Original Article

High risk of pulmonary embolism in acute respiratory distress syndrome related to COVID-19: an observational controlled-cohort study

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Background: COVID-19 may induce endovascular injury of pulmonary vessels and could be associated with increased risk of pulmonary embolism. The main objective was to compare the incidence of pulmonary embolism in patients with acute respiratory distress syndrome (ARDS) related to COVID-19 versus patients with pulmonary ARDS unrelated to COVID-19.

Methods: This is an observational controlled-cohort study performed at a single center of a university teaching hospital in France. The incidence of pulmonary embolism was prospectively assessed using computed tomography pulmonary angiography (CTPA) in patients with ARDS related to COVID-19 and compared to patients from a 3-year historical cohort of patients with pulmonary ARDS unrelated to COVID-19. In patients with ARDS related to COVID-19, CTPA was performed approximately 7 days after intubation or earlier in case of respiratory or hemodynamic worsening.

Results: CTPA was performed in 29 out of the 42 patients (69%) with ARDS related to COVID-19 and in 51 out of the 156 patients (33%) from the historical cohort of patients with pulmonary ARDS unrelated to COVID-19. Incidence of pulmonary embolism was 40% (17/42) in patients with ARDS related to COVID-19 and 3% (5/156) in the historical cohort (P=0.001). The proportion of patients with pulmonary embolism among all patients who had CTPA was 59% (17/29) in patients with ARDS related to COVID-19 and 10% (5/51) in the historical cohort (P=0.0001). After adjustment on the interval between ICU admission and computed tomography, COVID-19 remained independently associated with pulmonary embolism.

Conclusions: Pulmonary embolism was particularly frequent in patients with ARDS related to COVID-19, thereby suggesting that CTPA should be systematically performed in these patients.

Keywords: Acute respiratory distress syndrome (ARDS); COVID-19; pulmonary embolism; mechanical ventilation; computed tomography pulmonary angiography (CTPA)

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Introduction

COVID-19 due to severe acute respiratory syndrome coronavirus (SARS-CoV-2) may be complicated by acute respiratory distress syndrome (ARDS) with bilateral pulmonary infiltrates and profound hypoxemia requiring mechanical ventilation (1,2). Diffuse alveolar damage characterized by hyaline membranes, interstitial edema, cell necrosis and proliferation, is the morphological hallmark picture of the lung in patients with ARDS (3). Unlike common causes of ARDS, COVID-19 may induce endovascular injury of pulmonary vessels and could be associated with an increased risk of pulmonary embolism. Several series of clinical autopsies have found abnormally high rates of pulmonary embolism in deceased patients with ARDS related to COVID-19 (4,5). In a series of 11 clinical autopsies from Austria, pulmonary artery thrombosis was observed in all patients, in addition to usual diffuse alveolar damage (4). In another series of 12 clinical autopsies from Germany, pulmonary embolism was found to be the main reason of death in four patients (5).

Several clinical or radiological studies have also reported a high incidence of pulmonary embolism among patients with COVID-19 and respiratory failure, with a rate approximating 20% (6-10). However, computed tomography pulmonary angiography (CTPA) is not a routine exam in ARDS management, which is one reason why the actual incidence of pulmonary embolism in patients with ARDS has been inadequately studied.

This study aimed at determining whether the incidence of pulmonary embolism was actually higher in patients with ARDS related to COVID-19 than in patients with pulmonary ARDS unrelated to COVID-19.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6796).

Methods

Design and patients

This is a single-center observational controlled-cohort study including patients intubated with clinical criteria for ARDS (11).

Patients who did not require intubation and invasive mechanical ventilation were not included. In the studied group, all patients with ARDS related to COVID-19 (confirmed by positive RT-PCR) admitted to ICU between the 23rd March (first patient admitted for ARDS related to COVID-19) and 4th June 2020 (discharge date of the last patient) were included. In the control group, all medical charts were reviewed by two intensivists over a 3-year period (FR and VDR) to identify all intubated patients who met the criteria for pulmonary ARDS, i.e., related to pneumonia, aspiration, inhalation or lung contusion, whereas patients with extra-pulmonary ARDS were excluded (11). As pathogenic pathways could be different between pulmonary and extra-pulmonary ARDS, we decided to include only homogeneous patients with pulmonary ARDS characterized by direct insult of alveolar epithelium, and not patients with extra-pulmonary ARDS characterized by insult of pulmonary vascular endothelium (12). For all patients, prophylactic anticoagulation was administered as daily subcutaneous 4,000 IU enoxaparin in the absence of contraindication. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the local Ethics committee of Poitiers (registration number: CHU86-RECH-R2020-05-09). Given its observational nature, informed consent was waived.

Outcomes

The primary outcome was the proportion of patients with pulmonary embolism diagnosed using CTPA while under invasive mechanical ventilation. CTPA performed before ICU admission or before intubation was not retained in the analysis. When established, pulmonary embolism was classified as troncular, lobar, segmental or sub-segmental, based on the location of the most proximal endoluminal defect. The secondary outcome involved variables associated with pulmonary embolism among all patients having undergone CTPA.

As the pandemic occurred later in our region than in other parts of Europe, we were aware of a potential high risk of pulmonary embolism in patients with ARDS related to COVID-19. Consequently, we planned in advance to systematically perform CTPA approximately 7 days after intubation or earlier in case of respiratory or hemodynamic worsening, our objective being to confirm or rule out pulmonary embolism in all patients. By contrast, CTPA was not systematic in the control group with pulmonary ARDS unrelated to COVID-19, and was performed only in patients who had suspected pulmonary embolism or infectious pulmonary complication (pulmonary abscess or pleural empyema).

Statistical analysis

Continuous variables were given in mean ± standard deviation or median [25th–75th percentiles] and compared using the Student's *t*-test or the Mann-Whitney test as appropriate. Categorical variables were given in number and percentage and compared by means of the χ^2 test or the Fischer's exact test as appropriate.

Patients with ARDS related to COVID-19 were compared to those from the historical cohort with ARDS unrelated to COVID-19. Among patients who underwent CTPA, patients with pulmonary embolism were compared to those with no pulmonary embolism. Then, the variables associated with pulmonary embolism were assessed by means of multivariable logistic regression analyses. Given the fact that the estimated number of events was low, only two variables could be entered in the maximal model. A two-tailed P value of less than 0.05 was considered as indicating statistical significance. We used SAS software, version 9.4 (SAS Institute), for all the analyses.

Results

Study participants

Over the pandemic period, 50 patients were admitted to our ICUs for acute respiratory failure with confirmed COVID-19. Out of them, 42 patients required intubation and met the criteria for ARDS. CTPA was performed in 29 patients (69%), and repeated twice in 7 patients (17%).

In the historical 3-year cohort, 199 patients were admitted to our ICU for ARDS. After excluding the 43 patients with extra-pulmonary ARDS, 156 patients with pulmonary ARDS unrelated to COVID-19 were retained in the analysis including 49 patients (31%) with ARDS related to viral pneumonia. CTPA was performed in 51 patients (33%), and repeated twice in 5 patients (3%).

Patients with ARDS related to COVID-19 had a lower severity score at admission, less comorbidity except for a higher proportion of patients with hypertension, less severe hypoxemia within the first 48 hours of ARDS, and had lower mortality than those with ARDS unrelated to COVID-19 (*Table 1*).

Primary outcome

Incidence of pulmonary embolism was significantly higher in patients with ARDS related to COVID-19 than in those with ARDS unrelated to COVID-19: 40% (17/42) *vs.* 3% (5/156), P=0.001.

The proportion of patients with pulmonary embolism among those who had CTPA was also significantly higher in patients with ARDS related to COVID-19 than in the others: 59% (17/29) *vs.* 10% (5/51), P=0.0001 (*Table 1* and *Figure 1*). Patients with ARDS related to COVID-19 had lobar pulmonary embolism in 5/17 cases (29%), segmental embolism in 10 (59%) and sub-segmental embolism in 2 (12%). Eight patients (47%) had bilateral pulmonary embolism.

Secondary outcome

Among the 80 patients having undergone CTPA, 22 patients (28%) had pulmonary embolism including 17 patients (77%) with ARDS related to COVID-19 and 5 (23%) unrelated to COVID-19 (*Table 2*). The incidence of pulmonary embolism was significantly higher in ARDS related to COVID-19 than in the others: 59% (17/29) *vs.* 10% (5/51), P<0.0001. In patients who had pulmonary embolism, CTPA was performed later after intubation as compared to patients with no pulmonary embolism: 8 [6–12] *vs.* 2 [1–8] days, P=0.0015.

After multivariable logistic regression, ARDS related to COVID-19 remained independently associated with pulmonary embolism, even after adjustment on the duration between ICU admission and CTPA with an odds ratio of 13.0 (95% confidence interval, 4.0 to 41.7).

Discussion

In this single-center study, patients with ARDS related to COVID-19 had markedly higher incidence of pulmonary embolism than those with ARDS unrelated to COVID-19. Incidence of pulmonary embolism was 40% among all patients with ARDS related to COVID-19 and 59% among those who had CTPA, the actual incidence being between these 2 rates.

The proportion of patients with ARDS related to COVID-19 and confirmed diagnosis of pulmonary embolism (40%) was markedly higher than that reported in the literature, ranging from 17% to 24% among patients with respiratory failure (6-10). However, in the subgroup of ICU patients, one of these studies reported pulmonary embolism in 50% of patients who had CTPA, which was close to the 59% we have reported (8). Our study included only ARDS patients under invasive mechanical ventilation at the time of CTPA that was performed late in the course

Table 1 Comparison of patients with acute respiratory distress syndrome (ARDS) related to COVID-19 and those with pulmonary ARDS unrelated to COVID-19

Variable	COVID-19 ARDS (n=42)	Non-COVID ARDS (n=156)	P value
Characteristics of the patients			
Age, years	62±12	62±13	0.7274
Male sex, n (%)	33 (79%)	116 (74%)	0.5744
Body mass index, kg/m^2	30±5	29±8	0.8614
SAPS II at admission, points	38±11	55±22	0.0001
SOFA the day of admission, points	5±2	10±5	0.0001
Comorbidity			
Diabetes, n (%)	9 (21%)	24 (15%)	0.2567
Hypertension	22 (52%)	29 (19%)	0.1354
Underlying chronic cardiac disease, n (%)	0 (0%)	33 (21%)	0.0011
Underlying chronic lung disease, n (%)	0 (0%)	38 (24%)	0.0004
Active cancer, n (%)	0 (0%)	23 (15%)	0.0081
Immunodeficiency, n (%)	1 (2%)	44 (28%)	0.0004
Characteristics of ARDS			
Interval between the onset of respiratory symptoms and ICU admission, days	8 [5–10]	5 [2–7]	0.0001
Interval between ICU admission and intubation, days	0 [0–1]	1 [1–2]	0.4684
Severity of ARDS within the first 48 h			0.0004
Mild	2 (5%)	1 (1%)	–
Moderate	29 (69%)	64 (41%)	–
Severe	11 (26%)	91 (58%)	–
Ventilatory parameters			
Tidal volume, mL/kg	6.1±0.4	6.1±1.2	0.8244
Plateau pressure, cmH_2O	26±3	25±3	0.2465
PEEP, cmH_2O	13±3	12±4	0.2851
Driving pressure, cmH_2O	13±3	13±4	0.9903
Compliance of the respiratory system, mL/cmH_2O	31±7	32±12	0.7725
Treatments of ARDS			
Use of high-flow nasal oxygen before intubation, n (%)	17 (40%)	56 (36%)	0.5851
Use of NIV before intubation, n (%)	0 (0%)	13 (8%)	0.0529
Use of paralytic agents, n (%)	42 (100%)	129 (83%)	0.0037
Use of prone positioning, n (%)	32 (76%)	80 (51%)	0.0038
Use of steroids, n (%)	6 (14%)	13 (8%)	0.2450
ECMO, n (%)	6 (14%)	13 (8%)	0.2450

Table 1 (*continued*)

Table 1 (*continued*)

Variable	COVID-19 ARDS (n=42)	Non-COVID ARDS (n=156)	P value
Pulmonary embolism			
Computed tomography pulmonary angiography (CTPA), n (%)	29 (69%)	51 (33%)	0.0001
Diagnosis of pulmonary embolism, n (%)	17 (40%)	5 (3%)	0.0001
Diagnosis of pulmonary embolism among patients with CTPA, n/n total (%)	17/29 (59%)	5/51 (10%)	0.0001
Interval between ICU admission and CT, days	8 [6–12]	2 [1–8]	0.0001
Outcomes			
Duration of mechanical ventilation, days	17 [11–23]	11 [6–20]	0.0001
Length of ICU stay, days	21 [15–27]	13 [8–24]	0.0002
Ventilator-free days at day 28, days	11 [4–16]	0 [0–17]	0.0502
Death, n (%)	7 (17%)	70 (45%)	0.0009

Continuous variables are given in mean ± standard deviation and compared between the 2 groups using the Student's *t*-test, or given in median [25th–75th percentiles] and compared using a Mann-Whitney test according to their distribution, and categorical variables are given in number and percentage and were compared by means of the χ^2 test. ARDS, acute respiratory distress syndrome; SAPS, simplified acute physiological score; SOFA, sepsis organ failure assessment; ICU, intensive care unit; NIV, non-invasive ventilation; CTPA, computed tomography pulmonary angiography; ECMO, extra-corporeal membrane oxygenation.

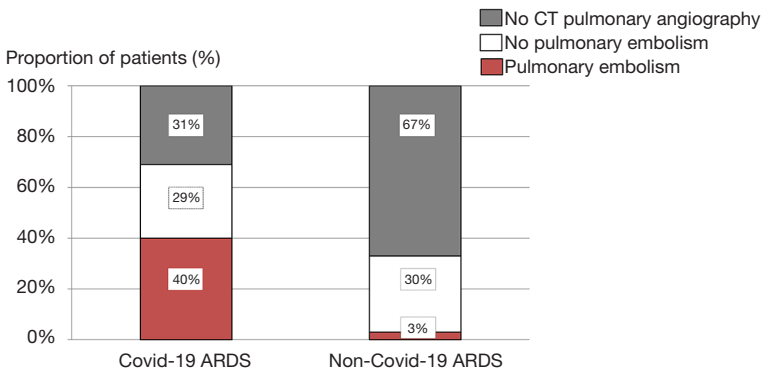

Figure 1 Bars showing the proportion of patients who had no computed tomography pulmonary angiography (CTPA) under mechanical ventilation (grey bars), those who had no pulmonary embolism on CTPA (white bars), and those who had confirmed diagnosis of pulmonary embolism on CTPA (red bars) in patients with ARDS related to COVID-19 and those with ARDS of non-COVID origin. The proportion of patients with pulmonary embolism was higher in COVID-19 ARDS than in those with ARDS of other origin (40% *vs.* 3%, P=0.0001). Although patients with COVID-19 ARDS had more frequently a CTPA than those with ARDS of other origin, the proportion of patients with confirmed diagnosis of pulmonary embolism among all patients who had CTPA was higher in COVID-19 ARDS than in the others (59% *vs.* 10%, P<0.0001). ARDS, acute respiratory distress syndrome.

of ARDS (8 days after ICU admission in median), and at times repeated if needed. In previous studies, CTPA was not systematic and was performed earlier which could explain why a number of pulmonary embolisms may have been overlooked.

To our knowledge, this is the first time that the incidence of pulmonary embolism was compared between ARDS related to COVID-19 and patients with pulmonary ARDS of other origin. Indeed, although several previous studies have compared the incidence of pulmonary embolism

Table 2 Comparison of patients with acute respiratory distress syndrome (ARDS) and pulmonary embolism and those with no pulmonary embolism among all patients who had computed tomography pulmonary angiography (CTPA) after intubation

Variable	Pulmonary embolism (n=22)	No pulmonary embolism (n=58)	P value
Characteristics of the patients			
Age, years	63 [57–69]	58 [52–65]	0.2445
Male sex (%)	20 (91%)	43 (74%)	0.1322
Body mass index, kg/m^2	27 [24–32]	29 [25–33]	0.3798
SAPS II at admission, points	39 [33–46]	49 [38–66]	0.0121
SOFA the day of admission, points	5 [4–10]	9 [6–14]	0.0136
Comorbidity			
Diabetes, n (%)	5 (23%)	15 (26%)	0.7778
Hypertension, n (%)	10 (45%)	18 (31%)	0.4338
Underlying chronic cardiac disease, n (%)	1 (5%)	6 (10%)	0.6668
Underlying chronic lung disease, n (%)	0 (0%)	11 (19%)	0.0297
Active cancer, n (%)	1 (5%)	4 (7%)	0.9999
Immunodeficiency, n (%)	2 (9%)	10 (17%)	0.4951
Reason for ARDS			<0.0001
COVID-19	17 (77%)	12 (21%)	
Non-COVID pulmonary ARDS, n (%)	5 (23%)	46 (79%)	
Characteristics of ARDS			
Interval between onset of respiratory symptoms and ICU admission, days	9 [5–11]	4 [1–10]	0.0921
Interval between ICU admission and intubation, days	1 [1–2]	1 [1–2]	0.9828
Severity of ARDS within the first 48 h			0.1356
Mild	0 (0%)	1 (2%)	
Moderate	16 (73%)	28 (48%)	
Severe	6 (28%)	29 (50%)	
Ventilatory parameters			
Tidal volume, mL/kg	5.9 [5.9–6.1]	6.0 [5.8–6.7]	0.2213
Plateau pressure, cmH_2O	26 [24–28]	27 [24–28]	0.9477
PEEP, cmH_2O	14 [12–15]	12 [10–15]	0.3497
Driving pressure, cmH_2O	13 [11–14]	13 [11–15]	0.5882
Compliance of the respiratory system, mL/cmH_2O	30 [27–36]	30 [24–35]	0.6173
Treatments of ARDS			
Use of paralytic agents, n (%)	21 (95%)	48 (83%)	0.2736
Use of prone positioning, n (%)	16 (73%)	27 (47%)	0.0460
Use of steroids, n (%)	6 (28%)	4 (7%)	0.0228
ECMO, n (%)	3 (14%)	4 (7%)	0.3865

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Pulmonary embolism (n=22)	No pulmonary embolism (n=58)	P value
Timing of CTPA			
Interval between ICU admission and CTPA, days	8 [6–12]	2 [1–8]	0.0015
Outcomes			
Duration of mechanical ventilation, days	18 [24–29]	12 [8–23]	0.0220
Length of ICU stay, days	22 [19–32]	17 [12–30]	0.0396
Ventilator-free days at day 28, days	10 [0–13]	5 [0–17]	0.6783
Death (%)	6 (27%)	17 (29%)	0.9999

Continuous variables are given in median [25th–75th percentiles] and compared using a non-parametric Mann-Whitney test. Categorical variables are given in number and percentage and were compared by means of the non-parametric Fisher exact test or the χ^2 test. ARDS, acute respiratory distress syndrome; SAPS, simplified acute physiological score; SOFA, sepsis organ failure assessment; ICU, intensive care unit; CTPA, computed tomography pulmonary angiography; ECMO, extra-corporeal membrane oxygenation.

between patients with ARDS related to COVID-19 and historical cohorts of ICU patients (6,7), they encompassed either non-selected ICU patients (6) or patients with septic shock (7). Helms and colleagues reported an incidence of pulmonary embolism of 17% in patients with ARDS related to COVID-19 versus only 1% in a historical cohort of ARDS of other origin (7). However, patients with ARDS unrelated to COVID-19 were identified from a historical cohort including patients with septic shock and probably patients with extra-pulmonary ARDS. By contrast, our historical cohort included all consecutive patients with pulmonary ARDS.

Limitations

The main limitation of this study is the retrospective nature of the analysis. In the historical cohort, only one-third of patients with pulmonary ARDS unrelated to COVID-19 underwent CTPA, and it was performed much earlier after ICU admission than in patients with ARDS related to COVID-19. Consequently, the actual incidence of pulmonary embolism in patients with ARDS unrelated to COVID-19 could be markedly underestimated. To date, no study has prospectively assessed the incidence of pulmonary embolism in ARDS and we cannot exclude the eventuality that is necessary to perform CTPA later in the course of ARDS. Although we prospectively planned systematic CTPA to confirm or rule out pulmonary embolism after around one week of mechanical ventilation in all patients with ARDS related to COVID-19, CTPA was nonetheless performed in only 69% of patients, either because they were extubated earlier or because they were too severe to undergo scanner.

Another limitation is that we did not perform routine ultrasound examination of the lower limb veins and consequently we cannot hypothesize the mechanism of pulmonary embolism. Whereas the incidence of deep venous thrombosis may also be particularly high in patients with COVID-19 reaching approximately 40 to 50% of cases (5,13,14), histological findings suggest that pulmonary embolism could be due to thrombosis of small pulmonary arteries rather than by thromboembolism (4).

Lastly, patients with ARDS related to COVID-19 had surprisingly few underlying chronic diseases, especially few chronic cardiac or lung diseases, and few cancers whereas these are strong risk factors for pulmonary embolism. The explanation is unclear but could in part be due to strict lockdown of patients at risk for COVID-19. Regardless the reason, this is in keeping with the recent French cohort including more than 4000 patients with COVID-19 in ICUs and reporting that only 7% of patients had underlying immunodeficiency (15).

In conclusion, pulmonary embolism was particularly frequent in patients with ARDS related to COVID-19, thereby suggesting that CTPA should be systematically performed during their ICU stay.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the local Ethics committee of Poitiers (registration number: CHU86-RECH-R2020-05-09). Given its observational nature, informed consent was waived.

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