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D-dimer levels as an associated factor for pulmonary embolism in COVID-19 patients in Critical Care Unit: A case-control study

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Abstract

Objective: Establish the association between the D-Dimer levels and pulmonary embolism (PE) in CT pulmonary angiogram (CTPA) in patients with COVID 19 in critical care.

Methodology*:* Case Control study in patients with diagnosis of COVID 19 in three critical care units during 2021 in Medellin. All patients had CTPA as a diagnostic method for PE.

Results*:* There were 135 cases and 136 controls, mean age 60 years old (IQ 51-70), 74.2 % were men. 39% had high blood pressure. Segmentary PE was found in 65.2%, lobar PE in 19.3% and 15.6% in the right or left pulmonary artery. We found that it is more likely to have PE if the D-Dimer value is more than 5000 ng/mL (ORa 7.8; IC95% 4.09-14.92).

Conclusion*:* D-Dimer is an independent factor that is associated with PE in patients with COVID - 19 in critical care, especially if the value is over 5000 ng/mL.

Keywords: Pulmonary Embolism; SARS-CoV2; Thrombosis; Intensive care unit; Overweight; CT Angiography

1. Introduction

The coronavirus (COVID - 19) is caused by the SARS CoV-2 virus. It created a pandemia with at least y millions of deaths in the world by March of 2024 [1]. In severe cases the clinical manifestations were respiratory failure, acute kidney injury (AKI) or thrombotic events [2]

The probable physiopathology of thrombotic events in patients who suffer from COVID-19 is an endothelial inflammation that creates micro thrombus which leads to deep vein thrombosis (DVT), PE, arterial thrombosis, heart attack and stroke [3, 4]. The arterial and venous thrombotic events have been widely described in patients with COVID-19, they are generated by excessive inflammation, hypoxia, prolonged rest and disseminated intravascular coagulation (DIC) [3-6].

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For the diagnosis of PE there are multiple image tests available like XRay, CTPA, Lung Ventilation Perfusion Scan (VQ Scan) and pulmonary angiography [7-9]. The CTPA most common indications are clinical suspicion of PE, High D-Dimer level [10] . In critical care unit patients, the PE diagnosis is difficult because of the low specificity of the biomarkers, limited physical examination and contraindications and limitations in the CTPA [11-13]

Since the initial phases of the COVID pandemic the D-Dimer has been associated with mortality but there is little information in the literature about the relationship between this biomarker and thrombotic events. D-Dimer has a high sensitivity but low specificity in the diagnosis of PE. Given the physiopathology features of COVID-19 it is important to know the role of D-Dimer in patients with possible PE.

The main objective of the study was to establish the association between the D-Dimer levels and PE in CTPA in patients with COVID 19 in a critical care.

2. Methods

2.1. Study Design

A case-control study was conducted on patients diagnosed with COVID-19 confirmed by molecular or antigen testing, who were admitted to the high dependency units of three institutions in the city of Medellín from January to December 2021. Patients who underwent chest CTPA for the diagnosis of pulmonary embolism were included. Patients without a D-dimer report were excluded.

2.2. Data Collection

Electronic medical records of hospitalized patients in high dependency units at three institutions in Medellín, Colombia, were reviewed. Cases were defined as patients diagnosed with pulmonary embolism by CTPA, and controls were those with a negative CTPA. To minimize classification bias, a second radiologist evaluated the images; for positive CTPA, confirmation by the second radiologist classified the patient as a case. In case of disagreement, a third evaluator determined the result. For negative CTPA, concordant reports from the second radiologist classified the patient as a control; discordant reports excluded the patient from the study. CTPA were acquired using 16 and 64-row CT scanners. Images were reconstructed at 1 mm and analyzed in all three planes.

2.3. Variables

Clinical characteristics such as age, sex, BMI, comorbidities, and the presence of ventricular dysfunction were evaluated. Troponin and D-dimer levels were collected. D-dimer values were converted to Fibrinogen Equivalent Units (FEU) ng/ml as necessary. D-dimer levels were categorized as <3000, 3000-5000, and >5000 FEU ng/ml based on literature and interim data analysis. Ventricular dysfunction and troponin levels were excluded from the analysis due to incomplete information in medical records (>10%).

2.4. Sample Size Calculation

To detect an odds ratio (OR) of at least 2.5 for the association between high D-dimer levels and PE, with an exposure rate of 88% based on the study by Helms and Cols [15], a total sample of 264 patients with a 1:1 case-control ratio was required, considering a confidence level of 95% and power of 80%. Patients were consecutively recruited until the required sample size was achieved.

2.5. Statistical Analysis

Univariate analysis was performed. For quantitative variables, measures of central tendency (means or medians) and dispersion (standard deviation or interquartile range) were reported based on variable distribution, verified using the Shapiro-Wilk test ($p<0.05$). For qualitative variables, absolute frequencies and proportions were reported. Student's t-test or Mann-Whitney U test was used for comparison based on variable distribution. Chi-square test was used for qualitative variables.

To estimate the association between D-dimer levels and PE, a binomial logistic regression model was used, adjusting for potential confounders. D-dimer was entered as a categorical variable based on the aforementioned categorization. Adjusted odds ratios (OR) with 95% confidence intervals were reported, with $p \leq 0.05$ considered significant. Data were analyzed using STATA® version 12 (StataCorp). The research protocol was approved by the Institutional Committee of Ethics for Research in Human Beings of Universidad CES (act No. 185).

3. Results

A total of 271 patients were included in the study (136 controls and 135 cases). The mean age was 60 years (IQR 51-70), with 74.2% being male. The median BMI was 27.9 (IQR 24.9 - 30.2). The most common comorbidity was arterial hypertension (HTN) in 39% of patients. Regarding the location of the PE. it was observed that 65.2% were segmental, 19.3% were lobar, and 15.6% were in the main branches.

Comparing patients who presented with PE and those who did not, differences were found in the median D-dimer levels between both groups (10788 vs 2862 respectively, p <0.0001). Regarding age, differences in mean age between cases and controls were found. No differences were found in the distribution of sex, median BMI, presence of diabetes, oncological history, autoimmune history, or history of previous thrombosis. (Table 1).

Table 1 Clinical characteristics with and without PE

Variable	**PE +**	**PE -**	**p**
Age(Mean, SD*)	55.9 (15.75)	64.4 (13.33)	0.001
D - Dimer ng/ml (Median, IQR**)	10788 (4674-17890)	2862 (1197-6825)	<0.0001
BMI*** (Median, IQR**)	27.65 (4,89)	28.19 (4.78)	0.36
	n (%)	n (%)	
Sex			0.115
Male	95 (70.4)	106 (77.9)	
Female	40 (29.6)	30 (22.1)	
High Blood Pressure			0.004
Yes	41 (30.4)	65 (47.8)	
No	94 (69.6)	71 (52.2)	
Diabetes mellitus			0.228
Yes	22 (16.3)	30 (77.9)	
No	113 (83.7)	106 (22.1)	
Oncologic disease			0.743
Yes	4 (3)	5 (3.68)	
No	131 (97)	131 (96.32)	
Autoimmune disease			0.992
Yes	4 (3)	4 (3)	
No	131 (97)	132 (97)	
Previous thrombotic event			0.079
Yes	3 (2.2)	9 (6.6)	
No	132 (97.8)	127 (93.5)	

*SD: Standard deviation, **IQR: interquartile range, BMI: Body mass index, D-dimer is expressed in Fibrinogen Equivalent Units (FEU)

For the multivariate analysis (Table 2) the model used included the variables with statistical significance. If there is no statistical significance, the variables considered by the literature and/or clinically important were included as possible confusion factors. There is a 6.8 more probability of having PE if the D-Dimer level is more than 5000 ng/mL compared with a level of 3000 ng/dL.

Table 2 Binomial logistic regression model for the outcome of PE

Variable	OR a	IC 95%	p
D-Dimer (ng/mL)			
<3000	1		
3000 - 4999	1.03	0.41 – 2.63	0.935
> 5000	7.81	4.092 – 14.92	0.001
Age			
> 60 years old	1		
< 60 years old	3.34	0.79 – 6.25	0.308
BMI			
Normal	1		
Overweight	0.27	0.13 – 0.56	0.001
Obesity	0.54	0.24-1.2	0.133
Sex			
Female	1		
Male	0.66	0.34 – 1.29	0.224
Diabetes Mellitus			
No	1		
Yes	1.49	0.89 – 3.26	0.308
High Blood Pressure			
No	1		
Yes	0.58	0.31 – 1.11	0.110
Previous thrombotic event			
No	1		
Yes	0.4	0.08 – 2.01	0.269

ORa: Adjusted Odds Ratio

4. Discussion

D-dimer has been extensively studied as one of the markers of fibrinogen degradation and has been associated as a highly sensitive but not very specific diagnostic test for thrombotic events, especially DVT and PE. During the COVID-19 pandemic, D-dimer has been associated not only as a predictor of thrombotic events but also linked to the inflammatory phase and as a predictor of disease severity [15, 16]. The prevalence worldwide of high D-dimer levels in hospitalized patients with COVID-19 was 36% [17]. In the research done by Gil-Mosquera [18], the D-dimer levels were 4.548 ng/mL [IQR: 2.292-25.969] versus 1.406 ng/mL [IQR: 684-3.894], p < 0,001, in patients with and without PE respectively; while our study showed that the levels were above the normal limit, median of 10.788 (IQR 4.674–17.890) for cases and 2.862 (IQR 1197–6.825) for controls. Studies before COVID-19 reported D-Dimer level much lower for thrombotic disease.

With the evolution of the pandemic, the study has shown that the levels of D-Dimer are 4 times higher in moderate and severe cases of the disease [5, 19-21]. In this study we found that the D-Dimer level is an independent factor associated with the presence or absence of PE (OR 7,81 IC95% 4.092 – 14.92), that why we propose that COVID-19 positive patients in critical care with clinical suspect of PE and limited access to CTPA, this results may help prioritize the resource, since in the pandemic high incidence there was a underdiagnosis of thrombotic events because there was limited access to

CTPA [22]. The results show that patients with COVID-19 and D-Dimer levels higher than 5000 ng/ml, should go to CTPA and start anticoagulation medicine.

Obesity is a risk factor for the development of thrombotic events and has higher mortality in patients with COVID-1923.24, patients have venous stasis, limited mobility, coagulation abnormalities (higher fibrinogen, plasminogen activator inhibitor –1, VII and VIII factor, Von Willebrand factor and platelet plasminogen activation, endothelial dysfunction, and worst mechanical ventilation). In the study we found 45% of the patients overweight and 28% in obesity, of these patients only 35.6% and 31.9% were PE positive respectively. Obesity was not a risk factor for developing PE (OR 0.54 IC95% 0.24-1.2 p 0.133).

In multiple studies, diabetes mellitus has been identified as an independent risk factor for severe illness caused by SARS-CoV-2 [15, 24, 25], with an increased incidence of thrombotic complications (47.1% vs 21.2%, p <0.001), and a two to three-fold higher mortality upon admission to the intensive care unit. Possible contributing factors include older age, hyperglycemia, the presence of comorbidities, and increased susceptibility to hyperinflammation.

In our study, it was found that only 19.2% of the patients had diabetes mellitus (DM), and of those, only 16.3% presented with pulmonary embolism (PE). When D-dimer levels were evaluated in diabetic patients, it was found that 51.29% had D-dimer levels >5000 FEU ng/dl, which is comparable to findings in other studies. However, upon entering the multivariate analysis, diabetes mellitus did not show statistical significance despite being recognized as a risk factor according to the literature.

The findings of obesity, sex, and high blood pressure could be explained by Prevalence-incidence bias (also known as Neyman Bias) [26] PE can lead to early death in patients with COVID-19 before a radiologic confirmation, this may underestimate or even reverse the direction of the association. However, it is important to note that the main objective of this study is not to estimate the associations for these variables [11, 13, 15, 24], Nevertheless, it is suggested that the reported association for the variable of interest may be underestimated. These considerations should be taken into account when analyzing the information, and a limitation of the study is declared despite working with incident cases. Additionally, the exclusion of two clinically and statistically important variables, troponin levels and ventricular dysfunction, due to lack of data in the medical records, is noted.

Strengths of the study include the double verification of CTPA by two different radiologists, allowing for control of classification and information bias. Given that the three institutions use different methods for measuring D-dimer, data were converted to FEU, which allows for uniformity in measurement and analysis. Our study is a multicenter case-control study conducted at three institutions in the city of Medellín, which expands the spectrum of the studied population.

Additional cohort studies are needed in institutions where CTPA is routinely performed upon admission of COVID-19 patients, which would also allow for the evaluation of the diagnostic performance of D-dimer in pulmonary embolism.

5. Conclusions

The D-dimer level is an independent factor associated with PE in patients with COVID-19 in critical care patients, especially if the level is more than 5000 ng/mL. This will help in the future with making clinical decisions in critical ill patients. For the prognosis of the disease based on the D-Dimer level more studies are required.

Compliance with ethical standards

Disclosure of conflict of interest

All of the authors disclose that we do not have any conflict of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any other author. Also, The investigation protocol was approved by the “Institutional Committee of Ethics for Research in Human Beings at Universidad CES” (Act N°185)

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