Full Length Article

Pulmonary embolism in patients with COVID-19 pneumonia: When we have to search for it?

L. Filippi [a,1], M. Sartori [a,b,1,*], M. Facci [a], M. Trentin [a], A. Armani [a], M.L. Guadagnin [a], P. Prandoni [a]

[a] *Alto Vicentino Hospital*
[b] *Università degli studi di Padova*

A B S T R A C T

Background: COVID-19 is still a global challenge in regard for management and therapy. Pulmonary embolism (PE) seems to have a higher prevalence in COVID-19 instead of non-COVID patients. Clinical and laboratory parameters related with PE are still unknown.
Methods: We conducted a retrospective unicentre study in Alto Vicentino Hospital between March 1st, 2020, and January 31st, 2021 in patients admitted for COVID-19 tested with a RT-PCR nasal swab. Data about patients studied with computed tomography pulmonary angiogram (CTPA) because of PE suspicion were collected, as their clinical and laboratory parameters too.
Results: 2621 patients were admitted for COVID-19 in Alto Vicentino Hospital between March 1st, 2020, and January 31st, 2021 and in 267 of them a CTPA was performed finding 50 PE (18.7%). Only non-Caucasian race (OR = 5.44; 95% CI 1.22–24.35; p = 0.027) and previous VTE (OR = 5.3; 95% CI 1.09–26.17; p = 0.039) were found to be independently associated with PE.
Conclusion: PE is a frequent complication of COVID-19 and clinician need high degree of suspicion because clinical and laboratoristic parameters cannot drive diagnosis.

1. Introduction

Coronavirus disease 2019 (COVID-19) is still a global challenge in health and non-health settings, given the high association with both morbidity and mortality [1].

In all age groups, and especially in elderly, the main targets of SARSCoV-2 infection are pulmonary epithelial cells, lymphocytes and vascular endothelium with global involvement of the organism, including significant haemostatic alterations [2].

Endothelial damage comes with an inflammation-driven activation of coagulation, resulting in an increased thrombotic risk. In particular, there is a high release of inflammatory mediators, increased levels of factor VIII, von Willebrand factor, fibrinogen and local fibrinolysis with increased D-dimer [3].

These conditions, together with the venous thromboembolism (VTE) risk in hospitalized patients, lead to an increased incidence of thrombosis [4]. The risk is greatly increased in patients hospitalized for COVID-19 disease, and, in particular, acute pulmonary embolism represents a potentially severe complication of the disease [5–8]. A recent meta-analysis report at 17.9% incidence of PE in emergency department, 23.9% in general wards and 48.6% in ICU [9]. In this regard, the most authoritative medical societies have suggested some recommendations for anticoagulation to prevent and treat these complications [10–12].

As we had the opportunity to perform computed tomography pulmonary angiograph (CTPA) in a broad number of patients admitted to our hospital during the current pandemic, because of the clinical suspicion of PE, we report here the prevalence of PE we observed. In addition, we assessed the association of several clinical and laboratory parameters with the risk of PE.

2. Materials and methods

We conducted a retrospective study in Alto Vicentino Hospital in

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Vicenza (Italy) evaluating all CTPA performed between March 1st, 2020, and January 31st, 2021 in patients with a positive reverse transcriptase polymerase chain reaction (RT-PCR) for Sars-CoV2 virus on nasopharyngeal swab. The RT-PCR test was developed in-house by the Microbiology Laboratory. CT angiograms were acquired on 64 row or greater scanners after injection of 50 to 75 mL of high concentration iodine contrast media, with the use of a bolus-tracking technique and a threshold of 160 HU to 250 HU in the main pulmonary artery. Images were reconstructed with a slice-thickness of 1 mm In Press in mediastinal and parenchymal windows. A single reader (ILL) classified pulmonary embolism location as main pulmonary, lobar, segmental or subsegmental arteries based on the location of the most proximal luminal defect.

Patient charts were reviewed for demographic, laboratory, and clinical outcome variables. The reason why patient had been referred for CTPA was obtained from electronic medical records, as well as the categorisation as intensive care unit (ICU) or sub-ICU or ward patient, the need for mechanical ventilation or non-invasive ventilation (NIV) and the respiratory worsening during hospitalisation. Information regarding laboratory tests (d-dimer, pCO2, P/F) and type of prophylactic anticoagulation was collected from clinical record. Wells-PE score [13] was calculated based on clinical variables (clinical signs and symptoms of DVT, probability of PE, heart rate, immobilization at least 3 day or recent surgery, previous diagnosed VTE, hemoptysis, presence of cancer). In patient with concomitant clinical symptoms of deep venous thrombosis (DVT) of the lower extremities, an echo color Doppler was performed and interpreted according to standardized criteria.

2.1. Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation, whereas non-normal distributed ones as median and interquartile range. Categorical variables were reported as numbers and percentages. Continuous normally-distributed variables were compared by using the Student *t*-test; Categorical variables were compared with chi-squared test, or Fisher exact test, when appropriate.

Univariable and multivariable logistic regression analyses were performed to evaluate the individual and independent association of clinical and laboratoristics variables with the occurrence of PE, and presented as odds ratio (OR) with by their 95% confidence intervals (CI). Multicollinearity was assessed using collinearity diagnostics. The variance inflation factors showed no significant collinearity (<2.5) among the covariates.

We used a parsimonious model including variables with p < 0.05 by the univariate test as a candidate for the multivariate analysis.

A multivariable logistic regression analyses were performed to evaluate the risk of in-hospital death in patients with vs. those without PE and presented as odds ratio (OR) with by their 95% confidence intervals (CI).

3. Results

Between March 1st 2020 and January 31st 2021, 2621 patients with RT-PCR test positive for Sars-CoV2 were admitted to our hospital. CTPA was performed in 267 (9%) patients. Relevant clinical and biological data are summarized in the Table 1, separately for patients with and without PE.

The population mean age was 69,9, and male sex rate was 64%. Out of 267 patients with COVID-19 who underwent CTPA, PE was shown in 50 (18.7%). As shown in Table 1, there were no differences between patients with and without PE with regard to sex, age, or nutritional status. PE patients were more likely to belong to the non-Caucasian race (10% versus 3.2%), and to have a high pre-test clinical probability of PE (>4) according to the Wells score (24% versus 9.7%). As shown in Table 1, there were no differences between patients with and without PE in terms of in-hospital setting, concurrent antithrombotic treatments

Table 1

Clinical and demographic features of the study population.

	PE present (n = 50)	PE non-present (n = 217)	p value
Males:females	31:19 (62%:38%)	141:76 (65%:35%)	0.692
Age (y)	68.86 [65.79–71.93]	70.12 [68.47–71.76]	0.505
Obesity (%)	10 (20%)	38 (17.6%)	0.069
Non-Caucasian race	5 (10%)	7 (3.2%)	0.037
Score Wells ≥4	12 (24%)	21 (9.7%)	0.006
Bed rest	27 (54%)	114 (52.5%)	0.852
Previous VTE	4 (8%)	4 (1.8%)	0.021
Active cancer	7 (14%)	10 (4.6%)	0.014
ICU setting	2 (4%)	9 (4.2%)	0.953
Sub-ICU setting	9 (18%)	35 (16%)	
Medical setting	39 (78%)	172 (79.6%)	
Fever onset >7 days	15 (30%)	72 (33.3%)	0.651
Steroids before CT scan	36 (72%)	161 (74.5%)	0.712
Prophylactic LMWH before CT scan	36 (73.5%)	156 (71.9%)	0.672
Therapeutic LMWH before CT scan	3 (6.1%)	15 (6.9%)	
DOAC before CT scan	1 (2%)	11 (5%)	
D-Dimer <500 before CT scan	4 (8%)	15 (7%)	<0.0001
D-Dimer 500–1500 before CT scan	6 (12%)	87 (41%)	
D-Dimer 1500–4000	7 (14%)	53 (25%)	
D-Dimer >4000	33 (66%)	57 (26%)	
Low platelet (<150,000) before CT scan	9 (18%)	36 (16.7%)	0.694
P/F < 100 before CT scan	13 (27.1%)	46 (22%)	0.203
P/F 100–200 before CT scan	18 (37.5%)	108 (51.7%)	
P/F > 200 before CT scan	17 (35.4%)	55 (26.3%)	
Tachypnea before CT scan	29 (58%)	106 (49.3%)	0.268
Low pCO2 (<35) before CT scan	21 (50%)	92 (47.7%)	0.784

P/F: PaO2/FiO2 ratio.

and several clinical and laboratory parameters, except for the baseline D-dimer, which was significantly higher in patients with than in those without PE. Indeed, a baseline D-dimer higher than 4000 ng/mL was found in 33 (66%) and 57 (26%), respectively (p < 0.001). At multiple logistic regression only non-Caucasian race (OR = 5.44; 95% CI 1.22–24.35; p = 0.027) and previous VTE (OR = 5.3; 95% CI 1.09–26.17; p = 0.039) were found to be independently associated with PE (Table 2).

As far as the thrombotic burden in patients with PE is concerned, 34% of PE patients had the involvement in the main and or the lobar pulmonary arteries, while in 46% of patients the most proximal location was in the segmental arteries, and in 17% in the subsegmental ones (Table 3.)

As shown in Table 4, the percentages of death from any cause (24,5% vs 16,4%; p = 0,180), of increase in the oxygenation modality (58% vs 47%; p = 0,160), and increase in intensity of care (42% vs 33%; p = 0,247) did not differ between patients with and without PE.

Table 2

Multivariable regression analyses for the occurrence of pulmonary embolism.

	OR ratio	95% CI	p value
Non-Caucasian race	5.44	1.22–24.35	0.027
Wells score < 4	0.68	0.27–1.72	0.420
Previous VTE	5.34	1.09–26.17	0.039
Associated cancer	2.34	0.725–7.529	0.155
D-Dimer 500–1500	0.29	0.069–1.26	0.100
D-Dimer 1500–4000	0.53	0.13–2.23	0.386
D-Dimer >4000	2.29	0.633–8.27	0.206

Table 3
Pulmonary embolism characteristics.

	PE (n 50/267)
Principal/lobar	17 (34%)
Segmentary	23 (46%)
Subsegmentary	10 (20%)

Table 4
In-hospital adverse events.

	Total (n = 267)	PE (n = 50)	Non-PE (n = 217)	p value
Death	47 (17.9%)	12 (24.5%)	35 (16.4%)	0.180
Increase in oxygenation	130 (49%)	29 (58%)	101 (47%)	0.160
Increase in care intensity	93 (35%)	21 (42%)	72 (33.3%)	0.247

4. Discussion

The incidence of PE we found in our cohort of patients (18.7%) is higher than observed in previous studies [14], but consistent with that reported in a recent meta-analysis of available investigations [15]. The relatively high rate is likely to be explained by the high proportion of patients with severe disease (20.7% of our cohort). Indeed, the rate of PE arising in patients admitted because of SARS CoV2 has been consistently found to increase according to the disease severity [15]. In addition, in agreement with several reports [16,17], symptomatic PE developed in spite of the adoption of thromboprophylactic measures in the vast majority of our patients, including all those with the most severe clinical presentation. Of interest, all patients underwent objective confirmation because of clinically symptomatic PE, and standardized methods and criteria were used to perform and interpret the CTPA. In agreement with most available investigations [16,17] most embolic complications involved peripheral (segmental or subsegmental) arteries in the absence of concomitant manifestations of DVT, thus providing an indirect support to the local origin of the thrombotic burden. The risk of PE was not influenced by the age and sex of the recruited individuals (p = 0.5 and 0.7, respectively), whereas it was significantly related to the non-Caucasian race (p = 0.04). These findings are consistent with those reported in investigations conducted in patients with infectious respiratory diseases other than the COVID one [11].

Of interest, hypocapnia, tachypnea, worsened respiratory pattern (i. e., the clinical manifestations that prompted the request of CTPA most), and the positivity of the pre-test clinical probability of PE according to the Wells score did not correlate with the development of PE, most likely because of the low specificity of clinical manifestations or parameters shared by the disease itself.

Surprisingly enough, the baseline value of the D-dimer test did not correlate with the development of PE, except for the little minority of patients with a baseline D-dimer exceeding 4000 ng/mL. In all other patients the clinical suspicion was as likely to be confirmed or confuted by CTPA. This finding is inconsistent with several available reports [15] and suggests that D-dimer as a standalone parameter is not a reliable marker of thromboembolic complications in a clinical scenario dominated by (severe) infectious/inflammatory disorders. Indeed, D-dimer is likely to correlate with the severity of COVID-19 disease irrespective of the occurrence of PE. The mechanism behind the development of VTE could be, in turn, the consequence of an inflammation-driven activation of coagulation. Indeed, infection is expected to induce tissue damage, activation of monocytes and macrophages, as well as the release of several substances, such as tissue factor, cytokines and interleukin, which in turn can activate the extrinsic pathway of coagulation and increase platelets activity [8]. In addition, endothelial dysfunction can promote microvascular thrombosis and impair the fibrinolytic system [9]. Finally, the use of drugs such as steroids may increase the thrombotic risk [10].

Whether the development of PE has the potential to impact patients' prognosis is controversial, as there are scientific contributions in favour and against this association [15,16]. We failed to show a correlation between PE and intensification of care or mortality.

Of relevant interest, a substantial proportion of our patients developed PE complication in spite of the systematic adoption (in almost 90%) of preventive doses of enoxaparin. Our findings are consistent with those reported in several recent reports [15,16] As the results of a recent randomized clinical trial failed to show any appreciable advantage of intermediate over preventive doses of enoxaparin in patients with severe disease [18], the heparin dosage associated with the best benefit-to-risk ratio remains to be identified.

Based on the retrospective design and the unavoidable selection of patients' candidates to CTPA, the interpretation of our study results requires caution. However, our findings suggest that the rate of PE complications in patients admitted to medical wards because of a SARSCoV-2 infection is high, whichever the disease severity, is not adequately preventable with the conventional doses of LMWH, and is virtually not predictable with the adoption of the most conventional clinical and laboratory parameters.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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