6)	0.27
Peak CRP (mg/dL)	98.8 (29.8–179.0)	100.4 (31.4–186.9)	79.0 (21.2–150.2)	0.023
Elevated troponin,[a] n (%)	276 (45.3)	209 (41.1)	67 (67.0)	<0.001
NT-proBNP (pg/mL)	304.5 (96.5–1193.0)	211 (87.5–660)	3094 (1298.0–6276.5)	<0.001
D-dimer (ng/mL)	870 (431.5–1803.5)	870 (430–1800)	870 (464–1876)	0.71

Continued

Table 1 *Continued*

Variables	Total (N = 696)	No history of atrial fibrillation (N = 590)	History of atrial fibrillation (N = 106)	P-value
Aspartate transaminase (u/L)	41 (26–63)	42 (27–64)	31 (21–63)	0.007
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (1.0–1.5)	<0.001

Values are reported as means ± standard deviations or medians (interquartile ranges).
ACE-i, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; ARNI, angiotensin re-ceptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (eGFR < 60 mL/min/m^2); CKD-EPI, chronic kidney disease epidemiol-ogy collaboration formula; CRP, C reactive protein; fever, temperature >37.5°C; eGFR, estimated glomerular filtration rate; FiO$_2$, fraction of inspired oxygen; INR, international normalized ratio; No., number of patients; NT-proBNP, N-terminal-pro-hormone brain natriuretic peptide.
^{a}Elevated troponin value was defined as above the 99% percentile of normal values.

also found that new-onset AF occurred in 12.5% of the patients and in 36 (52.9%) of them, it was the first episode of AF.

The proportion of patients hospitalized for COVID-19 with a history of AF ranged from 5% to 20% in previous reports.[8–10] In our experience, the high prevalence of AF history (15%) may be linked to the older age of our population (mean age was 67.4 ± 13.2 years) and the characteristics of our cohort with a high prevalence of cardiovascular comorbidities. From this perspective, the prognostic role of a history of AF should be interpreted in the context of other conditions contributing to the higher risk of death. Several studies suggest that the presence of pre-existing cardiovascular diseases identifies patients at higher risk of adverse COVID-19 outcomes.[11,12] It has been also shown a higher risk of development of cardiac arrhythmias following COVID-19 as well as the risk of worse clinical course in those patients who developed AF. Nevertheless, the prognostic role of AF history during COVID-19, on top of other established risk factors, has not yet been clearly described in previous reports. Only one multicentre cohort study showed higher odds of mortality among COVID-19 patients with AF history, but the study did not take into account significant confounders associated with COVID-19 severity, such as respiratory and laboratory parameters, including troponin plasma levels.[13]

Regardless of COVID-19, AF is a well-known CV risk factor in the general population associated with a high risk of mortality and CV complications.[14,15] Among patients admitted to intensive care unit, AF is an independent risk factor for weaning failure and is significantly associated with poor hospital outcome in mechanically ventilated patients, and with a higher percentage of respiratory failure due to ARDS, even in the absence of HF.[16] Our data confirm the prognostic role of AF, along with age and other well-known comorbidities, also in patients affected by COVID-19. The relationship between COVID-19 and AF seems to be bidirectional. AF may increase the incidence and severity of COVID-19 and COVID-19 may favour episodes of AF. The correlation between viral infection and onset AF is established, as well as risk factors and possible predictors. Nevertheless, our understanding of arrhythmic complications in COVID-19 is still evolving.[17]

SARS-CoV-2 uses direct binding with ACE2 to enter the host cells including type 2 pneumocytes, macrophages, cardiomyocytes, pericytes, and endothelial cells.[2] Plasma ACE2 activity is elevated in multiple conditions, including HF, hypertension, vascular disease, and AF, and is directly associated with more advanced atrial structural remodelling.[2] In this perspective, AF could increase susceptibility to SARS-CoV-2 infection, especially in case of advanced atrial disease, such as in older patients with multiple CV comorbidities. In addition, resulting systemic inflammation may overlap with the basal inflammatory state present in case of AF and may be a potential mechanism for worse outcomes.[18]

On the other hand, acute respiratory infections may represent a precipitant factor for new-onset or recurrent AF. Viral infection is associated with direct myocardial injury and inflammation, metabolic dysfunction, electrolyte abnormalities, dehydration, hypoxia, and activation of the sympathetic nervous system, all of which predispose to cardiac arrhythmia.[2]

During COVID-19 disease, especially in case of critical illness, new-onset AF can be promoted by arrhythmogenic triggers, such as prolonged hypotension, inadequate oxygen delivery, positive fluid balance, and previous vasopressor use. From this perspective, new-onset AF may represent both a marker of disease severity as well as a likely contributor to poor outcomes.

It is important to note that in our AF population, the rate of death was higher than for stroke or systemic embolic events. Our findings highlight that, as observed for the general population, among COVID-19 patients, AF increases the risk of worse outcome pointing out the need to adopt integrated multilevel prevention strategies to improve outcomes, beyond stroke prevention, as it is recommended in the AF Better Care (ABC) holistic pathway for integrated AF care, reported in the most recent ESC AF guidelines.[6]

In our report, the association between AF and worse outcome was not modified by previous or concomitant use of anticoagulant. This finding supports recent studies showing that neither antiplatelet therapy nor anticoagulant therapy before admission influenced the risk of hospital admission for COVID-19, as well as the risk of severe clinical presentation or death during hospitalization.[19] As previously shown by our group,[7] patients with AF, as well as patients with a history of HF, were less likely to be treated with corticosteroids. One possible explanation may be the prominent role of the cardiac involvement as a main cause of reduced survival and symptoms in these patients. This concept is corroborated by the slightly lower degree of COVID-19 severity at admission (higher values of PaO$_2$/FiO$_2$ ratio, lower SOFA score, and body temperature) in these patients with concomitant AF. Consistently, patients with AF were also less likely to receive antiviral therapy in this study.

Table 2 In-hospital management and outcome of the study population stratified by history of atrial fibrillation

Variables	Total (N = 696)	No history of atrial fibrillation (N = 590)	History of atrial fibrillation (N = 106)	P-value
In-hospital treatment				
Hydroxychloroquine, n (%)	580 (83.9)	500 (85.5)	80 (75.5)	0.010
Lopinavir/ritonavir, n (%)	185 (26.8)	153 (26.2)	32 (30.2)	0.39
Darunavir/ritonavir, n (%)	157 (26.8)	18 (17.0)	16 (18.0)	0.032
Tocilizumab, n (%)	80 (11.6)	76 (13)	4 (3.8)	0.006
Corticosteroids, n (%)	343 (49.6)	303 (51.8)	40 (37.7)	0.008
Antibiotics, n (%)	609 (88.1)	517 (88.4)	92 (86.8)	0.64
Heparin, n (%)	472 (73.1)	412 (75.3)	60 (60.6)	0.002
Ventilatory support[a]				
Oxygen support with FiO_2 <50%	301 (43.7)	240 (41.1)	61 (58.1)	0.001
Oxygen support with FiO_2 ≥50%	380 (55.9)	332 (57.6)	48 (46.2)	0.030
Non-invasive ventilation, n (%)	300 (43.5)	272 (46.4)	28 (26.9)	<0.001
Intubation, n (%)	103 (17.5)	102 (17.0)	4 (3.8)	<0.001
Too sick for intubation, n (%)	132 (22.7)	98 (20.2)	35 (34.3)	0.002
Outcomes				
Death, n (%)	164 (23.6)	123 (20.8)	41 (38.7)	<0.001
Cause of death				
Respiratory insufficiency	125 (67.6)	96 (68.1)	29 (65.9)	0.79
Acute MI	5 (2.7)	3 (2.1)	2 (4.5)	0.39
Pulmonary embolism	13 (7.0)	13 (9.2)	0 0	0.037
Multiorgan failure	31 (18.9)	21 (17.1)	10 (24.3)	0.97
Acute heart failure, n (%)	52 (9.4)	29 (6.3)	23 (25.3)	<0.001
Atrial fibrillation onset, n (%)	68 (12.5)	36 (7.9)	32 (36.8)	<0.001
STEMI, n (%)	11 (1.6)	10 (1.7)	1 (1.0)	0.56
NSTEMI, n (%)	17 (3.1)	11 (2.4)	6 (6.6)	0.033
Ventricular arrhythmia, n (%)	8 (1.2)	5 (0.9)	3 (2.9)	0.08
Stroke event	3 (0.4)	2 (0.3)	1 (1.0)	0.39
Bleeding	5 (2.7)	4 (2.8)	1 (2.3)	0.84
Pulmonary embolism, n (%)	52 (7.6)	49 (8.5)	3 (2.9)	0.046
Other thromboembolic events, venous or arterial, n (%)	61 (8.8)	56 (9.5)	5 (4.7)	0.11
ARDS, n (%)	100 (17.3)	94 (19.2)	6 (6.7)	0.004
Sepsis, n (%)	68 (10.1)	59 (10.3)	9 (8.7)	0.60
Acute renal failure, n (%)	72 (14.8)	55 (13.4)	17 (21.5)	0.06
Multiorgan failure, n (%)	34 (7.1)	23 (5.8)	11 (13.9)	0.010

Values are reported as means ± standard deviations or medians (interquartile ranges).
FiO_2, fraction of inspired oxygen; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PaO_2, oxygen partial pressure at arterial gas analysis; STEMI, ST-elevation myocardial infarction.
[a]Patients could receive more than one ventilatory support during hospitalization.

Proper pharmacological management of patients with COVID-19 infection and AF is required. Recommendations have recently been provided for the pharmacological management of patients with COVID-19 and concomitant AF, which include the effects and potential pro-arrhythmic interactions between antiarrhythmic drug, anticoagulants, and emerging COVID-19 pharmacotherapies. General recommendations for AF management in patients with COVID-19 are summarized in Table 4.[20,21]

Limitations

This study had some limitations. Our population was characterized by a relatively old age with a significant burden of CV comorbidities. Since residual confounding could not be excluded, the prognostic role of history AF should be interpreted accordingly. Nevertheless, the multivariable model used accounted for relevant clinical and demographic confounders. Not all patients were subjected to continuous electrocardiographic monitoring and the
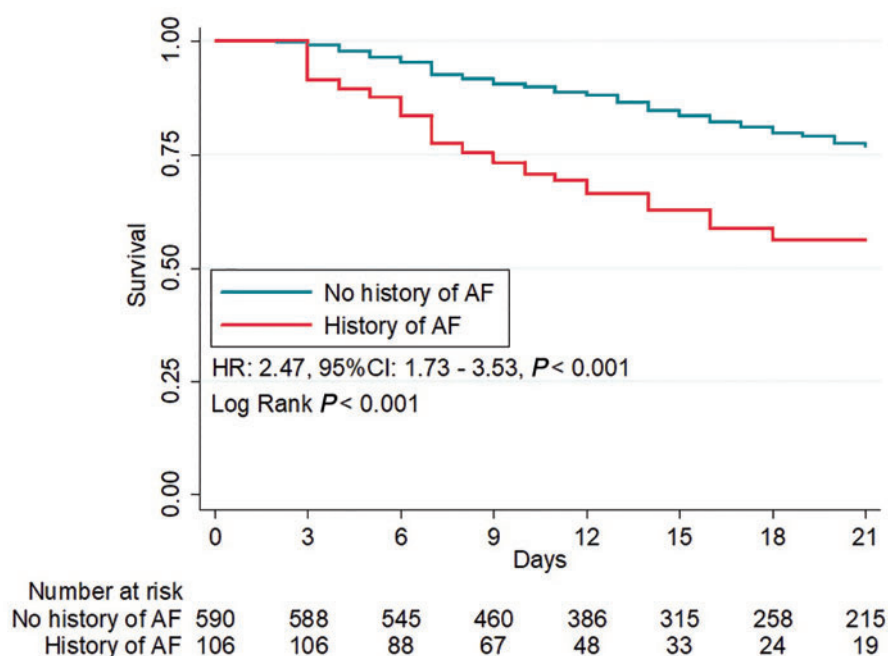
Figure 1 Kaplan–Meier survival curves stratified by history of AF. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

Table 3 Univariate and multivariable Cox regression model for in-hospital death

	Level/units	Univariable		Multivariable	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Clinical characteristics					
Age	+5 years	1.06 (1.05–1.08)	<0.001	1.28 (1.14–1.43)	<0.001
Gender	Male vs. female	1.32 (0.92–1.90)	0.125	2.12 (1.26–3.56)	0.005
Heart failure	Yes vs. no	2.44 (1.70–3.52)	<0.001	1.78 (1.05–3.03)	0.033
Hypertension	Yes vs. no	1.91 (1.37–2.67)	<0.001	1.01 (0.64–1.60)	0.96
Atrial fibrillation	Yes vs. no	2.47 (1.73–3.53)	<0.001	1.73 (1.06–2.84)	0.029
Ischaemic cardiomyopahty	Yes vs. no	2.28 (1.65–3.16)	<0.001	1.02 (0.63–1.66)	0.922
Treatment before hospitalization					
Anticoagulation therapy	Yes vs. no	1.43 (0.94–2.17)	0.091	0.73 (0.43–1.24)	0.250
Baseline findings					
Oxygen saturation	+5%	0.96 (0.95–0.98)	<0.001	0.96 (0.94–0.98)	<0.001
Laboratory measurements					
Red blood cell count	$+1 \times 10^6/\mu L$	0.68 (0.54–0.86)	0.001	0.51 (0.28–0.92)	0.025
Haemoglobin	+1 g/dL	0.92 (0.85–0.98)	0.018	1.15 (0.94–1.41)	0.183
eGFR (CKD-EPI)	+10 mL/min	1.13 (1.05–1.21)	0.001	0.99 (0.99–1.00)	0.280
CRP peak	+1 mg/dL	1.00 (1.00–1.00)	<0.001	1.37 (1.09–1.72)	0.007
Troponin	Elevated vs. normal	3.19 (2.24–4.55)	<0.001	1.58 (1.02–2.45)	0.040

CKD-EPI, chronic kidney disease epidemiology collaboration formula; CRP, C reactive protein; eGFR, estimated glomerular filtration rate.

diagnosis of AF was carried out through ECG. Therefore, the occurrence of paroxysmal AF may have been underdiagnosed. Echocardiographic data were available for a small proportion of subjects, limiting the possibility to assess the association between AF, death, and cardiac structure and function. Finally, our analysis lacks post-discharge follow-up data, thus we could not assess the occurrence of AF after hospitalization.
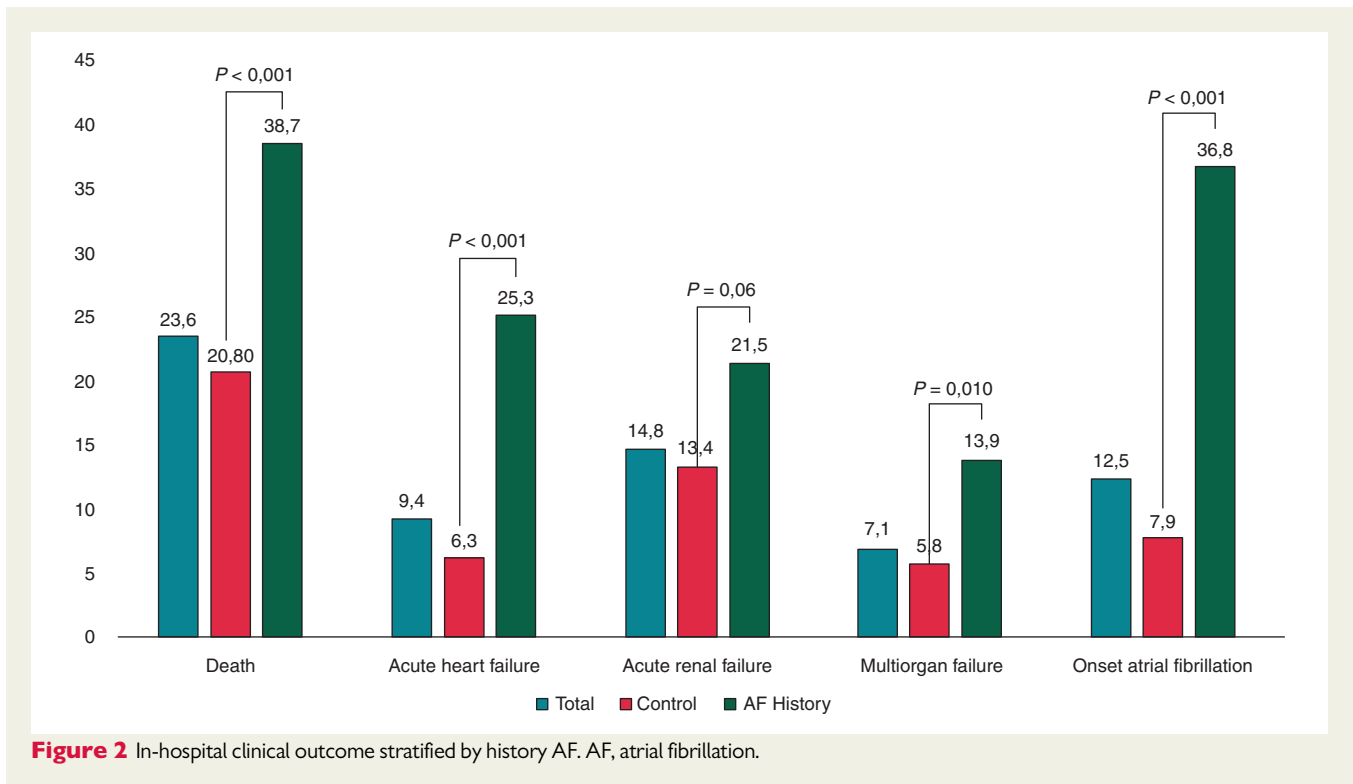
Figure 2 In-hospital clinical outcome stratified by history AF. AF, atrial fibrillation.

Table 4   General recommendations for AF management in patients with COVID-19

General recommendations

ECG is recommended in all patients with suspected COVID-19 infection at admission.

Is recommended to perform an ECG before the initiation of antiarrhythmic drug and ECG monitoring after initiation.

QT interval should be monitored in patients treated with class IA, IC, and III AADs, hydroxychloroquine/chloroquine, macrolide, fingolimod, and/or lopinavir/ritonavir.

Drug management

Classes IA and IC are contraindicated in COVID-19 patients on fingolimod.

Beta-blockers are recommended as a first-line therapy to rate control.

Calcium channel blockers are not recommended in acute myocarditis patients with decompensated HF.

Digoxin can be used in CHF or combination with β-blockers or calcium channel blockers for rate control.

Heparin is the anticoagulant of choice in hospitalized COVID-19 patients with AF, especially if patients are being treated with lopinavir/ritonavir.

Direct oral anticoagulants can be used in AF patients with COVID-19 after discharge without lopinavir/ritonavir.

Amiodarone can be used for rhythm and rate control in critically ill COVID-19 patients with CHF. Close monitoring with caution is recommended with concurrent lopinavir/ritonavir use. It is not recommended in patients undergoing treatment with fingolimod.

Flecainide or propafenone is a good option for pharmacological cardioversion in patients with no structural heart disease or coronary artery disease who are on fingolimod.

Ibutilide, flecainide, propafenone can be used for cardioversion in patients not treated with fingolimod and without structural heart disease or coronary artery disease.

AADs, anti arrhythmic drugs; AF, atrial fibrillation; CHF, chronic heart failure; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; HF, heart failure.
Modified from Ref.[20]

Conclusions

History of AF is a frequent comorbidity in patients hospitalized for COVID-19. It significantly contributes to worse clinical course with a higher mortality and in-hospital events, on top of other variables related with AF and COVID-19 severity. Atrial fibrillation history and careful electrocardiogram monitoring may be useful to stratify high-risk COVID-19 patients. Atrial fibrillation is an important risk factor to improve risk modelling of adults with COVID-19 and an optimal management of AF is necessary to potentially improve the outcomes.

Supplementary material

Supplementary material is available at *Europace* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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