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Research Article

Rethinking D-dimer's Role in the Diagnosis of Pulmonary Thromboembolism in Patients with COVID-19

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ABSTRACT

Background: D-dimer is a non-specific inflammatory marker that elevates in infections, thrombosis, and pregnancies. COVID-19 is a prothrombotic inflammatory disease, and it is common to find elevation of D-dimer in severe COVID-19 cases. The usefulness of D-dimer for the diagnosis of Pulmonary Thromboembolism (PE) in SARS CoV-2 has not been determined.

Objective: To determine the operational characteristics of D-dimer as a diagnostic method for PE in patients with COVID-19 treated at a university hospital in Bogotá, Colombia.

Methods: Study of diagnostic tests that included data from patients with COVID-19 with suspected PE who were screened with the index test (D-dimer measured by turbidimetric immunoassay technique) and reference test (Angiotomography of pulmonary arteries).

Results: Among the 209 patients analyzed, the prevalence of PE was 14.4%, D-dimer levels were significantly higher in the group of PE cases (2888 ng/Dl vs. 1114 ng/Dl; p=0.002). 80% of PE cases were submassive and 53% segmental. The operating characteristics for the reference cut-off point of the technique (>499 ng/mL) was Sensitivity: 93.9%, Specificity: 8.9%, Positive predictive value: 14.7%, Negative predictive value: 8.9%, proportion of false positives: 91.1% with a Youden J- index of 0.02. The area under the curve was 0.684. The coordinates of the curve showed a Youden J- index of 0.367 for a value of 2.281 ng/mL (4.5 times the reference value), using this cut-off point, we obtained a sensitivity of 60%, a specificity of 76%, PPV of 30%, NPV of 92%, and a proportion of false Negatives of 40%.

Conclusion: D-dimer does not have appropriate characteristics to be used alone for the diagnosis PE in patients with severe COVID 19. It can be used as part of a rational diagnostic process, being just as specific as the patient's signs and symptoms.

Keywords: COVID-19; D-dimer; Pulmonary embolism; Pulmonary angiotomography

Abbrivations: E: Specificity; LR+: Likelihood Ratio for the Positive Test; LR: Likelihood Ratio for the Negative Test; NPV: Negative Predictive Value; OR: Odds Ratio; PE: Pulmonary Embolism; PPV: Positive Predictive Value; S: Sensitivity

INTRODUCTION

D-dimer is an indicator of fibrin degradation formed by the sequential action of three enzymes, thrombin, Factor XIIIa, and plasmin; it behaves as a non-specific inflammatory marker that increases in various scenarios such as pregnancy, thrombosis, infection, trauma, sepsis, cancer [1]. Infection induced by SARS-CoV-2 can manifest with coagulopathy associated with inflammatory changes, with a prominent increment of fibrin degradation products such as D-dimer [2]. The presence of frequent thrombotic episodes and the relationship between disease severity and D-dimer levels have been described [3]. Although

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the pathogenesis of hypercoagulability attributed to COVID-19 is not fully understood, it has been possible to explain this condition based on Virchow's triad. The incidence of pulmonary thromboembolism in patients with COVID-19 is around 14%, with a mortality of 50% [4]. In order to improve outcomes in patients diagnosed with COVID-19, it is recommended timely diagnosis of PE and an adequate anticoagulation strategy. However, during the pandemic, indiscriminate use of anticoagulation based on high levels of D-dimer in patients with COVID-19 has been observed without consistently demonstrating better outcomes, nonetheless exhibiting variable bleeding rates [5,6].

Considering that SARS CoV-2 infection is a prothrombotic state, the most valuable operative characteristic of the D-dimer in the study of pulmonary thromboembolism in the non-COVID-19 patient population is the negative predictive value and the non-specificity of the D-dimer itself. We proposed this trial of diagnostic tests to rethink the diagnostic role of D-dimer in patients with SARS-CoV-2 infection.

METHODOLOGY

A study of diagnostic tests that included all patients diagnosed with COVID-19 confirmed by PCR and clinical suspicion of PE, that were admitted to a university hospital from the onset of the pandemic until December of 2020, all these patients undertook the index and the reference test. The information was retrieved from the clinical records of the institution after the approval from the ethics committee. Thoracic angiotomography with a protocol for PE was considered a reference test for diagnosing Pulmonary Thromboembolism; these were performed with a 64-slice Siemens Emotion Duo tomograph that belonged to the participating institution.

To determine the discriminatory capacity of the index test, contingency tables were constructed to establish a sensitivity, specificity, positive predictive value, negative predictive value, accuracy, diagnostic OR, Youden's J Index, and the positive and negative likelihood ratios using two cut-off points: the one indicated by the laboratory according to the technique used in the institution and the cut-off point with the highest Youden's J Index determined by the coordinates in a Receiver Operating Curve (ROC). The quantitative data were presented using central tendency and dispersion measures according to its distribution, and absolute and relative frequencies were used to describe qualitative variables. In this study thoracic angiotomography was considered the reference test for diagnosing pulmonary embolism with a sensitivity of 99.9% and a specificity of 100%. We calculated a sample size of 117 patients to determine total accuracy of the index test based on a previous publication that reported a sensitivity of 85% and a specificity of 88.5% for the incidence of venous thromboembolic disease using D-dimer versus thoracic angiotomography which had a sensitivity of 95% and a specificity of 99.999%, other parameters for this calculation were a confidence level of 95% and a power of 80% using the software for epidemic data analysis Epidat V4.2 [7]. Through the sampling module to calculate sample sizes for hypothesis testing for diagnostic tests in paired groups, since every patient underwent both tests. Operative characteristic and ROC curves were obtained using the statistical software SPSS V 26.

RESULTS

Computed thoracic angiotomography was performed on 214 patients diagnosed with COVID-19 and suspected PE, out of which three were excluded from the analysis due to the absence of a D-dimer result, and two patients in whom it was not possible to recover all the clinical data. All patients underwent D-dimer by turbidimetric immunoassay. Images from the lung vertices to the posterior costophrenic recesses were obtained, with 3-mm cuts, by previously administration of water-soluble contrast medium at an infusion rate of 3 ml/sec. For D-dimer the cut-off point of the reported technique is 499 ng/mL.

The analyzed sample consisted of 209 patients between 20 and 99 years; 60% of the patients were male, 44% had a history of arterial hypertension, and 14.4% had diabetes mellitus. The medians of the Wells and News scores were 1.5 and 5, respectively. Thirty-five patients were on mechanical ventilation, and 16.7% of the patients included in the sample died from the disease.

The prevalence of pulmonary thromboembolism in the sample was 14.4%, of which 80% was sub-massive, 53.6% had a sub-segmental location and 17.9% received systemic fibrinolysis. There were differences in the NEWS and WELLS scores, D-dimer, anticoagulation, days of hospital stay, and mortality between patients with and without PE (Table 1).

Table 1: Characterization of the patients included in the study.

Variable	Patients	PE	NO PE	P-value
	(-209)	-30	-179	
Male*	126 (60.3)	18 (64.3)	108 (62.1)	0.822*
Age‡	60.5 ± 17.7 (20-99)	63.4 ± 16.7 (27-99)	60.05 ± 15.6 (20-92)	0.277‡
Arterial hypertension*	92 (44)	13 (43.3)	79 (44.4)	0.915*
Mellitus diabetes*	30 (14.4)	5 (16.7)	25 (14)	0.778†
COPD*	24 (11.5)	5 (16.7)	19 (10.7)	0.357†
Cancer*	18 (8.6)	2 (6.7)	16 (9)	1†
NEWS Score§	5 ± 3 (0-12)	7 ± 3 (0-12)	5 ± 3 (0-12)	0.004§
WELLS Score§	1.5 ± 3 (0-11)	3 ± 4.5 (0-11)	1.5 ± 3 (0-9)	0.002§
WELLS Unlikely (≤4)*	159 (76.1)	17 (68)	142 (92.8)	0.001†
D-dimer ng/mL§	1230 ± 1920 (229-78270)	2888 ± 3349 (340-66880)	1114 ± 1420 (229-78270)	0.002§
Magnitude of Embolism*				
Massive	-	6 (20)	-	-
Sub-massive	-	24 (80)	-	-
Anatomical location*				
Subsegmental	-	15 (53.6)	-	-
Segmental	-	8 (28.6)	-	-
Lobar	-	3 (10.7)	-	-
Central	-	2 (7.1)	-	-
Thrombolysis*	-	5 (17.9)	-	-
Anticoagulation*	44 (21.1)	27 (90)	17 (9.5)	0.000†
Mechanic ventilation*	35 (16.7)	8 (26.7)	27(15.1)	0.116*
Days of mechanical ventilation §	9.5 ± 10.5 (1-82)	6.5 ± 21.25 (1-46)	10 ± 9.75 (1-82)	0.328§
ICU stay (days) §	10 ± 10.5 (1-83)	10 ± 13.8 (3-49)	9.5 ± 10.5 (1-83)	0.781§

Hospital Stay (days) §	5 ± 9 (1-99)	7 ± 9 (1-5)	5 ± 8 (1-99)	0.029§
Mortality*	35 (16.7)	10 (34.5)	25 (14.1)	0.014†

Note: *Absolute frequency (Percentage)-Chi-square; †Fisher's exact test; ‡ Means ± standard deviation (Minimum-maximum)-Student's T; § Median ± interquartile range (Minimum-maximum)- Mann Whitney U

Considering the cut-off point of the reported technique for the index test (499 ng/ml), D-dimer's sensitivity, specificity, and positive and negative predictive values were 93.3%; 8.9%; 14.7%, and 88.9%, respectively. The proportion of false positives for this cut-off point is 91.1%, and the overall accuracy is 21.1% (Table 2).

Table 2: D-Dimer operating characteristics for the 499 ng/mL cut-off.

	Confidence interval 95%			
Sensitivity (S)	93.3%	90.0%	a	96.7%
Specificity (E)	8.9%	5.1%	a	12.8%
Positive predictive value	14.7%	9.9%	a	19.5%
Negative predictive value	88.9%	84.6%	a	93.1%
False-positive rate	91.1%	87.2%	a	94.9%
False-negative rate	6.7%	3.3%	a	10.0%
Accuracy	21.1%	15.5%	a	26.6%
Diagnostic odds ratio	1.37	0.30	a	6.29
Youden's J Index	0.02	-	-	-
Likelihood Ratio (LR) +	1.02	0.97	a	1.08
Likelihood Ratio (LR) -	0.75	0.36	a	1.54
Prevalence in the sample	14.4%	9.6%	a	19.1%

The area under the ROC curve of the D-Dimer and the Wells Score for this sample was 68.4% and 67.5%, respectively. The D-dimer value with the highest Youden's J Index was 2.281 ng/Ml according to the coordinates of the ROC curve analysis (Figure 1).

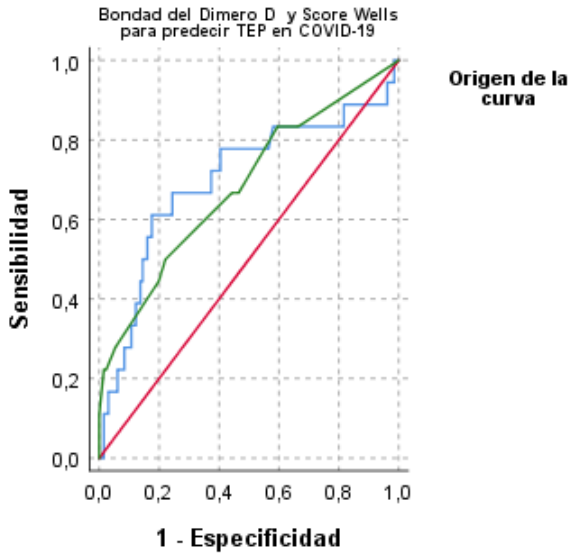

Figure 1: The area under the ROC curve Dimer D–Wells score versus classification by angiotomography for the diagnosis of PE. **Note:** (—) Dimero dvalor, (—) Linea de referencia, (—) Wells score.

A lower sensitivity of 60% {CI. 95% (53.4%-66.6%)}, greater specificity of 76.7% {CI. 95% (70.9%-82.4%)}, with a PPV of 30% and an NPV of 92%, and with a diagnostic OR of 4.93 {CI. 95% (2.30%-10.55%)}. Overall accuracy was greater than the cut-off point suggested by the laboratory technique (Table 3).

Table 3: D-Dimer operating characteristics for the 2281 ng/mL cut-off.

	Confidence interval 95%			
Sensitivity (S)	60.0%	53.4%	a	66.6%
Specificity (E)	76.7%	70.9%	a	82.4%
Positive predictive value	30.0%	23.8%	a	36.2%
Negative predictive value	92,0%	88.3%	a	95.7%
False-positive rate	23.3%	17.6%	a	29.1%
False-negative rate	40.0%	33.4%	a	46.6%
Accuracy	74.3%	68.4%	a	80.2%
Diagnostic odds ratio	4.93	2.30	a	10.55
Youden's J Index	0.367	-	-	-
Likelihood Ratio (LR) +	2.57	2.10	a	3.14
Likelihood Ratio (LR) -	0.52	0.42	a	0.65
Prevalence in the sample	14.4%	9.6%	a	19.1%

DISCUSSION

Critically ill patients with COVID 19 present elevated levels of D-dimer, associated with the severity of the disease, and could be considered a biomarker associated with a worse outcome without being frequently associated with the presence of thrombotic phenomena. The present study explored the usefulness of this test and the drawbacks of considering this test as a use-alone diagnostic tool for pulmonary embolism.

The sample size of this study is sufficient to determine the operational characteristics; more information was collected for consideration by the developer group, considering that this is valuable information that can provide a better understanding of the pathophysiological elements of SARS-CoV-2 infection.

The frequency of pulmonary embolism in this series was 14.3%, comparable to the study by SUH et al., which reported a cumulative incidence of 16.5% [8]. However, in more severe patients admitted to intensive care, the prevalence can be higher, up to 38% [9]. Although D-dimer values were higher in patients with a confirmed diagnosis of PE (2888 ng/m vs. 1114 ng/m; p=0.002), almost the entire sample studied (97.38%) had elevated D-dimer levels above the reference point of the laboratory technique, similar to other studies that also describe elevated values of D-dimer in COVID-19 [10].

In this series, age and comorbidities do not seem to be factors related to the presentation of pulmonary embolism since there were no differences in clinical characteristics such as hypertension, diabetes, or cancer between patients with COVID-19 who did or did not develop the event of interest, neither did age, unlike the study by Alonso-Fernandez et al. where elderly patients had a higher incidence of PE [11]. However, clinical severity does seem to be related to thromboembolic phenomena, given that the severity assessed by the news score was significantly higher in the group with PE. Traditional clinical assessment of patients with suspected PE in the non-COVID-19 population uses Wells score to guide clinical decision. Even though Wells score is not validated in COVID-19, it was significantly higher in patients with PE and showed an area under the curve of 0.675 comparable to that of D-dimer.

Patients with PE and COVID-19 have a worse course of the disease, with a greater need for intensive care, longer hospital stays, and a more critical requirement for invasive mechanical ventilation

[8,11]. In this series, PE is associated with higher mortality 34.5% vs. 14.1% (p=0.014). Elevated D-dimer levels, as described by Zhang et al., can predict hospital mortality in COVID-19, Zhang found a Hazard Ratio of 51.5 (p<0.001) [12]. Other risk factors described for PE in patients with COVID-19 are the absence of thromboprophylaxis and other inflammatory markers similar to D-dimer, such as elevated C-reactive protein [13].

There are multiple assays available on the market to detect D-dimer levels that may have different specificities. The technique we used in this study to measure D-dimer was the turbidimetric immunoassay, which has a sensitivity of 93% (89%-95%) and a specificity of 53% (46%-61%), which is moderate. Its main advantage is that the sensitivity is comparable to the automated ELISA method [14].

Elevation of D-dimer can occur in healthy patients due to expected fibrin degradation, but marked elevations reflect pathological conditions. In SARS-CoV-2 infection, the elevation of D-dimer has a multifactorial etiology. It not only reflects thrombotic states, but it may also be due to the excessive inflammatory response with the cytokine release and macrophage activation, diffuse intravascular coagulation, immobilization, and secondary hypoxia due to lung injury. These mechanisms result in Virchow's famous triad: endothelial injury, circulatory stasis, and hypercoagulability [15,16].

Given the low specificity of D-dimer for the diagnosis of PE in COVID-19, multiple studies are consistent with increasing the cut-off point to improve the operational characteristics of diagnostic performance [8,17-22].

In our study, we found that the operational characteristics of D-dimer for the diagnosis of PE at a cut-off point of 499 ng/ml have a sensitivity of 93.3% (CI 90%-96.7%) and a specificity of 8.9% (CI 5.1%-12.8%), when we adjusted to a higher cut-off point based on the best Youden's J Index, (2281 ng/ml) which represents almost 4.5 times the previous value. As expected, the operating characteristics were modified, the sensitivity decreased, but specificity increased. Regarding the area under the curve, the systematic review by Shu et al. reports an area under the curve for D-dimer of 0.737 for the diagnosis of PE slightly higher than that reported in this series, which was 0.684. However, neither of the two is an excellent discrimination; Shu reports operational characteristics for two cut-off points of D-dimer. The 500 mg/L limit had a sensitivity of 96% and a specificity of 10%, while the 1000 mg/L limit had sensitivity of 91% and specificity of 24, similar to the results of our cut-off point of 499 ng/ml. Shu also describes a high PPV of 89%, this characteristic is the most consistent with our results, confirming that as in the non-COVID-19 population, this may be one of the most important traits used to rule out the disease in patients with low clinical probability.

It is consistent that the elevation of D-dimer in patients with COVID-19, even in early phases, is a marker of poor prognosis but does not always reflect thrombotic phenomena [23,24], in such a way that if we increase the cut-off point of D-dimer, we can strengthen the diagnostic exercise of PE and implement safer therapies, initiate antithrombotic management with more evidence make rational use of pulmonary artery computed tomography, and avoid risky exposures to contrast media. However, it should not be forgotten that considering a higher cut-off point can increase the rate of false negatives, which could also lead to under diagnosis with the risk of related fatal outcomes [25].

Among this study's limitations is the nature of the single-center and retrospective study.

CONCLUSION

D-dimer does not have good diagnostic performance characteristics to consider it a surrogate for diagnosing PE in severe COVID-19 patients. It can be used as part of a rational diagnostic plan. Values of more than four times the maximum average reference value should be considered, and the high NPV can be considered to rule out PE in COVID-19 patients.

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Author contributions

Drs. Nieto, Valencia and Molano conceived the original study design. Professor Martinez designed and conducted statistical analysis for this study, revised results and translation. Dr. Nieto takes full responsibility for this manuscript. The rest of the authors entered data on the database, revised and double checked the data. All authors contributed to editing the manuscript and approved the final version.

CONFLICT OF INTEREST

No conflict exists for the specified authors.

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