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Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: A multicenter observational study

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ABSTRACT

Little is still known about the clinical features associated with the occurrence of acute respiratory distress syndrome (ARDS) in hospitalized patients with Coronavirus disease 2019 (COVID-19). The aim of the present study was to describe the prevalence of pre-admission antithrombotic therapies in patients with COVID-19 and to investigate the potential association between antithrombotic therapy and ARDS, as disease clinical presentation, or in-hospital mortality.

We enrolled 192 consecutive patients with laboratory-confirmed COVID-19 admitted to emergency department of five Italian hospitals. The study population was divided in two groups according to the evidence of ARDS at chest computed tomography at admission. Propensity score weighting adjusted regression analysis was performed to assess the risk ARDS at admission, and death during hospitalization, in patients treated or not with antiplatelet and anticoagulant agents.

ARDS was reported in 73 cases (38 %), who showed more likely hypertension compared to those without ARDS (57.8 % *vs* 49.6 %; P = 0.005). Thirty-five patients (18.5 %) died during the hospitalization. Not survived COVID-19 patients showed a statistically significant increased age (77 ± 8.31 *vs* 65.57 ± 8.31; *P = 0.001*), hypertension (77.1 % *vs* 53.5 %; *P = 0.018*) and coronary artery disease prevalence (28.6 % *vs* 10.2 %; *P = 0.009*). Both unadjusted and adjusted regression analyses showed no difference in the risk of ARDS at admission, or death during hospitalization, between patients treated or not with antiplatelets or anticoagulants.

Pre-admission antithrombotic therapy, both antiplatelet and anticoagulant, does not seem to show a protective effect in severe forms of COVID-19 with ARDS at presentation and rapidly evolving toward death.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel highly pathogenic human coronavirus recently recognized as the cause of the coronavirus disease 2019 (COVID-19). The outbreak sparked in Wuhan, capital city of Hubei province in China, and spread rapidly to other countries, reaching devastating pandemic proportion [1]. Italy is the one of the hardest hit countries by COVID-19, with more than 200,000 laboratory-confirmed cases by May 2, 2020 [2].

The clinical course of COVID-19 may be complicated by several life-threatening conditions including sepsis, respiratory failure, heart failure, acute kidney and cardiac injury, and septic shock [3]. Little is still known about the patient clinical characteristics predisposing to the occurrence of these life-threatening conditions.

Acute distress respiratory syndrome (ARDS) is one of the most frequent encountered complication of COVID-19, and has been associated with significantly lower patients' survival during hospitalization. Although its pathophysiology is not completely understood, the

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interplay between inflammation and coagulation seems to have a central role [4].

Whether anti-inflammatory drugs and anticoagulants might influence the onset of ARDS in COVID-19 has not yet been investigated.

The aim of this multicenter study was to evaluate the prevalence of antithrombotic therapies at admission in patients with COVID-19 and the potential association between antithrombotic therapy and ARDS, as disease clinical presentation, or in-hospital mortality.

2. Materials and methods

From a large cohort of 963 patients admitted from February 2020 to April 2020 for fever and dyspnea to Emergency Department (ED) of five Italian Hospitals (*Humanitas Hospital of Milan, Fatebenefratelli Hospital of Naples, Bergamo Hospital, Rivoli Hospital of Turin, Health Authority Bergamo East*), we enrolled 192 consecutive patients with laboratory confirmed COVID-19. The laboratory confirmation was achieved by real time quantitative reverse-transcription polymerase chain reaction (RT- PCR) assay on nose/throat swab or sputum sample positive for SARS-CoV-2.

At admission, all patients underwent medical history, physical examination and laboratory evaluation. Chest X-Ray and/or Computed Tomography (CT) scan were also performed to rule out pneumonia in one or multiple sites. The COVID-19 population was divided in two groups according to the diagnosis of isolated pneumonia or pneumonia with ARDS and according to in-hospital mortality. ARDS diagnosis was defined according to the Berlin definition [5].

The prevalence and the type of antithrombotic therapy have been compared between these groups. Discontinuation of antithrombotic therapy during hospitalization was considered as an exclusion criterion. The institutional ethics committee approved the protocol. Verbal and written informed consent for participation was provided for all patients.

2.1. Statistical analysis

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 chi-squared 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 propensity score 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 test, a p value < 0.05 was considered statistically significant. Analysis were performed by using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Clinical characteristic of the study population according to the presence or not of ARDS at admission.

	Overall (*N = 192*)	Patients without ARDS (*N = 119*)	Patients with ARDS (*N = 73*)	*P*
Males, n (%)	115 (59.9)	73 (61.3)	42 (57.5)	*0.710*
Age, mean years (SD)	67.7 (15.2)	66.1 (16.7)	70.3 (12.1)	*0.063*
Smoke, n (%)	16 (8.3)	11 (9.2)	5 (6.8)	*0.754*
Hypertension, n (%)	111 (57.8)	59 (49.6)	52 (71.2)	*0.005*
Diabetes Mellitus, n (%)	42 (21.9)	24 (20.2)	18 (24.7)	*0.582*
Dyslipidemia	23 (12.0)	12 (10.1)	11 (15.1)	*0.422*
Obesity, n (%)	26 (13.5)	16 (13.4)	10 (13.7)	*1.000*
Atrial fibrillation, n (%)	24* (12.5)	12 (10.1)	12 (16.4)	*0.286*
Heart Failure, n (%)	20 (10.4)	12 (10.1)	8 (11.0)	*1.000*
Previous Ischemic Stroke, n (%)	16 (8.3)	12 (10.1)	4 (5.5)	*0.394*
CKD, n (%)	12 (6.2)	4 (3.4)	8 (11.0)	*0.071*
CAD, n (%)	26 (13.5)	14 (11.8)	12 (16.4)	*0.483*
COPD, n (%)	26 (13.5)	19 (16.0)	7 (9.6)	*0.300*
Antiplatelet Therapy, n (%)	55 (28.6)	36 (30.3)	19 (26.0)	*0.643*
Anticoagulant Therapy, n (%)	26 (13.5)	15 (12.6)	11 (15.1)	*0.789*

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease. **13 paroxysmal, 7 persistent, 4 permanent.*

3. Results

The characteristics of the study population were reported in Table 1. The mean age was 67.7 ± 15.2 years; 115 (59.9 %) were males. ARDS was reported in 73 cases (38 %), who showed more likely hypertension compared to those without ARDS (57.8 % *vs* 49.6 %; $P = 0.005$).

55 COVID-19 patients (28.6 %) were on antiplatelet therapy at admission, among them 44 (22.9 %) were taking acetylsalicylic acid, 5 (2.6 %) P2y12 inhibitor and 6 (3.1 %) double antiplatelet therapy. They were older compared with those not taking antiplatelet drugs (73.7 ± 9.2 *vs* 65.2 ± 16.4; $P = 0.001$), and showed a higher prevalence of hypertension (78.2 % *vs* 49.6 %; $P = 0.001$), dyslipidemia (30.9 % *vs* 4.4 %; $P < 0.001$) and CAD (26.4 % *vs* 4.4 %; $P = 0.001$).

26 COVID-19 patients (13.5 %) were on anticoagulant therapy at admission, among them 18 (9.4 %) were taking non-vitamin K oral anticoagulant (NOAC) and 8 (4.2 %) was on well-controlled vitamin K oral anticoagulant (VKA). They showed older age than those not taking anticoagulant drugs (77.81 ± 9.46 *vs* 66.07 ± 15.35; $P < 0.001$), as well as higher prevalence of hypertension (80.8 % *vs* 54.2 %; $P = 0.02$), atrial fibrillation (84.6 % *vs* 1.2 %; $P < 0.001$), heart failure (30.8 % *vs* 7.2 %; $P = 0.001$), CKD (19.2 % *vs* 1.2 %; $P = 0.012$), previous stroke (23.1 % *vs* 6.0 %; $P = 0.011$) and CAD (30.8 % *vs* 10.8 %; $P = 0.009$).

Thirty-five patients (18.5 %) died during the hospitalization. Not survived COVID-19 patients showed a statistically significant increased age (77 ± 15.6 *vs* 65.6 ± 8.3; $P = 0.001$), hypertension (77.1 % *vs* 53.5 %; $P = 0.018$) and CAD prevalence (28.6 % *vs* 10.2 %; $P = 0.009$) (Table 2). Fig. 1 shows the proportion of death according to pre-admission antiplatelet and anticoagulant therapy.

In spite of the significant differences among survived and not survived COVID-19 patients in baseline characteristics, the inverse probability weighting produced a good covariate balance, with absolute standardized differences less than 10 % for all variables. Fig. 2 shows graphically how the antiplatelet and anticoagulant arms were more balanced in terms of allocation probability respect to patients were not taking anti-thrombotic drugs at admission. Unadjusted and adjusted regression models for the risk of ARDS and death according to pre-admission antithrombotic therapy was reported in Table 3. Pre-admission antithrombotic therapy with antiplatelets or anticoagulants did not result associated with increased risk of ARDS at admission and in-

Table 2
Clinical characteristics of COVID-19 patients survived and not survived during hospitalization.

	Survived Group (*N = 157*)	Not survived Group (*N = 35*)	*P*
Males, n (%)	95 (60.5)	20 (57.1)	*0.860*
Age, mean years (SD)	65.6 (15.6)	77.0 (8.3)	*< 0.001*
Hypertension, n (%)	84 (53.5)	27 (77.1)	*0.018*
Smoke, n (%)	13 (8.3)	3 (8.6)	*1.000*
Diabetes Mellitus, n (%)	33 (21.0)	9 (25.7)	*0.703*
Dyslipidemia	18 (11.5)	5 (14.3)	*0.860*
Obesity, n (%)	19 (12.1)	7 (20.0)	*0.336*
Atrial fibrillation, n (%)	20 (12.7)	4 (11.4)	*1.000*
Heart Failure, n (%)	14 (8.9)	6 (17.1)	*0.257*
Previous Ischemic Stroke, n (%)	13 (8.3)	3 (8.6)	*1.000*
CKD, n (%)	8 (5.1)	4 (11.4)	*0.311*
CAD, n (%)	16 (10.2)	10 (28.6)	*0.009*
COPD, n (%)	18 (11.5)	8 (22.9)	*0.132*
Antiplatelet Therapy, n (%)	45 (28.7)	10 (28.6)	*1.000*
Anticoagulant Therapy, n (%)	20 (12.7)	6 (17.1)	*0.678*

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

hospital mortality in COVID-19 patients.

4. Discussion

The main findings of the present study can be summarized as follows: a large proportion of patients admitted for COVID-19 is on treatment with antithrombotic agents; antithrombotic therapy stratified patients with older age and higher prevalence of comorbidities; patients who did not survived were older and showed higher prevalence of comorbidities; neither antiplatelet therapy nor anticoagulant therapy affected the risk of severe clinical presentation as ARDS at admission or death during hospitalization.

Among our study population including Italian hospitalized COVID-19 patients, we confirmed the epidemiological association between cardiovascular risk (CV) factors and the individual susceptibility to SARS-CoV2 infection, as previously described in Chinese and American cohort studies [6,7]. Particularly, hypertension, diabetes and coronary artery disease were the most prevalent comorbidities. Moreover, as previously showed by early Chinese data [8,9], the prevalence of CV diseases, in particular hypertension, was significantly increased in critically ill COVID-19 patients with ARDS compared to those with milder forms of disease and, in the same way, hypertension and CAD were significantly increased in non-survived COVID-19 patients compared to survivors.

Among our study population, the AF prevalence, as preexisting comorbidity at admission, was 12.5 %, higher than expected in general population [10]; however, no difference in AF prevalence has been shown in COVID-19 patients with more severe form of disease characterized by ARDS and poor clinical outcome.

The pathogenesis of ARDS in the clinical context of COVID-19 may be related to the direct effect of SARS-CoV-2 on alveolar epithelial cells and to indirect effects of infection-related hypoxia, both conditions predisposing to thrombotic events. Moreover, preliminary reports [11,12] suggest that a severe inflammatory response and disseminated intravascular coagulation (DIC) may occur in COVID-19 patients predisposing to microvascular pulmonary thrombosis.

Based on the pathophysiological hypothesis that COVID-19-induced ARDS patients may be driven by microvascular thrombotic processes, we decided to investigated if the pre-admission antithrombotic therapy, including both antiplatelet and anticoagulant drugs, might impact on the clinical course and prognosis of hospitalized COVID-19 patients.

In the present analysis, antithrombotic therapy before admission did not influence the clinical presentation COVID-19 in terms of ARDS and in-hospital mortality. These results suggest that the pathophysiology of microvascular pulmonary thrombosis in the clinical context of COVID-19-induced pneumonia is not influenced by pre-admission antithrombotic treatment, probably due to the complex interplay between clotting system activation and the SARS-CoV2 immuno-mediated inflammatory response, two processes that mutually reinforce each other.

Our results should be interpreted in light of the limitations related to the retrospective observational nature of the study. Larger multicenter prospective studies are required to confirm our preliminary

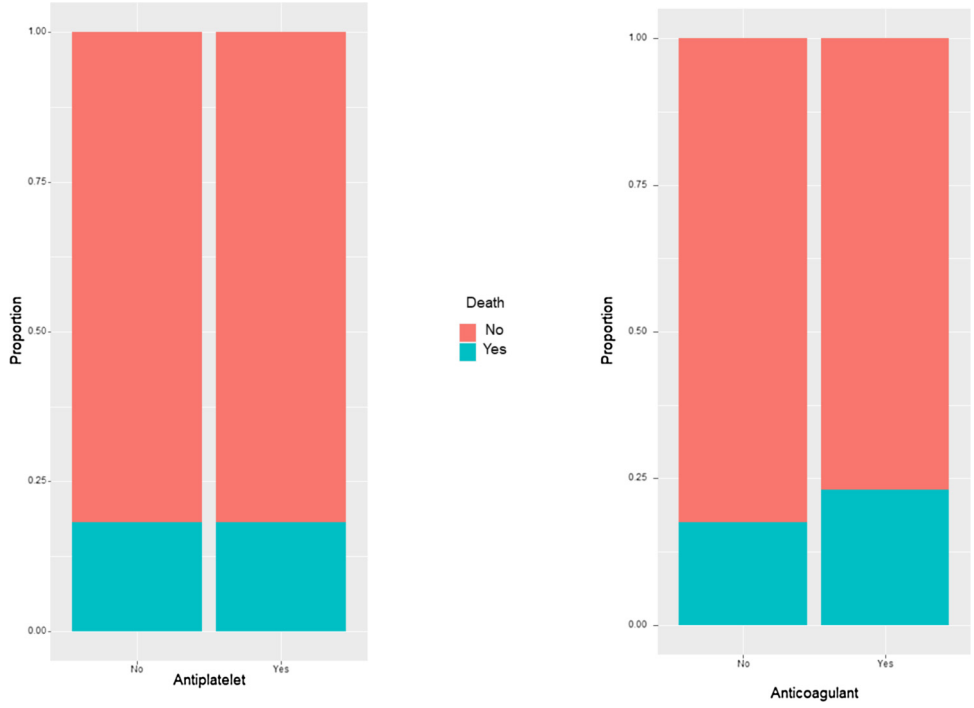

Fig. 1. Proportion of death among COVID-19 patients on antiplatelet and anticoagulant therapy.

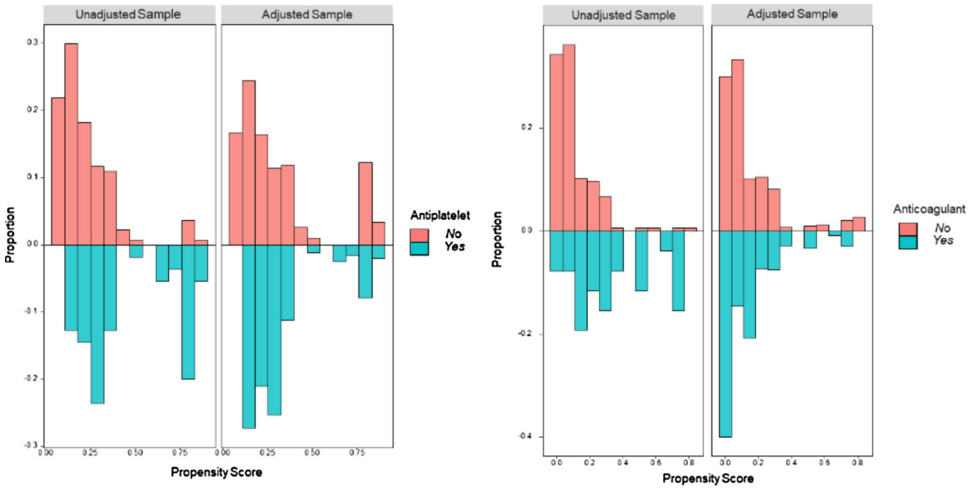

Fig. 2. Distributional balance of the propensity score in unadjusted and adjusted sample.

Table 3
Unadjusted and adjusted regression models for the risk of death and ARDS according to pre-admission antithrombotic therapy.

		Unadjusted			Adjusted		
		RR	**CI**	***P***	**RR**	**CI**	***P***
Death	**Anticoagulant**	1.42	0.53 – 2.47	0.493	1.15	0.29 – 2.57	0.995
	Antiplatelet	1.00	0.48 – 1.80	0.991	0.51	0.21 – 1.15	0.110
ARDS	**Anticoagulant**	1.13	0.64 – 1.67	0.629	1.24	0.56 – 2.08	0.465
	Antiplatelet	0.81	0.54 – 1.28	0.530	0.58	0.38 – 1.14	0.165

ARDS, acute respiratory distress syndrome; CI, confidence interval; RR, relative risk.

findings.

5. Conclusion

Although our results need confirmation by prospective studies including a larger population, the antithrombotic therapy, both antiplatelet and anticoagulant, does not seem to show a protective effect in severe forms of COVID-19 characterized by ARDS and rapidly evolving toward death.

Declaration of Competing Interest

No conflict of interest or any financial support to declare

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