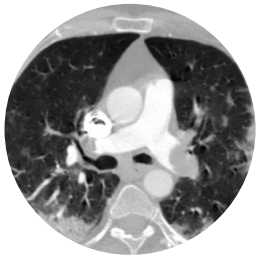

Prevalence of pulmonary embolism in patients with COVID-19, April - December 2020

Prevalencia de embolia pulmonar en pacientes con infección por COVID-19, abril-diciembre de 2020

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Summary
Introduction: Thrombotic events associated with COVID-19 infection contribute to higher morbidity and mortality of patients. The objective was to review the clinical and imaging characteristics of patients with suspected diagnosis of pulmonary embolism (PE) and COVID-19 infection, from April to December 2020. ***Methodology:*** Cross-Sectional observational study that included patients with a molecular diagnosis of SARS CoV-2 infection and chest computed tomography angiography (CT angiography) performed for suspected PE. Patients were divided into two groups (PE vs No PE). Qualitative variables were compared with each other with Pearson's Chi^2 test or Fisher's exact test, and quantitative variables were analized with the Student's T test or the Mann-Whitney U test. ***Results:*** 127 patients were included with a median age of 60 (IQR: 45-69) years, 68 (53.5%) were men and 23.6% (n = 30) presented PE. When comparing PE (n = 30) vs No PE (n = 97), the first group required more mechanical ventilation, extended days of hospitalization, higher mortality as well as higher levels of D-Dimer, all with statistically significant difference ($p < 0.05$). ***Conclusion:*** A quarter of patients with COVID-19 presented PE as a complication with high levels of D-dimer, a higher frequency of ventilatory assistance, more days of hospitalization and higher mortality.

Resumen
Introducción: Los fenómenos trombóticos asociados a COVID-19 contribuyen a una mayor morbimortalidad. El objetivo fue determinar las características clínicas e imagenológicas de pacientes con sospecha diagnóstica de embolia pulmonar (EP) y COVID-19, de abril a diciembre de 2020. ***Metodología:*** Estudio observacional transversal que incluyó pacientes con diagnóstico molecular de infección por SARS-CoV-2 y angiotomografía computarizada de tórax (Angio-TAC) realizada por sospecha de EP. Se dividieron los pacientes en dos grupos (EP vs. no EP). Se compararon entre sí variables cualitativas con la prueba Chi^2 de Pearson o la prueba exacta de Fisher, y se realizó la misma exploración con variables cuantitativas empleando la prueba T de Student o U de Mann-Whitney. ***Resultados:*** Se incluyeron 127 pacientes con una mediana de edad de 60 años (RIC 45-69) —68 (53,5 %) eran hombres— y el 23,6 % (n = 30) presentó EP. Al comparar EP (n = 30) vs. no EP (n = 97), se observó que en el primer grupo la mayoría requirieron ventilación mecánica, más días de hospitalización y tuvieron una mortalidad mayor, así como niveles más altos de dímero D, todos con diferencia estadísticamente significativa ($p < 0,05$). ***Conclusión:*** Una cuarta parte de los pacientes con COVID-19 sufrieron EP como complicación, con altos niveles de dímero D, mayor frecuencia de asistencia ventilatoria, más días de estancia hospitalaria y mayor mortalidad.

Introduction

Coronavirus is a non-segmented, encapsidated virus with a ribonucleic acid chain that belongs to the Coronaviridae family (1). Six types of coronaviruses have been identified that cause disease in humans: four of them produce mild respiratory symptoms, whereas the other two-MERS and SARS-have caused epidemics with high mortality rates (2).

In early December 2019 a new type of coronavirus, named SARS-CoV-2, was identified in Wuhan (China). Subsequently, coronavirus disease 2019 (COVID-19) was declared a global health emergency by the World Health Organization (WHO) (3).

Coronavirus infection 2019 (COVID-19) has common symptoms such as fever and cough, which can progress to pneumonia, acute respiratory distress syndrome (ARDS) and/or multisystem failure. Risk factors associated with worse outcome are advanced age, comorbidities, neutrophilia, organ dysfunction and coagulopathy (3, 4).

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The endothelial damage caused by COVID-19 is due not only to the direct viral lesion on the endothelium, but also to the systemic inflammatory response associated with the cytokine storm (5). This generates complications such as thrombotic phenomena, which contribute to significant morbidity and mortality (6,7). Pulmonary embolism (PE), deep vein thrombosis (DVT), ischemic stroke (IS) and acute myocardial infarction (AMI) are examples of complications described in patients with COVID-19 (6, 7). The pathophysiological mechanism in the context of viral disease is due to multiple factors such as excessive inflammation, hypoxia, immobilization and disseminated intravascular coagulation, which contribute to a prothrombotic state (6, 7). The present study aims to determine the prevalence of clinical and imaging characteristics of patients with a diagnostic suspicion of PE and confirmed infection by COVID-19, between April and December 2020.

Materials and Methods

Cross-sectional observational study that included patients with molecular diagnosis of SARSCoV- 2 infection and chest computed tomography angiography (CT angiography) performed for suspected PE, between April and December 2020.

Chest CT angiograms were retrieved from the institution's image storage and distribution system (PACS), performed in patients with clinical suspicion of PE between April and December 2020, who also had a molecular diagnosis of SARSCoV-2 infection. These images were interpreted independently by two radiologists specialized in Trauma and Emergency Radiology, who determined the imaging characteristics according to the presence or not of PE, its distribution and the imaging pattern of SARS-CoV-2 infection, among others. In case of disagreement, a third radiologist gave a blinded opinion (tie-breaker). The radiologists had no access to clinical or paraclinical information.

The medical records were reviewed in search of the clinical and laboratory variables contemplated in the present study. The analysis was carried out with the IBM SPSS Version 22 program, according to the proposed purposes; absolute and relative frequencies were used to describe the qualitative variables, and mean and standard deviation or median and interquartile ranges for the quantitative variables according to their distribution in the study population. Patients were divided into two groups according to the presence or absence of PE on CT angiography. Qualitative variables were compared with each other using Pearson's Chi2 test or Fisher's exact test, when any of the expected values was 5 or less. Similarly, the same exploration was carried out with quantitative variables using the Student's t-test or Mann-Whitney U test, according to their distribution. Interobserver variability was calculated using the kappa index.

The research was approved by the Ethics Committee of the institutions for its execution.

Results

A total of 127 patients with a median age of 60 years (RIC 45-69) were included, of whom 68 (53.5 %) were men. Seven out of ten patients were obese (73.2 %) and more than half (57 %) had hypertension as a history. Dyspnea, cough and fever were the most frequent symptoms at hospital admission with 82.6 %, 76.3 % and 73.2 %, respectively. Symptoms such as cardiorespiratory arrest and hemoptysis occurred only in patients with PE documented on Angio-CT (Table 1).

Table 1. Clinical characteristics of the patients (n = 127)

Antecedentes	*n* (%)
Obesity	93 (73,2)
Arterial hypertension	73 (57,4)
Diabetes *mellitus*	34 (26,7)
Dyslipidemia	26 (20,4)
Pneumopathy	14 (11)
Nephropathy	12 (9,4)
Heart disease	11 (8,6)
Symptoms	
Dyspnea	105 (82,6)
Cough	97 (76,3)
Fever	93 (73,2)
Chest pain	26 (20,4)
Gastrointestinal	18 (14,1)
Cardiorespiratory arrest	4 (3,1)
Syncope	4 (3,1)
Hemoptysis	4 (3,1)
Alteration of consciousness PE (+) on CT scan	
Yes	30 (23,6)
No	97 (76,3)
Treatment	
Anticoagulation	30 (100)
Percutaneous intervention	2 (6,6)
Thrombolysis	2 (6,6)

PE: Pulmonary embolism. CT: Computed tomography

Regarding imaging characteristics, in 23.6 % of patients (n = 30) CT angiography was positive for PE, with lobar and segmental compromise in 50 % and 80 % respectively (Figures 1 and 2). Of these 30 patients, right ventricular dysfunction was documented on echocardiography in only three cases, and concomitant DVT was found on lower limb Doppler assessment in only three patients. In the pulmonary parenchyma of patients with PE, 83.3% had a typical pattern for coronavirus infection, 23.3% had pulmonary infarction associated with PE, and concomitant pleural effusion was documented in only two patients (Table 2).

Table 2. Imaging characteristics of the patients

Angio-CT characteristics	*n* (%)
Distribution of pulmonary embolism (PE)	
Primary PE	2 (6,6)
Lobar PE	15 (50)
Segmental PE	24 (80)
Subsegmental PE	6 (20)
Associated pulmonary infarction	7 (23,3)
COVID-19 pattern	
Typical	25 (83,3)
Probable	3 (10)
Indeterminate	1 (3,3)
Atypical	1 (3,3)
Pleural effusion on Angio-CT	2 (6,6)
COVID-19 pattern on CXR	23 (76,6)
Pleural effusion on Rx	2 (6,6)
DVT	3 (10)
Right ventricular dysfunction	3 (10)

Regarding management, only two of the 30 patients with PE were taken to percutaneous management by interventional radiology for thrombectomy, and two more were managed with intravenous thrombolysis (Table 1). When comparing patients with PE (n = 30) and without PE (n = 97), it can be seen that in the first group the majority required ventilatory assistance with mechanical ventilation, required more days of hospital stay, had a higher mortality, as well as higher levels of D-dimer, all with statistically significant differences (Table 3).

Table 3. Comparison between patients with and without PE

	PE (*n* = 30)	No PE (*n* = 97)	*p* value < 0,05
Age, Me (RIC)	66,5 (58,7-74,2)	57 (43-67)	0,00308
D-dimer (ng/L)	5.129 (2.040-29.231)	749 (343-2.223)	0,00001
Mechanical ventilation, *n* (%)	22 (73,3)	34 (35)	0,0002
Days of hospitalization, Me (RIC)	13,5 (7-20)	5,5 (4-14,75)	0,015
Mortality, *n* (%)	8 (26,6)	11 (11,3)	0,039

The interobserver variability for all the variables evaluated was very good (almost perfect), with kappa indices above 0.8 (Table 4).

Table 4. Interobserver variability

Imaging characteristic	Kappa index
Presence of PE	0.93
Distribution of PE	0.89
Pulmonary infarction in Angio-CT	0.91
COVID-19 pattern on Angio-CT scan	0.88
Pleural effusion on Angio-CT	0.92

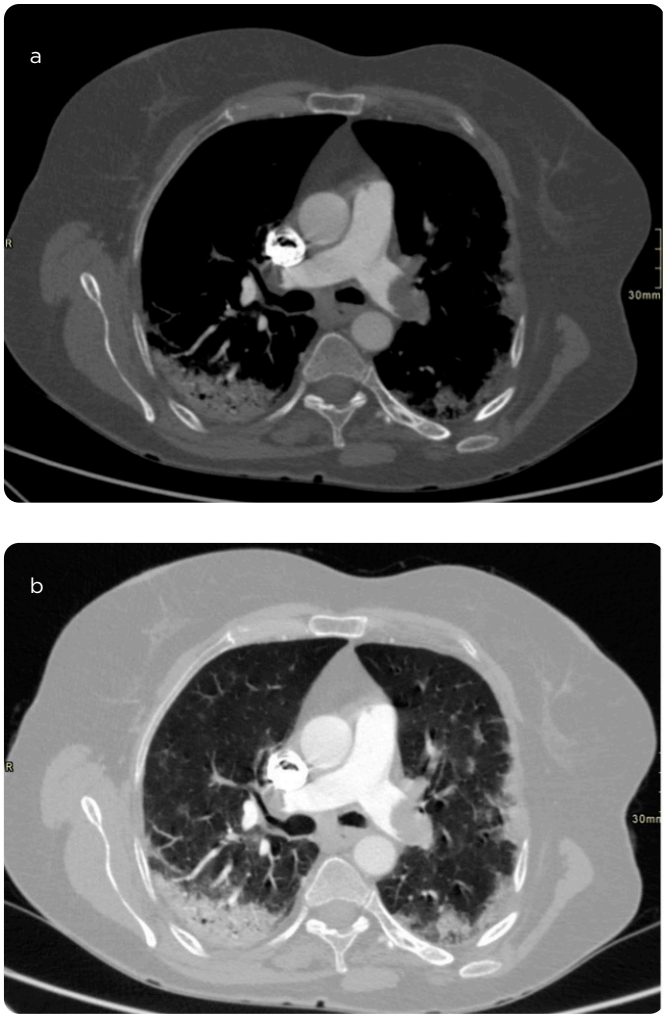

Figure 1. Chest CT angiography of a 59-year-old patient, a) lung window and b) mediastinal window. Positive findings for PE with bilateral involvement of main pulmonary arteries associated with bilateral subpleural consolidations predominantly in the lower lobes, in relation to COVID-19 viral pneumonia (typical pattern).

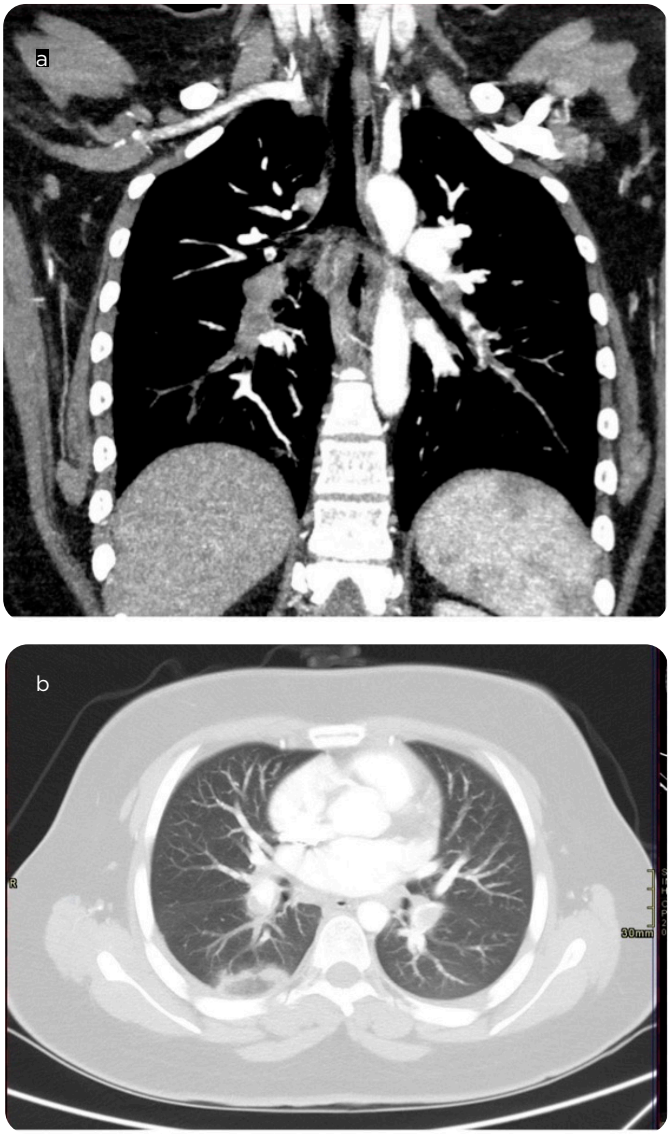

Figure 2. Chest CT angiography in a 35-year-old patient with syncope. a) coronal section in mediastinal window and b) axial section in lung window, showing bilateral lobar and segmental PE. Reverse halo sign of subpleural location in the apical segment of the right lower lobe due to pulmonary infarction, without other opacities suggestive of viral pneumonia.

Discussion

A clear link between inflammation and multi-organ damage has been described in patients with COVID-19. Proinflammatory cytokines, such as interleukin 6 (IL-6), IL-17A and tumor necrosis factor α are elevated in most patients with severe outcomes (7-9), considering that hypercoagulability is an important phenomenon of inflammatory states. Thus, proinflammatory cytokines are critically involved in abnormal clot formation, platelet hyperactivation and dysregulation in anticoagulant pathways (10).

Coagulopathy has been described in up to 50% of cases of COVID-19 with severe manifestations (11), represented especially in elevated concentrations of D-dimer and fibrin degradation products (10). Similarly, respiratory tract infection is a known risk factor in the development of PE in hospitalized patients (3). In recently published studies, the incidence of PE in patients with COVID-19 disease is between 23% and 30% (11-13), which is consistent with the present study, in which 23.6% of patients had positive Angio-CT. These PE rates are higher than what is normally found in critically ill patients without COVID-19 (1.3 %) (14) or in patients consulting the emergency department for other causes (3 %-10 %) (15).

Obesity in COVID-19 is associated with more severe disease (16). Poggiali et al. recently demonstrated that patients with a body mass index greater than 30 kg/m2 were 2.7 times more likely to develop PE (3, 17, 18). In this study, more than 73.2 % had obesity as a background.

As mentioned in the results, the median D-dimer in PE patients was 5,129 ng/L compared with 749 ng/L in the non-PE group (p 0.00001). A D-dimer > 1 ng/mL has been clearly identified as a poor prognostic factor in COVID-19 (4), with recent reports of a high incidence of thrombotic events in critically ill patients (7). A normal level of this dimer, moreover, allows exclusion of PE in ambulatory patients with a low or intermediate clinical probability of PE (18,19). Consistently, Poggiali et al. found a significant difference in D-dimer level between PE-positive and PE-negative groups (3). D-dimer thresholds of 900 (20), 2,400 (21) and 2,660 ng/L (15) have been described for the detection of all patients with PE or COVID-19.

As recently published by Grillet et al. (12), in the present study most patients with PE required ventilatory support with mechanical ventilation, required more days of hospital stay, and had a higher mortality. Bompard et al. (20) found a median hospital stay of 15 days (RIC 9-17) in patients with PE versus 8 days (RIC 4-12) in patients without PE, a finding similar to the median of 13.3 and 5.5 days in the respective groups of the study presented here. Other authors have found no significant difference in ICU admissions, need for intubation or length of hospitalization when comparing two groups based on the presence of PE.

Bompard et al. (20) recently analyzed a cohort of 135 patients with confirmed SARS-CoV-2 infection who underwent chest CT angiography for suspected PE. The majority (70 %) were men with a median age of 64 years, similar to the population included in our study. Of the 32 patients with PE, 10 were of proximal location (main or lobar branch) and in the remaining 22 the involvement was peripheral, a finding similar to that observed in the current study, in which 80 % of the patients had opacification defects in segmental branches.

The limitations of the study include those derived from a retrospective descriptive observational design with a small sample size. Likewise, it is pertinent to mention the possibility of selection bias when considering a population with a high pretest probability for PE, an aspect that favored a higher percentage of this complication in the patients included and also prevented the calculation of the incidence of PE in COVID-19 for the population studied. Due to the retrospective methodology, it was not possible to perform an in-depth analysis of possible confounding variables such as other comorbidities, hypercoagulability risk factors and thrombophilia. Finally, it is important to mention that the collection of patients was done in a period without vaccination, so the prevalence today could change, for which further studies are required.

Conclusions

A quarter of the patients with COVID-19 included in this study presented PE as a complication with high levels of D-dimer and mostly lobar and segmental involvement. Most of them required ventilatory assistance with mechanical ventilation, more days of hospital stay and higher mortality. The present study provides relevant information on the frequency of PE presentation in COVID-19 in our population, emphasizing the importance of early detection of this complication in patients who are at greater risk of developing thrombotic events and serious outcomes.

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