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# Pulmonary Embolism (PE) Prevalence in Mexican-Mestizo Patients With Severe SARS-COV-2 (COVID-19) Pneumonia At A Tertiary-Level Hospital: A Review

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**Abstract:** Since the report of the first case of COVID-19 in Wuhan, China, on December 31, 2019, several associated thrombotic complications have been reported, mainly venous thromboembolic events, and myocardial infarctions, in addition to peripheral arterial thrombosis and cerebral vascular events, which have been attributed to a hypercoagulable state. We aimed to know the prevalence and prognostic biomarkers in patients with pulmonary thromboembolism (PE) and SARS Cov-2 pneumonia. Hospitalized

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patients with SARS Cov-2 pneumonia who have had clinical, biomarker, and imaging data (chest angiography) of pulmonary thromboembolism were included. Descriptive statistics and prevalence rates were calculated. For the analysis between the groups, the paired Student's t and the Wilcoxon test were performed. CT angiography was performed on 26 patients at our institution, with a diagnosis of severe pneumonia secondary to SARS-CoV2. 9 of the patients (34.6%) had a venous thromboembolic disease. Type 2 DM was the most frequent comorbidity up to 55.5% of the total; it was followed by obesity and overweight in 55.5%, and in third place, by systemic arterial hypertension in 33.3% of the cases, 1 (11.1%) patient had chronic kidney disease and 1 (11.1%) patient with a history of cancer, only 1 patient met criteria and was treated with thrombolysis. 6 (66.6%) of the patients had segmental PE, 3 (33.3%) patients had subsegmental PE, and 4 (44.4%) patients presented pulmonary infarction. (Curr Probl Cardiol 2023;48:101208.)

## Introduction

**T**he emerging coronavirus disease (COVID-19) is caused by the new severe acute respiratory syndrome coronavirus (SARS-Cov-2), which is the cause of the ongoing pandemic that, as of March 29, 2022, had 481,756,671 confirmed cases and 6,127,981 confirmed deaths.<sup>1</sup> On the same date, in Mexico, one of the most affected Latin American countries, the number of confirmed cases was 5,935,727 and 337,070 deaths, according to the Government of Mexico.<sup>2</sup>

## Epidemiology

Since the report of the first case of COVID-19 in Wuhan, China, on December 31, 2019, several associated thrombotic complications have been reported, mainly venous thromboembolic events, and myocardial infarctions, in addition to peripheral arterial thrombosis and cerebral vascular events, which have been attributed to a hypercoagulable state.<sup>3-5</sup>

High prevalence of venous thromboembolic disease (VTE) has been reported in patients with COVID-19 in intensive care units (ICU) despite the use of thromboprophylaxis of up to 27% and arterial thrombotic

events in 3.7%. Being PE is the most frequent thrombotic complication in 81% of the cases.<sup>4</sup>

## Pathophysiology of Thrombus Formation

One hypothesis that has been related to the presence of pulmonary embolism in patients with SARS Cov 2 pneumonia is that the pathophysiology of thrombus formation is different since it is believed that thrombi are formed in the pulmonary vessels due to local inflammation process more than classic thrombi coming from other parts of the body, mainly the extremities.<sup>6</sup>

COVID-19 disease can lead to activation of systemic coagulation and thrombotic complications. The clinical spectrum of the disease is vast and nonspecific. Among the various clinical and biochemical parameters associated with poor prognosis, increased D-dimer levels have gained particular attention as a predictor of the development of acute respiratory distress syndrome (ARDS) and the need for admission to an intensive care unit (ICU) or death.<sup>7,8</sup>

On the other hand, the severity of the disease is also correlated with pro-inflammatory cytokines (IL-2, IL6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF- $\alpha$ ). The cause of the cytokine storm is not yet clear, though. These findings are consistent with the close connection between thrombosis and inflammation, 2 mutually reinforcing processes. Generally, with viruses, evidence suggests that inflammation of immune and non-immune cells can lead to an imbalance of pro and anticoagulant states during infection.<sup>9</sup> Since the endothelium plays an essential role in regulating homeostasis, and because it is altered in viral infections, the risk of hematological alterations is imminent. Additionally, the viral infection-induced elevation of von Willebrand factor, activation of the Toll-like receptor, and activation of the tissue factor pathway may play a role in the coagulant cascade, leading to the formation of cross-linked fibrin clots.<sup>10,11</sup>

## Laboratory Findings

High levels of C-reactive protein, leukopenia, lymphopenia, mild thrombocytopenia, prolonged prothrombin time (PT), and elevated levels of D-dimer and fibrinogen have been described within the characteristic laboratory findings. The diagnosis is confirmed by a real-time polymerase chain reaction (RT-PCR) test.<sup>4</sup>

## Histopathological Findings

The pulmonary histopathological findings reported are diffuse alveolar damage consistent with acute respiratory distress syndrome, hyaline membranes, activated pneumocytes, microvascular thromboembolism, capillary congestion, and protein-rich interstitial edema.<sup>12</sup>

## Thrombus Prophylaxis

Patients hospitalized for pneumonia due to COVID-19 should receive thrombus prophylaxis to prevent thromboembolic events if they do not have contraindications, and angiotomography continues to be the cornerstone for the diagnosis of PE, so it should be considered in patients with elevated D-dimers and sudden clinical deterioration.<sup>6</sup> Elevation of D-dimer, lymphopenia, age, and prolonged clotting times have been identified as independent predictors of thrombotic complications.<sup>4</sup>

## Methods

Venous thromboembolism (VTE) comprises deep venous thrombosis (DVT) and pulmonary embolism (PE), which can lead to death.<sup>13</sup> In an observational study at our institution, hospitalized patients with SARS-Cov-2 pneumonia with positive RT-PCR were selected; they had prognostic biomarkers (D-dimer, C-reactive protein, and ferritin). A chest CT angiography was performed to detect pulmonary thromboembolism with evidence of filling defects. Variables recorded included laboratory tests, comorbidities, and imaging findings.

## Demographics

A chest CT angiography was performed in 26 patients with severe pneumonia secondary to SARS-CoV2. It was found that 9 of the patients (34.6%) had a venous thromboembolic disease, of which 3 patients were of female gender and 6 male genders (Table 1). Among the comorbidities, type 2 DM was the most frequent, up to 55.5% of the total; it was followed by obesity and overweight in 55.5%. The third most frequent was systemic arterial hypertension in 33.3% of the cases.

Comparison of laboratory findings is shown in Table 2.

## Comorbidities

One patient (11.1%) had chronic kidney disease, and another (11.1%) patient had a cancer history. 7 (77.7%) of the patients were hospitalized,

**TABLE 1.** Demographic characteristics

Demographic characteristics	Patients with pneumonia (Covid-19 +)
Age	57.8 ± 13.9 y
Sex	Female 3 Male 6
BMI	28.8
Comorbidities	DMT2 5(55.5%) Obesity/overweight 5(55.5%) Systemic arterial hypertension 3(33.3%) Chronic kidney disease 1(11.1%) Cancer 1(11.1%)
Hospitalized with VTE	7(77.7 %)
Out-of-hospital with VTE	2(22.2 %)
Anticoagulation	Low molecular weight heparin 5 (55.5%) Low molecular weight heparin full dose 1 (11.1%) Unfractionated heparin 2 (22.2%) Oral anticoagulants 0 Systemic thrombolysis 1 (11.1%)

and 2 (22.2%) corresponded to outpatients. Five of the patients (55.5%) received low molecular weight heparin-based treatment; only 1 patient was treated with thrombolysis.

## Imaging Findings

In the tomographic findings, 9 patients presented PE, 1 patient had deep vein thrombosis and CNS arterial thrombosis, 6 (66.6%) of the patients had segmental PE, 3 (33.3%) subsegmental PE, 4 (44.4%) patients had pulmonary infarction and 2 (22.2%) pleural effusion (Fig 1). Age and laboratory findings were evaluated as predisposing factor

**TABLE 2.** Laboratory tests were performed on patients with and without PE

Variable	PE(+)	PE(-)	P-value
Age	49 ± 15.4	57.8 ± 13.9	0.199
Leukocytes	10,688 ± 5,268	8,914.3 ± 5,328.9	0.463
Lymphocytes	783.5 ± 341.4	1000 ± 374.2	0.183
Platelets	291,588 ± 12,9940	281,857 ± 14,6691	0.874
Fibrinogen g/l	539.56 ± 241.2	602.4 ± 232.7	0.567
D-dimer ng/ml	9,585.47 ± 12,850	14,870.3 ± 17,773.7	0.421
Ferritin ng/ml	1239.8 ± 1387.7	1178 ± 858.8	0.920
CRP mg /l	17,0.9 ± 90.2	15,7.63 ± 168.3	0.814
DHL UI/L	658.6 ± 257.7	420 ± 143.8	0.032*
Procalcitonin ng/mL	2.69 ± 5.9	0.7 ± 0.66	0.430
Troponin I ng/mL	77.36 ± 151.5	68.36 ± 81.4	0.902
CPK MB ng/dl	37.42 ± 35.3	22 ± 11.5	0.476

P-value (\*) < 0.05

**TABLE 3.** Tomographic findings of PE in the nine patients

Location of PE in patients with Pneumonia (Covid-19 +)	Number (percentage)
Pulmonary embolism	9 (34.6 %)
Central o lobar	0
Segmental	6 (66.6 %)
Subsegmental	3 (33.3 %)
Pulmonary infarction	4 (44.4 %)
Pleural effusion	2 (22.2 %)
Deep vein thrombosis of the pelvic limbs	1 (11.1 %)
CNS arterial thrombosis	1 (11.1 %)

for PE; however, all biochemical biomarker was found within normal parameters for the presence of venous thromboembolic disease.

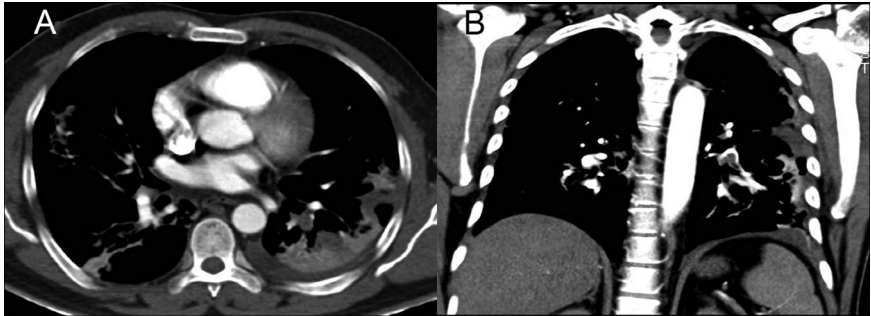
Table 3 shows the tomographic findings in PE.

## Discussion

Since the pandemic spread of SARS-CoV-2, there have been several anecdotal reports from colleagues of a high prevalence of thrombotic complications, including extracorporeal thrombosis of continuous veno-venous hemofiltration (CVVH) circuits, central venous access associated thrombosis, as well such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Most but not all of these complications occurred in patients admitted to the ICU, and most patients received routine thromboprophylaxis. We found only 1 report about using higher dose CVVH to prevent cytokine storm complicating COVID-19.<sup>14</sup>

PE should be suspected in hospitalized patients with sudden-onset dyspnea, increased oxygen requirement, hemodynamic instability, and dissociation between clinical manifestations and respiratory and hemodynamic status. Dyspnea can present in a severe and acute form, mainly in embolism of the main branches; however, in cases of distal PE, dyspnea may be mild and transient.<sup>15</sup>

Prevalences between 20 and 30% have been reported in foreign studies. There were no studies on the prevalence of PE in our population, so we undertook the task of investigating it in such a way that in 26 of the patients who underwent chest angiotomography, it was observed that 34.6% had pulmonary thromboembolism, 1 patient had deep vein thrombosis, and 1 patient had CNS arterial thrombosis. Pulmonary emboli in patients with COVID-19 showed a bilateral distribution in 6 (66.9%) patients, right in 5 (55.5%) patients, and left in 4 (44.4%) without patients



**FIG 1.** Chest CT angiography shows in axial (A) and coronal (B) planes multiple hypodense filling defects that occlude the entire left basal segmental branch, in addition to a hypodense, triangular image with a pleural base that does not enhance evincing an area of pulmonary infarction (Color version of figure is available online.)

with proximal involvement. Nine patients had the distal pulmonary vascular disease (segmental and subsegmental), and 4 of them also had pulmonary infarction. This finding is not frequently reported despite the distal predominance of PE in COVID-19.<sup>16</sup>

Our patients' comorbidities in order of frequency were type 2 DM, obesity and overweight, and subarachnoid hemorrhage. Some authors suggest that the elevation of D-dimers may be a prognostic marker of the evolution of the disease since they relate it to the activation of coagulation in response to an inflammatory response syndrome in patients with COVID-19 or even as a consequence direct from SARS-CoV-2 itself, however, in our series we did not document significant correlation in D-dimers and other biomarkers (lymphocytes, platelets, fibrinogen, ferritin, CRP, DHL, C-reactive protein, Troponin I and CPK MB) in patients with VTE and COVID-19, vs COVID-19 patients without VTE.<sup>17</sup>

The new emerging disease caused by SARS-CoV2 leads to the activation of systemic coagulation and thrombotic complications. It has been reported in ICUs in foreign countries that despite using thromboprophylaxis, there is up to 27% venous thrombosis and arterial thrombotic events in 3.7%, with PE being the most frequent thrombotic complication in 81% of cases. In our institution, an incidence of 36.4% of venous thromboembolic disease was obtained, with PE being the most frequent, the results are similar to foreign countries, and the figure is not negligible, so we should suspect it even when the patient with severe pneumonia secondary to SARS-CoV2 is found with thromboprophylaxis.



## Conclusions

The prevalence of PE is frequent in patients with COVID-19. Its higher prevalence may be related to the severity of the extent of lung parenchymal involvement. However, no significant differences have been found in the location of the embolic material or the degree of elevation of D-dimers between patients with PE and COVID-19 infection compared to patients with PE without COVID-19. As a finding of interest in our series, pulmonary infarction and pleural effusion were documented; however, more studies are required to determine which factors are associated with PE in patients with COVID-19 and better define the indications for pulmonary CT angiography.

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