Critical Care Explorations

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Factors Associated With Pulmonary Embolism Among Coronavirus Disease 2019 Acute Respiratory Distress Syndrome: A Multicenter Study Among 375 Patients

Abstract: Risk factors associated with pulmonary embolism in coronavirus disease 2019 acute respiratory distress syndrome patients deserve to be better known. We therefore performed a post hoc analysis from the COronaVirus-Associated DIsease Study (COVADIS) project, a multicenter observational study gathering 21 ICUs from France ($n = 12$) and Belgium ($n = 9$). Three-hundred seventy-five consecutive patients with moderate-to-severe acute respiratory distress syndrome and positive coronavirus disease 2019 were included in the study. At day 28, 15% were diagnosed with pulmonary embolism. Known risk factors for pulmonary embolism including cancer, obesity, diabetes, hypertension, and coronary artery disease were not associated with pulmonary embolism. In the multivariate analysis, younger age (< 65 yr) (odds ratio, 2.14; 1.17–4.03), time between onset of symptoms and antiviral administration greater than or equal to 7 days (odds ratio, 2.39; 1.27–4.73), and use of neuromuscular blockers greater than or equal to 7 days (odds ratio, 1.89; 1.05–3.43) were independently associated with pulmonary embolism. These new findings reinforce the need for prospective studies that will determine the predictors of pulmonary embolism among patients with severe coronavirus disease 2019.

Key Words: acute respiratory distress syndrome; coronavirus disease 2019; critically ill; pulmonary embolism; severe acute respiratory syndrome coronavirus 2; thrombotic complications

To the Editor:

Recent studies have suggested that patients with acute respiratory distress syndrome (ARDS) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (also known as coronavirus disease 2019 [COVID-19]) were at higher risk of pulmonary embolism (PE) (1–3). Risk factors associated with PE in these patients deserve to be better known. To do that, we performed a post hoc analysis from the COVADIS project, a multicenter observational study gathering 21 ICUs from France ($n = 12$) and Belgium ($n = 9$).

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MATERIALS AND METHODS

In participating ICUs, all consecutive patients with moderate-to-severe ARDS according to Berlin definition (4) (Pao_2/Fio_2 ratio under 200 mm Hg with a positive end-expiratory pressure of at least 5 mm Hg) and positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction seen between March 10, 2020, and April 12, 2020, were analyzed. This study was approved by appropriate regulatory committee in France and in Belgium in accordance with national regulation. Each patient was informed about the study. In case of incompetency, next of kin were informed. The requirement for written informed consent was waived. Each local investigator filled an electronic case report form to collect data (Castor EDC, Amsterdam, The Netherlands).

Among all collected data, demographics, known predisposing risk factors associated with thrombotic complications (5), management interventions delivered during ICU hospitalization, antiviral treatment, and immunomodulatory agents were kept for the current analysis. PE occurrence and mortality were recorded at day 28. To identify factors associated with PE, a post hoc multivariate logistic regression analysis with backward stepwise selection was performed. All variables associated with PE in univariate analysis with a p value of less than 0.20 were included. Statistical analysis was performed with R Version 3.5.0 and RStudio Version 1.1.453 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Three-hundred seventy-five patients were included in the study. The mean age was 63.5 ± 10.1 years, 77% were male, and 40% had a body mass index over 30 kg/m^2. The most frequent comorbidities were hypertension (58%), diabetes (26%), coronary artery disease (10%) and cancer, leukemia, or lymphoma (12%). Main treatments administrated are summarized in **Table 1**. Details in anticoagulation regimens were not collected but all patients received administrated anticoagulation at least at preventive dose.

At day 28, 55 patients (15%) were diagnosed with PE with a rate of 9.1 cases per 1,000 ventilator days and a mean duration of 7.2 ± 6.1 days between intubation and PE diagnosis. Deep venous thrombosis were more frequently found in patients with PE than in those without PE. Patients with PE tended to be younger, had longer interval between onset of symptoms and antiviral administration, and had longer duration of neuromuscular blockers use and of mechanical ventilation. However, known risk factors for PE including cancer, obesity, diabetes, hypertension, and coronary artery disease were not associated with PE. Furthermore, we did not find differences in disease severity, ventilator settings at admission, and antiviral strategies between patients with and without PE.

In the multivariate analysis, younger age (< 65 yr), time between onset of symptoms and antiviral administration greater than or equal to 7 days, and use of neuromuscular blockers greater

TABLE 1. Main Characteristics of the Critically Ill Patients With Coronavirus Disease 2019 Acute Respiratory Distress Syndrome

	Patients With Pulmonary Embolism (*n* = 55)	Patients Without Pulmonary Embolism (*n* = 320)	*p*
Age (yr)	61.1 ± 9.1	63.9 ± 10.3	0.06
Male	46 (84)	242 (76)	0.23
Body mass index (kg/m^2)	29.6 ± 4.7	29.8 ± 5.6	0.77
Comorbidities			
Hypertension	26 (53)	190 (59)	0.11
Diabetes mellitus	12 (22)	87 (27)	0.40
Coronary artery disease	8 (15)	28 (9)	0.21
Chronic heart failure	1 (2)	12 (4)	0.70
Cancer, leukemia, or lymphoma	4 (7)	40 (13)	0.36
Peripheral vascular disease	4 (7)	20 (6)	0.77
Chronic liver disease	2 (4)	10 (3)	0.69
Chronic renal disease	5 (9)	26 (8)	0.81
Autoimmune disease	0	12 (4)	0.23
Charlson score	1.3 ± 1.9	1.4 ± 1.9	0.83
Deep venous thrombosis	**11 (20)**	**24 (8)**	**0.003**
ICU therapy			
Invasive mechanical ventilation	55 (100)	320 (100)	1
Duration of mechanical ventilation at day 28 (d)	**18.3 ± 9.1**	**15.8 ± 9.1**	**0.048**
Neuromuscular blockers	48 (87)	266 (83)	0.56
Duration of neuromuscular blockers (d)	**9.5 ± 7.6**	**6.4 ± 5.4**	**< 0.001**
Inhaled pulmonary vasodilators	9 (16)	34 (11)	0.25
Prone positioning	45 (82)	255 (80)	0.86
Extracorporeal membrane oxygenation	6 (11)	35 (11)	1
Renal replacement therapy	13 (24)	61 (19)	0.43
Antiviral therapy	48 (87)	280 (88)	0.96
Lopinavir	10 (18)	71 (22)	0.50
Remdesivir	4 (7)	14 (4)	0.34
Hydroxychloroquine	39 (71)	199 (62)	0.21
Time between onset of symptoms and antiviral administration (d)	**10.0 ± 3.6**	**8.4 ± 4.3**	**0.02**
Steroids	13 (26)	64 (21)	0.47
Tocilizumab	0	9 (3)	0.37
Ventilator settings and oxygenation at admission			
Tidal volume (mL per kg of predicted body weight)	6.1 ± 0.7	6.3 ± 0.9	0.16
Positive end-expiratory pressure (cm of water)	11.9 ± 2.6	11.5 ± 2.9	0.35
Pao_2/Fio_2 (mm Hg)	132 ± 57	127 ± 49	0.53
Outcome			
ICU mortality at day 14	9 (16)	83 (26)	0.13
ICU mortality at day 28	16 (29)	118 (37)	0.27
Extubated at day 28[a]	19 (49)	137 (68)	0.25
Ventilator-free days at day 28[a]	7.4 ± 9.1	9.7 ± 8.4	0.13

[a]Patients who were dead at day 28 were excluded.

Values are mean ± SD or number of patients (percentage of total). Significant results are in boldface.

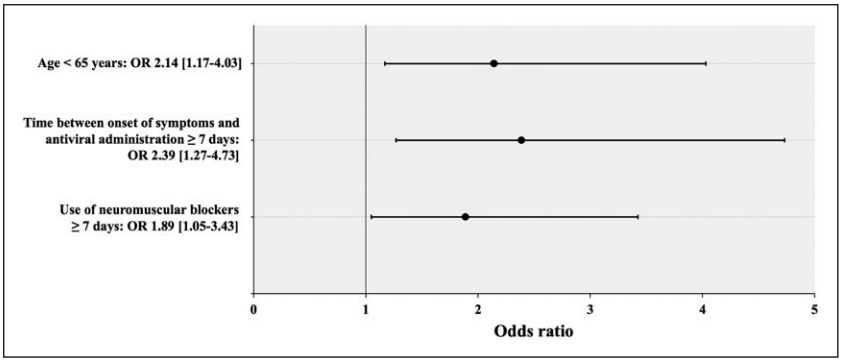

Figure 1. Multivariate logistic regression analysis of factors associated with pulmonary embolism among patients with coronavirus disease 2019 acute respiratory distress syndrome. OR = odds ratio.

than or equal to 7 days were independently associated with PE (**Fig. 1**). Younger age and time between onset of symptoms and antiviral administration greater than or equal to 7 days were also associated with overall thrombotic complications (PE and/or deep venous thrombosis).

DISCUSSION

Our study that includes a large population of COVID-19 ARDS with multicenter recruitment reports a PE incidence of 15%, identical to the incidence reported by Helms et al (2) in a smaller series of 150 patients. Although this incidence has to be seen as a lower bound as we likely underestimated the true incidence of PE because COVADIS study was not designed for systemic search for PE. This 15% incidence is however much higher than in non-COVID-19 patients with ARDS, which ranges between 1.3% and 2.5% (2, 6, 7). To know the mechanism and the factors associated with this higher incidence is of critical importance.

Thrombotic complications are considered to be a consequence of the interaction between patient-related risk factors and setting-related risk factors (5). In non-COVID-19 mechanically ventilated patients, the main independent risk factors for PE are male gender, high body mass index, history of cancer, and past medical history of deep venous thrombosis (8). The major finding of our work is that in nonselected patients with COVID-19 ARDS, these factors were not associated with PE. Furthermore, the fact that younger age was associated with higher risk of PE is fairly unexpected. These findings suggest that current guidelines should be adjusted. Indeed, in patients with severe COVID-19, the French Society of Thrombosis and Haemostasis currently proposes to consider routine therapeutic or intermediate-dose anticoagulation in those with risk factors such as cancer and obesity (9).

Use of neuromuscular blockers has been reported as an independent risk factor for deep venous thrombosis among critically ill patients (10). Neuromuscular blockers induce muscle paralysis, which is associated with pooling of blood in veins and stasis. Increased thoracic pressure due to mechanical ventilation can further slow blood velocity in veins. In the current study, we found that use of neuromuscular blockers and duration of mechanical ventilation were longer in patients with PE than in patients without PE. This may represent a modifiable risk factor worth to be evaluated in a randomized trial.

Antiviral therapies in COVID-19 are supposed to decrease viral load (11). The association between PE and delay in antiviral administration found in our study might incite to investigate the link between viral load and risk factors related to PE.

Our results should be interpreted with caution, as the study was not originally designed to investigate PE. In particular, there was no systematic strategy was used to search PE, and information regarding anticoagulation dose was not collected.

CONCLUSIONS

Based on the analysis of a large multicenter case series of COVID-19 ARDS, we found that: 1) at least 15% of patients with COVID-ARDS have PE; 2) known risk factors for PE were not associated with PE in the particular setting of COVID-19 ARDS; and 3) patients with PE had longer duration of mechanical ventilation and of neuromuscular blocker use. These new findings reinforce the need for prospective studies that will determine the predictors of PE among patients with severe COVID-19 (12).

Dr. Textoris is a part-time employee of bioMérieux, an IV diagnostics company, and Hospices Civils de Lyon, a university hospital. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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