Association Between Pulmonary Embolism and COVID-19 in Emergency Department Patients Undergoing Computed Tomography Pulmonary Angiogram: The PEPCOV International Retrospective Study

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Abstract (Word count 276)

Background: There have been reports of pro-coagulant activity in patients with COVID-19. Whether there is an association between pulmonary embolism (PE) and COVID-19 in the emergency department (ED) is unknown. The aim of this study was to assess whether COVID-19 is associated with PE in ED patients that underwent a CTPA?

Methods: A retrospective study in 26 EDs from 6 countries. ED patients in whom a computed tomographic pulmonary angiogram (CTPA) was performed for suspected PE during a 2-month period covering the pandemic peak. The primary endpoint was the occurrence of a pulmonary embolism on CTPA. COVID-19 was diagnosed in the ED either on CT or RT-PCR. A multivariable binary logistic regression was built to adjust with other variables known to be associated with PE. A sensitivity analysis was performed in patients included during the pandemic period.

Results: A total of 3358 patients were included, of whom 105 were excluded because COVID-19 status was unknown, leaving 3253 for analysis. Among them, 974 (30%) were diagnosed with COVID-19. Mean age was 61 years (19) and 52% were women. A pulmonary embolism was diagnosed on CTPA in 500 patients (15%). The risk of PE was similar between COVID-19 patients and others (15% in both groups). In the multivariable binary logistic regression model, COVID-19 was not associated with higher risk of PE (adjusted odds ratio 0.98, 95% confidence interval 0.76 to 1.26). There was no association when limited to patients in the pandemic period.

Conclusion: In ED patients that underwent CTPA for suspected PE, COVID-19 is not associated with an increased probability of PE diagnosis. These results were also

valid when limited to the pandemic period. However, these results may not apply to patients with suspected COVID-19 in general.

Introduction

COVID-19 is currently one of the greatest worldwide threats to public health, and a challenge for researchers and physicians. The reported mortality ranges from 0.1% to 8% depending on the disease severity.[1] COVID-19 viral pneumonia is associated with hypoxia, a hyper-inflammatory state and coagulopathy.[2,3] High rates of elevated D-dimers have also been reported in case series, which may be associated with worse outcomes.[4,5] Rapid identification of patients with COVID-19 who are at risk of pulmonary embolism (PE) may improve prognosis by early initiation of anticoagulant therapy.[6]

In the emergency department (ED), the diagnostic strategy for PE is well established. Several clinical decision rules (CDR) have been validated to safely limit the use of irradiative imaging studies (especially computed tomography pulmonary angiogram [CTPA], considered as the gold standard). These CDR are based on a Bayesian approach that combines pre-test probability (i.e. suspected PE prevalence in the studied population estimated by a score or physician gestalt) with the D-dimer result to stratify risk and guide indication for CTPA. Application of the Pulmonary Embolism Rule Out Criteria (PERC) may safely exclude PE in patients with low clinical probability.[7] Other CDR such as the Wells or revised Geneva scores (RGS) are also recommended, and the recent YEARS protocol may allow the D-dimer threshold to be raised whilst still safely limiting the use of CTPA.[8–10] All these rules were validated before the COVID-19 pandemic, and their safety is based on estimated PE prevalence in the studied population. Since COVID-19 is reportedly associated with an increased risk of thrombo-embolic events, and the validity of these CDR is unknown, it is possible that during this pandemic, conventional ED diagnostic strategies for PE is unsafe. Furthermore, since decision rules are derived in specified

populations, a rule that applies to a stratified subpopulation of ED patients may also not extrapolate to the general population. Conversely, even if COVID-19 causes an increase in the risk of venous thromboembolism in the general population, this may not translate into a higher risk among ED patients with suspicion of PE. The aim of our study is to assess if COVID-19 is associated with PE in ED patients who underwent a CTPA for suspected PE, and to assess whether RGS based diagnostic strategy is safe in this period.

Methods

Design

This was a multicenter retrospective study in 26 centers from France, Spain, Belgium, Italy, Chile and Canada. The study was approved by the steering committee of Assistance Publique – Hôpitaux de Paris. Local ethics committees in all participating countries approved the study. Due to its retrospective nature on de-identified data, an informed consent was waived in all participating countries.

Patients and data

All patients who underwent a CTPA for suspected PE during the study period were included. Roughly, the COVID-19 peaks of ED visits ranged from late March to mid-April 2020. Since we wished to include patients from both prior to and during the COVID-19 pandemic, the overall study period was comprised between February 1st to April 10th 2020. The study period slightly differed in the different centers as the COVID-19 pandemic peak occurred at different periods in the participating centers. In each country, we considered that COVID-19 epidemic started when more than 100

patients were diagnosed positive, respectively March 4th, 6th, 15th, 15th, 18th and 24th in Italy, Spain, France, Chile, Belgium and Quebec.

All CTPA performed for ED patients during this period were collected, and data from the ED visits were collected. Patients with no COVID-19 status, inconclusive CTPA for the diagnosis of PE, or in whom CTPA was performed for a reason other than "suspicion of PE" were excluded.

Study data were obtained from the electronic health system of each center by local study investigators. Baseline characteristics, risk factors for PE and items from conventional CDR were collected.

Objectives and endpoint

The primary objective of this study was to assess whether COVID-19 was independently associated with PE in ED patients that underwent a CTPA. Secondary objectives included the validation of conventional diagnostic strategies using a combination of the Revised Geneva Score (RGS) and D-dimer in this period (Table 1), and to assess the diagnostic performance of D-Dimer amongst COVID-19 patients.

The primary endpoint was the presence of a pulmonary embolism on CTPA. Each CTPA was analyzed and interpreted by senior Radiologist.

In cases of inconclusive CTPAs, the patient was excluded from analysis. COVID-19 status was defined with the following rule:

- Negative during the pre-pandemic period (defined as first 100 diagnosed cases in the country)
- Positive if RT-PCR was positive

- Positive if lung CT showed evidence of a COVID-19 lesion, i.e. ground-glass opacities or crazy paving.[11]

In cases where RT-PCR was not performed and CT was indeterminate or with non-specific abnormalities, the patient was excluded because his/her COVID-19 status could not be determined. In the absence of positive RT-PCR, a patient with CT interpreted as “unlikely COVID-19” was considered as non Covid-19. In these patients, severity of CT lesions were not reported. Severity of COVID-19 lesions were graded as recommended by French Society of Radiology and other reports as moderate (extent <25), extended (25%-<50%), severe (50%-75%) and critical (> 75%).[12,13]

A simplified RGS was calculated using data collected during the ED visit (Table 1). Due to the retrospective nature of collected data, we merged the two items “unilateral lower-limb pain” and “pain on lower-limb deep venous palpation and unilateral edema” as “clinical signs of deep venous thrombosis”, with a weighting of 2 points. D-dimer, C-reactive protein and leucocytes were also collected. CT findings were classified according to their probability of COVID-19 (likely, compatible, unlikely) and their severity (mild, moderate, severe, critical).[14]

Statistical Analysis

Baseline characteristics were expressed as number (%) for categorical variables and mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, depending on their distribution. Separate bivariate analyses were performed to determine the unadjusted association between PE and the following known risk factors: age, sex, heart rate, previous thrombo-embolic event, hemoptysis, clinical signs of deep venous thrombosis, estrogen intake and

surgery/immobilization within four weeks. In addition, severity of COVID-19 symptom, period (before/after pandemic onset) and country of admission were studied too. A direct multivariable binary logistic regression model was built taking into account all known risk factors: : age, sex, heart rate, previous thrombo-embolic event, hemoptysis, clinical signs of deep venous thrombosis, estrogen intake and surgery/immobilization within four weeks (P value inferior or equal to 0.2 in univariate analysis or forced into the model), and in addition center of admission. Multicollinearity was investigated using in first correlation matrix and in second tolerance and variation inflation parameters. Due to violation of linearity in the logic for age as a continuous variable, it was categorized in the model using quartile values.. Receiver-operating characteristic (ROC) curve and Youden index were used to calculate the optimal cut-off of D-dimers for PE diagnosis. Several goodness-of-fit tests were performed to determine model performance (Hosmer-Lemeshow test, Standard Pearson test, Osius-test, McCullagh-test, Informative Matrix (IM) test and Unweighted Sum of Squares test).

To validate the safety of a RGS-based diagnostic strategy, we compared the rate of PE diagnosed in patients with low to intermediate RGS RGS and D-dimer below the age-adjusted threshold (i.e. 500 µg/ml under 50 years, and age x 10 over 50 years) in patients with and without COVID-19.[15,16]

Since physicians' threshold for ordering a CTPA may have changed during the pandemic period, we ran a sensitivity analysis limited to patients in this period.

P values <0.05 were considered significant. SAS V.9.4 software (SAS Institute Inc., Cary, NC) was used for statistical analyses.

Results

During the study period, 3,358 patients were included in the 26 participating EDs, 52% of whom were included during the pandemic period. Amongst them, COVID-19 status could not be determined in 105 patients (figure 1). A total of 3,253 were analyzed. The mean age was 61 years (SD 19) and 1,695 (52%) were women. Baseline characteristics are reported in table 2. There was no difference in patient characteristic between the two periods pre/post pandemic (Suppl table 1). Nine hundred and seventy four patients were diagnosed with COVID-19; 530 (54%) were diagnosed with both positive RT-PCR and CT, 370 (38%) on CT only and 74 (8%) only with RT-PCT.

Pulmonary embolism was diagnosed in 500 patients (15%); 148 patients (15%) had a COVID-19 diagnosis and 352 (15%) did not (difference 0.3% [95% confidence interval [CI] -3% to 3%], unadjusted odds ratio 0.98 [95% CI 0.78 – 1.19]). Amongst the 500 patients with PE, 59 (15%) were isolated sub-segmental,. A RGS of 5 or more (considered as high risk) was associated with a higher risk of PE (23% vs 14%, difference 9% [95%CI 1.5% to 15.7%]).

In the multivariable logistic regression analysis, there was no association between COVID-19 and PE (adjusted OR = 0.98, 95% CI 0.761 to 1.26). Hosmer-Lemeshow p-value was 0.40. The other goodness-of-fit tests had a $p>0.05$ except for IM test ($p=0.01$) There was no period effect between pre and post pandemic onset date (OR 1.02, 95%CI 0.83 to 1.24, $p=0.72$). The sensitivity analysis limited to the pandemic period reported similar results: COVID-19 had an adjusted OR of 1.10 (95%CI 0.79 to 1.52) for the risk of PE (Suppl table 2). Another sensitivity analysis after excluding the 59 isolated sub-segmental PEs reported that COVID-19 had an adjusted OR of 0.97 95%CI=[0.74 – 1.26] for the risk of PEs.

The area under the receiving operator characteristics curve of D-dimer for the diagnosis of PE was 0.79 (95%CI 0.76 – 0.81) for the general population, and 0.81 (95%CI 0.77 – 0.85) in COVID-19 patients (figure 2).

A total of 207 patients had a non-high clinical probability and D-dimer below the age-adjusted threshold, among whom 4 had a PE; one in a COVID-19 patient and three in non COVID-19 patients. The percentage of false negative for the RGS with age-adjusted threshold was respectively of 1.4% and 2.2%.

Discussion

In this multicenter retrospective study, we report that COVID-19 is not associated with increased risk of PE diagnosis among ED patients who underwent a CTPA. The risk of PE was of 15% in both groups, and the adjusted OR of COVID-19 for PE was 1.01 (95% CI 0.81 to 1.27).

This result is in contrast to recent reports and case series that highlighted a higher risk of thrombo-embolism in COVID-19 patients.[17,18] In our study, we focused on ED patients, who are, by definition, at the beginning of the part of their hospitalized stage of disease. Recent reports suggested an increased risk of thrombo-embolic events in admitted patients, both to wards and the intensive care unit. These patients may be at higher risk both because they were identified at a later stage of the disease, and also after a potential period of immobilization. Furthermore, these previous reports were not comparative, and therefore no definitive conclusion of increased risk could be made. It is likely that COVID-19 is associated with higher risk of PE in the general population, but our reports suggest that this is not the case among ED patients with suspicion of PE. This is in line with studies including pregnant women, who in the general population are at increased risk of thrombo-embolic events. However, in ED patients with suspected PE, pregnancy was not reported to be associated with higher risk of PE.[19]

We included patients based on whether a CTPA was performed in the ED. This is because the diagnostic strategy to rule out PE in the ED is based on a Bayesian approach, where the work-up (especially regarding the order of a CTPA) depends on the pre-test probability, which is dependent on PE prevalence in the studied population. We conducted this study to assess if COVID-19 was associated with PE, because if confirmed, it could have led to a change in the diagnostic strategy. Our

results suggest that the current strategy may be safe during COVID-19 pandemic because the pre-test probability of PE does not seem to depend on the COVID-19 status. Furthermore, only one ‘low risk’ (non-high RGS and D-dimer below age adjusted threshold) patient was diagnosed with a sub-segmental PE among COVID-19 patients. However, since we only included patients that had had a CTPA performed, it is possible some patients with a non-high RGS and low D-dimer had a PE missed in the ED because a CTPA was not ordered.

Limitation

This study has several limitations. Firstly, patients were included only if a CTPA was performed in the ED. This means that all patients that had a suspicion of PE and a negative D-dimer and a non-high clinical probability of PE were excluded. This inclusion bias limits our ability to conclude whether or not these results can apply to the whole ED population with suspicion of PE, and moreover to the general population. Among included patients, it is possible that some underwent a CTPA for an alternate diagnosis such as aortic dissection. After screening all CTPA performed during the study period, the local investigator sought in the patient's file whether the CTPA may have been performed outside a suspicion of PE and subsequently excluded him/her. However, we may have missed some CTPAs with no clear listed indication and have a subsequent inclusion bias. Furthermore, it is possible that during the COVID-19 pandemic, emergency physicians may have had a lower threshold for ordering a CTPA especially because COVID-19 has been reported to be associated to higher risk of PE, and also because a lung CT was often performed to diagnose COVID-19. However, the patient's baseline characteristic was similar between the two periods (Supplemental table), and we found no period effect in the analysis (Supplemental table 2). Furthermore, the sensitivity analysis restricted to patients included in the pandemic period reported similar result, with no association between COVID-19 and risk of PE (Supplemental table 3). However, a bias may still exist since the potential risk of COVID-19 induced coagulopathy was not described at the beginning of the pandemic period but after a few weeks. This bias is limited because patients were included until april 10th, before physicians were aware of suspected COVID-19 induced coagulopathy. A sensitivity analysis with time forced in

the model as a categorical variables (weeks of inclusion) reports similar results with no effect of time (Supplemental table 4).

Second, defining the presence of COVID-19 in the ED may be difficult. We excluded 105 patients in whom COVID-19 status could not have been determined, but it is possible that other patients were wrongly classified. The reported sensitivity for the diagnosis of COVID-19 of RT-PCR ranges from 71%to 98% and 93% to 97% for lung CT.[20,21] To mitigate this, in this study, patients were considered to have COVID-19 if one or the other of the tests was positive, which limited the risk of false negatives. In 38% of cases, the diagnosis of COVID-19 was only adjudicated on CT. This is in part caused by the limited availability of RT-PCR testing in France, and the longer turnaround time for RT-PCR results compared to CT. In these patients, the sub-optimal specificity of CT could have led to false positives, and radiologists exhibited moderate performances in differentiating COVID-19 pneumonia from other viral pneumonia on lung CT.[22,23] This limit is inherent to our design, and represents a classification bias. However, this can be seen as a challenge faced in the day to day clinical practice of emergency medicine and patients with a suspected COVID-19. In our study, sensitivity of RT-PCR was 84% and false negative rate was 23%, which is consistent with what has been reported in the literature.[20] However, we cannot exclude that some COVID-19 patients may have had both false negative PCR and false negative CT.

In addition, we found a center effect and investigated this.It transpired that French EDs was a protective factor for PE (adjusted OR 0.61, 95%CI 0.48 – 0.78), which suggest different practice patterns across countries. This may reflect the fact that heterogenous data sources were combined, especially in light of the fact that French EDs dominated the sample size. The multivariable model adjusted the results for this

association, but whether this could affect the external validity of our results is unknown.

Last, as a retrospective study, although the case record form was standardized, there was no monitoring of data collection methods in the 6 countries and 26 sites. This was mitigated by making the data required as pragmatic and minimal as possible to satisfy the primary objective.

Conclusion

In ED patients that had CTPA performed for suspected PE, COVID-19 was not associated with a higher risk of PE. These results suggest that conventional diagnostic strategies for PE in ED patients with suspected COVID-19 are safe.

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Figure 1: Flow diagram. PE: pulmonary Embolism.

Figure 2: Receiving operator characteristic curves of D-dimer for diagnosis of pulmonary embolism in the emergency department.

A) whole population: area under the curve = 0.79, 95%CI=[0.76 ; 0.81]

B) COVID-19 patients: area under the curve = 0.81, 95%CI=[0.77 ; 0.85]

Variable	
Age > 65 years	1
Previous DVT or PE	1
Surgery or immobilisation within 1 month	1
Active malgnant condition	1
Clinical signs of DVT	2
Heart rate, beats/min	
75-94	1
≥ 95	1

Table 1: Simplified revised Geneva score. DVT: deep venous thrombosis. PE: pulmonary embolism. Score ranges from 0 to 8. High probability defined by a score > 4. From the original score,“unilateral lower-limb pain” and “pain on lower-limb deep venous palpation and unilateral edema” were merged as “clinical signs of deep venous thrombosis”, with a weigh of 2 points.

Variable	n	PE n=500	No PE n=2753
Age (years), mean (SD)			
Sex			
Female	3253	234 (45%)	1471 (53%)
ED from France	3253	358 (72%)	2276 (83%)
Post pandemic period	3253	252 (50%)	1642 (51%)
Comorbidities			
Chronic respiratory insuficiensy	3248	42 (8%)	276 (10%)
Hypertension	3247	207 (42%)	1087 (40%)
Chronic heart failure	3248	61 (12%)	476 (17%)
Chronic kidney failure	3245	26 (5%)	133 (5%)
ED presentation			
Chest pain	3245	179 (36%)	1075 (39%)
Shortness of breath	3249	349 (70%)	1731 (63%)
Syncope	3245	60 (12%)	384 (14%)
Delay from onset to ED visit, median (IQR)	2883	3 [1; 7]	3 [1;7]
Heart rate (/min) , mean (SD)	2893	97 (20)	93 (20)
Respiratory Rate (/min), mean (SD)	2297	23 (7)	23 (7)
SpO2 (%), median [IQR]	3104	96 [93; 98]	97 [94; 99]
Systolic blood pressure, mean (SD)	3191	134 (24)	137 (24)
Temperature (°C), mean (SD)	3123	36.8 (0.8)	37 (0.9)
Risk factors for PE			
Estrogen use	3236	12 (2%)	78 (3%)
Clinical signs of DVT	3247	101 (11%)	248 (9%)
Surgery or trauma requiring immobilisation within 1 month	3246	53 (11%)	168 (6%)
Past history of PE or DVT	3245	106 (21%)	279 (10%)
Hemoptysis	3245	15 (3%)	104 (4%)
Active malignancy	3246	68 (14%)	374 (14%)
Laboratory results			
D-dimer (ng/ml), median (IQR)	2495	4270 [1730; 10000]	1181 [762; 2105]
Leucocytes, mean (SD)	3106	10.6 (4.6)	9.1 (5.1)
C-reactive protein, median (IQR)	2758	23 [7; 83]	14 [4; 65]

Table 2: Baseline characteristics. ED: emergency department SD: standard deviation. IQR: Interquartile range. PE: pulmonary embolism. DVT: deep venous thrombosis

		PE		No PE
		n=500		n=2753
Signs of COVID-19				
Very likely		82 (16%)		470 (17%)
Compatible		54 (11%)		296 (11%)
Unlikely		364 (73%)		1987 (72%)
Extent of lesions	**n=127**		**n=711**	
Moderate		35 (28%)		197 (28%)
Extended		47 (37%)		238 (33%)
Severe		40 (31%)		255 (36%)
Critical		5 (4%)		21 (3%)
RT-PCR COVID-19				
Performed		202 (40%)		1136 (41%)
Positive		80 (16%)		524 (19%)
Confirmed COVID-19		148 (30%)		826 (30%)

Table 3: COVID-19 status. PE: pulmonary embolism. RT-PCR: reverse transcriptase polymerase chain reaction. Extent of lesions: Moderate < 25%, extended 25-50%, Severe 50-75% and Critical >75%.

Variable	Bivariate		Multivariate	
	OR [95%CI]	**p-value**	**OR [95%CI]**	**p-value**
Covid-19	0.95 [0.77 – 1.18]	0.66	0.98 [0.76 – 1.26]	0.86
Sexe male	1.34 [1.10 – 1.62]	**0.0035**	1.46 [1.18 – 1.80]	**0.0005**
Age (quartile)		**0.0033**		**0.0186**
[75 – 103]	1.70 [1.28 – 2.25]		1.63 [1.20 – 2.21]	
[63 – 75[	1.43 [1.07 – 1.92]		1.38 [1.01 – 1.89]	
[48 – 63[	1.45 [1.08 – 1.94]		1.33 [0.98 – 1.81]	
[18 – 48[	1		1	
Heart rate (bpm)	1.01 [1.00 – 1.01]	**0.0007**	1.01 [1.01 – 1.02]	**<0.0001**
Past thrombo-embolic event	2.41 [1.87 – 3.10]	**<0.0001**	2.32 [1.77 – 3.04]	**<0.0001**
Hemoptysis	0.81 [0.47 – 1.41]	0.46	0.84 [0.48 – 1.50]	0.56
Clinical sign of DVT	2.53 [1.95 – 3.28]	**<0.0001**	2.31 [1.73 – 3.08]	**<0.0001**
Recent immobilisation	1.93 [1.39 – 2.68]	**<0.0001**	1.92 [1.34 – 2.75]	**0.0004**
Active cancer	1.97 [0.73 – 1.30]	0.85	0.76 [0.56 – 1.05]	0.09

Table 4: Univariate and multivariable analysis, adjusted for center effect (p<0.001) Age according to quartile. DVT: deep venous thrombosis. ED: emergency department. Overall classification rate (precision of the model): 69%, Hosmer Lemeshow p value: 0.4.
Severity of CT lesion and pandemic period were not associated with PE (p=0.72 and p=0.54 respectively).