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► To cite this version:

Benjamin Planquette, Lina Khider, Alice Le Berre, Simon Soudet, Gilles Pernod, et al.. Adjusting D-dimer to lung disease extent to exclude Pulmonary Embolism in COVID-19 patients (Co-LEAD). *Thrombosis and Haemostasis*, 2022, 122 (11), pp.1888-1898. 10.1055/a-1768-4371 . hal-03722805

HAL Id: hal-03722805

<https://u-picardie.hal.science/hal-03722805v1>

Submitted on 7 Sep 2024

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Adjusting D-dimer to Lung Disease Extent to Exclude Pulmonary Embolism in COVID-19 Patients (Co-LEAD)

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Thromb Haemost 2022;122:1888–1898.

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received

July 31, 2021

accepted after revision

February 8, 2022

accepted manuscript online

February 10, 2022

article published online

October 17, 2022

DOI <https://doi.org/10.1055/a-1768-4371>

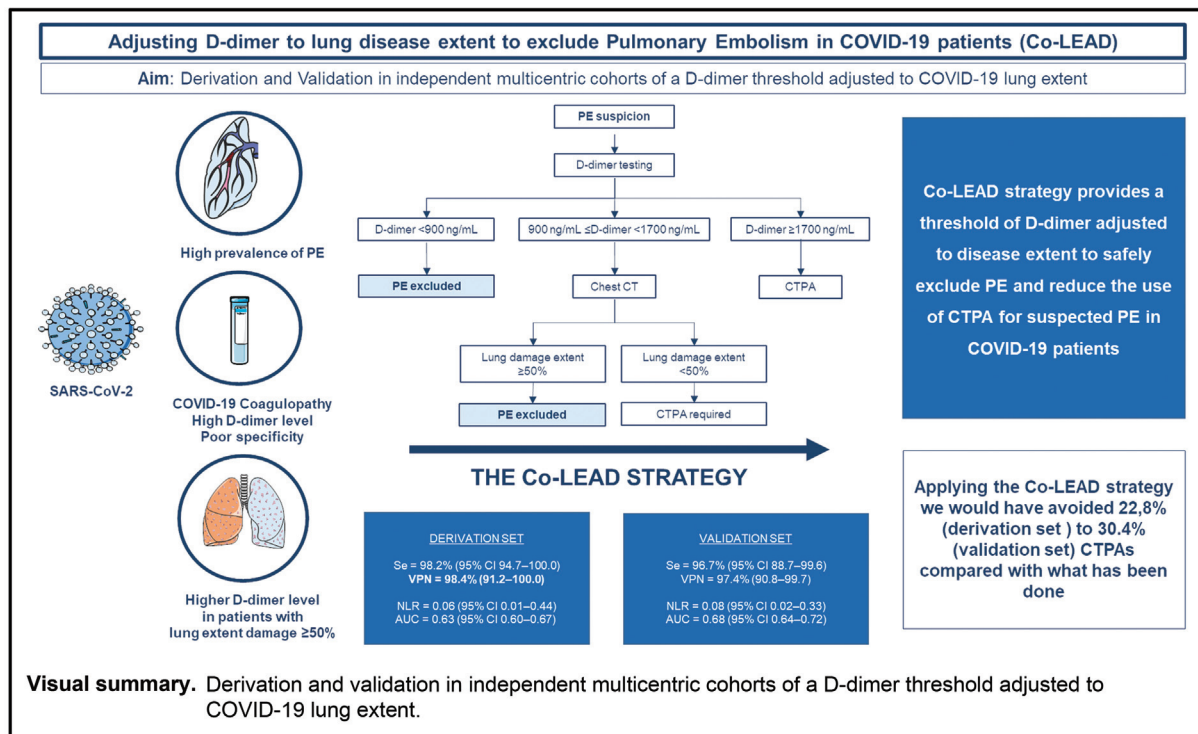
10.1055/a-1768-4371.

ISSN 0340-6245.

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Abstract

Objective D-dimer measurement is a safe tool to exclude pulmonary embolism (PE), but its specificity decreases in coronavirus disease 2019 (COVID-19) patients. Our aim was to derive a new algorithm with a specific D-dimer threshold for COVID-19 patients.

Methods We conducted a French multicenter, retrospective cohort study among 774 COVID-19 patients with suspected PE. D-dimer threshold adjusted to extent of lung damage found on computed tomography (CT) was derived in a patient set ($n = 337$), and its safety assessed in an independent validation set ($n = 337$).

Results According to receiver operating characteristic curves, in the derivation set, D-dimer safely excluded PE, with one false negative, when using a 900 ng/mL threshold when lung damage extent was $<50\%$ and 1,700 ng/mL when lung damage extent was $\geq 50\%$. In the derivation set, the algorithm sensitivity was 98.2% (95% confidence interval [CI]: 94.7–100.0) and its specificity 28.4% (95% CI: 24.1–32.3). The negative likelihood ratio (NLR) was 0.06 (95% CI: 0.01–0.44) and the area under the curve (AUC) was 0.63 (95% CI: 0.60–0.67). In the validation set, sensitivity and specificity were 96.7% (95% CI: 88.7–99.6) and 39.2% (95% CI: 32.2–46.1), respectively. The NLR was 0.08 (95% CI: 0.02–0.33), and the AUC did not differ from that of the derivation set (0.68, 95% CI: 0.64–0.72, $p = 0.097$). Using the Co-LEAD algorithm, 76 among 250 (30.4%) COVID-19 patients with suspected PE could have been managed without CT pulmonary angiography (CTPA) and 88 patients would have required two CTs.

Conclusion The Co-LEAD algorithm could safely exclude PE, and could reduce the use of CTPA in COVID-19 patients. Further prospective studies need to validate this strategy.

Keywords

- ▶ pulmonary embolism
- ▶ COVID-19
- ▶ D-dimer
- ▶ computed tomography
- ▶ diagnosis

Introduction

Prevalence of pulmonary embolism (PE) in patients with coronavirus disease 2019 (COVID-19) is high, and PE diagnosis is challenging in this specific population.^{1–8} COVID-19-

associated coagulopathy was described early on, as well as unusually high D-dimer levels in a large majority of patients.^{9–11} The D-dimer level seems to be proportional to the extent of lung damage, and was also identified as an independent risk factor of in-hospital mortality.¹⁰ PE is often

suspected in COVID-19 patients with respiratory symptoms, but the use of D-dimer to rule it out is a questionable strategy because of its increased levels even in the absence of venous thromboembolism (VTE). Therefore, current validated thresholds of D-dimer in non-COVID-19 outpatients with suspected PE may not help safely reduce the number of fruitless computed tomography (CT) pulmonary angiography (CTPA) in COVID-19 patients. Consequently, the International Society on Thrombosis and Haemostasis guidelines suggested to directly confirm diagnosis using standard-of-care objective testing, such as CTPA.¹² Most recent algorithms and guidelines aim to reduce imaging testing^{13–16}; however, due to the lack of specificity of clinical signs of PE and the difficulty to perform CTPA in the most severe COVID-19 patients, the application of such guidelines in current clinical practice is challenging and potentially leads to misdiagnosing PE or to excessively prescribe therapeutic anticoagulation without objective confirmation of PE. Therefore, ruling out PE using a specific threshold for D-dimer could be useful in reducing CTPA prescription, particularly in patients with severe COVID-19,¹⁷ and in facilitating the management of imaging examinations for other patients.¹⁸

The purpose of this study was to derive a new diagnostic algorithm for PE with a D-dimer cut-off value adjusted to the CT extent of lung damage, and to assess its safety for the exclusion of PE. To determine the D-dimer thresholds, we used a retrospective multicenter cohort study of COVID-19 patients with suspected PE (derivation set). We then performed an external validation in an independent multicenter cohort of COVID-19 patients with suspected PE.

Methods

Design and Setting

This study is a retrospective, multicenter cohort study sponsored by the Groupe Hospitalier Paris Saint Joseph (GHPSJ). The study design was approved by our institutional ethics committee (IRB number: IRB 00012157) and registered on the National Institute of Health data platform (INDS No. MR 4516150520). Patients' nonopposition to the use of their data for research was also collected in accordance with the European regulation (General Data Protection Regulation). Study reporting complied with the requirements of the STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) statement for observational studies in epidemiology (<https://www.strobe-statement.org>).

Derivation Set

Between March 1 and May 8, 2020, all COVID-19 patients with respiratory symptoms who had a CTPA for suspicion of PE were recorded in a database in two large academic hospitals in Paris, France: GHPSJ and Hôpital Européen Georges-Pompidou (HEGP).⁷ Patients from emergency rooms, general wards, or intensive care units (ICUs) were included if they were over 18 years of age, were admitted for COVID-19 with respiratory symptoms, and had a CTPA at baseline or during hospitalization for a suspected PE. Diagnosis of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection was confirmed

by a positive result of a reverse transcriptase polymerase chain reaction assay or highly suggestive CT findings of COVID-19 pneumonia.¹⁹ All the patients included were informed of the research protocol by letter, allowing them to express their opposition to the use of their data, according to French legislation and the institutional review board. The exclusion criterion was respiratory distress syndrome explained by another disease than COVID-19. The decision to perform a CTPA was not predefined and was left to the discretion of the clinicians in charge of the patients.²⁰ In most cases, PE was suspected because of dyspnea, acute respiratory failure, tachycardia, syncope, or respiratory worsening. To apply the European Society of Cardiology (ESC)'s diagnostic algorithm,¹³ the clinical probability of PE was calculated retrospectively using the simplified revised Geneva²¹ score on the same day of D-dimer collection. The clinical probability of PE was classified as probable or unlikely, and the D-dimer threshold was adjusted for age.¹⁵

Validation Set

During the initial COVID-19 outbreak, five French academic medical centers associated with the F-CRIN INNOVTE network (Saint Etienne University Hospital, Besançon University Hospital, Brest University Hospital, Grenoble-Alpes University Hospital, and Amiens University Hospital) recorded clinical, radiological, and biological data of all consecutive COVID-19 patients with respiratory symptoms who had a CTPA for suspicion of PE. All patients were included between February 12 and September 14, 2020. Diagnostic criteria for COVID-19 were identical to those of the derivation set. Similarly to the derivation set, the decision to perform a CTPA was not predefined and was left to the discretion of the clinicians in charge of the patients. In most cases, PE was suspected because of acute respiratory symptoms (chest pain, respiratory failure, or worsening respiratory status).

Laboratory Data

For the derivation set, D-dimer assays were either Vidas D-dimers (Biomérieux, Marcy-l'Etoile, France) or STA-Liatest D-Di (Diagnostica Stago, Asnières, France). For the validation set, D-dimer assays were either Vidas D-dimers, STA-Liatest D-Di, or Innovance D-Dimers (Siemens Healthcare Diagnostics, Marburg, Germany) according to local practice. D-dimer levels were reported in ng/mL. Analyses were performed on both sets of patients using the available D-dimer level within 24 hours prior to CTPA. As the D-dimer assays differed from one center to another, we checked whether their performance differed to exclude PE in patients with COVID-19. As the Vidas D-dimers is currently the assay with the best sensitivity and negative predictive value (NPV) in the non-COVID-19 population,²¹ we used it as the reference assay, like we would have in the general population.

CTPA Analysis

In both derivation and validation sets, all CTPAs were locally reviewed by two radiologists to determine whether the findings were highly suggestive, indeterminate, or nonsuggestive of COVID-19. The reading was performed according

to the recommendations of the European Society of Radiology and the European Society of Thoracic Imaging.¹⁹ Lung damage extent was classified into two groups: <50% or ≥50%.⁷ In each center, the same two radiologists locally confirmed or refuted the diagnosis of PE, and, if present, whether or not it was sub-segmental. Discrepancies were resolved through discussion with a third radiologist until consensus was reached.

Derivation of the Co-LEAD Algorithm

In the derivation set, we constructed receiver operating characteristic (ROC) curves to define a D-dimer cut-off value that could safely exclude PE in COVID-19 patients. We defined the threshold as the highest value associated with a maximum of one false negative.^{22,23} Then, as previously reported,²⁴ we found that D-dimer increased with lung damage extent, regardless of the presence of PE. Consequently, we constructed two ROC curves, one for patients with lung damage extent <50% and one for patients with lung damage extent ≥50%. Using the previous definition allowing for one false negative, we conceived a diagnostic algorithm for PE combining COVID-19-lung damage extent and adjusted D-dimer (Co-LEAD algorithm), with a different threshold for each lung damage extent category. We then evaluated the diagnostic performance of the proposed Co-LEAD algorithm in both derivation and validation sets using sensitivity (Se), specificity (Sp), positive predictive value (PPV), NPV, and negative likelihood ratio (NLR) defined as $(1 - Se/Sp)$, the area under the curve (AUC) of the strategy, number and proportion of patients with a false negative diagnosis, and number of CTPAs that could have been avoided if the Co-LEAD algorithm had been applied.

Statistical Analysis

Categorical variables are presented as number of patients (proportion) and quantitative variables as median with interquartile range (IQR). Ninety-five percent confidence intervals (95% CIs) of proportions were estimated using either the normal approximation or the binomial method when proportions were close to 0 or 1. Comparison of proportions was done, as appropriate, with the Chi-square or the Fisher test, and two means were compared by a standard *t*-test or a Mann-Whitney test, as appropriate. The NCSS Statistical software was used for calculations. A *p*-value <0.05 was deemed statistically significant. We calculated the corresponding diagnostic indexes: sensitivity, specificity, PPV, and NPV with 95% CI using the usual formula. The empirical (nonparametric) method of DeLong et al²⁵ was used to estimate AUC and compare the AUC of the derivation and the validation sets.

Results

Derivation Set Characteristics

Among 337 COVID-19 patients with CTPA for suspected PE, 70 (20.8%) patients were diagnosed with PE (►Table 1). The D-dimer level at the time of CTPA was available for 267 (79.2%) patients. The median D-dimer level was 1,340 ng/mL (IQR:

903–2,370) in patients without PE and 6,435 ng/mL (IQR: 2,935–3,750) in patients with PE (*p*<0.001). In patients without PE, the median D-dimer level was 1,269 ng/mL (IQR: 833–2,092) in patients with lung extent damage <50%, and 2,070 ng/mL (IQR: 1,270–3,404) in patients with lung extent damage ≥50% (*p*=0.009). In patients with PE, the median D-dimer level was 6,167 ng/mL (IQR: 2,887–12,940) in patients with lung extent damage <50% and 7,130 ng/mL (IQR: 3,376–14,500) in patients with lung extent damage ≥50% (*p*<0.001).

ESC Diagnostic Algorithm Performances in the Derivation Set

Fifty-eight (21.7%) Patients were classified as likely to have a PE, whereas 209 (78.3%) patients were classified as unlikely and D-dimer testing was recommended before CTPA to exclude PE (►Table 2). Considering all the variables of the Geneva revised simplified score, only two items differed between patients with and without PE: unilateral lower limb pain (10 [17.5%] vs. 8 [4.0%], *p*=0.003) and pain on lower limb deep vein palpation and unilateral edema (11 [19.3%] vs. 4 [2.0%], *p*<0.0001). Applied to our derivation set, this algorithm had the following performances: Se 100% (95% CI: 93.6–100.0), Sp 9.9% (95% CI: 6.3–14.8), PPV 22.8 (95% CI: 17.7–28.6), and NPV 100.0 (95% CI: 83.8–100.0). Thus, if this algorithm was used, 246 CTPAs would have been required. This diagnostic algorithm did not result in any false-negative cases.

Determination and Performances of D-dimer Threshold to Exclude PE in COVID-19 Patients

In the derivation set we obtained from the ROC curve a threshold of 900 ng/mL for the exclusion of PE (►Supplementary Fig. S1 [available in the online version]). The strategy relying on the use of this specific threshold in all the patients of the derivation set without previous estimation of clinical probability had the following performance: Se 98.2% (95% CI: 94.7–100.0), Sp 24.2% (95% CI: 18.4–29.9), PPV 25.6% (95% CI: 19.7–31.4), and NPV 98.1% (95% CI: 94.3–100.0). Among the 267 patients with a D-dimer value available at the time of CTPA, 52 had D-dimer level <900 ng/mL. If this strategy was used, we would have performed 215 CTPAs. The strategy relying on using this specific threshold in the 209 patients with PE considered as unlikely had the following performance: Se 98.2% (95% CI: 83.9–100.0), Sp 22.3% (95% CI: 16.8–28.5), PPV 25.1% (95% CI: 19.5–31.4), and NPV 97.9% (95% CI: 88.9–99.9). If this strategy was used, we would have performed 219 CTPAs.

D-dimer Assays' Performance According to the Lung Damage Extent

We then made sure the diagnostic performance of the D-dimer assays was similar in the two groups of lung damage extent (<50% vs. ≥50%) and that the differences in AUCs were not statistically significant (0.80, 95% CI: 0.66–0.89 vs. 0.87, 95% CI: 0.77–0.92, *p*=0.34, ►Supplementary Fig. S2 [available in the online version]). We obtained from the ROC curves a threshold of D-dimer for each subgroup (≥50%

Table 1 Clinical characteristics of the COVID-19 patients in the derivation set and the validation set

	Derivation set			Validation set			p-Value ^b
	Total (n = 337)	Patients with PE (n = 70)	Patients without PE (n = 267)	Total (n = 337)	Patients with PE (n = 66)	Patients without PE (n = 271)	
Age, y (median, IQR)	66 (55–80)	66 (54–80)	66 (55–79)	65 (55–74)	65 (55–73)	65 (55–74)	0.052
Male sex, n (%)	207 (61.4)	39 (55.7)	168 (62.9)	214 (63.0)	49 (75.4%)	165 (61.8)	0.47
Time from illness onset to CTPA, days (median, IQR)	7 (3–10)	7 (4–13)	7 (3–10)	7 (4–12)	11 (6–15)	7 (3–10)	0.096
D-dimer level, ng/mL (median, IQR)	1,644 (981–3,750)	6,435 (2,935–3,750)	1,340 (903–2,370)	1,600 (800–3,765)	5,340 (2,400–13,550)	1,285 (765–2,442)	0.71
BMI, kg/m ² (median, IQR)	26.3 (23.6–29.9)	29.7 (27.0–30.7)	26.1 (23.5–29.8)	27.5 (24.6–32.0)	27.5 (25.0–31.6)	27.4 (24.5–32.0)	0.003
Sub-segmental PE, n (%)		13 (18.6%)			10 (15.2%)		0.59
Risk factors for VTE							
Previous VTE, n (%)	24 (7.2)	5 (7.1)	19 (7.3)	27 (8.0)	5 (7.7)	22 (8.1)	0.69
Active cancer, n (%)	32 (9.6)	5 (7.2)	27 (10.2)	53 (15.6)	9 (13.8)	44 (16.2)	0.017
Lung damage extent ≥ 50%, n (%)	66 (26.1)	28 (40.0)	38 (22.5)	97 (29.0)	24 (36)	73 (27)	0.34

Abbreviations: BMI, body mass index; CTPA, computed tomography pulmonary angiography; IQR, interquartile range; PE, pulmonary embolism; VTE: venous thromboembolism.

^aComparison between patients with PE and without PE in the derivation set.

^bComparison between all patients of the derivation set and the validation set.

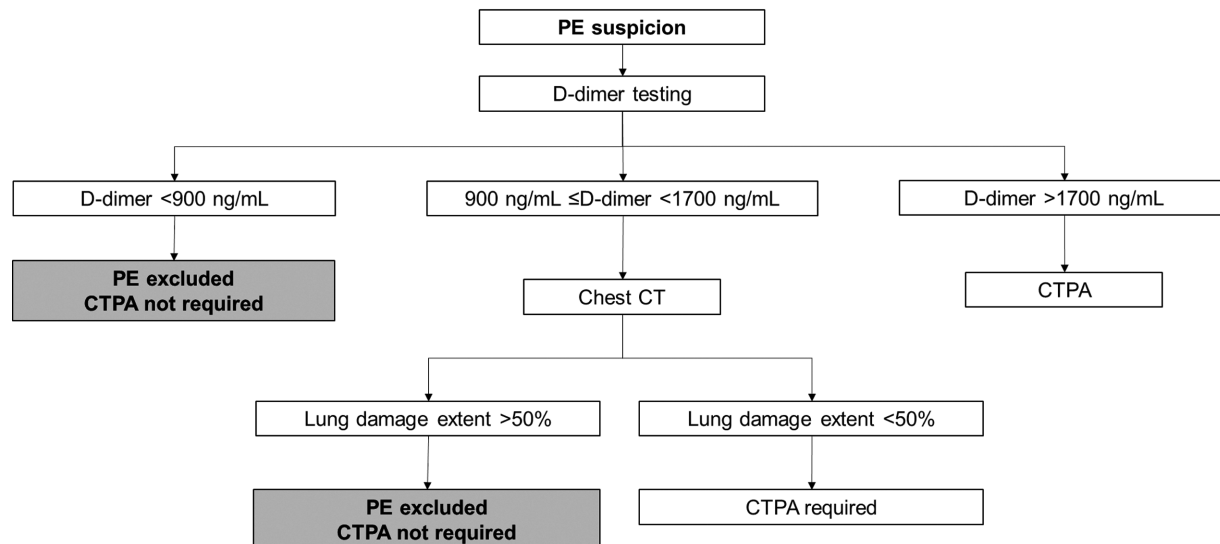
^cEvaluated at CT scan.

Table 2 Diagnostic performance of the different strategy

Derivation set (N = 267)	ESC guidelines	Clinical probability ^a then D-dimer <900 ng/mL	Clinical probability ^a then Co-LEAD	D-dimer <900 ng/mL	Co-LEAD
Number of patients in whom PE can be excluded	21	48	55	53	61
Se	100%	98% (95–100)	98% (95–102)	98% (95–100)	98% (95–100)
Sp	10% (6–14)	22% (17–28)	26% (20–31)	25% (19–30)	28% (22–35)
PPV	23% (18–28)	25% (19–31)	26% (20–32)	26% (20–32)	27% (21–33)
NPV	100%	98% (94–100)	98% (95–100)	98% (94–100)	98% (95–100)
NLR	0.0	0.08	0.07	0.07	0.06
Efficiency	246	219	212	215	206
Efficacy	3.5	3.2	3.1	3.1	3.0
Number of false negative	0	1	1	1	1

Abbreviations: NLR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity. Note: Efficiency: number of CTPA required; efficacy: number of CTPA scans needed to diagnose one pulmonary embolism.

^aClinical probability has been retrospectively assessed by the simplified revised Geneva Score.


Fig. 1 Combined strategy for PE suspicion in COVID-19 patients: Co-LEAD algorithm. PE, pulmonary embolism.

and <50%): 1,700 ng/mL in the subgroup $\geq 50\%$ and 900 ng/mL in the subgroup <50%. The strategy relying on the use of these specific thresholds in the derivation set without previous estimation of clinical probability (► **Supplementary Fig. S3** [available in the online version]) had the following performance: Se 98.2% (95% CI: 94.7–100.0), Sp 28.4% (95% CI: 24.1–32.3), PPV 26.7% (95% CI: 20.7–32.7), and NPV 98.4% (95% CI: 95.2–100.0). Among the 267 patients with a D-dimer value available at the time of CTPA, 52 had D-dimer level <900 ng/mL. If this strategy was used, we would have performed 206 CTPAs. The strategy relying on the use of these two specific thresholds in the 209 patients with PE considered as unlikely had the following performance: Se 98.2% (95% CI: 83.9–100.0), Sp 25.6% (95% CI: 19.8–32.0), PPV 25.9% (95% CI: 20.2–32.4), and NPV 98.2% (95% CI: 90.3–99.9).

If this strategy was used, we would have performed 212 CTPAs.

Derivation and Performance of the Co-LEAD Algorithm to Exclude PE in COVID-19 Patients

Using the previous definition allowing one false negative for the exclusion of PE, we conceived a diagnostic algorithm for PE combining lung extent and D-dimer-adjusted threshold (Co-LEAD, ► **Fig. 1**). The D-dimer threshold that safely excluded PE was 900 ng/mL in patients with lung damage extent <50% and 1,700 ng/mL in patients with lung damage extent $\geq 50\%$. The Co-LEAD algorithm entails that patients with a D-dimer level <900 ng/mL do not require CTPA, whereas those with a D-dimer level $\geq 1,700$ ng/mL require CTPA regardless of the disease extent. When the D-dimer

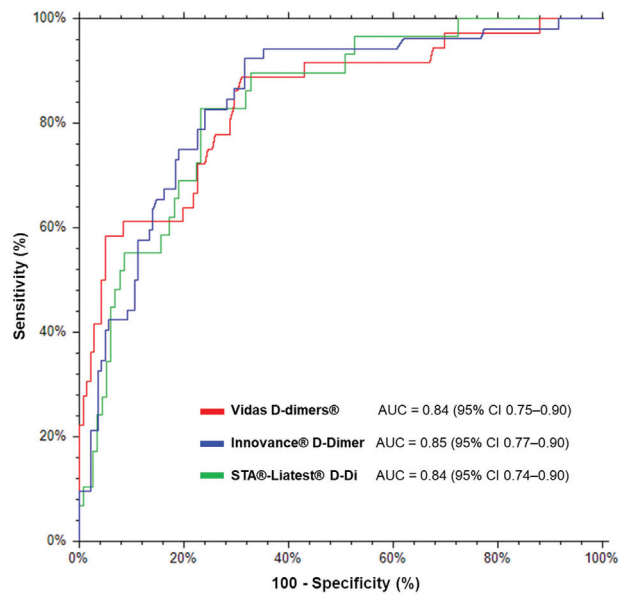


Fig. 2 Receiver-operating characteristic curves of D-dimer for PE diagnosis in COVID-19-suspected PE patients according to the D-dimer assay in the whole population (validation and derivation set). PE, pulmonary embolism.

level is between 900 and 1,700 ng/mL, patients with lung damage extent $\geq 50\%$ on CT do not require contrast injection, whereas those with lung damage extent $< 50\%$ need contrast injection to confirm PE. This strategy had the following performance: Se 98.0% (95% CI: 95.0–100.0), Sp 28.0% (95% CI: 22.0–35.0), PPV 27.0% (95% CI: 21.0–33.0), and NPV 98.0% (95% CI: 95.0–100.0). With this strategy, we would have performed 206 CTPAs and 88 patients would have had a two-step CT. The NLR of this strategy was 0.06 (95% CI: 0.01–0.44). The AUC for the Co-LEAD algorithm was 0.63 (95% CI: 0.60–0.67). As predefined, there was one false negative of the diagnostic algorithm (1.6%, 95% CI: 0.0–4.7). This patient was a 62-year-old woman with a single antero-basal segmental PE and a D-dimer level of 650 ng/mL.

External Validation of the Co-LEAD Algorithm

In the validation set, 337 COVID-19 patients had a CTPA for suspected PE, which was confirmed in 66 (19.6%) patients. The prevalence of PE did not differ between both sets

($p = 0.70$). Clinical characteristics of patients were similar, except for body mass index and active cancer (\blacktriangleright **Table 1**). D-dimer levels were available at the time of CTPA for 250 patients (74.2%) in the validation set, a similar value to that of the derivation set ($p = 0.12$).

In the validation set, the Co-LEAD algorithm had a Se of 96.7% (95% CI: 88.7–99.6), a Sp of 39.2% (95% CI: 32.2–46.1), a PPV of 33.9% (95% CI: 26.9–41.0), and a NPV of 97.4% (95% CI: 90.8–99.7) for the exclusion of PE (\blacktriangleright **Table 2**). The NLR was 0.08 (95% CI: 0.02–0.33). The AUC for the Co-LEAD algorithm in the validation set was 0.68 (95% CI: 0.64–0.72) and did not differ from the AUC in the derivation set ($p = 0.097$). There were two false-negative cases (2.6%, 95% CI: 0.0–6.2): a 58-year-old man with lung damage extent $< 50\%$, a D-dimer level of 750 ng/mL, and a segmental PE occurring 10 days after COVID-19 onset; and a 79-year-old man with active cancer, a lung damage extent $< 50\%$, a D-dimer level of 510 ng/mL, and a segmental PE 14 days after COVID-19 onset. No fatal PE occurred.

Using the Co-LEAD algorithm, in the 250 patients with a D-dimer level available at the time of CTPA, 76 (30.4%) CTPAs would have been avoided, representing a 25.6% increase of avoided CTPA compared with the aforementioned D-dimer threshold of 900 ng/mL.

Co-LEAD Algorithm Performance According to D-dimer Assays

In the pooled derivation and validation sets, the AUCs of the Vidas D-dimers, STA-Liatest D-Di, and the Innovance D-Dimer did not differ significantly: 0.84 (95% CI: 0.75–0.90), 0.84 (95% CI: 0.74–0.90), and 0.85 (95% CI: 0.77–0.90) respectively, $p = 0.94$ and $p = 0.93$; \blacktriangleright **Fig. 2**). We also evaluated the performance of the Co-LEAD algorithm according to the D-dimer assay used. As shown in \blacktriangleright **Table 3**, the NLR always remained below 0.15 regardless of the assay used.

Discussion

We propose a new diagnostic algorithm for PE in COVID-19 patients with suspected PE, Co-LEAD, that combines D-dimer values using specific thresholds pending extent of lung damage. This algorithm has a high sensitivity and a high NPV in both derivation and validation cohorts, making this algorithm effective

Table 3 Diagnostic performance of the Co-LEAD strategy according to the D-dimer assay used by centers

D-dimer assay	Centers	Patients (n)	Number of false negative with the Co-LEAD algorithm	Sensitivity	NPV	NLR
Vidas D-dimer	#1, #2	145	0	100.0 (97.9–100.0)	100.0 (97.9–100.0)	Not calculable
STA-Liatest D-Di	#0, #5, #2	178	1	97.2 (91.9–100.0) ^a	97.8 (93.6–100.0)	0.09 (0.06–0.17)
Innovance D-Dimer	#3, #4	194	2	96.2 (90.9–100.0) ^a	96.3 (91.3–100.0)	0.11 (0.02–0.19)

Abbreviations: NPV, negative predictive value; NLR, negative likelihood ratio.

Note: Centers: #0 GHPSJ, #1 HEGP, #2 CHU Brest, #3 CHU Besançon, #4 CHU Amiens, and #5 CHU Grenoble-Alpes.

^aOne-sided 97.5% confidence interval.

to exclude PE. To our knowledge, this is the first study proposing an algorithm aiming at diagnosing PE in patients with COVID-19.

PE is a frequent complication of COVID-19¹⁻⁷ that concerns a large number of patients at different stages of the disease. A high prevalence of PE was described in critically ill patients.^{2,7,26} However, PE should not be considered as a late complication of COVID-19, but rather as a specific and potentially early manifestation. Thus, in several reports, half of PEs were diagnosed within 48 hours of admission.^{3,7,27}

The diagnosis of PE is challenging in COVID-19 patients and the diagnostic algorithms recommended by international guidelines for the outpatient population¹³ might not be as useful because patients with COVID-19 have high D-dimer levels even in the absence of VTE. To date, noncontrast CT has been considered the first-line imaging tool and has quickly become a cornerstone in both the diagnostic workup and follow-up of SARS-CoV-2 infection.¹⁹ At admission or during follow-up, respiratory symptoms suggestive of PE are frequent and may lead to contrast injection in almost all COVID-19 patients. It is thus necessary to derive and validate a specific algorithm dedicated to this population, as it seems inappropriate to perform CTPA to all COVID-19 patients. First, faced with a sudden influx of patients, it is necessary to rationalize radiological examinations. Second, COVID-19 patients seem more likely to present renal impairment,¹⁷ and the benefit-risk balance of contrast injection should be carefully weighted. The Co-LEAD strategy results in an important reduction (16% when compared with ESC algorithm) in contrast dye injection, which seems relevant to reduce the risk of renal impairment/failure, a poor prognosis criterion in critically ill COVID-19 patients.¹⁷ Third, patient transportation is logistically difficult, particularly for the most severe cases, and increases the risk of exposing other patients and medical staff to the virus. The role of D-dimer in COVID-19 is still a matter of debate: some suggest using D-dimer to suspect or to confirm VTE,²⁸⁻³⁰ while others use D-dimer to initiate anticoagulant treatment outside of the usually recommended practices.^{31,32} Indeed, the so-called "super-high" COVID-19 D-dimer level led us to forget that D-dimer testing is not specific but remains sensitive enough to safely exclude PE. It was observed that D-dimer is correlated to severity and mortality in COVID-19 patients.^{9,10,33} Moreover, the D-dimer level at hospital admission for COVID-19 is associated with an increased in-hospital mortality, independent of VTE.³⁴

The present Co-LEAD algorithm is the first algorithm designed to exclude PE in COVID-19 patients by using a D-dimer threshold adjusted to COVID-19 lung damage extent. Age-adjusted D-dimer¹⁵ or, more recently, clinical probability-adjusted D-dimer threshold^{14,16,35} already showed excellent performances in non-COVID-19 patients. Since the damage extent on CT seems to be associated with the intensity of COVID-19 coagulopathy,²⁴ and some reported that PE occurred more frequently in the affected lung areas, D-dimer was adjusted here for lung extent damage on CT scan.³⁶ Given that CT is the routine examination performed in all hospitalized patients with COVID-19 requiring oxygen therapy, information about the extent of lung damage is almost always available. The Co-LEAD algorithm seems to

have a better diagnostic performance than the algorithm using age-adjusted D-dimer of the ESC guidelines. Unfortunately, we were not able to compare the performance of Co-LEAD with the YEARS algorithm on the derivation set because the post-hoc calculation of the clinical probability according to YEARS was not feasible due to missing data.

In contrast to recommended algorithms,¹³ Co-LEAD was constructed without using a pretest clinical probability score. This choice was guided by our results showing comparable diagnostic performances when the algorithm was applied to all patients in the derivation set rather than to those with unlikely clinical probability according to the simplified revised Geneva score. Lastly, as previously reported, a minority of COVID-19 patients had a high clinical pretest probability and would have been directly eligible for CTPA. Not assessing clinical probability simplifies the Co-LEAD algorithm and could improve its safety by reducing the risk of misuse, as already shown for the PERC rule.³⁷⁻³⁹ In fact, like the recent 4PEPS strategy, Co-LEAD offers a diagnostic strategy for PE and results in a nonnegligible reduction in CTPA. Even if performances of the three D-dimer assays show interesting results, performances can differ from one D-dimer assay to another. Innovance D-Dimer and STA-Liatest D-Di have indeed a higher NLR, and therefore a slightly lower performance, as already described in the non-COVID-19 population.^{21,40} This could explain the two false-negative cases observed in the validation set, for whom the Innovance D-Dimer assay was used. D-dimer assays may not have identical results due to differences in antibody specificity because of variable affinity for high- or low-molecular-weight fibrin degradation products and/or cross-linked and non-cross-linked fibrin derivatives.

Our study has several limitations. First, regarding the applicability of this algorithm, a major limit should be pointed out for patients with D-dimer between 900 and 1,700 ng/mL, as it requires performing two scans: a first step including a noncontrast chest CT to assess the extent of the disease, and then a CTPA according to the lung damage extent. We are aware of the difficulties in assessing CT images in real time, and this two-step protocol could be skipped by using the 900 ng/mL threshold in all COVID-19 patients. The Co-LEAD strategy moderately improves the efficacy and the efficiency compared to a strategy based only on an adapted threshold of 900 ng/mL, by allowing to avoid six iodine injections. It does nevertheless impose a two-step CT. However, it has been shown that the extent of COVID-19 lesions on CT is stable over time beyond the 10th day of illness⁴¹; the Co-LEAD thresholds could thus be used on the previous CT scan results, especially in the most severe patients whose transport to the radiology department is neither simple nor safe.⁴²

Second, it is important to remember that nontransportable critically ill COVID-19 patients were not included in both derivation and validation sets because they were not able to have CTPA. Therefore, the Co-LEAD diagnostic algorithm was not evaluated in a population of unstable critically ill patients. On the other hand, it is important to specify that the population included is heterogeneous, with both

outpatients from emergency departments and inpatients from general wards or ICUs. We can assume that the characteristics of these patients could be different.

Third, our study is probably underpowered. It would have been desirable to get 100 events instead of 66 PEs in the validation cohort.⁴³ The upper limit of the 95% CI of the false-negative rate of the Co-LEAD algorithm is above the recommended 3%.²³ To evaluate the performances of the current ESC guidelines in the derivation set, the clinical probability for PE was calculated retrospectively. Lastly, due to the retrospective nature of our study, we cannot exclude an indication bias of CTPA performance. This strategy should therefore be validated in a management study including a 3-month patients' follow-up, allowing for identification of thromboembolic complications following the exclusion of PE in patients managed without CTPA.

Conclusion

The Co-LEAD algorithm using the D-dimer level with thresholds adapted to the lung damage extent excludes PE in COVID-19 patients with a high sensitivity and high NPV in both derivation and validation sets. This algorithm could reduce the number of CTPA required to manage COVID-19 patients with a suspected PE. Further prospective management studies are required to confirm this strategy in patients with COVID-19 and a suspected PE.

What is known about this topic?

- D-dimer is usually prescribed in COVID-19 patients to assess disease prognosis.
- D-dimer specificity is reduced in COVID-19 patients.

What does this paper add?

- D-dimer level is associated to lung damage extent.
- D-dimer threshold could be safely adjusted in COVID-19 patients to exclude pulmonary embolism.

Funding

The authors gratefully acknowledge the Assistance Publique – Hôpitaux de Paris for their support in bringing this project to life, and the Groupe Hospitalier Paris Saint Joseph for sponsoring it.

Conflict of Interest

T.M. reports personal fees and nonfinancial support from Bayer Healthcare SAS, personal fees and nonfinancial support from Incyte Biosciences, France, nonfinancial support from Alexion Pharma, France, nonfinancial support from Abbott, France, nonfinancial support from Amgen SAS, nonfinancial support from Boehringer Ingelheim, France, nonfinancial support from Bristol-Myers Squibb, no-financial support from MSD France, outside

the submitted work; F.C. reports grants from Pfizer, personal fees from Bayer, other from Boehringer; grants, personal fees, and other from BMS; personal fees and other from Astra-Zeneca, other from GSK, personal fees from LEO-Pharma, other from Actelion, outside the submitted work; S.S. reports grants from LEO-Pharma, personal fees from Bayer, personal fees from BMS Pfizer, outside the submitted work; N.G. reports personal fees and nonfinancial support from Boehringer Ingelheim, personal fees and nonfinancial support from Bayer, personal fees from Bristol-Myers Squibb/Pfizer, personal fees from LEO-Pharma, personal fees from Aspen, outside the submitted work; O.S. reports grants, personal fees, and nonfinancial support from Bayer; grants, personal fees, and nonfinancial support from BMS; personal fees and nonfinancial support from Sanofi Aventis; personal fees and nonfinancial support from Boston Scientific; personal fees from Pfizer; grants, personal fees, and nonfinancial support from MSD; grants and personal fees from Boehringer Ingelheim; grants from Daiichi Sankyo; personal fees from Chiesi; personal fees and nonfinancial support from BTG, outside the submitted work; L.K. reports personal fees from Bristol-Myers Squibb/Pfizer, outside the submitted work; M.A.S. reports personal fees and nonfinancial support from Bristol-Myers Squibb/Pfizer, personal fees and nonfinancial support from Bayer SA, grants, personal fees, and nonfinancial support from Leo-Pharma, personal fees from Aspen, outside the submitted work; R.C. reports personal fees from Aspen, outside the submitted work; D.M.S. reports grants from Boehringer Ingelheim, personal fees from Bayer, personal fees from Bristol-Myers Squibb/Pfizer, personal fees from Leo-Pharma, personal fees from Aspen, personal fees from Carmat, outside the submitted work; E. M. reports personal fees and nonfinancial support from Bayer, personal fees from Bristol-Myers Squibb/Pfizer, personal fees from Novartis, outside the submitted work; . N.M. reports grants and personal fees from Bayer Healthcare, grants and personal fees from BMS Pfizer, personal fees from Astra-Zeneca, personal fees from Terumo, grants and personal fees from Abbott, outside the submitted work; L.F. reports personal fees from Janssen, personal fees from Sanofi, personal fees from General Electrics, nonfinancial support from Guerbet, grants from Invectys, nonfinancial support from Philips, nonfinancial support from Ariana Pharma, nonfinancial support from Evolucare, outside the submitted work. All the other authors have nothing to declare.

Acknowledgments

We would like to acknowledge all nurses, technicians, and physicians involved in the vascular medicine, internal medicine, respiratory medicine, intensive care, clinical investigation center, and hematology departments of the Georges Pompidou European Hospital and Cochin Hospital for their help in taking care of patients and including them in the study.

The authors would also like to express their sincere condolences for the sudden loss of their very own Prof. Guy Meyer. Prof. Meyer was a force in developing practice-changing diagnostic algorithms and treatment strategies for VTE. He was a compassionate doctor, well-appreciated teacher, a remarkable mentor, and a friend to all. He will be dearly missed.

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