Influence of antithrombotic treatment given before to hospital admission on COVID-19 patients

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Abstract:

Nothing is known regarding the clinical characteristics associated with the incidence of acute respiratory distress syndrome (ARDS) in hospitalised Coronavirus illness 2019 patients (COVID-19). The purpose of this study was to characterise the incidence of pre-admission antithrombotic medications in patients with COVID-19 and to examine the potential connection between antithrombotic therapy and ARDS as clinical disease presentation or in-hospital mortality.

We enrolled 192 consecutive patients admitted to the emergency departments of five Italian hospitals with laboratory-confirmed COVID-19. The study population was separated into two groups based on the presence of ARDS on admission chest computed tomography. A propensity score weighted regression analysis was used to estimate the risk of ARDS at admission and death during hospitalisation in patients treated or not with antiplatelet and anticoagulant medications.

73 cases (38%) were diagnosed with ARDS and were more likely to have hypertension than those without ARDS (57.8% vs. 49.6%; P = 0.005). Thirty-five patients (18.5%) passed away while hospitalised. Patients who did not survive COVID-19 had statistically significant increases in 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 10.5%; P = 0.009). Both unadjusted and adjusted regression models revealed no difference in the risk of ARDS at admission or mortality during hospitalisation between antiplatelet and anticoagulant-treated and untreated patients.

Pre-admission Antithrombotic medication, including antiplatelet and anticoagulant, does not appear to be protective in severe cases of COVID-19 presenting with ARDS and fast progressing to mortality.

1. Introduction

SARS-CoV-2 is a novel, highly deadly human coronavirus recently identified as the cause of coronavirus sickness in 2019. (COVID-19). The outbreak began in Wuhan, the capital of China's Hubei region, and swiftly spread to neighbouring nations, reaching pandemic proportions [1]. Italy is among the countries hardest impacted by COVID-19, with over 200,000 laboratory-confirmed cases expected **by May 2, 2020** [2]. Many life-threatening diseases, including sepsis, respiratory failure, heart failure, severe renal and cardiac

damage, and septic shock, may worsen the clinical course of COVID-19 [3]. Nothing is known about the clinical characteristics of patients that predispose them to these life-threatening illnesses.

Acute respiratory distress syndrome (ARDS) is one of the most often observed complications of COVID-19, and it has been related to significantly reduced hospital survival rates for patients. The relationship between inflammation and coagulation seems crucial in its pathophysiology [4], even though its aetiology is not fully understood.

It has not yet been determined whether anti-inflammatory medications and anticoagulants may influence the onset of ARDS in COVID-19.

This multicenter study aimed to assess the prevalence of antithrombotic treatments upon admission in patients with COVID-19, as well as any potential association between antithrombotic therapy and ARDS, as illness clinical presentation, or in-hospital mortality.

Methods:

We enrolled 192 consecutive patients with laboratory-confirmed COVID-19 from a large cohort of 963 patients admitted from February to April 2020 for fever and dyspnea to the 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). Real-time quantitative reverse-transcription polymerase chain reaction (RT- PCR) assay on nose/throat swab or sputum sample positive for SARS-CoV-2 provided laboratory confirmation.

Upon admission, all patients were given a medical history, physical examination, and laboratory evaluation. A chest X-ray and computed tomography (CT) scan were also conducted to rule out pneumonia in one or many sites. The COVID-19 population was separated into two groups based on the presence or absence of pneumonia with acute respiratory distress syndrome (ARDS) and in-hospital mortality. The diagnosis of ARDS was based on the Berlin definition [5].

We evaluated the prevalence and kind of antithrombotic treatment between these groups. The discontinuation of antithrombotic therapy during hospitalisation was assessed as an exclusion criterion. The institution's ethical committee authorised the protocol. All patients provided verbal and written informed consent for participation.

Statistical analysis

The Kolmogorov–Smirnov and Shapiro–Wilk tests distributed continuous data. Normally distributed data were expressed as the mean, and standard deviation (SD), while non-normally distributed variables were described as the median and interquartile range (IQR). Numbers and percentages were supplied for categorical variables.

Student's t-test was used to compare regularly distributed continuous data, whereas the Mann-Whitney U test was utilised to evaluate non-normally distributed continuous variables. Categorical variables were compared using the chi-square test or the Fisher exact test when applicable. Using logistic regression models, the unadjusted and adjusted risk ratios (RR) for the outcomes of interest were determined and presented as RR with their 95% confidence intervals (CI). We employed propensity score weighting to account for the possibility of selection bias in treatment assignment between the two study groups (average treatment

effect weights). The propensity score model was created by integrating all pre-procedural covariates potentially associated with the outcome and treatment decision, irrespective of their statistical significance or collinearity with other variables included in the model. Age, smoking, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, coronary artery disease (CAD), heart failure, obesity, dyslipidemia, stroke, and chronic kidney disease were baseline factors included in the propensity score model (CKD). Following weighting, standardised mean differences were computed to evaluate the balance of all covariates included in the propensity score model; values more than 0.10 were deemed statistically significant for differences across groups.

A p-value 0.05 was considered statistically significant for all tests.

Version 3.5.1 of R was used to conduct analyses (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 details the characteristics of the study population. 67.7 15.2 years was the mean age; 115 (59.9%) were men. 73 cases (38%) were diagnosed with ARDS and were more likely to have hypertension than those without ARDS (57.8% vs. 49.6%; P = 0.005).

At the time of admission, 55 COVID-19 patients (28.6%) were on antiplatelet medication, with 44 (22.9%) using acetylsalicylic acid, 5 (2.6%) P2y12 inhibitors, and 6 (3.1%) receiving dual antiplatelet therapy. They were older (73.7 9.2 vs 65.2 16.4; P = 0.001) and had a greater prevalence of hypertension (78.2% vs 49.6%; P = 0.001), dyslipidemia (30.9% vs 4.4%; P 0.001), and coronary artery disease (26.4% vs 4.4%; P = 0.001). At admission, 26 COVID-19 patients (13.5%) were on anticoagulant medication, with 18 (9.4%) receiving non-vitamin K oral anticoagulant (NOAC) and 8 (4.2%) on well-controlled vitamin K oral anticoagulant (VKA). They had a 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), chronic kidney disease (19.2% vs 1.2%; P = 0.012), prior stroke (23.1% vs 6.0%; P = 0.011), and coronary artery disease (30.8% vs Thirty-five patients (18.5%) passed away while hospitalised. Patients who did not survive COVID-19 had a statistically significant increase in 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 10.5%; P = 0.009). (Table 2). The proportion of deaths according to pre-mission antiplatelet and anticoagulant medication is depicted in Figure 1.

Notwithstanding the significant disparities in baseline characteristics between COVID-19 patients who survived and those who did not, the inverse probability weighting achieved a solid covariate balance, with absolute standard deviations of less than 10% for all variables. Antiplatelet and anticoagulant arms were more evenly distributed in allocation probability among patients who did not use antithrombotic medicines at admission, as depicted in Figure 2. Table 3 displays the unadjusted and adjusted regression models for the likelihood of ARDS and death according to pre-mission antithrombotic treatment. In COVID-19 patients, pre-admission antithrombotic medication with antiplatelets or anticoagulants was not linked with an elevated risk of ARDS at admission or in-hospital death.

Discussion:

Patients who did not survive were older and showed a higher prevalence of comorbidities. Both antiplatelet and anticoagulant therapy did not affect the risk of severe clinical presentation as ARDS at admission. These findings can be summed up as follows: many patients admitted for COVID-19 are on treatment with antithrombotic agents.

The epidemiological link between CV risk factors and individual susceptibility to SARS-CoV2 infection, as established in Chinese and American cohort studies [6,7], was confirmed in our study sample, which included hospitalised COVID-19 patients from Italy. Individual vulnerability to SARS-CoV2 infection has been linked to preexisting conditions such as hypertension, diabetes, and coronary cardiovascular risk (CV) factors, as revealed in Chinese and American cohort studies [6,7]. The most common co-existing conditions included high blood pressure, diabetes, and heart disease. Early Chinese data [8,9] also demonstrated that the prevalence of CV diseases, especially hypertension, was significantly higher in critically ill COVID-19 patients with ARDS compared to those with milder forms of illness and that the majority of hypertension and CAD was similarly higher in non-survivors of COVID-19 compared to survivors.

The prevalence of AF among the patients in our study was 12.5%, which is greater than what is seen in the general population [10]. However, AF prevalence has yet to be reported in COVID-19 patients with a more severe form of the disease, characterised by ARDS and poor clinical outcomes.

The direct effects of SARS-CoV-2 on alveolar epithelial cells and indirect effects of infection-related hypoxia, which predispose to thrombotic events, may contribute to the development of ARDS in the clinical context of COVID-19. Furthermore, recent data [11,12] suggest that COVID-19 individuals may be predisposed to pulmonary microvascular thrombosis due to a robust inflammatory response and disseminated intravascular coagulation (DIC).

We hypothesised that pre-admission antithrombotic therapy, including both antiplatelet and anticoagulant drugs, might affect the clinical course and prognosis of hospitalised COVID-19 patients due to the pathophysiological hypothesis that microvascular thrombotic processes may drive COVID-19-induced ARDS patients.

This study found that pre-admission anticoagulation did not affect the clinical presentation of COVID-19 concerning ARDS or in-hospital mortality. Given the complex interplay between clotting system activation and the SARS-CoV2 immuno-mediated inflammatory response, these findings suggest that pre-admission antithrombotic treatment does not affect the pathophysiology of pulmonary microvascular thrombosis in the clinical context of COVID19-induced pneumonia.

This study's weaknesses can be attributed to the fact that it was conducted based on past data. Confirmation of our preliminary findings requires more extensive multicenter prospective trials.\

Conclusion:

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

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
Age, mean years (SD)	67.7 (15.2)	66.1 (16.7)	70.3 (12.1)	0
Smoke, n (%)	16 (8.3)	11 (9.2)	5 (6.8)	0
Hypertension, n (%)	111 (57.8)	59 (49.6)	52 (71.2)	0
Diabetes Mellitus, n	42 (21.9)	24 (20.2)	18 (24.7)	0
(%) Dyslipidemia	23 (12.0)	12 (10.1)	11 (15.1)	
Obesity, n (%)	26 (13.5)	16 (13.4)	10 (13.7)	1
Atrial fibrillation, n (%)	24* (12.5)	12 (10.1)	12 (16.4)	0

Heart Failure, n (%)	20 (10.4)	12 (10.1)	8 (11.0)	1
Previous Ischemic	16 (8.3)	12 (10.1)	4 (5.5)	0
Stroke, n (%) CKD, n (%)	12 (6.2)	4 (3.4)	8 (11.0)	
CAD, n (%)	26 (13.5)	14 (11.8)	12 (16.4)	0
COPD, n (%)	26 (13.5)	19 (16.0)	7 (9.6)	0
Antiplatelet Therapy, n	55 (28.6)	36 (30.3)	19 (26.0)	0
(%) Anticoagulant	26 (13.5)	15 (12.6)	11 (15.1)	
Therapy, n (%)				

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

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.

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