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# Pulmonary Embolism in COVID-19 Patients:

# Awareness of an Increased Prevalence

**Running Title:** *Poissy et al.; COVID-19 and Pulmonary Embolism*

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**Data sharing:** Data, analytic methods, and study materials are available to other researchers upon request by email

We report a case-series of COVID-19 patients with pulmonary embolism (PE) in our institution. Lille University Hospital is the tertiary care center for the North-of-France, the 2nd French region in population density (189 p/km$^2$), also considered as a "metabolic" area with high number of overweight patients. The study was approved by the Institutional data protection authority of Lille University Hospital.

Among the 107 first consecutive confirmed COVID-19 patients admitted in ICU for pneumonia from Feb 27th to March 31th, we noticed an unexpected high number of PE during their stay in ICU, 22(20.6%) at the time of analysis (April 9th), within a median time from ICU admission of 6 days (range 1 to 18 days). To determine whether this represents an increase in the expected incidence of PE over a similar time interval, we analyzed the files of 196 patients hospitalized in our ICU during the same time interval in 2019. Despite a similar severity score at entrance in ICU, the frequency of PE in our COVID-19 series was twice higher than the frequency we found in this control period, (20.6% vs 6.1%; absolute increase risk of 14.4%, 95%CI 6.1 to 22.8%). It was also twice higher than the 7.5% frequency of PE in the 40 Influenza ICU patients admitted between 1stJanuary to 31thDecember 2019 (3PE, absolute increase risk 13.1%, 95%CI 1.9 to 24.3%). A qualitative description of main characteristics of PE cases in the different periods are reported in the Table.

Taking into account the ICU duration at time of analysis, we estimated the cumulative incidence of PE using Kalbfleisch and Prentice-method by taking into account death (n=15) and discharge alive (n=48) as competing events; the 22 patients still hospitalized in ICU without PE at the time of analysis (median[range] ICU length of stay=15 days [10 to 30] days) were treated as censored observations. At 15 day of ICU admission, cumulative incidence of PE in COVID-19 ICU patients was estimated to 20.4% (95%CI, 13.1 to 28.7%). Regarding main data at ICU admission (using univariable Fine and Gray model to estimate subhazard

ratios (SHRs) of PE), D-Dimers (SHR per log-SD increase=1.81; 95%CI,1.03 to 3.16), plasma factor VIII activity (SHR per log-SD increase,1.73; 95%CI,1.10 to 2.72), and factor Willebrand antigen levels (SHR per log-SD increase,1.69; 95%CI,1.12 to 2.56) values seem to be associated with a greater PE risk.

At the time of PE diagnosis, 20/22 patients were receiving prophylactic antithrombotic treatment (UFH or LWMH) according to the current guidelines in critically ill patients[1,2]. One patient with a history of DVT was receiving fluindione with INR in the therapeutic range and one patient was receiving therapeutic UFH because of atrial fibrillation. The criteria for decision to perform Computed Tomography Pulmonary Angiography (CTPA) were suspicion of PE upon admission and/or acute degradation of hemodynamic or respiratory status. All CTPA were performed with multi-bar CT with no difference in the injection protocol whether the CTPA was performed for PE diagnosis or not. The number of CTPA was higher in COVID-19 patients than in the ICU patients hospitalized during the same time period in 2019. This historical control group reflects the global practice in our ICU. Because only 34% of patients from this group suffer from respiratory failure requiring CTPA (see Table), a potential bias of an increased detection of PE in COVID-19 patients could have been generated. That is why we compared COVID-19 patients to Influenza patients admitted in ICU for respiratory failure in 2019. Even if the number of CTPA performed in Influenza patients was higher than in patients with COVID-19, less PE were identified, reinforcing the increase risk of PE in COVID-19 patients. The low number of associated DVT in COVID-19 patients may suggest that they have pulmonary thrombosis rather than embolism.

Pulmonary embolism frequency has not yet been reported in the different series of COVID-19 patients. All our patients received thromboprophylaxis according to the current recommendations for critically ill medical patient. However, we suspect that the high obesity prevalence in our patient-group contributes to the increased PE frequency[3]. Due to the lack of

specific studies in this population, the recommendations do not mention an adaptation of prophylaxis regimen in overweight patients nor a need for monitoring of anti-factor Xa concentration. Furthermore, heparin could have benefic impacts in COVID-19 infection, but the effective dose and monitoring is discussed, in particular in very high-risk patients, with high BMI or according to other criteria such as D-dimers[4]. Indeed, during the H1N1-flu pandemic, some centers reported an increased thrombotic risk in severe patients with ARDS and suggested the use of higher doses of heparin[5].

In conclusion, there is an urgent need for replication in a much larger scale of our data on PE frequency in COVID-19 infection in ICU-patients. Failure to identify and accurately manage this risk could worsen the prognosis of patients with COVID-19.

**Disclosures**

None

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**Table.** Number of CT Pulmonary Angiography performed for suspicion of PE, Number and main characteristics of Pulmonary Embolism (PE) Events in Intensive Care Unit from COVID-19 pandemic period by comparison to the same period in 2019 and to influenza patients in 2019

| | **Study period** | | |
|---|---|---|---|
| | **2019,** February 27th to March 31th (all ICU patients*, n=196) | **2019,** 1st January to 31th December (Influenza ICU patients (PCR+), n=40) | **2020,** February 27th to March 31th (COVID-19 ICU patients, (PCR+), n=107) |
| Number of chest CT scans, n (%) | 50 (25.5) | 20 (50.0) | 36 (33.6) |
| Number of CTPA, n (%) | 30 (15.3) | 17 (42.5) | 34 (31.8) |
| Number of CTPA performed for a PE diagnosis, n (%) | 20 (10.2) | 8 (20.0) | 34 (31.8) |
| Number of PE cases (%) | 12 (6.1) | 3 (7.5) | 22 (20.6)** |
| Bilateral, n (%) | 8 (66.6) | 0 *** | 8 (40.0) § |
| Proximal, n (%) | 2 (16.6) | 0 *** | 2 (10.0) § |
| Segmental, n (%) | 6 (50.0) | 0 *** | 11 (55.0) § |
| ARDS, n (%) | 14 (7.1) | 15 (37.5) | 67 (62.6) |
| Intubation, n (%) | 84 (42.9) | 17 (42.5) | 67 (62.6) |
| Doppler ultrasound, n (%) | 12 (6.1) | 2 (5.0) | 8 (7.5) |
| DVT, n (%) | 9 (4.6) | 1 (2.5) | 5 (4.7) |
| **Patients with Pulmonary Embolism** | | | |
| Age, years, median (range) | 66 (30 to 72) | 71 (57 to 72) | 57 (29 to 80) |
| Men, n (%) | 8 (66.7) | 2 (66.7) | 13 (59.1) |
| Body mass index, median (range) | 29 (18 to 42) | 26 (16 to 52) §§ | 30 (22 to 53) |
| SOFA at admission, median (range) | 8 (1 to 16) | 2 (1 to 9) | 4 (0 to 14) |
| SAPS II at admission, median (range) | 53 (23 to 69) | 41 (34 to 65) | 40 (18 to 78) |
| ARDS, n (%) | 5 (41.7) | 2 (66.7) | 17 (77.3) |
| Intubation, n (%) | 8 (66.7) | 3 (100.0) | 17 (77.3) |
| DVT associated to PE, n (%) | 7 (58.3) | 1 (33.4) | 3 (13.6) |

* Reasons for hospitalization in this group were : acute respiratory failure (34%), sepsis/septic shock (19%), strokes and other neurological disorders (10%), non septic shock (6%), cardiac arrest (6%), intoxications (6%), metabolism disorders (4%), post-operative conditions (5%), microangiopathies (1.5%), acute kidney injury (1.5%) and others (7%: pancreatitis, self-hanging injury, severe trauma, gas embolism). ** corresponding to an absolute increase of 14.4% (95%CI, 6.1 to 22.8%) against control group of ICU patients admitted from February 27th to March 31th 2019 and 13.1% (95%CI, 1.9 to 24.3%) against and control group of Influenza ICU patients admitted January 1th to December 31th 2019.*** The 3 PE identified in Influenzae patients were unilateral and subsegmental § 2 missing values. §§1 missing value Abbreviations: BMI=body mass index; CT=computed tomography; CTPA= CT pulmonary angiography; ICU=intensive care unit; PCR= Polymerase Chain Reaction; PE=pulmonary embolism; SAPSII= Simplified Acute Physiology Score, The SAPS II score provides an estimate of the risk of death without having to specify a primary diagnosis. It includes physiological variables, type of admission and underlying disease variables. Point score between 0 and 163 predicts mortality between 0% and 100%.; SOFA=Sequential Organ Failure Assessment, is a mortality prediction score that is based on the degree of dysfunction of six organ systems. The score is calculated on admission and every 24 hours, ranging from 0 (normal) to 4 (high degree of dysfunction/failure) for each organ failure. ARDS=Acute Respiratory Distress Syndrome