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Predicting pulmonary embolism in patients infected with COVID-19 based on D-dimer levels and days between diagnosis of the infection and D-dimer determination

Ignasi Garcia-Olivé[1,2,3,4], Helena Sintes[1,4], Joaquim Radua[5,6,7,8], Jordi Deportos[9], Isabel Nogueira[10], Cristian Morales-Indiano[11], Jorge Abad Capa[1,2,3,4], Antoni Rosell[1,2,3,4]

[1]Department of Respiratory Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [2]CibeRes, Ciber de Enfermedades Respiratorias, Spain; [3]Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain; [4]Departament de Medicina, Universitat Autònoma de Barcelona, Spain; [5]Imaging of Mood- and Anxiety-Related Disorders (IMARD) group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [6]CIBERSAM, Madrid, Spain; [7]Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [8]Department of Clinical Neuroscience, Stockholm Health Care Services, Stockholm County Council, Karolinska Institutet, Stockholm, Sweden; [9]Department of Nuclear Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [10]Department of Radiology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [11]Department of Clinical Analysis and Biochemistry, Laboratori Clínic Metropolitana Nord, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Correspondence: Ignasi Garcia Olivé, Department of Respiratory Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Spain.
E-mail: igarcia.germanstrias@gencat.cat
https://orcid.org/0000-0001-7698-5107

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Abstract

Ruling out pulmonary embolism (PE) can be challenging in a situation of elevated D-dimer values such as in a case of COVID-19 infection. Our objective was to evaluate the difference in D-dimer values of subjects infected with COVID-19 in those with PE and those without and to analyze the predictive value of D-dimer for PE in these subjects based on the day of D-dimer determination.

This was an observational, retrospective study, conducted at a tertiary hospital. All subjects with PCR-confirmed COVID-19 infection requiring hospital admission at our institution between the months of March and April 2020 were included in the study. We compared D-dimer levels in subjects who went on to develop a PE and those who did not. We then created a model to predict the subsequent development of a PE with the current D-dimer levels of the subject. D-dimer levels changed over time from COVID-19 diagnosis, but were always higher in subjects who went on to develop a PE. Regarding the predictive model created, the area under the curve of the ROC analyses of the cross-validation predictions was 0.72. The risk of pulmonary embolism for the same D-dimer levels varied depending on the number of days elapsed since COVID-19 diagnosis and D-dimer determination. To conclude, D-dimer levels were elevated in subjects with a COVID-19 infection, especially in those with PE. D-dimer levels increased during the first 10 days after the diagnosis of the infection and can be used to predict the risk of PE in COVID-19 subjects.

Introduction

At the beginning of the COVID-19 outbreak a number of authors suggested that the infection could directly impact cardiovascular disease, either by increasing the risk of severe disease

and death in subjects with preexisting cardiovascular disease, or by the association of COVID-19 infection with multiple direct and indirect cardiovascular complications, including acute myocardial injury, myocarditis, arrhythmias and venous thromboembolism (VTE) [1]. Since then, elevated D-dimer levels in subjects infected with COVID-19 have been associated with a poorer outcome [2,3], while anticoagulant treatment has been associated with decreased mortality in subjects with markedly elevated D-dimer [4].

D-dimer levels, which are a useful tool for allowing clinicians to rule out pulmonary embolism (PE) [5], have been described as elevated in subjects with COVID-19[6], both in those with VTE or PE and those without [7,8].

In this context of elevated D-dimer values, ruling out PE can be even more challenging than it was previously. Thus, our objective was to analyze the predictive value of D-dimer for PE in COVID-19 subjects, and to evaluate whether the risk of pulmonary embolism is influenced by the number of days elapsed from COVID-19 diagnosis and D-dimer determination.

Materials and Methods

Location

This was an observational, retrospective study, conducted at a hospital in Badalona (Barcelona, Spain). Hospital Universitari Germans Trias i Pujol is a tertiary hospital with 600 beds. It is also a referral hospital for an area with a population of 700,000.

Study subjects

All subjects with a PCR-confirmed COVID-19 infection requiring hospital admission at our institution between the months of March and April 2020 were included in the study. All D-dimer determinations between day 0 (day of PCR confirmation) and day 30 (30 days after the diagnosis) were considered. Subjects with a CT or CT-SPECT PE diagnosis were considered to have PE. Subjects without suspicion of PE, without a CT-scan or CT-SPECT, or with a diagnostic procedure that did not confirm PE were considered not to have a PE. The end of follow up was established as the day of discharge in subjects without PE and the day of diagnosis in subjects with confirmed PE.

Plasma D-dimer measurements

Blood samples were collected in 3.8% (0.129 M) sodium citrate (anticoagulant) tubes (BD Vacutainer) and plasma was obtained by 10-minute centrifugation at 3000 rpm. All plasma samples were analyzed within two hours of collection. Plasma D-dimer concentration was measured using a latex-enhanced immunoassay (Hemosil D-Dimer HS 500, Instrumentation Laboratory) on an automated coagulation analyzer (ACL TOP 750, Instrumentation Laboratory). D-dimer levels were expressed in fibrinogen equivalent units (FEUs). At our institution, the cutoff established for VTE exclusion was 0.5 µg/mL (FEU).

Statistical analysis

Comparison of D-dimer levels

The first aim of this study was to investigate the differences in D-dimer levels in subjects who went on to develop a PE and those who did not, depending on the time elapsed from COVID-19 diagnosis. To investigate these relationships, we created boxplots and conducted tests to compare the D-dimer levels of subjects who later developed a PE and subjects who did not in the time elapsed since COVID-19 diagnosis.

It must be noted that the numbers of D-dimer measurements on a given day were relatively small for subjects who developed a PE (range: 2-17 measurements per day). To have larger sample sizes for the boxplots and the comparison tests, we divided the time since COVID-19 diagnosis into groups of three days. When a subject had two or more D-dimer measurements in one of these groups of three days, we averaged them.

To statistically compare D-dimer levels of subjects who went on to develop a PE and those who did not in each group of three days, we had planned to perform t-tests of the logarithm of the D-dimer levels (to approximate normality). However, our measurement device truncated D-dimer levels higher than 7.65 µg/mL, and we therefore had to replace t-tests with Tobit models, which can handle censored dependent variables [9].

To assess whether results were similar in subjects in different age or sex groups, we repeated the boxplots and comparisons separately for subjects <65 years old, subjects >65 years old, and for males and females.

Creation of a prediction model

The second aim of this study was to provide clinicians with a model that would allow them to predict the subsequent development of a PE based on the current D-dimer levels of the subject.

To create this model: a) we first standardized the D-dimer levels to remove the effects of time elapsed since the diagnosis of COVID-19; b) we conducted a logistic regression in which the dependent variable was the development of pulmonary embolism (yes *vs.* no) and the independent variable was the highest standardized D-dimer level of each subject; c) we then created an empty matrix in which the columns were the number of days since COVID-19 diagnosis and the rows were the D-dimer levels (0.50, 1.00, *etc.*); and d) we filled each cell of the matrix with the estimated probability of developing a pulmonary embolism, as predicted using the coefficients of the logistic regression and the standardized D-dimer level of the cell (Table 1).

To standardize the D-dimer levels, we first applied a robust locally weighted regression [10] in which the dependent variable was the logarithm of the D-dimer levels in subjects who did not develop a PE, while the independent variable was the number of days elapsed since the COVID-19 diagnosis. This regression yielded the expected D-dimer levels as a function of time in subjects who did not develop a PE. We then removed these expected levels from the logarithm of the actual D-dimer levels of each subject.

We did not include the effects of age or sex in the logistic regression because in preliminary analyses we had found that they were not statistically significant.

To validate the model, we used a leave-one-out cross-validation approach. In each iteration, we used all subjects except the i^{th} subject to create the model, obtaining a matrix of rounded probabilities as in Table 1. We then simulated the use by a clinician of this matrix to predict whether the i^{th} subject would develop a pulmonary embolism. This division into a "training sample" (to create the model) and a "test sample" (the excluded subject that we predicted) was performed many times, so that each subject was the test sample once. With this algorithm, we were able to predict the development of a PE in all subjects, but the subjects used to create the prediction model and the subjects used to test it were always different.

Finally, to summarize the accuracy of the model, we conducted a ROC analysis in which the dependent variable was the (true)

development of a pulmonary embolism, and the independent variable was the probability of pulmonary embolism found in the cross-validation. Again, to assess whether results were similar in subjects with different age or sex groups, we repeated the ROC analysis for subjects <65 years old and subjects >65 years old, as well as for males, and females.

All analyses were conducted in R with the packages VGAM [11] and pROC [12].

Results

After excluding subjects without a D-dimer measurement, subjects with PE and D-dimer determination obtained only the same day or after the diagnosis of PE, 782 subjects were included in the analysis (Figure 1), of whom 34 went on to develop a PE (see Table 2 for a description of the participants). 2,200 measurements

Table 1. Probability (in %) of pulmonary embolism according to the number of days elapsed since COVID-19 diagnosis and the D-dimer levels.

D-dimer levels (g/ml)	Days after the COVID-19 diagnosis																													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
0.05	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.50	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
1.00	4	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
1.50	5	5	4	4	4	3	3	3	3	3	3	3	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
2.00	6	6	5	5	5	4	4	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4
2.50	7	7	6	6	5	5	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	5
3.00	8	8	7	7	6	6	5	5	5	4	4	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5
3.50	9	9	8	7	7	6	6	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6
4.00	10	9	9	8	8	7	6	6	6	6	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7
4.50	11	10	10	9	8	8	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	
5.00	12	11	10	10	9	8	8	7	7	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	8
5.50	12	12	11	10	10	9	8	8	7	7	7	7	6	6	6	6	7	7	7	7	7	7	7	7	7	8	8	8	8	8
6.00	13	12	12	11	10	9	9	8	8	7	7	7	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	9	9	
6.50	14	13	12	11	11	10	9	9	8	8	8	7	7	7	7	7	7	7	8	8	8	8	8	8	8	9	9	9	9	9
7.00	15	14	13	12	11	10	10	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	10
7.65	15	15	14	13	12	11	10	10	9	9	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	10	10	10	10	10

If a patient has two or more D-dimer levels, use the higher probability.

Table 2. Basic description of the participants.

	All patients	Patients who did not develop a PE	Patients who later developed a PE
All patients:			
Number (%)	782	748 (95.7%)	34 (4.3%)
Age in years (SD)	62.2 (15.7)	62.1 (15.8)	63.8 (12.9)
Females %	41.2%	41.0%	44.1%
<65 years old patients:			
Number (%)	407	391 (96.1%)	16 (3.9%)
Females %	40.0%	40.2%	37.5%
>65 years old patients:			
Number (%)	375	357 (95.2%)	18 (4.8%)
Females %	42.4%	42.0%	50.0%
Male patients:			
Number (%)	460	441 (95.9%)	19 (4.1%)
Age in years (SD)	61.9 (15.2)	61.9 (15.4)	61.3 (10.7)
Female patients:			
Number (%)	322	307 (95.3%)	15 (4.7%)
Age in years (SD)	62.6 (16.3)	62.4 (16.4)	66.9 (15.0)

PE, pulmonary embolism.

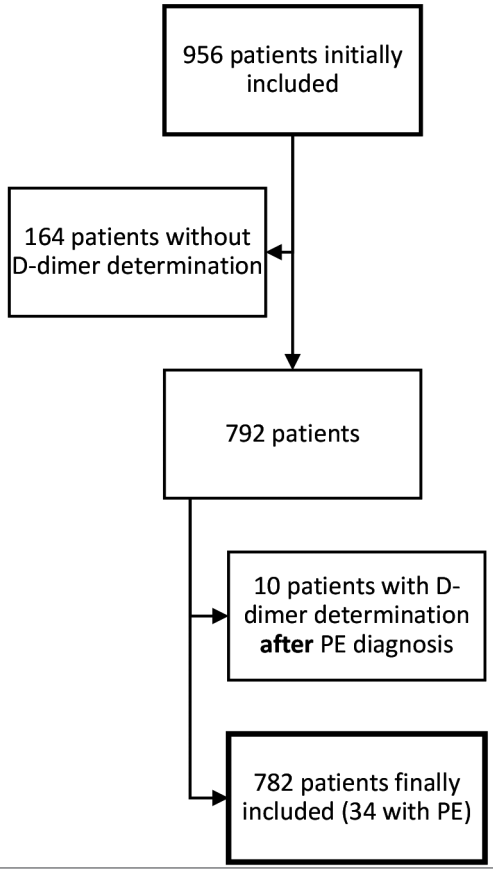

Figure 1. Flowchart of the selection of patients finally included in the analysis. PE, pulmonary embolism.

of D-dimer levels were performed during the studied time span, of which 152 were from subjects who went on to develop a PE. Median time from COVID-19 diagnosis to PE diagnosis was 15 days (interquartile range: 9-20, range: 1-46), and median time from a D-dimer measurement to the PE diagnosis was 10 days (interquartile range: 5-16, range: 1-43). Median stay was 11 days (interquartile range 5-20, range 0-51). For those who died median stay was 7 days (interquartile range 4-11, range 0-37).

Comparison of D-dimer levels

As can be observed in Figure 2, D-dimer levels changed over time from COVID-19 diagnosis, but were always higher in subjects who went on to develop a PE. Tobit models found that these differences were statistically significant during the first 17 days following COVID-19 diagnosis (p was 0.040 for 0-2 days, 0.016 for 3-5 days, <0.001 for 6-8 and 9-11 days, and 0.003 for 12-14 and 15-17 days). Differences were no longer statistically significant after the 17th day from diagnosis, but this later period included few measurements from subjects who went on to develop a PE (from two to six measurements per three day group). Results were similar when we analyzed subjects <65 years old, subjects >65 years old, male subjects and female subjects separately.

Box plots showed several outlying D-dimer levels in the first nine days in the group of subjects that did not develop PE. The presence of these outlying observations might indicate deviations from a normal distribution, which may affect the estimation of the statistical significance of the comparisons. To assess whether this is the case, we repeated the comparisons of D-dimer levels of subjects who went on to develop a PE and those who did not using non-parametric Wilcoxon tests. The statistical significance was nearly identical (p was 0.036 for 0-2 days, 0.008 for 3-5 days, <0.001 for 6-8 and 9-11 days, 0.005 for 12-14, 0.003 for 15-17 days, and no longer statistically significant after the 17th day).

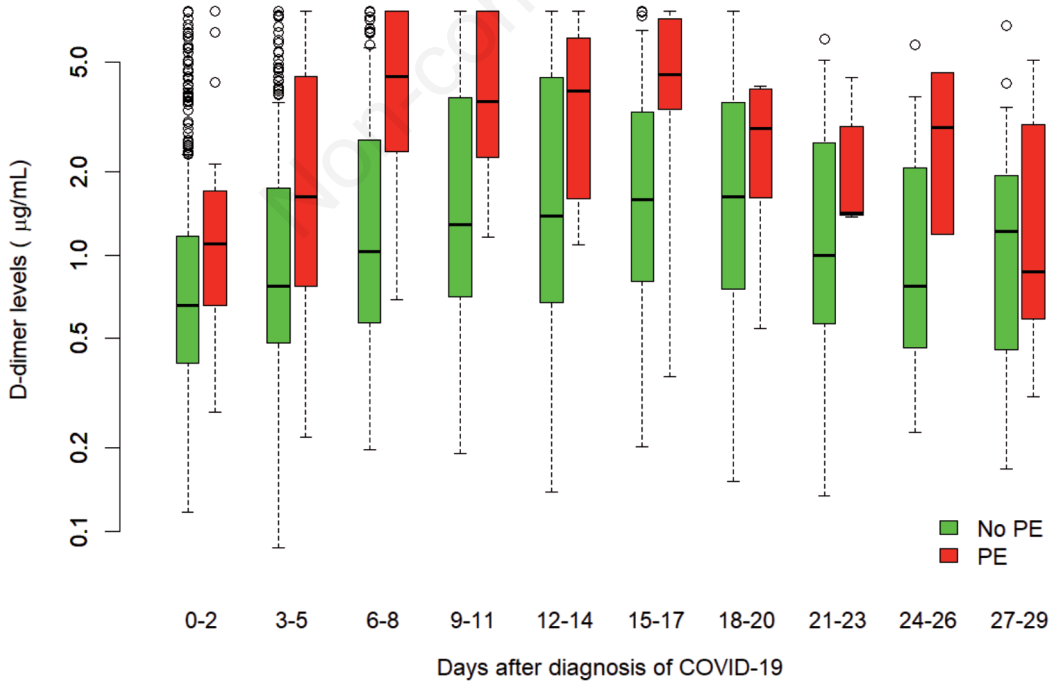

Figure 2. Boxplot of the relationship between D-dimer levels and pulmonary embolism (PE) depending on the time since the diagnosis of COVID-19. Our measurement device truncated D-dimer values higher than 7.65 µg/ml.

Prediction models

We provide the matrix with the estimated probability of pulmonary embolism according to the number of days since the diagnosis of COVID-19 and D-dimer levels in Table 1. If a subject has two or more D-dimer levels, the clinician should look at the probabilities associated to the different D-dimer levels and select the one with the greatest probability.

As shown in Table 3, the area under the curve of the ROC analyses of the cross-validation predictions was 0.72 (fair). It increased to 0.80 or 0.77 when the ROC analyses only included <65 years old or male subjects, while it decreased to 0.64 or 0.65 when they only included >65 years-old or female subjects. To provide clinicians with more practical estimates of the accuracy (and thus to what extent should they trust the probabilities), we then calculated the area under the curve for males <65 years old, females <65 years old, >65 years old, and >65 years old females. The area under the curve reached 0.83 (good) for males <65 years old, remained at 0.73 and 0.72 (fair) for females <65 years old and males >65 years old, and decreased to 0.65 (poor) for females >65 years old. All ROC analyses were statistically significant (the 95% CI did not include 0.50), with the only exception of the one for females >65 years old.

Discussion

In our study, COVID-19 infection was associated with elevated levels of D-dimer which were higher in subjects who developed PE. D-dimer levels increased during the first 10 days after the diagnosis of infection and slowly decreased after the 15th day. Higher D-dimer levels were associated with an increased risk of PE. Thus, for example, a subject with a determination of D-dimer of 7.00 mg/mL on the day of diagnosis had a probability of 15% of presenting a PE during hospitalization.

The association between COVID-19 infection and elevated D-dimer values has been described in the literature [3,13,14], and those subjects with higher D-dimer levels are observed to be more likely to present a poorer outcome [2,15]. Tang and cols described that anticoagulant treatment was associated with decreased mortality in subjects with markedly elevated D-dimer [4]. Since then, many authors have described an association between COVID-19 and an elevated risk of VTE [16-21].

In a situation in which elevated D-dimer values and respiratory failure are common, ruling out PE can be even more challenging than previously supposed, making it desirable to obtain cut-off values to improve the diagnostic accuracy of D-dimer for PE. Although the clinical utility of a fixed upper limit for a normal D-dimer level has been called into question, at our institution this limit has been set at 0.5 µg/mL. In our previous analysis [8], the baseline D-dimer level in our control group (without PE) was 1.6 µg/mL. Thus, a fixed upper limit for a normal D-dimer level does not seem to be useful in order to rule out PE in subjects infected with COVID-19.

Leonard-Lorant *et al*. [7] reported that a D-dimer threshold of 2669 µg/l detected all subjects with pulmonary embolus on chest CT scans. In another French study conducted by Artifoni *et al.* [14] including 71 non-ICU subjects, D-dimer levels at hospital admission were significantly higher in those who developed VTE with a median of 1.63 µg/ml *vs* 0.63 µg/ml. The negative predictive value of a baseline D-dimer level <1.0 µg/ml for PE was 98%, while it was 100% when taking into account the latest available D-dimer level prior to VTE. When comparing VTE positive *vs* VT negative subjects, Stoneham *et al.* reported that a D-dimer threshold of >2 µg/mL was present in 78% of subjects with VTE and only 33% of subjects without VTE [21]. Cui and colleagues, using a D-dimer cut-off value of 1.5 µg/ml, described a sensitivity, specificity and negative predictive value of 85.0, 88.5 and 94.7%, respectively [16]. In our model, a subject with a D-dimer determination of 2.50 µg/ml had a probability of approximately 5% of presenting a PE, which seems to be in line with previous findings [7].

Our study has several limitations. First, it is a retrospective study. Secondly, the time of evolution is based on laboratory confirmation of COVID-19 infection, while the symptoms had certainly begun earlier. Thirdly, at our institution, necropsies have not been performed on subjects infected with COVID-19. Thus, subjects with sudden death and suspected PE have not been included in the study. And lastly, not all subjects were diagnosed using the same technique, as at our institution both CT-scan and SPECT-CT are commonly used for the diagnostic assessment of PE.

The main new finding of this work is that the risk of developing PE depends on the day of Covid-19 determination. Thus, a D-dimer level of 5.50 □g/mL is associated with a probability of D-dimer of 12% if the determination is made on the first day after confirmation of COVID-19, but the associated probability is 6% if determination of D-dimer occurs 12 days later (please note that if a subject has two or more D-dimer levels, we must use the higher probability).

In short, we have detected an increase in D-dimer levels in subjects with COVID-19 infection, especially in those with PE. D-dimer levels increased during the first 10 days after the diagnosis of infection, and slowly decreased after the 15th day. The risk of pulmonary embolism for the same D-dimer levels varied depending on the number of days since the diagnosis of COVID-19 and D-dimer determination. In our opinion, prospective studies should be carried out in order to set a limit of normal D-dimer values for COVID-19 patients. Until then, we recommend serial determination during their hospital stay.

Table 3. Area under the curve (AUC) of the ROC analyses of the cross-validation predictions of pulmonary embolism.

	AUC (95% CI)
All patients	0.72 (0.63-0.81)
<65 years old patients	0.80 (0.70-0.90)
>65 years old patients	0.64 (0.51-0.78)
Male patients	0.77 (0.66-0.89)
Female patients	0.65 (0.52-0.78)
<65 years old male patients	0.83 (0.71-0.95)
<65 years old female patients	0.73 (0.55-0.91)
>65 years old male patients	0.72 (0.53-0.91)
>65 years old female patients	0.58 (0.39-0.77)

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