Clinical Outcomes of Pulmonary Embolism in Mexican Patients With COVID-19

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Abstract
Coagulation abnormalities have been reported in COVID-19 patients, which may lead to an increased risk of Pulmonary Embolism (PE). We aimed to describe the clinical characteristics and outcomes of COVID-19 patients diagnosed with PE during their hospital stay. We analyzed patients with PE and COVID-19 in a tertiary center in Mexico City from April to October of 2020. A total of 26 (100%) patients were diagnosed with Pulmonary Embolism and COVID-19. We observed that 14 (54%) patients were receiving either prophylactic or full anticoagulation therapy, before PE diagnosis. We found a significant difference in mortality between the group with less than 7 days (83%) and the group with more than 7 days (15%) in Intensive Care Unit (P = .004); as well as a mean of 8 days for the mortality group compared with 20 days of hospitalization in the survivor group (P = .003). In conclusion, there is an urgent need to review antithrombotic therapy in these patients in order to improve clinical outcomes and decrease hospital overload.

Keywords
thromboembolism, COVID-19, pulmonary embolism

Introduction
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) infection is characterized by fever and respiratory symptoms, however, patients infected with SARS CoV-2 may present with a broad clinical spectrum, ranging from an asymptomatic disease to acute respiratory distress syndrome and multi-organ failure. Patients with COVID-19 infection have been reported to suffer from coagulation abnormalities consistent with infection-induced inflammatory changes, in addition, Ackermann and colleagues reported the presence of endothelial lesions, such as intercellular union disruption, disrupted cell membranes and cellular edema in the pulmonary endothelium during their post mortem study of 7 lungs obtained from patients who died from COVID-19. Not only do these patients often go through a hypercoagulability state but are also prone to suffer from prolonged immobilization; this leads critically ill patients to an increased risk of Venous Thromboembolism (VTE) and Pulmonary Embolism (PE). A VTE prevalence of 25% has been reported in patients with severe COVID-19 Pneumonia, similar to what Porfidia and colleagues reported in their meta-analysis. In addition, a PE prevalence of 8% was reported by Fauvel and colleagues in a multicentre study. In contrast, Porfidia and colleagues reported an overall incidence of 12%. Liao et al reported an overall incidence of 15.3% in their meta-analysis and Bompard and colleagues reported an overall incidence of 24%. Furthermore, COVID-19 patients presenting with Acute Respiratory Distress Syndrome (ARDS) have been reported to have a 5-fold risk of PE despite anticoagulation, with a 31% incidence of thrombotic complications reported in ICU patients despite the use of thrombotic prophylaxis. VTE has been associated with a poor prognosis and PE may be a turning point in these patients due to the increased hypoxemia and cardiac collapse. We aimed to describe the clinical
characteristics and outcomes of 26 COVID-19 patients diagnosed with PE during their hospital stay in a tertiary referral center for COVID-19 in Mexico City.

**Methods**

We performed a retrospective analysis of Mexican patients diagnosed with PE and COVID-19 during their hospitalization in a tertiary referral center for COVID-19 in Mexico City. All patients included in our study arrived at our emergency department between April the 24th of 2020, to October the 7th of 2020 and were then admitted to our institution. PE diagnosis protocol was initiated when patients presented clinical signs and/or symptoms. Demographic variables, comorbidities as well as laboratory results, mortality rate and severity of the disease were obtained from these patients retrospectively. 

Chi² and Fisher’s were used to compare proportions. Student’s t test or Mann-Whitney U tests to compare means between the patients who died and survivors; we also compared means between patients requiring intensive care unit (ICU) and non-ICU ward patients; we performed a regression multivariate analysis and a Pearson’s correlation analysis for mortality; a P value < .05 was considered statistically significant. The analysis was completed with the statistical software SPSS 25 (IBM, Armonk, NY, USA). This study was approved by research and ethics committee in our institution.

**Results**

A total of 26 (100%) patients were diagnosed with PE and COVID-19 during our study period, 21 (81%) were men and the mean age was 56.8 years. In terms of these patients’ comorbidities, 10 (38%) were obese, 5 (19%) had arterial hypertension and 5 (19%) suffered from type 2 diabetes mellitus. Regarding specific risk factors for VTE, 1 (4%) patient suffered from a thrombophilic disorder, 2 (8%) had reduced mobility and 18 (69%) presented with heart or respiratory failure on admission; no patient had a history of recent trauma, hormonal therapy or previous VTE. On admission, 20 (77%) patients presented with a NEWS score ≥ 7 and only 5 (19%) had a Padua score ≥ 4. In terms of laboratory values, the mean D dimer was 15,140 ng/ml, the mean LDH was 615.11 UI/l, the mean platelet count was 263,576 /ml, the mean ferritin was 1707.2 mcg/l, the mean CRP was 18.19 mg/L and the mean creatinine was 1.2 mg/dl. We observed that 12 (46%) and 2 (8%) patients were receiving prophylactic and total anticoagulation, respectively, before PE diagnosis. Following PE diagnosis, only 2 (8%) patients were treated with Alteplase and 24 (81%) were treated with anticoagulation alone. A mean of 7 days was found between admission and the occurrence of PE in our study group.

During hospitalization, 12 (46%) patients were admitted to the Intensive Care Unit for more than 3 days, with a mean Length of Stay (LOS) of 17 days in the ICU; 13 patients (50%) were intubated, and 8 (31%) died.

| Table 1. Comparison of Patients’ Demographics and Comorbidities Between Groups. |
|---------------------------------|-----------------|-----------------|-----------|
|                                | Alive (n = 18)  | Deceased (n = 8) | P value  |
| Age                            | 53.8 (SD 13.6)  | 63.3 (SD 9.5)   | (0.09)   |
| Male                           | 14              | 7               | (0.5)    |
| Female                         | 4               | 1               | (0.5)    |
| Type 2 diabetes mellitus       | 4               | 1               | (0.56)   |
| Arterial hypertension          | 4               | 1               | (0.56)   |
| Obesity                        | 8               | 2               | (0.42)   |
| Padua Score ≥ 4                | 4               | 1               | (0.56)   |
| News Score ≥ 7                 | 14              | 6               | (0.87)   |

| Table 2. Mean Results for Laboratory Findings on Admission and Hospitalization Events Between Groups.a |
|---------------------------------------------------------------|-----------------|-----------------|-----------|
|                                | Alive (SD)      | Deceased (SD)   | P value   |
| Hospitalized                  | 21.8 (10.8)     | 8.1 (7)         | (0.003)   |
| News                           | 7.9 (2.8)       | 8.8 (2.1)       | (0.42)    |
| Padua                          | 2.6 (1.2)       | 2.3 (0.9)       | (0.56)    |
| Ferritin (mcg/l)              | 1143.5 (1303)   | 2660 (5004)     | (0.24)    |
| CRP (mg/l)                    | 17.7 (10.8)     | 21.3 (5.8)      | (0.38)    |
| Platelets                     | 240,388 (68410) | 315,750 (15860) | (0.09)    |
| Leucocytes                    | 10,394 (4326)   | 13,137 (5323)   | (0.18)    |
| Creatinine (mg/dl)            | 1.2 (0.8)       | 1.2 (0.4)       | (0.8)     |

Abbreviations: CRP, C-reactive protein.

*Student’s t Test.

| Table 3. Medians and Interquartile Range for Non-Normally Distributed Laboratory Findings on Admission and Hospitalization Events Between Groups Using Mann-Whitney U. |
|---------------------------------------------------------------|-----------------|-----------------|-----------|
|                                | Alive (IQR)     | Deceased (IQR)  | P value   |
| D Dimer (ng/ml)               | 5,669 (19,527)  | 12,836 (25,256) | (0.68)    |
| Time admission/diagnosis      | 3.0 (14.5)      | 1.0 (4.0)       | (0.46)    |
| LDH (UI/l)                    | 490 (222)       | 580 (300)       | (0.12)    |
| Lymphocytes                   | 7.7 (7.2)       | 2.8 (7.3)       | (0.23)    |
| P/L ratio                     | 275 (331)       | 467 (683)       | (0.08)    |
| Neutrophiles/Lymphocytes      | 12 (27)         | 12 (14)         | (0.65)    |

Abbreviations: LDH, lactic acid dehydrogenase; P/L, platelets/lymphocytes.

In Table 1 we present the comorbidities between the groups, furthermore, we found no significant differences between the group that survived and the patients that died. We found a significant difference in mortality between the group with less than 7 days (83%) in ICU and the group with more than 7 days (15%) in ICU (P = .004); as well as a mean of 8 days for the mortality group compared with 20 days of hospitalization in the survivor group (P = .003). We did not find significant differences in the laboratory markers between both groups, but lymphocytes and platelets-to-lymphocyte ratio (P/L) showed important differences (Tables 2 and 3). We found that the mean age of the patients in ICU was 50 (SD 10) compared with 62
The retrospective, single center design of our study implies numerous of important limitations, nevertheless, to our knowledge, no previous study has attempted to describe the differences in morbidity and mortality in a group of COVID-19 patients diagnosed with PE in a non-critical-only context. Even though critically ill patients tend to die earlier, there is still a high proportion of ICU admissions along with the increased LOS in survivor patients, which makes this disease particularly challenging in terms of hospital management, hence, it becomes essential to improve treatment and prevention strategies in these patients in order to avoid hospital overload.

It is well known that thromboprophylaxis with Low-Molecular-Weight Heparin (LMWH) or Unfractionated Heparin (UH) is paramount in these patients, however, there is still an urgent need to review and adapt thrombotic prophylaxis in patients with SARS CoV-2 infection.

**Table 4. Multivariate Regression Analysis for Mortality.**

| Standardized coefficients B | t | 95% CI Sig. |
|-----------------------------|---|----------|
| Age                        | −.002 | −.008 | −.029 - .029 | 0.99 |
| LOS (days)                 | −1.39 | −1.95 | −1.57 - .227 | 0.12 |
| D-Dimer (ng/ml)            | −.299 | −1.07 | .000 - .000 | 0.34 |
| Time from admission to diagnosis (days) | .717 | 1.44 | −.034 - .109 | 0.22 |
| NEWS scale                 | .383 | 1.22 | −.096 - .222 | 0.28 |
| Padua scale                | −.332 | −1.10 | −.525 - .226 | 0.33 |
| LDH (UI/l)                 | .100 | .123 | −.002 - .002 | 0.90 |
| Ferritin (mcg/l)           | −.283 | −.327 | .000 - .000 | 0.76 |
| CRP (mg/l)                 | −.601 | −1.31 | −.098 - .035 | 0.26 |
| Platelets                  | 1.42 | 1.66 | .000 - .000 | 0.17 |
| Lymphocytes                | 1.21 | 1.32 | −.126 - .035 | 0.25 |
| P/L ratio                  | −1.96 | −2.05 | −.006 - .001 | 0.10 |
| Neutrophiles               | .682 | 1.08 | −.084 - .191 | 0.33 |
| Creatinine                 | 1.21 | 2.25 | −.450 - 4.36 | 0.08 |
| Leucocytes                 | −.698 | −1.14 | .000 - .000 | 0.31 |
| Neutrophiles/Lymphocytes   | −.201 | −.672 | −.026 - .016 | 0.53 |

Abbreviations: LOS, length of hospitalisation; LDH, lactic acid dehydrogenase; CRP, C-reactive protein; P/L, platelets/lymphocytes.

(12) in patient who did not required ICU care (P = .015). We also found a NEWS Score of 7 (SD 3.1) in the no ICU requirements compared with 9.3 (SD 1.4) for the ICU group (P = .025).

In Table 4, we describe the regression analysis, we did not find any significant association with mortality and the factors evaluated in this analysis; we found a negative correlation between mortality and LOS (r = −.55, n = 22, P = .004) and lymphocytes (r = −.36, n = 22, P = .04).

**Discussion**

It has been reported that COVID-19 patients with PE may have a mortality rate of up to 45% higher in comparison to non-COVID-19 cases. We found a mortality rate of 31% in our study group. Regarding critically ill patients, Contou D and colleagues reported an ICU mortality of 69% (13/16) in their study group, however, they did not compare those patients with a non-critically ill group. Furthermore, we found a significantly higher mortality of 83.3% for the group with less than 7 days in ICU compared with 15% in the more than 7 days in the ICU group (P = .004) this probably means that patients with severe disease tend to die earlier. D-Dimer levels have been reported to predict mortality in COVID-19 patients as it is a sign of inflammatory induced changes, however, we did not find D-Dimer levels to have a significant difference in mortality in our study group, which appears to be consistent with the meta-analysis performed by Chi and colleagues. Even though a D-Dimer greater than 1, 000 ng/ml has been identified as a risk factor for poor outcome in COVID-19 patients, in our study we did not find such patients to have a significant difference in mortality, although the later could be due to the small number of patients compared. Even though the presence of a single measurement of D-Dimer may not be associated with mortality in similar patients, authors like Valero et al have proposed that dynamic changes in this measurement have been found to be associated with such outcome. Hence, D-Dimer has been proposed as a safe way to exclude the presence of PE in COVID-19 patients, however, it should not be used as a positive marker of thrombosis due to the lack of specificity.

In terms of laboratory findings, a cross-sectional study performed by Dubois-Silva et al showed that inflammatory markers in patients with PE were increased in comparison to what has been reported in the literature for the COVID-19 context, although no comparisons were made between PE diagnosed patients who survived and those who did not. Furthermore, in our study group we found that patients with PE and COVID who died had higher, although non-significant, platelet count, lymphocytes and greater platelet-to-lymphocyte ratio. This tendency leads us to believe that an increased inflammatory response may be responsible for the greater mortality in these patients and may be an important predictor of mortality.

In addition, our study reported that 50% of our patients developed PE despite prophylactic anticoagulation, which is more than double of what was reported by Chi et al in their meta-analysis. Although authors like Fauvel and colleagues have reported that prophylactic anticoagulation during hospitalization lowered the occurrence of PE and mortality in comparison to those patients who did not receive any, we believe that such risk remains high; as reported by Bompard and colleagues in their multi centric study in which more than 50% of their PE diagnosed patients received prior prophylactic anticoagulation. Hence, we should review the current guidelines in order to improve clinical outcomes in COVID-19 patients.

On the other hand, some authors discuss the possibility of a different pathogenesis of PE in COVID-19 patients. They raise the possibility of pulmonary thrombi instead of pulmonary embolism, on account of a low incidence of DVT in their series. Pulmonary thrombi in this group of patients is probably a result of vascular damage associated with SARS CoV-2 and severe inflammation. Hence, high-dose heparin may not only be futile, but it may also be dangerous. The retrospective, single center design of our study implies numerous of important limitations, nevertheless, to our knowledge, no previous study has attempted to describe the differences in morbidity and mortality in a group of COVID-19 patients diagnosed with PE in a non-critical-only context. Even though critically ill patients tend to die earlier, there is still a high proportion of ICU admissions along with the increased LOS in survivor patients, which makes this disease particularly challenging in terms of hospital management, hence, it becomes essential to improve treatment and prevention strategies in these patients in order to avoid hospital overload.

It is well known that thromboprophylaxis with Low-Molecular-Weight Heparin (LMWH) or Unfractionated Heparin (UH) is paramount in these patients, however, there is still an urgent need to review and adapt thrombotic prophylaxis in patients with SARS CoV-2 infection.
More evidence is needed regarding the increase in doses of thromboprophylaxis with LMWH and/or UH in order to prevent PE. Moreover, the use of other forms of thromboprophylaxis such as compression stocks may aid in the prevention of PE in COVID-19 infected patients.

Authors’ Note
All authors contributed to study conception, data collection, investigation, writing, critical reviews and revision, final approval of the article, and accountability for all aspects of the work.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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