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.

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Letter to the Editor

Pre-admission atrial fibrillation in COVID-19 patients: Prevalence and clinical impact

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic human coronavirus recently recognized as the cause of the coronavirus disease 2019 (COVID-19). Italy is one of the hardest-hit countries by COVID-19, with more than 414,000 laboratory-confirmed cases by October 18, 2020 [1]. Atrial fibrillation (AF) represents a frequent comorbidity and may complicate the clinical course of COVID-19 patients during the hospitalization [2]. However, little is still known about the prognostic impact of pre-existent AF in patients with COVID-19. This multicenter cohort study aimed to evaluate whether the history of AF is associated with the risk to develop severe forms of COVID-19 and in-hospital mortality.

All consecutive patients with laboratory-confirmed COVID-19 admitted to the emergency department of ten Italian Hospitals from March 15th to April 15th, 2020, were included in the present study. The medical history, physical examination, electrocardiographic and laboratory data, and pharmacological therapy have been collected. The study population has been dichotomized into two groups according to the pre-existence or not of AF, as comorbidity. The study outcome measures included acute respiratory distress syndrome (ARDS), both at admission or developed during the hospitalization, and in-hospital mortality. ARDS was defined based on PaO_2/FIO_2 values and clinical criteria according to the Berlin definition [3]. The study outcomes were assessed by the local investigating centers. The institutional ethics committees approved the study.

The distribution of continuous data was tested with the Kolmogorov–Smirnov and the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD), whereas non-normal distributed ones as median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. Continuous normally-distributed variables were compared by using the Student *t*-test; differences between non-normally distributed variables were tested with the Mann-Whitney U test. Categorical variables were compared with the chi-square test, or Fisher exact test, when appropriate. The unadjusted and adjusted risk ratios (RR) for the outcomes of interest were calculated using logistic regression models and presented as RR with their 95% confidence intervals (CI). We used propensity score weighting to account for potential selection bias in treatment assignment between the two study groups (average treatment effect weights). The propensity score model was developed incorporating all pre-procedural covariates potentially related to the outcome and/or treatment decision regardless of their statistical significance or collinearity with other variables included in the model. The following baseline covariates were included in the model: age, smoke, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, coronary artery disease (CAD), heart failure, obesity, dyslipidemia, stroke, and chronic kidney disease (CKD). After weighting, standardized mean differences were calculated to assess the balance for all covariates included in the propensity score model; values higher than 0.10 were considered statistically significant for differences among groups. For all tests, a p-value <0.05 was considered statistically significant. The analysis was performed by using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

The study included 467 consecutive hospitalized patients with COVID-19. The mean age was 66.9 ± 14.6 years; 294 (63%) were males. The median follow-up was 28 days (IQR: 12–45). Pre-admission AF was reported in 122 cases (25.1%); of them, 12 (2.6%) were paroxysmal, 57 (12.2%) were persistent, and 53 (11.3%) were permanent forms. Patients with AF history were older than those without (71.3 ± 12.4 vs 65.3 ± 15.0 years; $P<0.001$) and were more frequently treated with oral anticoagulants (OACs) (40.9% vs 11.0%; $P<0.001$). The low percentage of OACs therapy among AF patients was related to the general practitioners' habit of switching OACs to low molecular weight heparin before the hospitalization, as part of empirical COVID-19 treatments. AF patients continued the pre-admission anticoagulant drug and dosing regimen during the hospitalization.

OACs therapy was reported in 11.0% of patients without history of AF, due to prosthetic heart valve (n: 22), previous venous thromboembolic events (n: 11), or hematological disorders (n: 5). No other difference was found in terms of comorbidities and/or pharmacological treatment, except for the history of stroke, which was prevalent in AF group (13.9% vs 7.2%; $P = 0.042$). ARDS was reported in 124 cases (26.5%) at admission to the emergency department, and in 169 cases (36.2%) during the hospitalization. In-hospital mortality occurred in 107 cases (22.9%). Fig. 1 shows the proportion of any ARDS, ARDS at admission, ARDS during the hospitalization, and mortality between the study groups. At propensity score weighted logistic regression model, history of AF was significantly associated with an increased risk of any ARDS (RR: 1.38; $P = 0.021$); a milder association, not statistically significant, was observed for the risk of ARDS during the hospitalization (RR: 1.78; $P = 0.074$). We found no statistical association between pre-existent AF and in-hospital mortality.

This study showed that pre-admission AF was present in about 25% of the overall population, confirming that history of AF is frequently reported in COVID-19 patients requiring hospitalization. Pre-existing AF seemed to be independently associated with the risk of ARDS, a life-threatening complication of COVID-19, more likely developed during the hospitalization. However, we found no difference in the risk of death between patients with AF vs. those without.

Despite much-emerging data about the epidemiological association between cardiovascular diseases (CVD) and COVID-19 [5], little is still known about the prevalence of AF as pre-admission comorbidity and no data are still provided about its prognostic role in infected patients [4, 6–8].

A recent Italian study including 99 patients hospitalized for COVID-

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19 in Northern Italy, reported an AF prevalence of 19%, which increased to 36% in those with other cardiovascular diseases, and to 42% among those who did not survive [4]. In a small report including 35 geriatric patients with COVID-19, the AF history was present in 75% of the study population [6]. According to the COVID-19 Task Force of the Italian National Institute of Health, 24.5% of 355 non-surviving COVID-19 patients (mean age 79.5 years, 70% men) showed AF before the SARS-CoV-2 infection [7]. Moreover, data provided by the New York State Department of Health reported that AF occupies the seventh position among COVID-19 comorbidities [8].

Whether AF should be considered a condition predisposing to a worse outcome in COVID-19 patients is still debated. In the present analysis, the pre-existing AF influenced the clinical outcome of COVID-19 patients in terms of ARDS development, particularly during the hospitalization, suggesting that AF should be considered a red flag for the risk of worsening respiratory disease. A possible explanation linking the pre-existing AF and the ARDS incidence in the setting of COVID-19 might be the increased ACE2 expression in individuals with AF, which may promote both the cell entry mechanisms of the SARS-CoV-2 and the inflammatory host response [9]. From this perspective, AF may be the phenotypic expression of underlying inflammatory substrate favoring, and then amplified by, COVID-19 and leading to worse respiratory impairment. In the present analysis, the pre-existing AF did not impact on in-hospital mortality. This result was consistent with previous findings from a cohort study including COVID-19 patients admitted to the intensive care unit [10].

The present study has several limitations, including the retrospective nature of the analysis and the relatively small number of patients enrolled. Due to the multicentre study design, we included subjects from different wards, with heterogeneous clinical characteristics and treated according to the local protocols. The inclusion of patients from different centers throughout the Italian territory, however, may contribute to the generalizability of our results. Although we found a higher rate of death in patients with previous history of AF vs. those without, there was no statistical association at propensity score weight analysis, probably due to the limited power of our study. Larger multicenter prospective studies are required to confirm our preliminary findings.

In conclusion, AF is a frequent pre-existing comorbidity in hospitalized patients with COVID-19 and seems to be independently associated with the risk of ARDS during hospitalization, albeit in absence of a significant effect on the risk of mortality. AF patients with COVID-19 should be considered more vulnerable and at a higher risk of worsening respiratory disease, and need a close clinical monitoring during the in-hospital course.

Declaration of Competing Interest

No conflict of interest or any financial support to declare

Appendix

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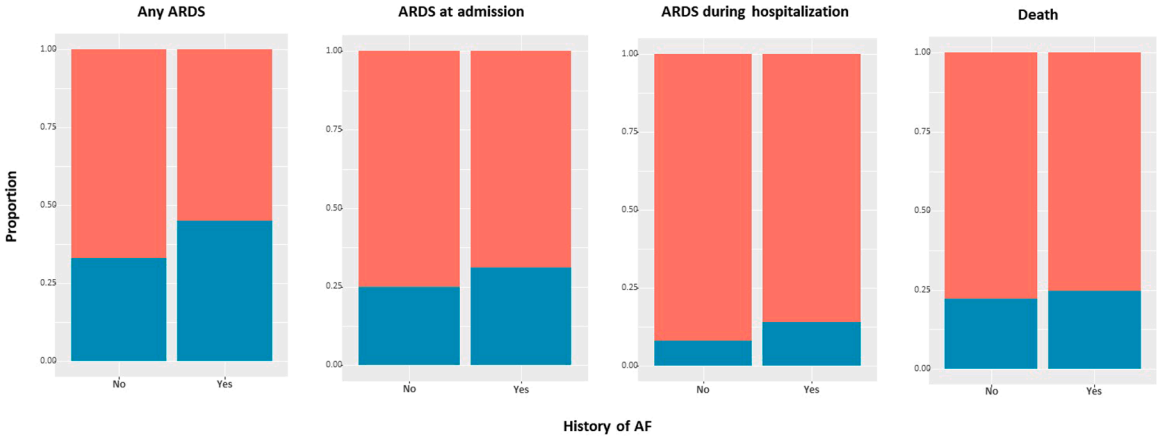

	Unweighted				Weighted			
	RR	LCI	UCI	*P value*	RR	LCI	UCI	*P value*
Any ARDS	1.41	1.11	1.71	*0.006*	1.38	1.05	1.70	*0.021*
ARDS at admission	1.34	0.97	1.76	*0.071*	1.25	0.87	1.70	*0.212*
ARDS during hospitalization	1.64	0.89	2.79	*0.098*	1.78	0.95	3.12	*0.074*
Death	1.11	0.75	1.55	*0.578*	0.94	0.61	1.37	*0.754*

Fig. 1. Proportion of any ARDS, ARDS at admission, ARDS during hospitalization and death between COVID-19 patients with vs. without history of AF (upper panel). Unweighted and weighted effect of AF history on the risk of any ARDS, ARDS at admission, ARDS during hospitalization, death (lower panel). Risk ratios (RR); Lower confidence interval (LCI); Upper confidence interval (UCI) and P values are represented.

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