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Age-related reduction in D-dimer cut-off specificity: Diagnostic relevance in geriatric patients

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ABSTRACT

Introduction: D-dimer testing is widely used to exclude pulmonary embolism (PE), but its specificity declines sharply with age. Evidence in very old adults is limited, as most validation studies include few patients aged ≥80 years. This study aimed to identify and validate a clinically appropriate D-dimer threshold for geriatric patients.

Methods: Two large cohorts of adults evaluated for suspected PE in a Geriatric Emergency Department were included. The derivation cohort included 1617 patients; the validation cohort included 2861 patients. D-dimer performance was assessed using ROC analysis, and specificity was compared across the conventional 500 μg/L FEU cut-off, the age-adjusted threshold, a fixed 1000 μg/L FEU threshold, and the optimized threshold. PE diagnosis was confirmed by CT pulmonary angiography.

Results: D-dimer levels increased with age, inflammation, and renal dysfunction. In the derivation cohort, the conventional cut-off showed low specificity, particularly in patients aged ≥90 years. The age-adjusted threshold improved performance but remained insufficient in the oldest age groups. An optimized threshold of 1050 μg/L FEU provided the best balance between sensitivity (100% in the derivation cohort and 97.8% in the validation cohort) and specificity, with a negative predictive value of 99.8%. This threshold correctly reclassified 23% of patients who were false-positive at the 500 μg/L FEU cut-off.

Conclusion: In very old adults, the conventional D-dimer cut-off is clinically inadequate, and the age-adjusted threshold remains suboptimal. A threshold of 1050 μg/L FEU, validated in two very old geriatric cohorts, offers a safer and more specific alternative for ruling out PE in geriatric emergency care.

1. Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major cause of morbidity and mortality in older adults [1], where diagnosis is often challenging due to atypical presentations and multimorbidity [2]. Clinical signs and symptoms of PE are notoriously nonspecific in geriatric patients, frequently overlapping with heart failure, infections, chronic lung disease, and functional decline, leading to both under- and over-diagnosis [3]. In Italy, the incidence of PE and its related mortality rates are substantial, particularly in the oldest age groups, underscoring the need for accurate and age-appropriate diagnostic strategies [4]. Because clinical signs and symptoms lack specificity, diagnostic algorithms combining pre-test probability assessment and D-dimer testing have become standard practice in emergency medicine [5]. The D-dimer assay is widely recognized as a highly sensitive tool for excluding PE in

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low-risk patients [6–8]. However, its specificity is limited, particularly in older adults, where D-dimer concentrations increase physiologically due to chronic inflammation, endothelial dysfunctions, reduced renal clearance, and the cumulative burden of comorbidities [9] – a phenomenon consistent with the inflammaging framework [10]. As a consequence, the conventional cut-off of 500 μg/L FEU becomes increasingly unreliable with advancing age, generating a high proportion of false positives and leading to unnecessary imaging, increased incidence of contrast-induced nephropathy [11], as well as increased costs. To address this limitation, age-adjusted D-dimer thresholds [ADC = patient's age × 10 μg/L] have been proposed and validated in adult populations [12,13]. However, these studies included relatively few patients aged ≥80 years, leaving uncertainty regarding the performance of age-adjusted thresholds in the oldest old, where D-dimer elevations are highly prevalent and often unrelated to acute thrombosis.

Moreover, emerging evidence suggests that in very old adults, D-dimer levels may rise in a nonlinear fashion, influenced more by systemic inflammation and frailty than by chronological age alone [14]. This raises the possibility that age-adjusted thresholds may remain insufficiently specific in geriatric emergency settings, where multimorbidity, acute illness, and chronic inflammatory states frequently coexist.

Given these gaps, there is a pressing need to identify clinically meaningful D-dimer thresholds tailored to geriatric patients, with particular attention to the oldest age groups, to improve diagnostic efficiency and reduce unnecessary imaging without compromising safety. The present study addresses this need by analyzing one of the largest cohorts of very old adults evaluated for suspected PE in a Geriatric Emergency Department.

Specifically, we aimed to: (1) characterize age-related changes in D-dimer levels; (2) assess the diagnostic performance of conventional, age-adjusted, and optimized thresholds; and (3) validate the proposed cut-off in an independent cohort.

2. Materials and methods

2.1. Study design and setting

This retrospective observational study was conducted at the Geriatric Emergency Department (GED) of the IRCCS INRCA Hospital in Ancona (Italy), a tertiary referral center specialized in geriatric and multimorbidity care. All procedures adhered to the Declaration of Helsinki and were approved by the Ethics Committee of the Marche Region (PROBIOLAB project, approval n. 64/2025). Retrospective analyses of anonymized clinical data do not require individual informed consent and clinical decisions were not influenced at all.

2.2. Study population and clinical evaluation

Two independent cohorts were analyzed. The derivation cohort included 1617 consecutive patients (962 females, 655 males) admitted to the GED between January 2013 and February 2014 with available D-dimer measurements. Patients were evaluated for suspected PE based on clinical judgment and standard diagnostic pathways, including assessment of pre-test probability using the Wells or revised Geneva score [15,16]. The validation cohort consisted of 2861 patients (1741 females, 1120 males) admitted between 2020 and 2025, used exclusively to confirm the diagnostic performance of the proposed D-dimer threshold.

Patients with low pre-test clinical probability (PTP) and a negative D-dimer were not subjected to further imaging, in accordance with international guidelines [17]. Patients with a positive D-dimer test or high PTP underwent confirmatory imaging. PE diagnosis was established through: CT pulmonary angiography (CTPA) showing segmental or more proximal intraluminal filling defects, or Ventilation-perfusion (V/Q) scintigraphy demonstrating a high-probability pattern. These criteria align with established diagnostic standards [5].

Plasma samples were collected at presentation and analyzed immediately using the Innovance® D-dimer immunoturbidimetric assay (Siemens Healthineers, Italia) on the Sysmex CS-2100i platform. This assay has demonstrated high sensitivity (98.8%) and moderate specificity (34.2%) at the conventional cut-off of 500 μg/L FEU [9]. Values <500 μg/L FEU were considered negative.

Demographic characteristics, comorbidities, and laboratory parameters were extracted from electronic medical records. Variables included: white blood cell count (WBC), C-reactive protein (CRP), hemoglobin (Hb), red blood cell count (RBC), platelet count, blood urea nitrogen (BUN), creatinine and estimated glomerular filtration rate (eGFR). CRP was included due to its known association with systemic inflammation and age-related coagulation activation [14].

2.3. Statistical analyses

Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± SD; non-normal variables as median [IQR]. Categorical variables were described as number (percentage). Group comparisons were performed using: Mann-Whitney *U* test for non-normal variables, Student's *t*-test for normally distributed variables, and Chi-square test for categorical variables. The age-related distribution of D-dimer concentrations was graphically assessed using scatter plots with D-dimer values on a logarithmic scale and a locally estimated scatterplot smoothing (LOESS) curve.

Diagnostic performance of D-dimer was evaluated using Receiver Operating Characteristic (ROC) curves and Areas Under the Curve (AUC). Sensitivity and specificity were calculated for the conventional 500 μg/L FEU cut-off, the age-adjusted cut-off (age × 10 μg/L FEU for patients aged >50 years), a fixed 1000 μg/L FEU cut-off, and the proposed 1050 μg/L FEU cut-off. Pairwise differences in specificity between the 1050 μg/L FEU threshold and the alternative cut-offs were assessed using McNemar's test. In addition, a sensitivity analysis restricted to patients aged ≥80 years was performed to assess the robustness of the findings in the oldest patients.

A multivariable logistic regression model was applied to identify predictors of false-positive D-dimer results in patients >60 years without PE. Covariates included age, WBC, CRP, Hb, RBC, platelets, BUN and eGFR. Inflammation-related variables were included due to their known impact on D-dimer elevation in older adults [14].

All analyses were performed using IBM SPSS Statistics version 27.0. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics and D-dimer levels according to age and clinical variables

A total of 1617 patients were included in the derivation cohort (Table 1). The median age was 85 years [IQR 80–89]. The median D-dimer concentration was 1200 [550–2990] μg/L FEU, and 358 (22.1%) patients had D-dimer values below the conventional 500 μg/L FEU threshold. PE was confirmed in 42 patients (2.6%). Baseline demographic and laboratory characteristics of the derivation and validation cohorts are reported in Table 1.

D-dimer concentrations increased progressively with age ($p < 0.01$), a trend observed in both sexes (Fig. 1). Among patients aged >60 years, those with confirmed PE had significantly higher D-dimer levels than those without PE ($p < 0.001$). Stratification by inflammatory and renal markers showed that patients with WBC >10,000/μL, CRP >0.5 mg/dL, or eGFR ≤30 mL/min exhibited higher median D-dimer values (Table 2).

Table 1
Description of clinical and biochemical characteristics of the patients of the derivation and validation cohorts.

	Derivation cohort ($n = 1617$)	Validation cohort ($n = 2861$)
Age (yrs)	85 [80–89]	84 [80–88]
D-dimer (μg/L FEU)	1200 [550–2990]	1180 [510–3160]
Pulmonary embolism (Yes/No)	42/1575	93/2768
WBC × 10^3/μL	8.4 [6.6–11.2]	8.3 [6.3–11.4]
RBC × 10^6/μL	4.18 ± 0.65	4.14 ± 0.69
Hemoglobin (g/dL)	12.38 ± 1.95	12.20 ± 2.05
Platelets × 10^3/μL	215.0 [171.0–268.7]	216.0 [170.0–273.0]
Sodium (mmol/L)	137 [134–139]	137 [134–140]
Potassium (mmol/L)	4.0 [3.7–4.4]	4.1 [3.7–4.4]
CRP (mg/dL)	2.91 [0.59–8.39]	1.60 [0.30–6.60]
Urea (mg/dL)	48 [36–75]	52 [38–78]
Creatinine (mg/dL)	1.1 [0.8–1.5]	1.1 [0.8–1.5]
eGFR (mL/min)	54 [36–75]	53 [35–72]

Data are median [IQR] for continuous non-normal variables and mean ± SD for continuous normal variables; eGFR: estimated Glomerular Filtration Rate.

3.2. Diagnostic performance of D-dimer in the derivation cohort

ROC curve analysis identified 1050 μg/L FEU as the cut-off providing the highest specificity while maintaining 100% sensitivity (Fig. 2). At this threshold, specificity reached 46%, compared with 23% using the conventional 500 μg/L FEU cut-off. Using the 1050 μg/L FEU threshold, 377 patients (23.3%) initially classified as false positive at 500 μg/L FEU were correctly reclassified as true negatives.

Diagnostic performance differed across the evaluated thresholds (Table 3). In the overall derivation cohort, the 1050 μg/L FEU cut-off maintained 100% sensitivity and achieved a specificity of 46.3%, compared with 22.5% for the conventional 500 μg/L FEU cut-off, 37.7% for the age-adjusted cut-off, and 44.7% for the 1000 μg/L FEU cut-off. The improvement in specificity with the 1050 μg/L FEU threshold was statistically significant compared with all alternative thresholds. In a sensitivity analysis restricted to patients aged ≥80 years, the findings were consistent, with 100% sensitivity and a specificity of 39.7% for the 1050 μg/L FEU cut-off, compared with 15.4%, 32.4%, and 37.9% for the 500 μg/L FEU, age-adjusted, and 1000 μg/L FEU thresholds, respectively. To investigate factors associated with false-positive D-dimer results, we performed a multivariable logistic regression analysis in patients aged >60 years without PE. Among the variables examined, only age and CRP were independently associated with a D-dimer value >1050 μg/L FEU (Table 4).

3.3. Validation of the proposed D-dimer cut-off in an independent cohort

The independent validation cohort included 2861 patients, whose baseline demographic and laboratory characteristics are summarized in Table 1. Ninety-three patients (3.3%) were diagnosed with PE. Using the 1050 μg/L FEU threshold, the assay identified 91 true positives and 1189 true negatives, with only 2 false negatives and 1579 false positives. This corresponded to a sensitivity of 97.8% (95% CI, 92.4–99.7%); a specificity of 43.0% (95% CI, 41.1–44.8%); a Negative Predictive Value (NPV) of 99.8% (95% CI, 99.4–100.0%), with a Positive Predictive Value (PPV) of 5.4% (95% CI 4.4–6.6%). The overall diagnostic accuracy was 44.7% (95% CI, 42.9–46.6%). Of the two false-negative cases, one had an upper-lobar PE, whereas the other had a very small upper-lobar embolism.

Table 2
D-dimer levels and their correlation with pulmonary embolism, WBC, CRP and eGFR in patients of derivation cohort aged >60 years.

	D-dimer levels median [IQR]	P
Pulmonary embolism (yes)	11,790 [5342–17,245]	<0.001
Pulmonary embolism (no)	1205 [580–2917.5]	
WBC ≤ 10,000/μL	1040 [510–2240]	<0.001
WBC > 10,000/μL	1940 [830–4280]	
CRP ≤ 0.5 mg/dL	825 [487.5–2052.5]	<0.001
CRP > 0.5 mg/dL	1320 [620–3287.5]	
eGFR ≤ 30 mL/min	2030 [915–4317.5]	<0.001
eGFR > 30 mL/min	1150 [550–2767.5]	

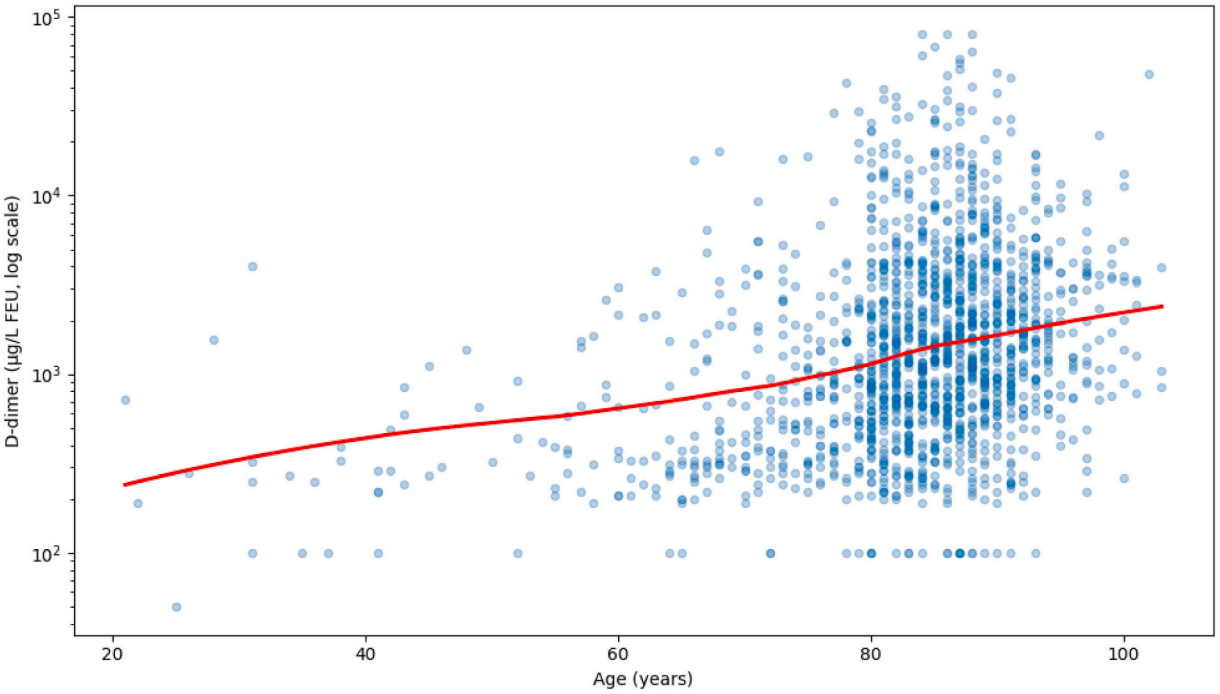


Fig. 1. Distribution of plasma D-dimer concentrations according to age in the derivation cohort.
Scatter plot of individual D-dimer values by patient age. D-dimer concentrations are reported in μg/L FEU on a logarithmic scale. The red line represents the LOESS-smoothed trend. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

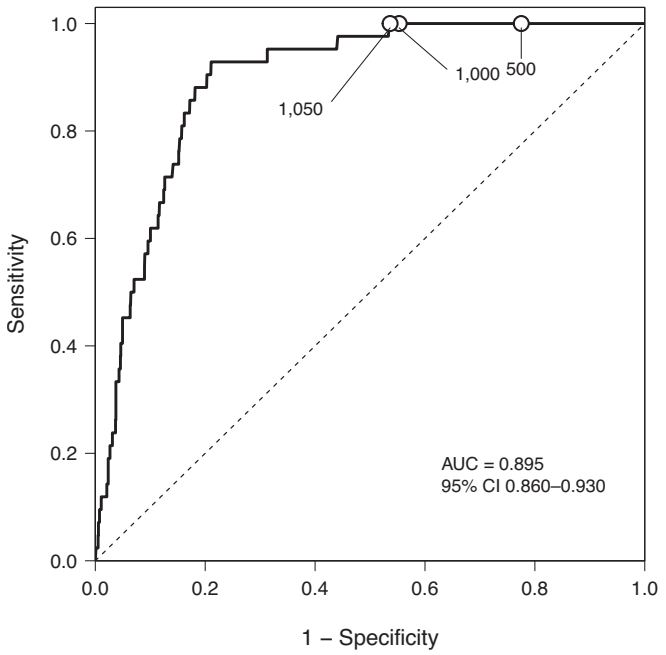


Fig. 2. Receiver Operating Characteristic (ROC) curve analysis for D-dimer in the diagnosis of Pulmonary Embolism for patients of the derivation cohort. The 500 μg/L FEU, 1000 μg/L FEU, and 1050 μg/L FEU thresholds are indicated on the curve.

4. Discussion

The present study confirms that the diagnostic behavior of D-dimer in very old adults differs substantially from that observed in younger populations, with a marked age-related decline in specificity and a high prevalence of elevated values unrelated to acute thromboembolism. This phenomenon has been consistently described in the literature, where D-dimer is recognized as a sensitive but poorly specific biomarker, particularly in the presence of comorbidities, inflammation, and age-related physiological changes [6,11,14]. However, this study extends this knowledge by analyzing one of the oldest and largest geriatric cohorts ever evaluated for suspected PE, with a median age of 85 years and more than 70% of patients aged ≥80 years. This demographic profile is rarely represented in diagnostic accuracy studies, including those validating age-adjusted D-dimer thresholds [18,19].

The prevalence of PE in our derivation cohort was relatively low (2.6%) compared with previous diagnostic studies in elderly patients, in which PE prevalence ranged from approximately 20% to 24% [20]. This difference likely reflects the characteristics of our geriatric emergency setting, where very old and multimorbid patients frequently present with nonspecific symptoms and substantial diagnostic uncertainty. Indeed, clinical manifestations of PE in older adults are often atypical or nonspecific, requiring a high index of clinical suspicion [21]. In this context, D-dimer testing is frequently used at a low clinical threshold to exclude PE, thereby increasing the number of patients tested and reducing the proportion of confirmed events.

The extremely advanced age of our cohorts is a unique strength. Most large studies on D-dimer include patients with mean ages between 55 and 65 years [22], and even meta-analyses of age-adjusted thresholds contain only a small proportion of patients aged ≥80 years [23]. In contrast, our dataset reflects the real-world geriatric population of emergency departments, where multimorbidity, frailty, and chronic inflammation are the norm rather than the exception [24]. This demographic context is essential for interpreting D-dimer values, as aging is associated with progressive activation of coagulation pathways, endothelial dysfunction, and chronic low-grade inflammation — the biological framework known as inflammaging [10,25].

In our derivation cohort, only 22% of patients had D-dimer values below the conventional 500 μg/L FEU threshold, confirming that this cut-off is largely unsuitable for geriatric emergency care. Specificity fell below 10% in patients aged ≥90 years, a finding consistent with prior reports showing that D-dimer loses nearly all discriminatory capacity in oldest old [26,27]. This raises important concerns regarding overdiagnosis, unnecessary imaging, and contrast-agent exposure, which carry increased risk of acute induced injury and adverse events in frail older adults [28,29].

Although the age-adjusted D-dimer threshold improves specificity in adults [30], our data show that in oldest old it remains insufficiently calibrated to the nonlinear, inflammation-driven rise in D-dimer typical of advanced age. This limitation has also been highlighted in a recent study evaluating modern diagnostic strategies such as the YEARS rule and the Adjust-Unlikely approach [31], but this analysis was conducted in a relatively young population (maximum age 74 years) and therefore provides no evidence regarding very old adults. In the overall derivation cohort, the 1050 μg/L FEU threshold provided a modest but statistically significant gain in specificity compared with both the age-adjusted and the fixed 1000 μg/L FEU thresholds, while maintaining 100% sensitivity. Crucially, these findings were confirmed in the sensitivity analysis restricted to patients aged ≥80 years. This makes it not simply "higher" than age-adjusted value, but genuinely better aligned with geriatric physiology.

The optimized threshold of 1050 μg/L FEU identified in our study

Table 4
Logistic regression analysis of the features suggestive of false positives in patients above age 60 and without pulmonary embolism.

Variable	B	Exp (B)	95% CI	*P* value
Age	0.053	1.054	1.024–1.085	≤0.001
WBC	0.046	1.047	0.999–1.097	0.054
CRP	0.090	1.094	1.052–1.138	≤0.001
Hemoglobin	−0.121	0.886	0.732–1.073	0.217
RBC	0.037	1.038	0.594–1.815	0.896
Platelet count	<0.001	1.000	0.997–1.002	0.742
BUN	0.006	1.006	1.000–1.012	0.059
eGFR	0.008	1.008	0.996–1.020	0.215

Table 3
Diagnostic performance of different D-dimer thresholds in the derivation cohort and sensitivity analysis restricted to patients aged ≥80 years.

Population	Patients, n (PE)	Cut-off	Sensitivity, %	Specificity, %	p vs 1050 μg/L FEU
Overall derivation cohort	1617 (42)	500 μg/L FEU	100.0	22.5	<0.001
		Age-adjusted	100.0	37.7	<0.001
		1000 μg/L FEU	100.0	44.7	<0.001
		1050 μg/L FEU	100.0	46.3	–
Patients aged ≥80 years	1285 (38)	500 μg/L FEU	100.0	15.4	<0.001
		Age-adjusted	100.0	32.4	<0.001
		1000 μg/L FEU	100.0	37.9	<0.001
		1050 μg/L FEU	100.0	39.7	–

PE, pulmonary embolism. Age-adjusted cut-off was defined as patient age × 10 μg/L FEU for patients aged >50 years. *P* values refer to paired comparisons of specificity between each threshold and the 1050 μg/L FEU threshold using McNemar's test.

provided the best balance between sensitivity and specificity, maintaining 100% sensitivity in the derivation cohort and 97.8% sensitivity in the validation cohort, with an excellent negative predictive value of 99.8%. These findings align with recent evidence suggesting that a modest upward adjustment of D-dimer thresholds can safely reduce imaging in selected populations [32–34]. Importantly, this threshold allowed the correct reclassification of nearly one quarter of patients who would have been considered false positives using the conventional cut-off, thereby reducing unnecessary CT pulmonary angiography – a clinically meaningful improvement in geriatric emergency care.

Our multivariable analysis further supports the biological plausibility of the proposed threshold. Among patients without PE, age and CRP were the only independent predictors of D-dimer values ≥1050 μg/L FEU, reinforcing the central role of inflammation in driving non-specific D-dimer elevations in older adults. This observation is consistent with mechanistic studies showing that CRP, IL-6, and other inflammatory mediators contribute to coagulation activation and fibrin turnover in aging populations [25,35]. These findings underscore the need to interpret D-dimer within a broader clinical and biological context in geriatric patients, rather than relying solely on thresholds derived from younger cohorts.

Several limitations must be acknowledged. First, the retrospective design may introduce selection bias, as inclusion depended on D-dimer testing performed during routine clinical care. More importantly, confirmatory imaging was not systematically performed in all patients, resulting in a potential partial verification bias. Patients with low pre-test probability and a negative D-dimer did not undergo imaging; therefore, undetected PE events among non-imaged patients cannot be completely excluded. This may have resulted in an overestimation of sensitivity and negative predictive value. Second, a direct comparison with clinical-probability–adjusted algorithms such as YEARS was not possible because the individual clinical variables required to retrospectively reconstruct these strategies were not systematically available in our dataset. Third, information on anticoagulation therapy was not available; however, anticoagulation typically lowers D-dimer levels and would therefore bias results toward improved specificity rather than the opposite [14]. Fourth, we lacked follow-up data to identify delayed PE diagnoses, although the high negative predictive value observed in both cohorts suggests that missed events are unlikely. Finally, D-dimer assays are method-specific, and our findings may not be directly generalizable to other analytical platforms [5,36].

In conclusion, our study demonstrates that the conventional D-dimer cut-off is clinically inadequate in very old adults and that an optimized threshold of 1050 μg/L FEU improves specificity without compromising safety. Given the unique age composition of our cohorts, these findings provide robust, geriatric-specific evidence that may inform future diagnostic algorithms and contribute to more judicious use of imaging in the emergency evaluation of suspected PE.

5. Conclusions

In this study, conducted in one of the oldest and largest geriatric cohorts ever evaluated for suspected pulmonary embolism, we found that the conventional D-dimer cut-off of 500 μg/L FEU is clinically inadequate for very old adults, yielding extremely low specificity and a high burden of unnecessary imaging. The age-adjusted threshold improved performance but remained insufficiently calibrated to the nonlinear, inflammation-driven rise in D-dimer typical of advanced age.

An optimized threshold of 1050 μg/L FEU provided the best balance between sensitivity and specificity, maintaining excellent safety (sensitivity 97.8–100%, NPV 99.8%) while substantially reducing false positives across all age strata. Importantly, this cut-off is the only one validated in a population with a median age of 85 years, making it more appropriate for geriatric physiology than thresholds derived from younger cohorts. Future studies should prospectively evaluate the 1050 μg/L FEU threshold within a structured diagnostic management algorithm incorporating clinical pre-test probability. In particular, systematic follow-up of patients in whom PE is excluded without imaging will be essential to confirm safety and quantify the potential reduction in unnecessary CTPA before routine clinical implementation. These findings support further prospective evaluation of a geriatric-specific D-dimer threshold and provide a basis for future diagnostic management studies aimed at reducing unnecessary imaging without compromising safety.

Abbreviations

[ADC]	Age adjusted DD Cut-off level
AUC	Areas Under the Curve
BUN	Blood Urea Nitrogen
CHF	Congestive Heart Failure
CRP	C-Reactive Protein
CTPA	Computed Tomography Pulmonary Angiography
CVST	Cerebral Venous Sinus Thrombosis
DD	D-Dimer
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
GED	Geriatric Emergency Department
PE	Pulmonary Embolism
PTP	Pre-test clinical Probability
RBC	Red Blood Cell
ROC	Receiver Operating Characteristic
SD	Standard Deviation
VTE	Venous Thromboembolism
WBC	White Blood Cell

CRediT authorship contribution statement

Francesca Marchegiani: Writing – original draft, Visualization, Data curation, Conceptualization. **Roberta Galeazzi:** Resources, Investigation, Data curation. **Luca Antognoli:** Software, Formal analysis, Data curation. **Fausto Moroni:** Validation, Methodology, Data curation. **Stefania Appolloni:** Investigation, Formal analysis, Data curation. **Antonio Cherubini:** Writing – review & editing, Resources, Methodology. **Fabio Salvi:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis. **Sara Cecchini:** Writing – review & editing, Investigation. **Enrico Paci:** Writing – review & editing, Supervision, Resources. **Fabiola Olivieri:** Writing – review & editing, Supervision, Resources. **Jacopo Sabbatinelli:** Writing – review & editing, Visualization, Data curation.

Ethics declaration

The authors have NOT obtained informed consent from participants or their legal representatives. According to the Italian regulations, retrospective analyses of anonymized clinical data do not require individual informed consent and clinical decisions were not influenced at all.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the Ethics Committee of the Marche Region. (Approval No. 64/2025)

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Declaration of competing interest

None declared.

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