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RESEARCH LETTER

Contribution of Atrial Fibrillation to In-Hospital Mortality in Patients With COVID-19

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Atrial fibrillation (AF) shares with coronavirus infective disease-19 (COVID-19) a higher prevalence of older age, cardiovascular risk factors, and comorbidities.[1–3] Among patients with COVID-19, a history of AF is reported in ≈20% of cases,[4] and new-onset AF represents a common complication, especially in those with a more severe disease.[1–3] We specifically investigated the prognostic role of AF on in-hospital outcome in consecutive patients admitted for COVID-19 in 3 Italian Institutions (Hospitals of Novara, Vercelli, and Chieti).

We retrospectively included consecutive patients aged ≥18 years hospitalized for COVID-19 from February to May 2020. The study protocol was approved by the institutional ethical committee (Institutional Review Board code CE 97/20), and patients gave informed consent to participate. All patients received a 12-lead ECG on admission. Additional electrocardiograms were performed every 48 hours in patients receiving QT-interval prolonging drugs (>90% of the whole population) or when clinically indicated. Patients were divided according to presence (either historical or new-onset) or absence of AF during the hospitalization for COVID-19. Historical AF was defined as a past medical history of AF.

Primary end point was in-hospital all-cause mortality in patients with versus those without AF and in patients with different AF subtypes (historical and new-onset) versus those without AF. The following end points were also evaluated during in-hospital stay: cardiovascular mortality and severe acute respiratory distress syndrome. Logistic regression models were used to estimate the independent association between AF and study end points, including demographic factors, comorbidities, laboratory findings, and in-hospital treatments.

A total of 637 patients were enrolled; 503 (79%) patients had no AF, and 134 (21%) had in-hospital AF (historical in 79 patients and new-onset in 55). Compared with patients without AF, those with AF were older and presented a higher prevalence of female sex, arterial hypertension, diabetes, cardiomyopathy, peripheral artery disease, chronic kidney disease, and chronic obstructive pulmonary disease. White blood cell count and C-reactive protein were increased and PaO_2/FiO_2 was reduced in the subset with new-onset versus historical AF.

In-hospital mortality was higher in patients with AF (44.4% versus 22.1% in those without, P=0.001); 30-day estimated survival rates by Kaplan-Meier method were 39.6% (95% CI, 27.8%–50.8%) versus 59.4% (51.4%–66.5%), respectively (log-rank P<0.001; Figure [A]). The incidence of cardiovascular death and severe acute respiratory distress syndrome during the hospitalization was also increased in the AF group (10.3% versus 5.2%, P=0.039; 37.8% versus 24.5%, P=0.042; respectively). At logistic regression analysis, AF (historical and new-onset) was significantly associated with higher risk of all-cause death (odds ratio [OR], 2.44 [95% CI, 1.18–5.07]; P=0.016); other independent predictors of

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†A list of all COVID-UPO Clinical Team members is given in the Appendix.

For Sources of Funding and Disclosures, see page 214.

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
COVID-19	coronavirus infective disease-19
OR	odds ratio

mortality were older age (OR, 1.07 [95% CI, 1.04–1.1]; *P*=0.001), history of cancer (OR, 2.19 [95% CI, 1.06–4.52]; *P*=0.034), and increased neutrophils count (OR, 1.06 [95% CI, 1.02–1.09]; *P*=0.001). Cardiovascular death (OR, 3.2 [1.2–9.5]; *P*=0.03) and in-hospital development of severe acute respiratory distress syndrome (OR, 1.96 [95% CI, 1.07–3.6]; *P*=0.03) were also independently associated with AF.

A difference in absolute increase of in-hospital mortality was observed comparing patient with AF versus without AF across different CHA_2DS_2-VASc score strata, when available: CHA_2DS_2-VASc 0 to 1 (N=156): 33.3% versus 6.2%, 27.1% absolute increase; CHA_2DS_2-VASc 2 to 3 (N=171): 59.3% versus 24.3%, 35.0% absolute increase; CHA_2DS_2-VASc >3 (N=285): 41.1% versus 32.3%, 8.8% absolute increase (*P* for interaction 0.02).

Patients with new-onset AF showed an increased incidence of in-hospital death (49.1% versus 36.7%), cardiovascular mortality (14.6% versus 5.1%), and severe acute respiratory distress syndrome (49.1% versus 29.7%) compared with those with historical AF. The 30-day estimated survival rates were 44.3% (95% CI, 27.7%–59.6%) in patients with historical AF (*P*=0.007 versus no AF) and 30.8% (17.4%–45.2%) in those with new-onset AF (*P*<0.001 versus no AF; Figure [B]). Using patients without AF as reference, logistic regression analysis indicated a significant increase in the risk of all-cause death in those with new-onset AF (OR, 3.34 [95% CI, 1.54–7.25]; *P*=0.002); the increase was not significant in patients with historical AF (OR, 1.26 [95% CI, 0.58–2.74]; *P*=0.55).

This study indicates that AF, especially new-onset, is an independent predictor of in-hospital all-cause mortality, cardiovascular death, and more severe clinical pattern in patients admitted for COVID-19. Given the risk of residual confounding, such association does not prove causation, as AF can be only a risk marker. Nevertheless, multiple adjustments for potential confounders and the finding that in-hospital AF was associated with lower survival mainly in patients with low or intermediate CHA_2DS_2-VASc score (ie, with fewer comorbidities) support that AF might, at least in part, directly impact mortality. Furthermore, patients with new-onset AF had a more severe COVID-19 presentation. This supports that new-onset AF is related to the degree of inflammatory and hypoxemic viral insult, and may further enhance the hypercoagulable state, endothelial dysfunction, and oxidative stress of COVID-19 patients, with consequent worsening in prognosis. The authors will make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results.

ARTICLE INFORMATION

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Disclosures

None.

APPENDIX

The following investigators also participated the COVID-UPO Clinical Team: Emanuele Albano: Umberto Dianzani, Gianluca Gaidano, Alessandra Gennari, Carla Gramaglia, Martina Solli, Ailia Giubertoni, Alessia Veia, Carlo Cisari, Paolo Amedeo Tillio, Paolo Aluffi Valletti, Francesco Barone Adesi, Michela Barini, Daniela Ferrante, Simona De Vecchi, Matteo Santagostino, Antonio Acquaviva, Elisa Calzaducca, Francesco Giuseppe Casciaro, Federico Ceruti, Micol Giulia Cittone, Davide Di Benedetto, Ileana Gagliardi, Greta Maria Giacomini, Irene Cecilia Landi, Raffaella Landi, Giulia Francesca Manfredi, Anita Rebecca Pedrinelli, Cristina Rigamonti, Eleonora Rizzi, Carlo Smirne, Veronica Vassia, Roberto Arioli, Pietro Danna, Zeno Falaschi, Alessio Paschè, Ilaria Percivale, Domenico Zagaria, Michela Beltrame, Matteo Bertoli, Alessandra Galbiati, Clara Ada Gardino, Maria Luisa Gastaldello, Valentina Giai Via, Francesca Giolitti, Ilaria Inserra, Emanuela Labella, Ilaria Nerici, Laura Cristina Gironi, Edoardo Cammarata, Elia Esposto, Vanessa Tarantino, Elisa Zavattaro, Francesca Zottarelli, Tommaso Daffara, Alice Ferrero, Ilaria Leone, Alessandro Nuzzo, Giulia Baldon, Sofia Battistini, Emilio Chirico, Luca Lorenzini, Maria Martelli, Emanuela Barbero, Paolo Boffano, Matteo Brucoli, Massimiliano Garzaro, Alberto Pau, Stephanie Bertolin, Letizia Marzari, Gianluca Avino, Massimo Saraceno, Umberto Morosini, Alessio Baricich, Marco Invernizzi, Silvia Gallo, Claudia Montabone, Samuel Alberto Padelli, Lucio Boglione, Filippo Patrucco, Luigia Salamina, Francesca Baorda, Eleonora Croce, Irene Giacone.

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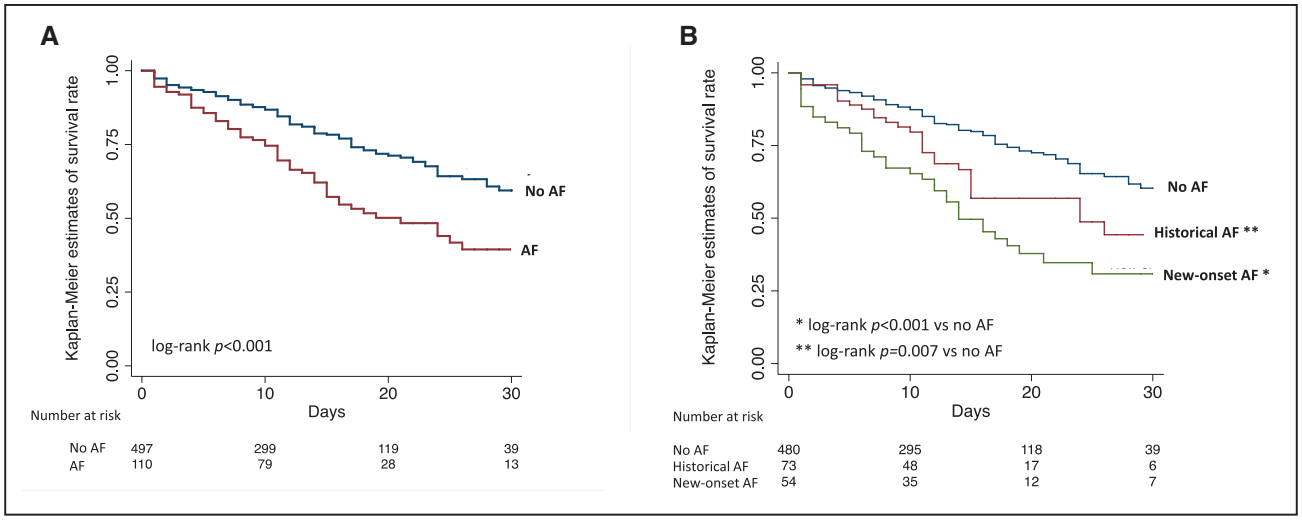

Figure. Kaplan-Meier curves at 30 days.
Estimates of survival stratified by presence/absence of atrial fibrillation (AF; **A**) and by AF subtypes (**B**) are illustrated.