A higher D-dimer threshold for predicting pulmonary embolism in patients with COVID-19: a retrospective study

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Abstract

Purpose COVID-19 raises D-dimer (DD) levels even in the absence of pulmonary embolism (PE), resulting in an increase in computed tomography pulmonary angiogram (CTPA) requests. Our purpose is to determine whether there are differences between DD values in PE-positive and PE-negative COVID-19 patients and, if so, to establish a new cutoff value which accurately determines when a CTPA is needed.

Methods This study retrospectively analyzed all COVID-19 patients who underwent a CTPA due to suspected PE between March 1 and April 30, 2020, at Ramón y Cajal University Hospital, Madrid (Spain). DD level comparisons between PE-positive and PE-negative groups were made using Student’s t test. The optimal DD cutoff value to predict PE risk in COVID-19 patients was calculated in the ROC curve.

Results Two hundred forty-two patients were included in the study. One hundred fifty-one (62%) were men and the median age was 68 years (IQR 55–78). An increase of DD (median 3260; IQR 1203–9625 ng/mL) was detected in 205/242 (96%) patients. 73/242 (30%) of the patients were diagnosed with PE on CTPA. The DD median value was significantly higher (p < .001) in the PE-positive group (7872, IQR 3150–22,494 ng/mL) compared with the PE-negative group (2009, IQR 5675–15,705 ng/mL). The optimal cutoff value for DD to predict PE was 2903 ng/mL (AUC was 0.76 [CI 95% 0.69–0.83], sensitivity 81%). The overall mortality rate was 16% (39/242).

Conclusion A higher threshold (2903 ng/mL) for D-dimer could predict the risk of PE in COVID-19 patients with a sensitivity of 81%.

Keywords COVID-19 • Pulmonary embolism • Computed tomography pulmonary angiogram • D-dimer • Retrospective study

Key points • Pneumonia and coagulation disorders are some of the clinical manifestations of COVID-19. In this regard, coagulation markers such as D-dimer can be increased even in the absence of pulmonary embolism.
• D-dimer role in pulmonary embolism (PE) risk estimation in COVID-19 patients is limited. Dyspnea can be present in uncomplicated COVID-19 pneumonia as well as in PE. Elevated D-dimer values could be a normal finding in COVID-19 patients but they could also be a reflection of PE.
• A higher D-dimer threshold for pulmonary embolism risk prediction in COVID-19 patients could lead to a reduction in computed tomography pulmonary angiogram requests, avoiding health system overwhelming.

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Introduction

A viral disease caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) emerged in December 2019 in Wuhan, China, and spread globally in the initial months of 2020. Spain has been one of the most affected countries during the initial phases of the pandemic, with more than 230,000 cases (5.1% of worldwide number) and 27,000 deaths (9%) [1].

The main clinical manifestations of COVID-19 are not only pneumonia but also coagulation disorders [2, 3]. A prothrombotic state can occur due to endothelial damage and coagulation cascade activation and is possibly related to thromboembolic phenomena [4–8].

In this regard, COVID-19 has been shown to raise blood markers such as D-dimer (DD), which has been found to be significantly higher than in bacterial lung infection [9]. Likewise, a high risk of pulmonary embolism (PE) has been described in COVID-19 patients [10–17].

As a result, the DD role in PE risk estimation in COVID-19 patients has left both clinicians and radiologists facing a dilemma: on the one hand, dyspnea can be present in uncomplicated COVID-19 pneumonia as well as in PE; on the other hand, elevated DD values could be a normal finding in COVID-19 patients but they could also be a reflection of PE. This issue has led to a significant increase in computed tomography pulmonary angiogram (CTPA) requests in radiology departments.

Thus, the purpose of this study is to determine whether there are any differences between DD values in PE-positive and PE-negative COVID-19 patients and, if so, to establish a new cutoff value to help radiologists and clinicians more accurately determine when a CTPA is needed.

Materials and methods

This study was approved by the Research Ethics Committee of our hospital. The need for patient informed consent was waived because of its retrospective nature. Data was anonymized to avoid any identification risk.

Study design and participants

The study retrospectively included data from consecutive patients with COVID-19 diagnostic criteria (see the “Definitions” section) that underwent a CTPA due to PE clinical suspicion from March 1 to April 30, 2020, at our institution (Ramón y Cajal University Hospital, Madrid, Spain).

A total of 402 CTPA exams were performed during the study period. One hundred forty-seven CTPAs belonging to patients who did not meet COVID-19 diagnostic criteria were excluded. Thirteen patients with COVID-19 criteria underwent two CTPAs during the study period. For these 13 cases, only the second CTPA was included. A total of 242 patients were included in the final analysis. The selection algorithm is summarized in Fig. 1.

Definitions

The main COVID-19 criterion was a positive result in RT-PCR (real-time reverse transcriptase-polymerase chain reaction) testing. However, since the reported sensitivity of RT-PCR is somewhat low [18–20], the combination of typical clinical, laboratory, and imaging (chest x-ray or CT) findings was also considered as COVID-19 criteria, provided that common bacterial and viral pathogens that cause pneumonia were excluded based on microbiological analysis [21].

Conditions which could cause a negative outcome such as chronic pulmonary diseases, high blood pressure, diabetes, dyslipidemia, immunosuppression by any cause, obesity, smoking habit, cancer, hepatic, cardiac, or renal chronic failure were included as comorbidities.

Several timepoints were defined, namely, the symptoms onset date, the emergency department arrival date, the CTPA date, and the death or discharge date.

Data collection

Epidemiological, demographic, laboratory, and outcome data was extracted from electronic medical records. The interval between CTPA exams and processing of laboratory data was

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**Fig. 1** Flow diagram of the study participants. COVID-19, coronavirus disease 2019; CTPA, computed tomography pulmonary angiogram
less than 2 days in all cases. All data was evaluated by three
physicians (AG, JQ, and MH) using a standardized collection
form, and a fourth physician (SV) checked for any differences
among the data collected by the three primary reviewers.

CTPA image acquisition

CTPA exams were performed on a 320-detector CT scanner
(Aquilion One, Canon Medical Systems LTD, Otawara,
Japan). The whole chest was craniocaudally scanned from
the lung apex to the lowest hemidiaphragm in the supine po-
sition. All patients were instructed to hold their breath to min-
imize motion artifacts. To reach optimal intraluminal contrast
enhancement, an automatic bolus-tracking technique using
the pulmonary trunk as region of interest and a threshold of
100 HU was performed, with a fix time delay of 5 s to image
acquisition. CTPA images were acquired during a single
breath-hold. Two different protocols were used, depending
on the hemodynamic conditions of the patient:

1. Helical CTPA: 40 mL of non-ionic iodinated contrast
with a flow rate of 5 mL/s, use of central detectors and
movement of the table, approximately 3 s duration and
low radiation dose (2–3 mSv). This protocol was chosen
in normal hemodynamic conditions.
2. Volumetric CTPA: 15–20 mL of non-ionic iodinated con-
trast with a flow rate of 5 mL/s, use of all (320) detectors
allowing for 16 cm of body surface coverage, 350 ms
duration and minimum radiation dose (< 1 mSv). This
protocol was chosen if a rapid blood flow was presumed
(young patients, tachycardia…).

The slice thickness was 0.5 mm. The image data was post-
processed and transferred to the Picture Archiving and
Communication System (PACS).

Image interpretation

PE radiological diagnosis was established as per recent guide-
lines [22, 23]. PE was classified according to laterality (uni-
lateral or bilateral), most proximal affected artery (trunk,
main, lobar, segmental, or subsegmental arteries), and location
(right upper lobe, middle lobe, right lower lobe, left upper
lobe, or left lower lobe). CT signs of right ventricle overload
(right ventricular enlargement, flattening of the interventricu-
lar septum, and/or inferior vena caval contrast reflux) were
also recorded.

A descriptive analysis of COVID-19 pulmonary radiologi-
cal findings on CTPA was made (using both mediastinal and
lung window settings). The presence and distribution of
ground-glass opacities, consolidation, crazy-paving, reticular
pattern, fibrotic-appearing changes (subpleural bands, bron-
chiectasis, bronchial and arterial architectural distortion, and
honeycombing), and barotrauma signs were described. Pleural
findings (thickening, retraction, or effusion) and lymphade-
nopathy were also recorded. Several findings could be de-
scribed at the same time.

Statistical analysis

Continuous variables were presented as a median with an
interquartile range (IQR). Categorical variables were de-
scribed as a number and percentage (%).

Patient characteristics in the PE-positive or PE-negative
groups along with the survivor and non-survivor groups were
compared using Student’s t test, χ² test, or Fisher’s exact test
where appropriate, providing the 95% confidence interval
(95% CI) and p value.

The optimal D-dimer cutoff point for PE was evaluated
using ROC and AUC and expressed as sensitivity and
specificity.

A two-sided α of less than 0.05 was considered statistically
significant. Statistical analyses were done using IBM®
SPSS® Statistics 25.0 (2020) software.

Results

Baseline characteristics of COVID-19 patients (Table 1)

Two hundred forty-two patients were included in the final
analysis. The median age was 68 years (IQR 55–78, range
29–96) and most patients were men 151/242 (62%).

Comorbidities Comorbidities were present in nearly 73%
(176/242) of the patients. The median of comorbidities per
patient was 1.75 (0–3). The most common were hypertension
(42%, 102/242), dyslipidemia (24%, 59/242), diabetes (18%,
44/242), and cancer (10%, 24/242). Chronic pulmonary dis-
ease(s), immunsuppression by any cause, obesity, smoking
habit, and hepatic, cardiac, or renal chronic failure were less
commonly described in the electronic medical records.

Clinical timepoints The median time from onset of COVID-19
symptoms to hospital admission was 7 days (IQR 4–13). The
median time from admission to CTPA was 7 days (IQR 1–
16.5). The median length of stay was 18 days (IQR 8–28).

Laboratory results An elevated DD level (median 3260 ng/
/mL, IQR 1203–9625 ng/mL, normal laboratory ranges of <
500 ng/mL) was detected in 205/242 (96%) patients. It was
also found that fibrinogen and CRP were above normal limits
in most patients. White blood cell count, lymphocytes, neu-
rophils, hemoglobin, and platelet count were within normal
limits.
PE incidence 73/242 (30%) patients were PE-positive and 169/242 (70%) were PE-negative. Of note, only in 5 PE-positive patients deep vein thrombosis (DVT) was documented.

Outcomes 150/242 patients (62%) were discharged, 39/242 patients (16%) died during hospitalization, and 53/242 patients (22%) remained hospitalized by the end of April.

Radiological findings (Table 2)

COVID-19 findings

Opacities The main findings were ground-glass opacities (152/242, 62.8%), consolidation (64/242, 26.4%), crazy-paving pattern (57/242, 23.6%), and reticular pattern (57/242, 23.6%).

Table 1 Baseline characteristics of COVID-19 patients

| Variable | Value |
|----------|-------|
| Patients: | 242 |
| Basic demographics: | |
| Age | 68 (IQR 55–78, range 29–96) years |
| Sex | Male = 151 (62%); Female = 91 (38%) |
| Comorbidities: | |
| Hypertension | 102 (42%) |
| Dyslipidemia | 59 (24%) |
| Diabetes | 44 (18%) |
| Cancer | 24 (10%) |
| Clinical timepoints: | |
| Days of symptoms before admission | 7 (4–13) days |
| Time from hospital admission to CTPA | 7 (1–16.5) days |
| Length of stay | 18 (8–28) days |
| Laboratory results: | |
| D-dimer (ng/mL) | 3260 (1203–9625) ng/mL (0–500 ng/mL) |
| White blood cell count (10^3/μL) | 10.2 (6.4–12.2) 10^3/μL (4–11 10^3/μL) |
| Lymphocytes (10^3/μL) | 2.11 (0.8–1.1) 10^3/μL (1–5 10^3/μL) |
| Neutrophils (10^3/μL) | 7.36 (4.2–10) 10^3/μL (1.5–7 10^3/μL) |
| Hemoglobin (g/dL) | 12.9 (11.5–14.5) g/dL (13–17.5 g/dL) |
| Platelet count (10^3/μL) | 255.6 (165.3–312) (10^3/μL) (140–400 (10^3/μL)) |
| Fibrinogen (mg/dL) | 514.8 (336–740) mg/dL (150–400 mg/dL) |
| CRP (mg/L) | 64.2 (4.7–96.5) mg/L (0–5 mg/L) |
| PE incidence: | |
| PE-positive: | 73 (30%) |
| PE-negative: | 169 (70%) |
| Main outcomes: | |
| Discharged | 150 (62%) |
| Hospitalized | 53 (22%) |
| Non-survivors | 39 (16%) |

Data are median (IQR) or n (%). In laboratory results, those parameters in italics were above normal limits. COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CTPA, computed tomography pulmonary angiogram; PE, pulmonary embolism; SI, International System of Units

Distribution The opacities were predominantly peripheral in 208/242 patients (86%) and predominantly central in 34/242 patients (14%).

Laterality The opacities were bilateral in 207/242 patients (94%), and only 13/242 patients (5.9%) had unilateral involvement (right lung in 10/242 patients [4.5%] and left lung in 3/242 patients [1.4%]).

Location The opacities were diffuse in most patients (162/242, 67%), whereas 48/242 patients (20%) had a lower lung field predominance, 25/242 patients (10.3%) had a middle-lung field predominance, and 15/242 patients (6.2%) had an upper-lung field predominance.

Other findings included fibrotic-appearing changes (52/242, 21.5%), pleural effusion (40/242, 16.5%), lymphadenopathy (22/242, 9%), and barotrauma signs (10/242, 4.1%).
Figure 2 shows examples of CTPAs from two PE-negative patients with typical COVID-19 radiological findings.

**PE imaging findings**

Among the 73 patients with PE, 35 patients (48%) had bilateral involvement.

In 46/73 patients (63%), filling defects involved the segmental and subsegmental arteries. Lobar arteries were involved in 17/73 patients (23.3%), main pulmonary arteries in 8/73 (11%), and pulmonary artery trunk in 2/73 patients (2.7%).

The most commonly involved sites were the right lower lobe (48/242, 67%), the left lower lobe (30/242, 41%), and the middle lobe (29/242, 40%), followed by the right upper lobe (27/242, 37%) and left upper lobe (25/242, 34.3%).

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| Table 2  | Radiological findings |
|----------|-----------------------|
| Variable | Value                 |
| COVID-19 (242) |                         |
| Opacities: |                         |
| GGO      | 152 (62.8%)            |
| Consolidation | 64 (26.4%)        |
| Crazy paving | 57 (23.6%)           |
| Reticular pattern | 57 (23.6%)       |
| Distribution: |                         |
| Peripheral | 208 (86%)            |
| Central    | 34 (14%)              |
| Laterality: |                         |
| Bilateral  | 207 (85.5%)           |
| Right/left lung | 10 (4.1%)/3 (1.2%)  |
| Location:  |                         |
| Diffuse    | 162 (67%)             |
| Upper/middle/lower lung field predominance | 15 (6.2%)/25 (10.3%)/48 (20%) |

Other findings:
- Fibrotic appearance: 52 (21.5%)
- Pleural effusion: 40 (16.5%)
- Lymphadenopathy: 22 (9%)
- Barotrauma signs: 10 (4.1%)

**Pulmonary embolism (73)**

| Laterality: |                         |
| Unilateral  | 38 (52.1%)             |
| Bilateral   | 35 (47.9%)             |

| Most proximal affected artery: |                         |
| Pulmonary artery trunk | 2 (2.7%) |
| Main pulmonary arteries  | 8 (11%)    |
| Lobar pulmonary arteries | 17 (23.3%) |
| Segmental pulmonary arteries | 36 (49.3%) |
| Subsegmental pulmonary arteries | 10 (13.7%) |

Location:
- Right upper lobe: 27 (37%)
- Middle lobe: 29 (39.7%)
- Right lower lobe: 48 (67.1%)
- Left upper lobe: 25 (34.3%)
- Left lower lobe: 30 (41.1%)

| Signs of right ventricle overload: | 15 (20.5%) |

Data is expressed in n (%). Findings could coexist. COVID-19, coronavirus disease 2019; GGO, ground-glass opacities; PE, pulmonary embolism
Signs of right ventricle overload were recorded in 15/73 patients (20.5%).

Figure 3 corresponds to a CTPA from a COVID-19 patient with PE findings.

**PE-positive and PE-negative group comparison (Table 3)**

Statistically significant differences were found between the PE-positive and PE-negative groups for neutrophils and DD levels. Age, sex, comorbidities, outcome, clinical timepoints, and laboratory results (white blood cell count, lymphocytes, hemoglobin, platelet count, fibrinogen, and CRP) did not show statistical differences.

Neutrophil median value was higher in the PE-positive group (8.3 [IQR 5.4–11] \(10^3/\mu L\)) compared to the PE-negative group (5.7 [IQR 4–9.5] \(10^3/\mu L\)), \(p = .02\).

The DD median value was 7872 ng/mL (IQR 3150–22,494) in the PE-positive group and 2009 ng/mL (IQR 5675–15,705) in the PE-negative group. There was a significant difference in DD levels between the two groups with \(p < .001\).

The optimal cutoff value for DD in the ROC curve to predict PE was 2903 ng/mL, which yielded a sensitivity of 81% and a specificity of 59%. AUC for PE was 0.76 (CI 95% 0.69–0.83, \(p < .001\)) (Fig. 4).

Table 4 illustrates different ranges of DD along with their sensitivity and specificity based on the ROC curve. With the optimal cutoff value of 2903 ng/mL, 98 CTPAs would have been saved but 13 PE would have been missed. A cutoff value of 1733 ng/mL would provide a sensitivity of 90% (7 out of 73 cases would have been missed in our sample) and a specificity of 51.4%, saving 72 CTPAs. A cutoff value of 1219 ng/mL would provide a sensitivity of 95.7% (3 out of 73 cases would have been missed) and a specificity of 37%, saving 56 CTPAs.
A total of 39/242 deaths (16%) occurred during hospitalization. A comparison between non-survivors (deceased patients) and survivors (discharged patients [150/242, 62%]) was made. Patients that remained hospitalized by the end of this study were excluded of this analysis (53/242, 22%).

Statistically significant differences were found for age (75 [IQR 71–80] vs. 65 [IQR 62–67] years, \( p < .001 \)), DD (7863 [2710–28,664] vs. 2433 [1093–6088] ng/mL, \( p = .01 \)),

| Variable                  | PE-positive (73) | PE-negative (169) | \( p \) value |
|---------------------------|------------------|-------------------|--------------|
| Age                       | 67 (55–82)       | 66 (55–77.5)      | \( p = .7 \) |
| Sex (men)                 | 50 (68.5%)       | 101 (59.8%)       | \( p = .2 \)  |
| Comorbidities             | 49 (67%)         | 127 (75%)         | \( p = .2 \)  |
| Clinical timepoints:      |                  |                   |              |
| Days of symptoms before admission | 7 (3–12) days   | 7 (4–13) days     | \( p = .7 \)  |
| Time from hospital admission to CTPA | 5 (0–13) days   | 8 (1–18) days     | \( p = .2 \)  |
| Length of stay            | 18 (10–28) days  | 17 (7–28) days    | \( p = .6 \)  |
| Laboratory results:       |                  |                   |              |
| D-dimer (ng/mL)           | 7872 (3150–22,494) ng/mL | 2009 (5675–15,705) ng/mL | \( p < .001 \) |
| White blood cell count (10³/μL) | 10 (7.4–13.2) 10³/μL | 7.7 (6.1–11.6) 10³/μL | \( p = .05 \) |
| Lymphocytes (10³/μL)      | 4 (0.8–1.7) 10³/μL | 1.1 (0.8–1.6) 10³/μL | \( p = .14 \) |
| Neutrophils (10³/μL)      | 8.3 (5.4–11) 10³/μL | 5.7 (4–9.5) 10³/μL | \( p = .02 \) |
| Hemoglobin (g/dL)         | 13.2 (12.2–14.7) g/dL | 13 (11.2–14.4) g/dL | \( p = .1 \) |
| Platelet count (10³/μL)   | 220 (163.8–279.3) (10³/μL) | 242 (165.3–324) (10³/μL) | \( p = .4 \)  |
| Fibrinogen (mg/dL)        | 503.3 (286.7–693.2) mg/dL | 574 (350.3–740) mg/dL | \( p = .1 \) |
| CRP (mg/L)                | 36 (8.5–105.9) mg/L | 22 (3.2–90.5) mg/L | \( p = .2 \) |
| Outcome:                  |                  |                   |              |
| Discharged                | 41 (56.2%)       | 110 (65.1%)       | \( p = .1 \) |
| Hospitalized              | 15 (20.5%)       | 37 (21.9%)        |              |
| Non-survivors             | 17 (23.3%)       | 22 (13%)          |              |

Data are median (IQR) or \( n \) (%). Those results in italics show statistical differences between groups. CRP, C-reactive protein; PE, pulmonary embolism.
neutrophils (9.04 [7.6–10.5] vs. 6.5 [5.9–7.1] \(10^3/\mu L\), \(p < .001\)), platelet count (203.6 [167–240.3] vs. 283.3 [260.6–306] \(10^3/\mu L\), \(p = 0.002\)), and CRP (122.7 [84.6–160.8] vs. 45.7 [36.1–55.3] mg/L, \(p < .001\)).

Sex, comorbidities, PE incidence, median length of stay until death or discharge, and other laboratory parameters (white blood cell count, lymphocytes, hemoglobin, and fibrinogen) showed no statistically significant differences between groups.

### Discussion

This retrospective study included 242 patients with coronavirus disease 2019 (COVID-19) that underwent a computed tomography pulmonary angiogram (CTPA) due to clinical suspicion of pulmonary embolism (PE). Since COVID-19 has shown to raise D-dimer (DD) levels even in the absence of PE, we tried to demonstrate statistically significant differences in DD values between PE-positive and PE-negative COVID-19 patients and to establish a more adequate DD cutoff value to assess CTPA indication in these patients. The PE-positive group showed higher DD values than the PE-negative group (7872 vs. 2009 ng/mL, respectively, \(p < .001\)). The optimal DD cutoff according to receiver operating characteristic (ROC) curve was 2903 ng/mL (81% sensitivity and 59% specificity).

As hypothesized in other studies, COVID-19 patients requiring hospital assistance were more frequently older men with metabolic risk factors, such as hypertension, dyslipidemia, or diabetes [24–27]. The median time from symptoms onset to hospital admission (7 days) was in accordance with previous research [27].

The incidence of PE was 30% (73/242), similar to that reported by other recent studies [10, 12, 28–30]. Three recent studies showed disparity results [31–33]. Of note, only 5/73 patients with PE had a confirmed diagnosis of deep vein thrombosis (DVT). It has been proposed that in situ microvascular thrombosis could be responsible for the strikingly high incidence of pulmonary thromboembolic events in the absence of DVT [6, 34]. However, an underestimation of the actual DVT incidence may have occurred, since many institutions restricted the use of Doppler ultrasound to rule out DVTs in COVID-19 patients [8, 35]. Other studies with smaller samples were insufficient to successfully clarify the actual DVT incidence [36], although recently published studies have stated that DVT events were frequently reported, suggesting that lower limb deep vein ultrasonography is necessary to detect DVT in COVID-19 patients [37–39]. Additional research is necessary to provide a deeper insight on this matter.

Along with previous studies, we found that a high DD is common in COVID-19 patients. In our sample, 96% (205/242) of the patients showed a DD value above normal limits (median 3260 ng/mL, [IQR 1203–9625]). Despite elevated DD levels in most patients, the PE-positive group showed higher values than the PE-negative group (7872 vs. 2009 ng/mL, respectively, \(p < .001\)), similarly to other studies [28, 30–33]. Thus, DD along with other clinical and laboratory data can be used as a tool to effectively assess pre-CTPA PE risk in COVID-19 patients. However, the cutoff point should be reasonably higher than in non-COVID-19 patients.

The optimal cutoff point for DD in the ROC curve for our sample was 2903 ng/mL, which is slightly higher than the previously reported by Leonard-Lorant et al. (2600 ng/mL) and Alonso-Fernández et al. (2500 ng/mL); compared to theirs, our study has a larger sample size (242 vs. 106 [Leonard-Lorent et al.] and 30 [Alonso-Fernández et al.]) and a longer follow-up period (2 months vs. 1 month).
[Leonard-Lorant et al.] and 11 days [Alonso-Fernández et al.]). This threshold of 2903 ng/mL yields a sensitivity of 81% and a specificity of 59%, and an area under the curve (AUC) of 0.76 (CI 95% 0.69–0.83, p < .001). Leonard-Lorant et al. results showed a higher sensitivity (100%) and specificity (67%), although AUC data was not reported. Alonso-Fernández et al. showed similar sensitivity and specificity like in our study (80% and 51%, respectively). However, guidelines usually demand a higher sensitivity [22]; a cutoff value between 1221 and 1721 ng/mL (sensitivity 91–94%, specificity 37–45%) could be more appropriate in this case.

The overall mortality rate in our sample (16%) was slightly higher than that reported in previous research [26, 27]. This may be due to the fact that our study had a longer follow-up period. Older age (75, IQR 71–80 years) and higher DD levels (7863 ng/mL, IQR 2710–28,664), among other laboratory parameters, were found in the non-surviving group, similarly to available published data [26].

We acknowledge some limitations to our study. First, this was a retrospective analysis conducted at a single center; therefore, information and management strategies could be different compared to other hospitals, and patient baseline characteristics and mortality rates may not be representative. Second, patients included in this study were diagnosed at one of the “red zones” in Europe; this could have led to overestimation of negative outcomes in patients due to health system overwhelming. Third, factors such as variable administered treatments, need of mechanical ventilation, admission to intensive care units, and dynamic changes in laboratory parameters were not examined but could have been helpful to better define the DD role in estimating the PE risk and in establishing a model predicting mortality.

In conclusion, COVID-19 has shown to raise D-dimer (DD) levels even in the absence of pulmonary embolism (PE). Despite high DD levels in most patients, the PE-negative group showed higher DD values than the PE-positive group. Our results suggest that a higher DD threshold (2903 ng/mL) instead of the standard DD cutoff value could more accurately predict the risk of PE in COVID-19 patients with a sensitivity of 81%.

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Code availability Not applicable.

Authors’ contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sofía Ventura-Díaz, Juan V Quintana-Pérez, Almudena Gil-Boronat, and Marina Herrero-Huertas. The first draft of the manuscript was written by Sofía Ventura-Díaz and all authors commented on previous versions of the manuscript. Review and editing was performed by Sofía Ventura-Díaz and Juan V Quintana-Pérez. All authors read and approved the final manuscript.

Data availability All data and statistic software accomplish field standards.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by the Research Ethics Committee of our hospital.

Consent to participate and publish The need for patient informed consent was waived because of its retrospective nature. Data was anonymized to avoid any identification risk.

Abbreviations AUC, Area under the curve; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CTPA, Computed tomography pulmonary angiogram; DD, D-dimer; IQR, Interquartile range; PE, Pulmonary embolism; ROC, Receiver operating characteristic; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

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