Received: 16 July 2024 | Revised: 21 August 2024 | Accepted: 22 August 2024

DOI: 10.1111/acem.15032

ORIGINAL ARTICLE

Failure rate of D-dimer testing in patients with high clinical probability of pulmonary embolism: Ancillary analysis of three European studies

Héloïse Bannelier MD[1] | Thomas Kapfer MD[2] | Mélanie Roussel MD[3] | Yonathan Freund PhD[4] | Karine Alame MD[1] | Pierre Catoire MD[1] | Amélie Vromant MD[1]

[1]Emergency Department, Pitié Salpêtrière Hospital, Paris, France

[2]Emergency Department, Saint Joseph Hospital, Paris, France

[3]Emergency Department, Univ Rouen Normandie, CHU Rouen, Rouen, France

[4]IMProving Emergency Care FHU, Sorbonne Université, Paris, France

Correspondence
Héloïse Bannelier, Emergency Department, Pitié Salpêtrière Hospital, 83 boulevard de l'Hôpital 75013 Paris, France.
Email: heloise.bannelier@aphp.fr

Abstract

Background: In patients with a high clinical probability of pulmonary embolism (PE), the high prevalence can lower the D-dimer negative predictive value and increase the risk of diagnostic failure. It is therefore recommended that these high-risk patients should undergo chest imaging without D-dimer testing although no evidence supports this recommendation.

Objective: The objective was to evaluate the safety of ruling out PE based on D-dimer testing among patients with a high clinical probability of PE.

Methods: This was a post hoc analysis of three European studies (PROPER, MODIGLIANI, and TRYSPEED). Patients were included if they presented a high clinical probability of PE (according to either the Wells or the revised Geneva score) and underwent D-dimer testing. The D-dimer–based strategy ruled out PE if the D-dimer level was below the age-adjusted threshold (i.e., <500 ng/mL in patients aged less than 50 and age × 10 ng/mL in patients older than 50).

The primary endpoint was a thromboembolic event in patients with negative D-dimer either at index visit or at 3-month follow-up. A Bayesian approach estimated the probability that the failure rate of the D-dimer–based strategy was below 2% given observed data.

Results: Among the 12,300 patients included in the PROPER, MODIGLIANI, and TRYSPEED studies, 651 patients (median age 68 years, 60% female) had D-dimer testing and a high clinical probability of PE and were included in the study. PE prevalence was 31.3%. Seventy patients had D-dimer levels under the age-adjusted threshold, and none of them had a PE after follow-up (failure rate 0.0% [95% CI 0.0%–6.5%]). Bayesian analysis reported a credible interval of 0.0%–4.1%, with a 76.2% posterior probability of a failure rate below 2%.

See related article on page 186 and 187

Presented at ACEP 2024 Research Forum, Las Vegas, NV, September 2024.

Supervising Editor: Alice M Mitchell.

Conclusions: In this study, ruling out PE in high-risk patients based on D-dimer below the age-adjusted threshold was safe, with no missed PE. However, the large CI of the primary endpoint precludes a definitive conclusion.

KEYWORDS
Bayesian analysis, computed tomography pulmonary angiography, D-dimer, emergency department, emergency medicine, probability scores, pulmonary embolism, revised Geneva, Wells

INTRODUCTION

Pulmonary embolism (PE) is commonly suspected in the emergency department (ED). It is critical to accurately diagnose this potentially deadly condition to ensure effective management and treatment. A workup strategy for the diagnosis of PE is considered safe if its failure rate is less than 2%.[1]

Both European and American guidelines recommend a sequential approach. The clinical probability of PE is assessed using clinical decision rule (Wells, revised Geneva score) or unstructured estimation (gestalt), categorized as low, moderate, or high.[2,3] If the risk of PE is low or moderate, a diagnostic strategy based on D-dimer levels is advised due to its high negative predictive value. PE is ruled out if the D-dimer level is below the age-adjusted threshold (i.e., less than 500 ng/mL in patients younger than 50 and age multiplied by 10 ng/mL in patients older than 50). If not, chest imaging, preferably computed tomography pulmonary angiography (CTPA), is recommended.[4] However, performing D-dimer testing is not recommended for patients with a high clinical probability of PE. Due to the high prevalence of PE in this population, relying solely on D-dimer testing may result in a lower negative predictive value and increase the risk of diagnostic failure. Therefore, guidelines recommend that high-risk patients should systematically undergo chest imaging without D-dimer testing.[2]

This recommendation is based on a very low level of evidence, with very scarce data published on the negative predictive value of D-dimers in these high-risk patients. Therefore, it remains uncertain whether it is safe to exclude PE based on D-dimer levels in patients with a high clinical probability. The objective of the study was to evaluate the safety of D-dimer testing in high-risk patients by estimating the failure rate of the D-dimer strategy and the likelihood that this rate is below 2%.

METHODS

Study design

This was a post hoc analysis of three European studies: PROPER, MODIGLIANI, and TRYSPEED. The PROPER and MODIGLIANI cohorts are prospective studies. The PROPER trial was a cluster-randomized noninferiority trial in France that compared the Pulmonary Embolism Rule-out Criteria (PERC)-based diagnostic strategy with the conventional strategy in patients with a low gestalt clinical probability of PE.[5] The MODIGLIANI study was a cluster-randomized noninferiority trial in France and Spain that compared the usual strategy of age-adjusted D-dimer threshold with the YEARS strategy in patients with low or moderate gestalt clinical probability of PE.[6] In both studies, patients were followed up at 3 months. Occurrence of thromboembolic events during follow-up was confirmed by an adjudication committee. For patients lost to follow-up, death records were queried. Any death during follow-up was analyzed by the adjudication committee. A sudden unexplained death was considered a thromboembolic event if it could not be excluded.

TRYSPEED was a retrospective study in six European countries, which included patients who underwent CTPA in the ED for suspected PE. The study aimed to evaluate temporal trends in the use of CTPA, diagnosis of PE, and type of PE. All patients underwent chest imaging, and no follow-up was conducted.[7] An inconclusive CTPA was previously defined as a CTPA that could not adequately assess the segmental level. All items of the Wells and revised Geneva score were collected in those studies, except for the "absence of alternative diagnosis" included in the Wells score, which was not available in the TRYSPEED database.

The protocols of all three studies were approved by ethics committees. As a secondary analysis on anonymized data, patient consent was waived for this study.

Population

Patients were included if they had a high clinical probability of PE and a D-dimer measurement in the ED. Patients who had a high clinical probability of PE and underwent D-dimer testing were sourced from the PROPER, MODIGLIANI, and TRYSPEED databases. In the PROPER and MODIGLIANI cohorts, a high PE clinical probability was defined as having either a Wells score greater than 6 or a revised Geneva score greater than 10. Although these cohorts aimed to evaluate patients with a low clinical probability of PE assessed through clinical gestalt, some patients were still classified as high risk because the Wells and Geneva scores objectively quantify risk, sometimes revealing a higher risk level than the clinician's initial assessment. The revised Geneva score was solely used for patients in the TRYSPEED database due to the lack of the "absence of alternative diagnosis" item required for the Wells score.

The PROPER cohort consisted of 1916 patients from 14 EDs in France, who visited the ED between 2015 and 2016 with a low gestalt clinical probability of PE. The MODIGLIANI cohort included 1414 patients from 16 EDs in France and two in Spain, who had low to moderate clinical gestalt probability of PE and did not have a negative PERC. The TRYSPEED study included 8970 patients who underwent CTPA in the ED for suspected PE, from 26 European EDs across six countries, during the first 7 days of each month from January 2015 to December 2019. Patients were excluded if they had missing D-dimer value or no Wells and no revised Geneva score available and if there was no assessment of PE by either a CTPA or a 3-month follow-up.

Endpoints

The primary endpoint was the failure rate of the D-dimer–based strategy. A failure was defined by a missed PE, i.e., a thromboembolic event in a patient with a negative D-dimer result (below the age-adjusted threshold), occurring either at the index visit or during the 3-month follow-up. The secondary endpoint assessed the failure of the strategy using a 500 ng/mL D-dimer threshold, also measured either at the index visit or during the 3-month follow-up.

To compare with the recommended strategy of CTPA with no D-dimer testing, an exploratory analysis aimed to estimate the negative predictive value of CTPA in these patients. In the PROPER and MODIGLIANI cohorts, patients were followed up at 3 months. A failure of CTPA was diagnosed as a negative CTPA at index visit and an ultimate diagnosis of thromboembolic event at 3 months. Because patients were not followed up in the TRYSPEED study, the failure rate of CTPA could not be determined.

Statistical analysis

Patient characteristics were expressed as categorical variables and were reported with their respective values and proportions (%). Numeric variables were presented as medians along with their interquartile ranges (IQRs). The age-adjusted D-dimer threshold was defined as 500 ng/mL for patients younger than 50 years and 10 times the age in ng/mL for patients 50 years and older. Additionally, the performance of the strategy using a fixed 500 ng/mL threshold was also assessed. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were estimated.

The failure rate of a diagnostic strategy can be defined in two different manners. First, it can be defined as the failure rate of the global strategy, i.e., the total number of missed PEs by the strategy divided by the total number of patients tested. In patients with a low prevalence of PE, this failure rate can be misleading as previously reported.[8,9] Secondly, a more conservative approach aims to focus on the subgroup of patients affected by the tested strategy. In this study, this only applied to patients with a negative D-dimer value.

A conservative approach was used in this study, which specifically evaluated the D-dimer false-negative rate, and the failure rate was defined as the ratio of the number of diagnosed PEs with negative D-dimer divided by the total number of patients with a negative D-dimer value. The confidence interval (CI) for the failure rate was reported at the 95% level.

A Bayesian approach has also been used to estimate the posterior probability that the failure rate of the strategy is below 2%. This probability indicates the likelihood that excluding PE in high-risk, negative–D-dimer patients is safe, according to data. Dispersion of parameter estimates is expressed by credible interval (with highest-density method), which are analogous to CIs used in frequentist statistics. If this interval for the D-dimer failure rate excludes 2%, we could conclude that the test is sufficiently safe to be used even in patients with a high clinical probability of PE. We consider that the negative D-dimer could safely exclude PE in the studied group if the posterior probability that the failure rate is below 2% is estimated over 95%.

RESULTS

A total of 3330 patients were screened from the PROPER and MODIGLIANI studies and 8970 patients from the TRYSPEED study. Out of those 12,300 patients, 10,365 patients were excluded as they did not meet the criteria of high risk of PE. Another 384 patients were excluded as their Wells or revised Geneva score was not available, 97 patients were excluded from the PROPER and MODIGLIANI cohort due to incomplete follow-up, 113 were excluded from the TRYSPEED database due to inconclusive CTPA, and 2963 patients were excluded as they had missing D-dimer value. Some patients met more than one exclusion criterion. Finally, a total of 651 patients who underwent D-dimer testing and had a high clinical probability of PE were included in the analysis, as shown in Figure 1. Out of those patients, 584 (90%) were from the TRYSPEED study.

The median (IQR) age of the participants was 68.0 (54.0–80.0) years, and 392 (60.2%) were female. A total of 204 PEs were diagnosed, resulting in a prevalence of 31.3%. The baseline characteristics are detailed in Table 1.

Failure rate of D-dimer

Seventy patients had D-dimer levels below the age-adjusted threshold, and none of them had a PE after follow-up, indicating a failure rate of 0.0% (95% CI 0.0%–6.5%). Bayesian analysis reported a credible interval of 0.0%–4.1%, with a 76.2% posterior probability of a failure rate below 2%.

Additionally, 48 patients had D-dimer levels below the fixed 500 ng/mL threshold, and none of them had a PE after follow-up, resulting in a failure rate of 0.0% (95% CI 0.0%–7.4%). Bayesian analysis reported a credible interval of 0.0%–5.9%, with a 62.8% posterior probability of a failure rate below 2%. Table 2 describes predictive statistics and their 95% credible intervals of age-adjusted

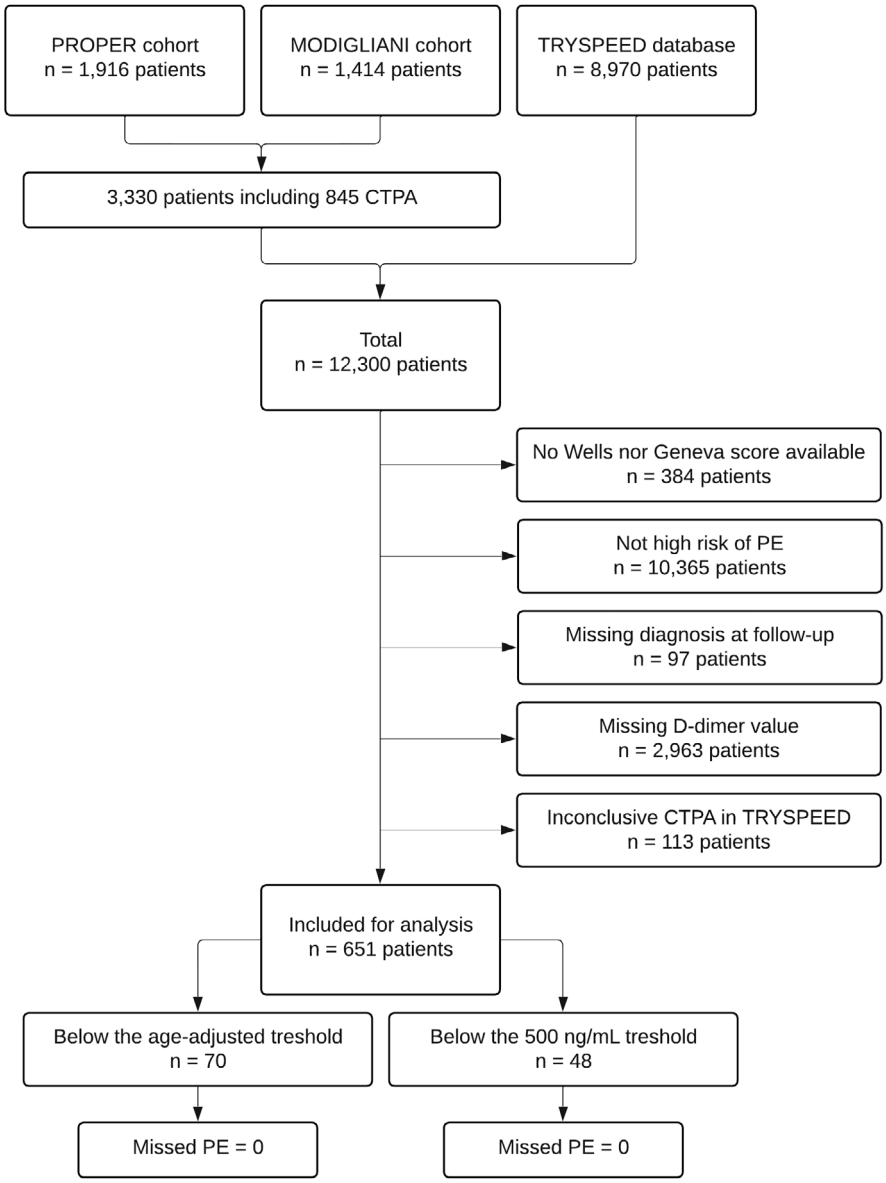

FIGURE 1 Flowchart. CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

and 500-fixed D-dimer thresholds. The positive predictive value (PPV) observed with the age-adjusted D-dimer strategy is higher compared to the fixed 500 strategy. The difference in denominators—581 for the age-adjusted strategy versus 603 for the fixed 500 strategy—reflects the total number of patients who tested positive under each approach. This difference suggests that the fixed 500 strategy produces more false positives. The age-adjusted D-dimer strategy, by yielding fewer false positives, consequently enhances its PPV compared to the fixed 500 strategy.

Overall failure rate of the strategy

Among the 651 patients with a high clinical risk, including patients with negative and positive D-dimer value, no PE was missed at follow-up. The failure rate of the overall strategy was 0.0% (95% CI 0.0%–0.6%). Bayesian analysis reported a credible interval of 0.0%–0.5%, with a less than 10^{-5} probability that the failure rate for the strategy is greater than 2%. Exploratory analyses of the MODIGLIANI and PROPER cohorts revealed that among the 845 patients who underwent CTPA in the ED, six were diagnosed with PE at 3-month follow-up despite not being diagnosed in the ED, indicating a CTPA failure rate of 0.7% (95% CI 0.3%–1.6%).

DISCUSSION

In this retrospective analysis of 651 patients with high clinical probability of PE from three European studies, no cases of PE were found in patients with high clinical suspicion and D-dimer levels below the

TABLE 1 Population characteristics.

	PROPER and MODIGLIANI (*n* = 67)	TRYSPEED (*n* = 584)	Overall (*n* = 651)
History and clinical signs			
Age (years)	59.0 (37.5–72.5)	69.0 (55.0–81.0)	68.0 (54.0–80.0)
Gender, feminine	52 (77.6)	340 (58.2)	392 (60.2)
Cancer	2 (3.0)	95 (16.3)	97 (14.9)
History of thromboembolic event	26 (38.8)	196 (33.6)	222 (34.1)
Estrogen use	6 (10.3)	19 (3.3)	25 (3.8)
Recent immobilization	9 (13.4)	92 (15.8)	101 (15.5)
Systolic blood pressure (mm Hg)	140 (130–156)	138 (123–155)	138 (124–155)
Heart rate (beats/min)	97 (81–108)	96 (84–109)	96 (84–109)
SpO_2 (%)	98 (96–99)	96 (94–98)	97 (94–98)
Temperature (°C)	36.8 (36.5–37.0)	36.9 (36.5–37.3)	36.9 (36.5–37.3)
Respiratory rate (breaths/min)	—	20 (17–25)	20 (17–25)
Syncope	5 (7.5)	61 (10.5)	66 (10.2)
Signs of deep vein thrombosis	64 (95.5)	555 (95.0)	619 (95.1)
Hemoptysis	5 (7.5)	16 (2.7)	21 (3.2)
PE is the most likely diagnosis	32 (47.8)	—	32 (47.8)
Biomarkers			
D-dimer (ng/mL)	640 (280–2500)	1870 (1060–4170)	1790 (942–4050)
D-dimer under 500 ng/mL threshold	27 (40.3)	21 (3.6)	48 (7.4)
D-dimer under age-adjusted threshold	31 (46.3)	39 (6.7)	70 (10.8)
Clinical decision rules			
Wells score	6 (5–8)	—	6 (5–8)
Revised Geneva	12 (12–14)	13 (11–14)	13 (12–14)
Outcomes			
PE	17 (25.4)	187 (32.0)	204 (31.3)

Note: Data are reported as median (IQR) or *n* (%).

Abbreviation: PE, pulmonary embolism.

age-adjusted threshold. None of these patients developed PE during follow-up, resulting in a failure rate of 0.0% (95% CI 0.0%–6.5%). However, the wide CI precludes a definitive conclusion about the safety of this D-dimer–based strategy. Bayesian analysis reported a 76.2% posterior probability that the failure rate is below 2%. The failure rate of the overall strategy among all high clinical risk patients was 0.0% (95% CI 0.0%–0.6%), with a less than 10^{-5} probability that the failure rate for the defined strategy is greater than 2%. The low specificity of D-dimer testing using an age-adjusted threshold in this cohort, calculated at 15.7%, suggests that while the test may be safe, its clinical utility could be limited, as it may result in a high number of false positives, leading to additional testing. Our study focuses on high-risk patients and addresses a gap in the existing literature by studying the safety of D-dimer testing in a population that is typically excluded from such analyses.

One of the main strengths of this study is the large cohort of patients with high clinical probability of PE, recruited from several EDs across Europe. This broad and diverse patient base enhances the generalizability of our findings. In addition, the rigorous follow-up procedures employed in the PROPER and MODIGLIANI studies, including telephone interviews and adjudication committees, ensure a high level of data accuracy regarding thromboembolic events. The exploratory analysis revealed that the failure rate of CTPA in these cohorts was 0.7%. Despite CTPA being considered the criterion

TABLE 2 Predictive statistics of D-dimer thresholds among high-risk PE patients using Bayesian analysis.

D-dimer threshold	Age-adjusted	Fixed 500 ng/mL
PPV	204/581	204/603
	35.1% (31.3%–39.0%)	33.8% (30.1%–37.7%)
Negative predictive value	70/70	48/48
	100% (95.9%–100%)	100% (94.1%–100%)
Posterior probability that failure rate is below 2%	76.2%	62.8%
Sensitivity	100% (98.6%–100%)	100% (98.5%–100%)
Specificity	15.7% (12.5%–19.2%)	10.7% (8.1%–13.8%)
Positive likelihood ratio	1.19 (1.13–1.23)	1.12 (1.08–1.16)
Negative likelihood ratio	0.0 (0.0–0.09)	0 (0.0–0.14)

Abbreviations: PE, pulmonary embolism; PPV, positive predictive value.

standard for PE diagnosis, with a high sensitivity and specificity, it is not infallible. Recognizing the limitations of CTPA helps refine diagnostic approaches. This underscores the importance of considering other diagnostic strategies, such as D-dimer testing, even in high-risk patients. However, further validation of these findings in larger cohorts is necessary to ensure the safety of the D-dimer strategy for these patients.

LIMITATIONS

Our study presents some limitations. First, the post hoc nature of the analysis may introduce biases inherent to retrospective analyses. Another limitation to consider is the heterogeneity of the included studies. One study relies solely on retrospective CTPA data without a 3-month follow-up, while the others include prospective follow-up. The lack of follow-up and the exclusion of inconclusive CTPA in the TRYSPEED study might result in an underestimation of the strategy's failure rate. Since most of the patients are from the TRYSPEED study, which is retrospective with no subsequent follow-up, D-dimer levels are compared mostly to CTPA results rather than to the usual clinical follow-up period. However, it is important to note that if a patient had a PE at 3 months but not at initial evaluation on CTPA (i.e., patients from the TRYSPEED study), this would correspond to a failure of CTPA and not related to our aim of assessing failure rate of D-dimer.

Although patients in the current analysis have been identified as having a high probability of PE based on the Wells or revised Geneva scores, they might still be inherently at lower risk because the original studies (PROPER and MODIGLIANI) were designed to evaluate patients with a low probability of PE as assessed by clinical gestalt. This difference occurs because the Geneva and Wells scores objectively quantify risk by incorporating specific criteria, offering a more consistent approach to risk assessment that can reveal a higher risk level than the clinician's initial impression. Therefore, the study population's characteristics might not accurately represent the broader population of high-risk patients.

There is also a significant difference in the percentage of negative D-dimer rates between the TRYSPEED study and the other two cohorts, despite similar rates of PE positivity. This disparity may be attributed to the fact that TRYSPEED includes only patients who have undergone CTPA, a procedure less likely to be performed if D-dimer results are negative. In contrast, the PROPER and MODIGLIANI cohorts include all patients with suspected PE, and we analyze those who had a D-dimer test regardless of whether they were scanned. This highlights the heterogeneity of the included studies and diminishes the comparability of these databases. Finally, excluding patients with missing data, such as D-dimer values and follow-up information, could introduce selection bias, potentially affecting the validity of our results.

CONCLUSIONS

In this study, ruling out pulmonary embolism in high-risk patients based on D-dimer below the age-adjusted threshold was safe, with no missed pulmonary embolism. However, the sample size was not large enough to draw a definitive conclusion on the safety of this strategy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Héloïse Bannelier https://orcid.org/0009-0000-6443-9248
Mélanie Roussel https://orcid.org/0000-0003-2467-8484
Yonathan Freund https://orcid.org/0000-0002-0262-3848

REFERENCES

1. Dronkers CEA, van der Hulle T, Gal GL, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15(5):1040-1043.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41(4):543-603.
3. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous

thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226-3256.
4. Douma RA, le Gal G, Söhne M, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. *BMJ*. 2010;340:c1475.
5. Freund Y, Cachanado M, Aubry A, et al. Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients: the PROPER randomized clinical trial. *JAMA*. 2018;319(6):559-566.
6. Nze Ossima A, Ngaleu Siaha BF, Mimouni M, et al. Cost-effectiveness of modified diagnostic strategy to safely rule-out pulmonary embolism in the emergency department: a non-inferiority cluster crossover randomized trial (MODIGLIA-NI). *BMC Emerg Med*. 2023;23:140.
7. Roussel M, Bloom B, Taalba M, et al. Temporal trends in the use of computed tomographic pulmonary angiography for suspected pulmonary embolism in the emergency department. *Ann Intern Med*. 2023;176(6):761-768.
8. Freund Y, Roussel M, Kline J, Roy P-M, Bloom B. The failure rate does not equal the false-negative rate: a call for tailoring diagnostic strategy validation in low prevalence populations. *J Thromb Haemost*. 2021;19(7):1832-1833.
9. Behringer W, Freund Y. Clinical translation of diagnostic studies: pitfalls of the usual reported characteristics. *Eur J Emerg Med*. 2021;28(3):165-166.

How to cite this article: Bannelier H, Kapfer T, Roussel M, et al. Failure rate of D-dimer testing in patients with high clinical probability of pulmonary embolism: Ancillary analysis of three European studies. *Acad Emerg Med*. 2025;32:116-122. doi:10.1111/acem.15032