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

Protective role of chronic treatment with direct oral anticoagulants in elderly patients affected by interstitial pneumonia in COVID-19 era

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ACEIs, angiotensin-converting enzyme;
ARBs, angiotensin II receptor blockers;
BMI body mass index;
COVID-19, coronavirus disease 2019;
DAPT, dual antiplatelet therapy;
DOAC, direct oral anticoagulants;
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Since December 2019, coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health emergency [1]. Elderly patients affected by chronic heart disease showed a high mortality risk in the setting of COVID-19 interstitial pneumonia [2,3]. This study aimed to assess if pharmacological cardio-active treatment reduce mortality risk in the setting of COVID-19 interstitial pneumonia.

We retrospectively enrolled elderly patients affected by COVID-19 interstitial pneumonia between February 25, 2020, and April 20, 2020. All the patients were affected by chronic heart disease (CHD) and they were followed in the divisional outpatient clinic of the Cardiology Unit of the Policlinico of Modena Hospital. The follow-up ended on May 5, 2020. The only endpoint of the study was all-cause mortality. This study was approved by the local Ethical Committee (protocol number AOU 0012597).

Continuous variables were expressed as mean ± one SD or median (range) values; and categorical data as percentages or proportions. All dichotomous variables were compared for the study outcome utilizing the $\chi 2$ test; and continuous variables using analysis of variance or Mann-Whitney U test, as appropriate. Survival probabilities were estimated with the Kaplan-Meier method and survival curves were plotted and compared between groups using the log-rank test. Multivariate Cox regression model was utilized to determine the independent risk factors for mortality. $P < 0.05$ was statistically significant.

The entire population counted 70 patients, aged > 70 years (median age: 79 years; range: 70–92), with known CHD and a diagnosis of SARS-Cov-2 infection confirmed by nasopharyngeal swab. The majority of our patients were affected by bilateral (n = 58; 82.8%) interstitial pneumonia, confirmed by chest x-ray and/or chest CT images.

During follow-up, 31 patients/70 (44.3%) died. Those who died were older, showed more cardiovascular risk factors (especially hypertension, obesity, and diabetes) and coronary or cerebro-vascular disease (**Table 1**).

The most important and strongest data from our study refers to anticoagulant chronic intake prevalence in the survivor group (48.7%; $p < 0.001$) respect to other pharmacological treatments.

A total of 26/70 patients (37.1%) were treated with direct oral anticoagulants (DOAC) which underlying indication was pulmonary embolism (n = 7; 26.9%), deep vein thrombosis (n = 6; 23%) or atrial fibrillation (n = 13; 50%). The majority of our patients received rivaroxaban (n = 11; 42.3%); followed by apixaban (n = 9; 34.6%), edoxaban (n = 4; 15.4%), and dabigatran (n = 2; 7.7%). The effect of male gender and chronic utilization of DOAC in influencing mortality were plotted in **Fig. 1**, panel A and B, respectively.

Only three parameters increased mortality risk. The strongest was age; then the male gender and the chronic DOAC intake (multivariate analysis reported in **Table 2**).

Our study demonstrated that elderly patients affected by interstitial pneumonia have a severe prognosis, with a mortality risk of around 40%. Considering the octogenarian mortality rate is 30% in Italy [4], our patients had a 1.5 - 2-fold increased risk. The higher mortality rate of our population mainly depends on the presence of a large number of cardiovascular risk factors, a finding confirmed by epidemiological studies in many countries [5]. Age represents the most powerful independent and prognostic factor in the multivariate analysis. On the contrary, hypertension, obesity, and diabetes were not significant maybe because their prevalence is often age-related. Male gender, which represents a self-determining factor, not depending on age, was significantly associated with mortality risk. The latter finding is a consolidated hallmark in Italy [6].

It is important to underline that any of the drugs chronically taken for the cardiovascular disease increased mortality risk. Following our assumption, we should not interrupt cardio-active drugs in elderly patients affected by cardiovascular disease and COVID-19.

Most cardio-active drugs did not influence mortality risk. Among these, we underline the neutral role of the renin-angiotensin system inhibitors: angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), confirmed by several studies [7,8].

The most important finding of our study is the demonstrated

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Table 1
Baseline characteristics of the study population.

parameter	Died	Survived	p
n	31 (44.3%)	39 (55.7%)	
Age, years, median (range)	85 (74–92)	73 (70–85)	< 0.0001
Risk factors for cardiovascular diseases			
Male gender	61.3% (*n* = 19)	41.0% (*n* = 16)	0.01
Hypertension	74.2% (*n* = 23)	51.3% (*n* = 20)	0.01
type II Diabetes Mellitus	32.2% (*n* = 10)	20.5% (*n* = 8)	0.03
Hypercolesterolemia	41.9% (*n* = 13)	43.6% (*n* = 17)	0.5
Obesity (BMI > 30 Kg/m^2)	22.6% (*n* = 7)	15.4% (*n* = 6)	0.04
Pre-existing chronic heart diseases			
Coronary artery disease	51.6% (*n* = 16)	46.7% (*n* = 18)	0.06
Cerebro-vascular disease	12.9% (*n* = 4)	10.2% (*n* = 4)	0.09
Aortic or Mitral valvulopathy	16.1% (*n* = 5)	15.4% (*n* = 6)	0.1
Chronic heart failure	48.4% (*n* = 15)	46.7% (*n* = 18)	0.5
Hystory of pulmonary embolism	9.7% (*n* = 3)	10.2% (*n* = 4)	0.9
Chronic obstructive pulmonary disease	16.1% (*n* = 5)	15.4% (*n* = 6)	0.3
Chronic renal failure	22.6% (*n* = 7)	20.5% (*n* = 8)	0.1
Chronically* taken drugs			
Aspirin	58.1% (*n* = 18)	61.5% (*n* = 24)	0.3
P2Y12 Inhibitors	12.9% (*n* = 4)	15.4% (*n* = 6)	0.2
DAPT	6.4% (*n* = 2)	7.7% (*n* = 3)	0.1
DOAC	22.6% (*n* = 7)	48.7% (*n* = 19)	0.001
Beta-blockers	48.4% (*n* = 15)	47.6% (*n* = 10)	0.7
Statins	38.7% (*n* = 12)	41.0% (*n* = 16)	0.9
ACEIs	58.1% (*n* = 18)	61.5% (*n* = 24)	0.6
ARBs	29.0% (*n* = 9)	30.8% (*n* = 12)	0.7
Calcium-antagonists	9.7% (*n* = 3)	10.2% (*n* = 4)	0.9

* *chronically taken drugs refer to therapies regularly taken by the patient for at least 6 months. ACEIs = angiotensin converting-enzyme inhibitors; ARBS = angiotensin II receptors blockers; BMI = body mass index; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulants.*

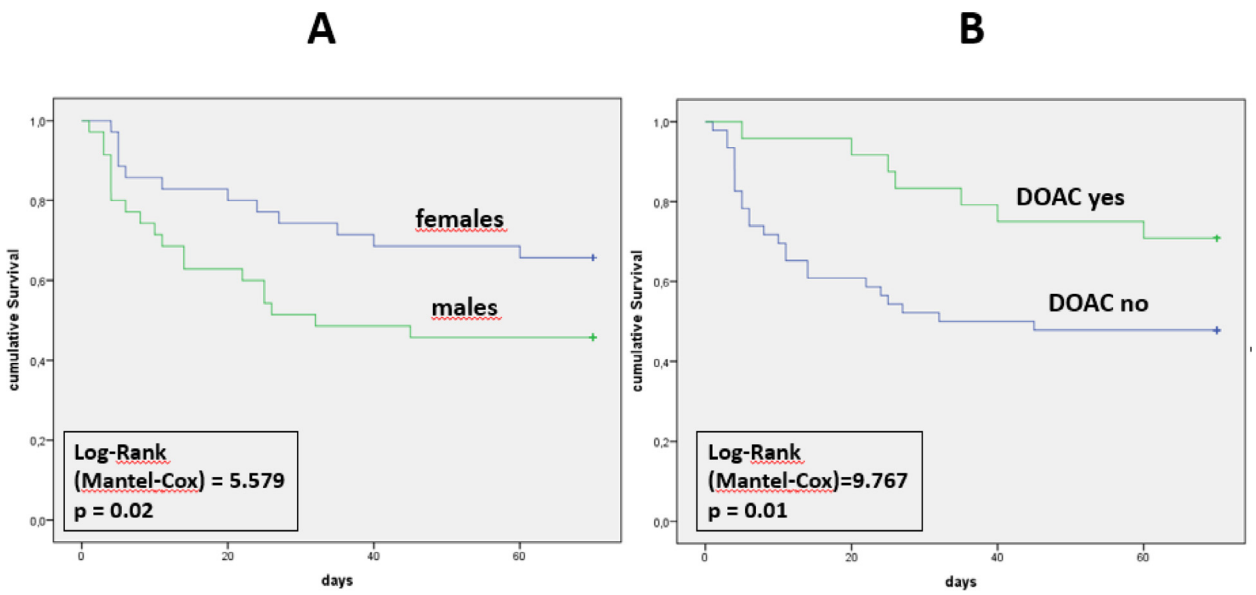

Fig. 1. Effect of gender (Panel A) and DOAC (Panel B) and on mortality.

Table 2
Results of the multivariate analysis.

parameter	T	Wald	Hazard ratio (95% CI)	p
Age	.33	30.5	1.39 (1.24 – 1.57)	< 0.0001
DOAC	−1.69	11.9	0.38 (0.17 – 0.58)	0.01
Male gender	1.57	5.7	1.49 (1.11 - 1.63)	0.02

protective role of anticoagulant drugs. Chronic DOAC intake is an independent parameter associated with a decreased mortality risk in our population. COVID-19 is mainly treated as a primary pulmonary disease, but according to the available literature, it is a more complex disease. Recent observations suggest a pivotal role of vascular damage (a sort of endothelitis, associated with thrombosis of the small pulmonary vessels) [7]. Therefore, mortality risk would not be conducted to the acute respiratory distress syndrome alone, but also the thrombosis in pulmonary and other district vessels [7,9].

According to these findings, anticoagulant treatment with a prophylactic dose of low molecular weight heparin reduced mortality in patients with COVID-19 [10]. In this scenario, the role of DOAC, the most powerful drugs that directly inhibit coagulation factors, is easy to understand. We believe that the importance of DOAC lies in the chronic intake, which is the only one capable of guaranteeing a real defense against thrombosis since the early stages of the disease, even before the onset of symptoms.

Further studies on a larger population of patients, possibly

randomized, are needed to confirm the protective role of DOAC in reducing the mortality risk in COVID-19 patients with pre-existing cardiac diseases.

CRediT authorship contribution statement

Rosario Rossi: Data curation, Formal analysis, Writing - original draft. **Francesca Coppi:** Conceptualization, Project administration, Supervision, Writing - review & editing. **Marisa Talarico:** Data curation, Formal analysis, Writing - original draft. **Giuseppe Boriani:** Conceptualization, Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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