Diagnostic Accuracy of D-Dimers for Predicting Pulmonary Embolism in COVID-19-Patients

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Abstract

Importance: Proinflammatory and hypercoagulable states with marked elevation seen in D-Dimer levels have been accurately described in patients infected by the SARS-CoV2 even without pulmonary embolism (PE).

Objectives: To compare D-dimers values in patients infected by the novel Coronavirus 2019 (COVID-19) with and without PE and to establish an optimal D-dimer cut-off to predict the occurrence of PE, which guides pulmonary computed tomography angiography (CTPA) indication.

Methods: We retrospectively enrolled all COVID-19-patients admitted between October first and November 22th, 2020, at the University Hospital Center of Mohammed VI, Oujda (Morocco), suspected to have PE and underwent a CTPA. Demographic characteristics and blood test results were compared between PE-positive and PE-negative. The receiver operating characteristics (ROC) curve was constructed to establish an optimal D-Dimer cut-off to predict the occurrence of PE.

Results: The study population consisted of 84 confirmed COVID-19-patients. The mean age was 64.93 years (SD 14.19). PE was diagnosed on CTPA in 31 (36.9%) patients. Clinical symptoms and in-hospital outcomes were similar in both groups except that more men had PE (p = .025). The median value of D-dimers in the group of patients with PE was significantly higher (14 680[IQR 33620-3450]ng/mL compared to the group of patients without PE 2980[IQR 6870-1600]ng/mL [P < .001]. A D-dimer at 2600 ng/mL was the optimal cut-off for predicting PE with a sensitivity of 90.3%, and AUC was .773[CI 95%, .667 − .876).

Conclusion: A D-dimer cut-off value of 2600 ng/mL is a significant predictor of PE in COVID-19-patients with a sensitivity of 90.3%.

Keywords

COVID-19, threshold, d-dimers, coagulopathy, pulmonary embolism

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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was first raised in December 2019 in China, caused a novel coronavirus disease 2019 (COVID-19), resulting in a global pandemic.1 Proinflammatory and hypercoagulable states with marked elevations seen in D-Dimer levels have been accurately described in the COVID-19-disease even in patients without pulmonary embolism (PE).2 Furthermore, D-dimer in COVID-19-patients is associated with the severity, mortality and admission in the intensive unit care (ICU).3–5 However, little is known about the pathogenesis of hypercoagulability. The three elements of the triad of Virchow appear to

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be involved. Several reports suggested that the infection induced an endothelial cell dysfunction,6–8 hyperviscosity and hypoxia.9,10 The stasis of blood flow due to immobilization can occur in all hospitalized patients. In addition, coagulation abnormalities such as elevated fibrinogen, factor VIII and Neutrophil extracellular traps have been reported in patients with COVID-19.11 Recently a large meta-analysis reported a pooled incidence at 15.3% of COVID-19-patient developing PE.12 Moreover, patients who required intensive care are more likely to develop PE.13 We aimed to assess D-dimer’s diagnostic accuracy for pulmonary embolism in a retrospective study of hospitalized COVID-19 patients.

**Materials and Methods**

For this retrospective analysis with anonymized data, informed consent and approval from the local ethics committee were obtained.

The study was carried out in a single center at the University Hospital Center of Oujda (Morocco) between October first and November 22th, 2020. We enrolled all COVID-19-patients confirmed by a positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction test (RT-PCR) suspected to have pulmonary embolism who underwent a pulmonary computed tomography angiography (CTPA) for clinical reasons or elevated D dimer. Demographic data were recorded for these patients and categorized as ICU or ward patients and the need for mechanical ventilation. The D-dimer level at the time of PE suspicion was also obtained. CT acquisitions were performed using standard CTPA protocols. Two experienced radiologists analyzed images and evaluated the COVID-19 disease extent, the distribution of pulmonary thromboembolic disease. We excluded incomplete CTPA examinations. In addition, by quantitative visual CT, the COVID-19-pattern was evaluated scoring acute COVID-19-related lung inflammatory lesions. This assessment consisting of 0 (0%), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%), or 4 (76%-100%) for each lobe. By summing up five lobe ratings, the overall severity score was obtained.14

The statistical analysis was performed with the statistical software SPSS version 21. The study population was divided into PE-positive and PE-negative groups. We analyzed the normal distribution of quantitative variables by performing the Shapiro-Wilk test. Non-parametric tests were used to compare non-normally distributed variables expressed as median with interquartile range (IQR). Otherwise, an unpaired Student’s t-test was used to compare normally distributed variables defined as mean and standard deviation. The categorical variables were expressed as frequency and percentages, and the comparison between the two groups was made using the Pearson Chi-Square test of Fisher’s Exact test. A Two-tailed P-value <.05 was considered statistically significant. The Receiver Operating Characteristic (ROC) curve was plotted to assess the diagnostic accuracy of the d-dimer for predicting pulmonary embolism.

**Results**

**Study Population**

The study population consisted of 84 confirmed-RT-PCR-COVID-19-patients. The main reasons for CTPA indications were clinical worsening (56%) and/or elevated D-dimer (28%). The median age was 64.93 years (SD 14.19); 52 (61.9%) were men, and common comorbidities of the whole population included hypertension (27.4%), diabetes mellitus (44%) and obesity (8.3%). Mean days between admission and suspicion of PE were 6.2. No statistically significant differences between patients with pulmonary embolism and those without pulmonary embolism were observed except that more men had PE (p = .025). Both groups showed similar in-hospital outcomes, and all patients received thromboprophylaxis. Mortality was similar in patients with and without pulmonary embolism group (41.9% vs 43.4% respectively). The demographical characteristics and in-hospital outcomes of patients are shown in Table 1.

**Table 1. Demographical characteristics and in-hospital outcomes of COVID-19 of the study population**

|                          | Whole population N = 84 | PE-positive N = 31 (36.9%) | PE-negative N = 53 (63.1%) | P-value  |
|--------------------------|-------------------------|-----------------------------|-----------------------------|----------|
| Age                      | 64.93(SD 14.19)         | 68.35(SD 11.48)             | 62.92 (SD 15.30)            | .091     |
| Gender                   |                         |                             |                             | .025*    |
| Males                    | 52 (61.9%)              | 24 (77.4%)                  | 28 (52.8%)                  |          |
| Females                  | 32 (38.1%)              | 7 (22.6%)                   | 25 (47.2%)                  |          |
| Hypertension n (%)       | 23 (27.4%)              | 5 (16.1%)                   | 18 (34%)                    | .077     |
| Smoking n (%)            | 8 (9.5%)                | 1 (3.2%)                    | 7 (13.2%)                   | .133     |
| Dyslipidemia n (%)       | 11 (13.1%)              | 3 (9.7%)                    | 8 (15.1%)                   | .478     |
| Diabetes n (%)           | 37 (44%)                | 13 (41.9%)                  | 24 (45.3%)                  | .766     |
| Body Mass Index (BMI) kg/m² | 26 (27-25)              | 26(27-25)                   | 26(28-24.86)                | .963     |
| Systolic pressure (mmHg) | 136 (149.75-123.75)     | 133(140-120)                | 139(151-129)                | .065     |
| Sa02 (%)                 | 75 (84-65)              | 75(85-68)                   | 73(81.5-63.5)               | .282     |
| Service of admission n (%) |                       |                             |                             |          |
| ICU                      | 67 (79.8%)              | 23 (74.2%)                  | 44 (83%)                    | .331     |
| Conventional wards       | 17 (20.2%)              | 8 (25.8%)                   | 9 (17%)                     |          |
| Mechanical ventilation n (%) |                       | 11 (35.5%)                  | 18 (34%)                    | .887     |
| Mortality n (%)          | 36 (42.9%)              | 13 (41.9%)                  | 23 (43.4%)                  | .896     |
| In-hospital stay (days)  | 11.50 (IQR 19.75-7)     | 10 (IQR 23-5)               | 12 (IQR 18.5-8)             | .673     |
Of the 84 patients, 67 (79.8%) were in the intensive care unit (ICU), of whom 29 (34.5%) were either intubated or on ECMO. 23 (74.2%) of the patients in the ICU had PE. 17 (20.2%) patients were admitted in general wards, of whom 8 (25.8%) had PE. The mortality rate of the whole population was 42.9% (36/84). The median duration of the hospital stay of the individuals was 11.50 days.

There were no significant differences between patients with and without pulmonary embolism regarding laboratory findings except D-dimer levels (14 680 [IQR 33620-3450]ng/mL et 2980 [IQR 6870-1600]ng/mL respectively [P < .001]. Biological findings are summarized in Table 2.

### CTPA Findings

Among the 31 (36.9%) patients with PE, 9 patients (29%) had bilateral involvement (Figure 1); 9 (29%) patients had segmental and subsegmental pulmonary embolism (Figure 2). Lobar arteries were involved in 10 (32.3%) patients and 8 (25.8%) involved in the pulmonary artery (AP) et 4 (12.9%) in the pulmonary artery trunk (TAP). No significant difference was observed between patients with PE and those without PE in the degree of CT abnormalities related to COVID-19 (p = .525). However, 54.8% (17/31) of patients with pulmonary embolism had more than 75% of the lung parenchyma affected by COVID-19.

The receiving operating characteristic (ROC) curve showed a DD level of 2600 ng/mL as the optimal threshold to predict pulmonary embolism in COVID-19-patients with a sensitivity of 90.3% and specificity of 49.1% (AUC: .773; CI .667 − .876), p < .001). (Figure 3) The logistic regression analysis showed D-dimer >2600 ng/mL as a strong predictor of pulmonary embolism with a sensitivity of 90.3% (OR: .111; 95% CI; .030−.411). The sensitivity and specificity of different DD levels reported from the ROC curve are summarized in Table 3.

### Discussion

The COVID-19-disease has been reported to increase the level of D-dimers (DD) even in patients without pulmonary embolism. We aimed to compare D-dimer levels in COVID-19-patients with and without pulmonary embolism and to establish an optimal threshold of D-dimer value to predict the occurrence of pulmonary embolism, which guides CTPA indication. Our current study included 84 RT-PCR-confirmed COVID-19-patients suspected to have a pulmonary embolism. The median value of D-dimer in the group of patients with pulmonary embolism was significantly higher (14 680 [IQR 33620-3450]ng/mL compared to the group of patients without pulmonary embolism 2980 [IQR 6870-1600]ng/mL [P < .001]. The ROC curve determines a D-dimer level of 2600ng/mL as the optimal threshold [90.3% sensitivity and 49.1% specificity]. However, no other differences were observed except more men had PE [P = .025].

Pulmonary embolism is the most prevalent thromboembolic complication reported in COVID-19-patients.15,16 In our study population, the incidence of pulmonary embolism is 7.17% (31/432), almost similar to some studies reporting rates of 2.8 to 6.6%.15,17,18 However, some recent large meta-analyses reported a pooled incidence of PE of 14.7 to 17.6% of COVID-19-patient developing PE, which is quite higher than in precedent studies.12,19–21 In our cohort, only 19.44% (84/432) underwent a CTPA. Therefore, underdiagnosed PE may assume that there were in the silent PE population, relatively asymptomatic or severe patients to undergo CTPA. In our study, the rate of PE is 36.9% (31/84), and our results are in line with some similar studies reporting a PE rate of 37%22 and 38%.18 However, it is slightly higher than other studies in the literature reporting PE rates of 27.2%-33%15,23,24

Among our cohort of COVID-19-patients, 67 (74.2%) were hospitalized in the ICU of whom, 29 (34.5%) required

### Table 2. Biological characteristics at the time of PE suspicion

|                          | Whole population N = 84 | PE-positive n = 31 (36.9%) | PE-negative n = 53 (63.1%) | P-value |
|--------------------------|-------------------------|---------------------------|----------------------------|---------|
| D-Dimer (ng/mL)          | 3915 (20 522-1765)      | 14 680 (33 620-3450)       | 2980 (6870-1600)            | <0.01** |
| Lactate Dehydrogenase (U/L) | 730.50 (898.75-480.25)  | 801 (1030-480)             | 670 (883.5-472.5)           | .266    |
| Prothrombin time (%)     | 67.76 (SD 13.44)        | 68.22 (SD 11.16)           | 67.49 (SD 14.71)            | .811    |
| Cephalin activated time  | 1.065 (1.355-1)         | 1.07 (1.15-1)              | 1.06 (1.495-1)              | .237    |
| International Normalized Ratio (INR) | 1.22 (1.30-1.152)     | 1.25 (1.34-1.17)           | 1.21 (1.275-1.14)           | .328    |
| Fibrinogen (g/L)         | 5.8 (7.20-3.725)        | 5.1 (7.2-2.8)              | 5.9 (7.2-4.1)               | .171    |
| White blood cells (elements/mm³) | 13.87.10³ (18.10³-9.98.10³) | 14.5.10³                  | 13.41.10³                   | .27     |
| Platelets cells (elements/mm³) | (317.25.10³-157.75.10³) | (18.47.10³-11.3810³)       | (17.47510³-8.71510³³)       | .538    |
| Lymphocytes cells (elements/mm³) | 62.10³(1.052.10³-4.55.10³) | 62.10³(8.51.10³-4.5.10³)  | 62.10³(1.19.10³-4.6.10³)   | .663    |
| Ferritin (ng/mL)         | 1147 (2257-327.681.10)  | 1382 (2277-729)            | 2347 (1051.188.10)          | .24     |
| Troponin us (ng/L)       | 47.40 (208.960)         | 62.20 (188.87)             | 243.77 (10.17)              | .77     |
| Urea (g/L)               | .495 (742-35)           | .54 (72-37)                | .47 (75-34)                 | .507    |
| Creatinine (mg/L)        | 9.155 (13.915-6.937)    | 9.59 (13.8-47.24)          | 9.14 (47.6-27)              | .732    |
| Fast Blood Glucose (g/L) | 1.395 (2.041-1.0725)    | 1.38 (2.04-1.05)           | 1.41 (2.055-1.09)           | .753    |
| C-Reactive Protein (mg/L) | 187.92 (99.31)          | 174.23 (SD 94.14)          | 195.93 (SD 102.23)          | .337    |
| Procalcitonin (ng/mL)    | .37 (1.23-16)           | .335 (777-167)             | .5 (2.09-15)                | .338    |
mechanical ventilation (Table 1). Out of them, 23 (34.3%) had PE; however, no statistical difference was found between patients with and without pulmonary embolism regarding the service of admission. In contrast to our results, some authors have reported that patients in the ICU are more likely to develop PE than those hospitalized in general wards. This could be explained by a more significant number of patients in the ICU. (67 vs 17) In our study, gender was statistically different between patients with and without pulmonary embolism as more men had PE. (P = .025) (Table 1) Our results are in line with several studies but in contrast with some other studies. Moreover, the male gender has also been associated with the severity of the COVID-19 infection.

No significant correlation between the occurrence of pulmonary embolism and severity of COVID-19-disease on CTPA was observed. However, contrast results were found in other studies compared to our cohort. These findings suggest that there may be prothrombotic states in critically ill patients.

Our cohort study showed that DD levels were higher in patients with pulmonary embolism than those without pulmonary embolism (14,680 [IQR 33620-3450] ng/mL; 2980 [IQR 6870-1600] ng/mL, respectively). (P < .001) Many previous studies support our findings. Furthermore, D-dimer has been reported to be associated with the severity and mortality in COVID-19-patients.

In our cohort, the ROC curve showed an optimal threshold of DD at 2600 ng/mL (90.3% sensitivity and 49.1% specificity), which is higher than some DD cut-off values reported in several previous studies. Cui S and al demonstrated that if they considered a threshold of 1.5 µg/mL for D-dimer to predict venous thromboembolism (VTE), the sensitivity and specificity were 85.0%, 88.5%, respectively, but if they considered 3.0 µg/

Figure 1. CTPA of a 79-year-old female with diabetes mellitus and COVID-19 infection confirmed by a positive RT-PCR. DD value was 11,400 ng/mL. CTPA performed 2 days after admission showed: (A) Axial reformatting (parenchymal window) within regions of diseased lung. (B) Axial reformatting (mediastinal window) with Filling defects affected both main pulmonary arteries (yellow arrows).

Figure 2. CTPA of a 65-year-old male with diabetes mellitus and COVID-19 confirmed by a positive RT-PCR. DD value was 56,200 ng/mL. CTPA performed 10 days after admission showed: (A) Axial reformatting within regions of diseased lung (B) Axial reformatting (mediastinal window) with a filling defect affected the left segmental branch artery (yellow arrow).
mL as the cut-off value, the sensitivity, specificity, were 76.9%, 94.9%. Compared to our study, we enrolled almost the same number of patients, but we focused mainly on PE in patient with COVID-19 instead of VTE in general. In addition, with a higher cut-off value (2600 vs 1500), our study showed a higher sensitivity (90.3% vs 85%). Although lower specificity was observed in our study (49.1% vs 88.5%), guidelines recommend a higher sensitivity. In the study of Alonso-Fernández and al, at the same specificity (49.10% vs 51%), our study recorded the highest sensitivity (90.3% vs 80%) with a higher DD threshold (2600 vs 2500). This could be explained by a larger sample size of patients in our study (81 vs 30).

Ventura Diaz S and al demonstrated in their study that a higher DD threshold of 2903 ng/mL could predict the occurrence of pulmonary embolism with a sensitivity of 81% and a specificity of 59%. Although our optimal cut-off was 2600 ng/mL with a sensitivity of 90.3% and specificity of 49.1%, a highest threshold for DD of 3120 ng/mL could predict the occurrence of pulmonary embolism with the sensitivity and specificity of 87.1% and 50.9% respectively. Furthermore, a threshold of 3285 ng/mL yields 83.9% and 50.9% of sensitivity and specificity, respectively. Almost similar sensitivity was observed when a threshold of 3315 ng/mL was used (80.6% vs 81%). Compared to this study, we
enrolled a small number of patients (84 vs 242), but our study demonstrates that a higher cut-off value (3285 vs 2903 ng/mL) yields the highest sensitivity (83.9% vs 81%). However, the study of Leonard-Lorant et al.29 which enrolled 106 COVID-19-patients, showed a 100% of sensitivity with a DD threshold of 2660 ng/mL. This is higher compared to our study, with almost the same cut-off value for DD.

The mortality rate was 36% in our study population. Some previous studies reported 12.2%-16%,26,33 which was slightly lower than in our cohort. Small sample size with a prevalence of men (61.9%) and ICU patients (79.8%) are factors that could explain the higher rate of mortality recorded. Moreover, many biological findings such as ferritin, fibrinogen, and procalcitonin were found elevated in the non-surviving group. These findings were similar to the data reported in the literature.28

Our study limitations include its relatively small sample size and its retrospective form carried out at a single center. Therefore, the potential presence of unmeasured confounding factors cannot be ruled out. Despite these limitations, this study showed a high pulmonary embolism rate in patients with moderate and severe COVID-19 disease, showing D-dimer as a strong predictor of PE and may potentially guide therapy and determine the prognosis.

To the best of the authors’ knowledge, this is the first study in Morocco and North Africa to report the rate of PE in COVID-19-patients. Nevertheless, by reporting a high prevalence of pulmonary embolism, the present study could strengthen current knowledge about the COVID-19 disease.

**Conclusion**

Pulmonary embolism is the most prevalent thrombotic event in patients with COVID-19. Although COVID-19 increases D-dimer (DD) levels in the absence of pulmonary embolism, higher DD values were found in the patients with pulmonary embolism group compared to those without pulmonary embolism group. Our findings indicate that an optimal threshold of 2600 ng/mL could predict the occurrence of pulmonary embolism in COVID-19-patients with a sensitivity of 90.3%. Furthermore, a higher threshold of DD value (3285 ng/mL) could predict the occurrence of PE with a sensitivity of 83.9%. Elevated D-dimer levels (>2600 or >3285 ng/mL) were significant predictors of PE.

| D-Dimer Cut-off (ng/mL) | Sensitivity | Specificity |
|------------------------|-------------|-------------|
| 965 to 2190            | 96.8% to 93.5% | 15.1% to 43.4% |
| 2405                   | 90.3%       | 43.4%       |
| 2470                   | 90.3%       | 45.3%       |
| 2550                   | 90.3%       | 47.2%       |
| 2600                   | 90.3%       | 49.1%       |
| 2795                   | 87.1%       | 50.9%       |
| 3120                   | 87.1%       | 50.9%       |
| 3285                   | 83.9%       | 50.9%       |
| 3315                   | 80.6%       | 50.9%       |

**Table 3.** Sensitivity and specificity of different DD levels reported from the ROC curve. When a threshold of 1295 ng/mL was used, sensitivity and specificity was 96.8% and 79.2% respectively, saving 11 CTPAs but one of 31 PE would have been underdiagnosed. When a threshold of 2405 ng/mL was used, sensitivity and specificity was 90.3% and 56.6% respectively saving 26 CTPAs but 3 PE would have been underdiagnosed. When an optimal threshold of 2600 ng/mL was used, sensitivity and specificity was 90.3% and 50.3% respectively saving 29 CTPAs however 3 out of 31 cases would have been underdiagnosed. A higher threshold of 3285 ng/mL yields a sensitivity of 87.1% missing 4 out of 31 cases and a specificity of 49.1%, saving 31 CTPAs.

**Ethics Approval and Informed Consent**

Approval from the local ethics committee was obtained. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

**Data Availability**

Data are available from the corresponding author by request.

**Author Contributions**

F. Laouan Brem: conception, literature review, analysis, data collection, writing- review & editing. A. Boudouh: conception, software, writing-review & editing. Y. Amane: conception, software, writing- review & editing. M.A. Bouazzoua: conception, software, analysis. C. Miri: conception, software, writing-review & editing. H. Rasras: conception, software, writing- review & editing. S. Nasri: conception, methodology, supervision. N. Abda: conception, methodology, analysis, supervision. I. Skiker: conception, methodology, supervision. H. Kousmi: conception, methodology, supervision. Z. Bazid: conception, methodology, supervision. N. El Ouaifi: conception, methodology, supervision.

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