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 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

MATERIALS AND METHODS

In participating ICUs, all consecutive patients with moderate-to-severe ARDS according to Berlin definition (4) (Pao2/Fio2 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/m2. 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 regimen 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 than or equal to 7 days, and use of in anticoagulation regimens were not collected but all patients received administrated anticoagulation at least at preventive dose.

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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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/m²)        | 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  |
| $P_{aO_2}/F_{Io_2}$ (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*           | 19 (49)                                  | 137 (68)                                      | 0.25  |
| Ventilator-free days at day 28* | 7.4 ± 9.1                                    | 9.7 ± 8.4                                     | 0.13  |

*Patients who were dead at day 28 were excluded.

Values are mean ± so or number of patients (percentage of total). Significant results are in boldface.
Critical Care Explorations

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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