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AGE-ADJUSTED D-DIMER IN SUSPECTED PULMONARY EMBOLISM: SAFETY AND REDUCTION IN CT PULMONARY ANGIOGRAPHY

DÍMERO-D AJUSTADO PELA IDADE NA SUSPEITA DE EMBOLIA PULMONAR: SEGURANÇA E REDUÇÃO DA ANGIOTOMOGRAFIA PULMONAR

DÍMERO D AJUSTADO POR EDAD EN LA SOSPECHA DE EMBOLIA PULMONAR: SEGURIDAD Y REDUCCIÓN DE LA ANGIOTOMOGRAFÍA PULMONAR

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ABSTRACT

A fixed D-dimer threshold becomes less specific with increasing age, leading many older adults with suspected pulmonary embolism to undergo imaging despite the absence of thromboembolism. Age adjustment aims to preserve safe exclusion while improving the usefulness of a negative result. This structured narrative review synthesizes PubMed-indexed management studies, diagnostic accuracy analyses, evidence syntheses, and guidelines identified through focused searches and targeted retrieval through October 8, 2026. In appropriately selected adults with non-high pretest probability, the usual threshold is 500 µg/L in fibrinogen equivalent units up to age 50 and age multiplied by 10 µg/L thereafter. In ADJUST-PE, the three-month thromboembolic failure rate among patients with D-dimer above 500 µg/L but below the age-adjusted threshold was 0.3%, with a 95% confidence interval of 0.1% to 1.7%. Among eligible patients aged at least 75 years, the proportion in whom pulmonary embolism could be excluded using D-dimer increased from 6.4% to 29.7%. RELAX-PE supported safety in routine outpatient care, while individual-patient meta-analysis demonstrated a smaller average efficiency gain across broader populations. These benefits depend on correct assessment of clinical probability, a sufficiently sensitive validated assay, and accurate interpretation of laboratory units. Evidence from combined YEARS and age-adjusted strategies should not be attributed to age adjustment alone. Age-adjusted D-dimer can safely reduce the need for CT pulmonary angiography in suitable patients, particularly

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older outpatients, while high clinical probability, hemodynamic instability, anticoagulant exposure, and assay uncertainty require different diagnostic considerations.

Keywords: D-dimer. Age Adjustment. Pulmonary Embolism. CT Pulmonary Angiography.

RESUMO

Um limiar fixo de D-dímero torna-se menos específico com o avanço da idade, levando muitos idosos com suspeita de embolia pulmonar a serem submetidos a exames de imagem, apesar da ausência de tromboembolismo. O ajuste pela idade visa preservar a segurança da exclusão diagnóstica e, ao mesmo tempo, aumentar a utilidade de um resultado negativo. Esta revisão narrativa estruturada sintetiza estudos de manejo, análises de acurácia diagnóstica, sínteses de evidências e diretrizes indexados no PubMed, identificados por meio de buscas direcionadas e recuperação específica de dados realizada até 8 de outubro de 2026. Em adultos adequadamente selecionados e sem alta probabilidade pré-teste, o limiar habitual é de 500 µg/L (em unidades equivalentes de fibrinogênio) até os 50 anos de idade e, a partir dessa idade, a idade multiplicada por 10 µg/L. No estudo ADJUST-PE, a taxa de falha tromboembólica em três meses entre pacientes com D-dímero acima de 500 µg/L, porém abaixo do limiar ajustado pela idade, foi de 0,3% (intervalo de confiança de 95%: 0,1% a 1,7%). Entre pacientes elegíveis com 75 anos ou mais, a proporção daqueles em quem a embolia pulmonar pôde ser excluída utilizando o D-dímero aumentou de 6,4% para 29,7%. O estudo RELAX-PE corroborou a segurança da estratégia na assistência ambulatorial de rotina, enquanto uma meta-análise de dados individuais de pacientes demonstrou um ganho médio de eficiência menor em populações mais amplas. Esses benefícios dependem da avaliação correta da probabilidade clínica, do uso de um ensaio validado com sensibilidade adequada e da interpretação precisa das unidades laboratoriais. As evidências provenientes de estratégias combinadas (como o protocolo YEARS e o ajuste pela idade) não devem ser atribuídas exclusivamente ao ajuste pela idade. O uso de D-dímero ajustado pela idade pode reduzir com segurança a necessidade de angiotomografia pulmonar em pacientes adequados, especialmente idosos atendidos em regime ambulatorial; por outro lado, situações como alta probabilidade clínica, instabilidade hemodinâmica, uso de anticoagulantes e incerteza quanto ao ensaio exigem abordagens diagnósticas distintas.

Palavras-chave: D-dímero. Ajuste pela Idade. Embolia Pulmonar. Angiotomografia Pulmonar.

RESUMEN

El umbral fijo de dímero D pierde especificidad con el aumento de la edad, lo que lleva a muchos adultos mayores con sospecha de embolia pulmonar a someterse a pruebas de imagen a pesar de no presentar tromboembolia. El ajuste según la edad tiene como objetivo mantener la seguridad al descartar la enfermedad y, al mismo tiempo, mejorar la utilidad de un resultado negativo. Esta revisión narrativa estructurada sintetiza estudios de manejo, análisis de precisión diagnóstica, síntesis de evidencia y guías clínicas indexados en PubMed, identificados mediante búsquedas dirigidas y recuperación específica de información hasta el 8 de octubre de 2026. En adultos seleccionados adecuadamente con una probabilidad pretest no alta, el umbral habitual es de 500 µg/L (en unidades equivalentes de fibrinógeno) hasta los 50 años, y a partir de esa edad, la edad multiplicada por 10 µg/L. En el estudio ADJUST-PE, la tasa de fracaso tromboembólico a tres meses entre pacientes con niveles de dímero D superiores a 500 µg/L pero inferiores al umbral ajustado por edad

fue del 0,3 % (intervalo de confianza del 95 %: 0,1 % - 1,7 %). Entre los pacientes elegibles de 75 años o más, la proporción en la que se pudo descartar la embolia pulmonar mediante el dímero D aumentó del 6,4 % al 29,7 %. El estudio RELAX-PE respaldó la seguridad de este enfoque en la atención ambulatoria habitual, mientras que un metaanálisis a nivel de paciente individual demostró una ganancia de eficiencia promedio menor en poblaciones más amplias. Estos beneficios dependen de una evaluación correcta de la probabilidad clínica, del uso de una prueba validada con suficiente sensibilidad y de una interpretación precisa de las unidades de laboratorio. Los resultados derivados de estrategias combinadas (como YEARS y el ajuste por edad) no deben atribuirse únicamente al ajuste por edad. El uso de dímero D ajustado por edad puede reducir de forma segura la necesidad de realizar angiotomografía pulmonar (angio-TC) en pacientes adecuados, especialmente en pacientes ambulatorios de edad avanzada; no obstante, situaciones como una alta probabilidad clínica, inestabilidad hemodinámica, tratamiento anticoagulante previo e incertidumbre sobre la prueba requieren consideraciones diagnósticas diferentes.

Palabras clave: Dímero D. Ajuste por Edad. Embolia Pulmonar. Angiotomografía Pulmonar.

1 INTRODUCTION

Suspected pulmonary embolism is a frequent diagnostic problem because its symptoms overlap with many cardiopulmonary illnesses and because neither an isolated symptom nor a positive biomarker establishes the diagnosis. Contemporary evaluation combines clinical pretest probability with D-dimer testing or imaging according to the patient's risk and stability. This sequence permits exclusion without imaging in selected patients while directing those with higher probability toward objective diagnostic testing.[1,2,3]

D-dimer reflects the degradation of cross-linked fibrin and is sensitive to acute thromboembolism, but it also increases in many conditions that do not represent pulmonary embolism. The specificity of a conventional threshold declines substantially with age, making a positive result common in older adults who do not have venous thromboembolism. Age adjustment was developed to improve the proportion of useful negative tests without abandoning the requirement for a compatible clinical probability assessment.[4,5]

CT pulmonary angiography provides essential diagnostic information when indicated, yet indiscriminate imaging exposes patients to radiation, iodinated contrast, and the consequences of incidental or uncertain findings. Reducing imaging requires evidence that anticoagulation and further testing can safely be withheld, rather than merely showing that a revised threshold produces fewer positive laboratory results. Prospective management studies therefore provide the central evidence for age-adjusted D-dimer, with diagnostic accuracy studies supplying complementary information about test performance.[6,7]

2 OBJECTIVE

This review examines the safety and diagnostic efficiency of age-adjusted D-dimer thresholds in adults evaluated for suspected acute pulmonary embolism. It assesses the evidence for avoiding CT pulmonary angiography, distinguishes prospective management outcomes from retrospective estimates, and compares age adjustment with related probability-based strategies. It also addresses laboratory units, assay differences, special populations, and implementation practices that determine whether the evidence can be applied safely.

3 METHODS

A focused PubMed search was conducted on October 8, 2026, using the expression ("age-adjusted"[Title/Abstract] OR "age adjusted"[Title/Abstract]) AND ("D-

dimer"[Title/Abstract] OR "D dimer"[Title/Abstract]) AND ("pulmonary embolism"[Title/Abstract] OR "Pulmonary Embolism"[MeSH Terms]). An upper publication-date limit of October 8, 2026, was applied without a lower date limit, yielding 204 records. Targeted retrieval added diagnostic guidelines, foundational derivation and validation studies, YEARS and PEGeD management studies, pregnancy-specific evidence, and studies addressing anticoagulation and laboratory assays.

Records were selected for their relevance to adult suspected pulmonary embolism, diagnostic safety, imaging avoidance, or limitations of threshold interpretation. PubMed metadata and available primary-source text were examined for study design, clinical probability criteria, assay information, denominators, imaging outcomes, and follow-up events. Prospective management studies were distinguished from retrospective reclassification, and mixed adaptive strategies were identified separately from age adjustment alone.

This is a structured narrative evidence review, with purposive selection rather than an exhaustive systematic review. No protocol was registered, no independent duplicate screening or formal risk-of-bias instrument was applied, and no new pooled effect estimate was calculated. All references were verified against PubMed records, and published sensitivity, specificity, efficiency, and three-month failure rates were treated as distinct outcomes.

4 RESULTS AND DISCUSSION

4.1 CLINICAL PROBABILITY DETERMINES THE ROLE OF D-DIMER

A negative D-dimer is useful when the probability of pulmonary embolism before testing is sufficiently low that a sensitive assay can reduce the remaining probability to an acceptable level. This assessment can use a validated Wells or revised Geneva pathway, with the threshold interpreted according to the probability categories used by that pathway. The biomarker should not be ordered as an indiscriminate screen for all patients with dyspnea or chest pain because nonspecific positive results can initiate avoidable imaging.[1,2]

In patients with a very low clinical probability, a validated pulmonary embolism rule-out criteria pathway may avoid even D-dimer testing when all criteria are negative. Patients who require biomarker testing are a different population from those already excluded by such a rule, and older age alone makes the standard PERC rule positive. Age-adjusted D-dimer

therefore has particular value after appropriate risk assessment in older adults, while remaining a component of an algorithm rather than a replacement for clinical evaluation.[8,9]

A high clinical probability or hemodynamic instability changes the diagnostic priority toward urgent evaluation and imaging appropriate to the circumstances. The 2026 multisociety guideline supports age-adjusted D-dimer in adults with low or intermediate clinical probability and recognizes YEARS as an alternative validated approach. This endorsement does not justify using a negative age-adjusted value to overrule a high-probability presentation or to delay the evaluation of an unstable patient.[2,3]

4.2 THRESHOLD CALCULATION AND LABORATORY UNITS

For commonly used high-sensitivity assays reported in fibrinogen equivalent units, the conventional threshold is 500 µg/L up to age 50, with age in years multiplied by 10 µg/L used thereafter. A 70-year-old therefore has a threshold of 700 µg/L FEU, equivalent to 700 ng/mL FEU or 0.70 mg/L FEU. The arithmetic is simple, but the laboratory's reporting units, assay validation, and definition of a negative value must be established before the threshold is applied.[6,8]

Fibrinogen equivalent units and D-dimer units are different calibration conventions and cannot be treated as identical labels attached to the same numerical result. ACEP guidance specifies an age-times-five threshold for eligible assays reported in D-dimer units, whereas the familiar age-times-ten expression applies to FEU assays. A generic formula entered into an electronic record without identifying the assay and unit convention can therefore produce clinically important classification errors.[8,10]

For an illustrative 70-year-old with non-high clinical probability, a result of 620 µg/L FEU falls above the fixed threshold but below the age-adjusted threshold. The same number in DDU would not carry the same interpretation, and a result at or above the applicable cutoff requires the next diagnostic step under the chosen pathway. Examples clarify the calculation but do not replace local laboratory agreement on a validated threshold or the assessment of whether the patient qualifies for D-dimer exclusion.[6,11]

4.3 INTERPRETING DIAGNOSTIC SAFETY

Sensitivity measures the proportion of patients with disease who have a positive test under a specified reference standard, whereas a management-study failure rate measures subsequent events in patients classified as not requiring treatment. The latter is conditional

on the complete pathway, its eligibility criteria, and the decision to withhold imaging or anticoagulation. A high sensitivity estimate therefore cannot by itself demonstrate that a new threshold can safely replace a prospectively validated diagnostic strategy in a different population.[5,6]

Negative predictive value additionally depends on disease prevalence and can change when a strategy is transferred from outpatient care to a higher-risk population. The value of a negative result should consequently be interpreted with the pretest probability and study setting, rather than assumed from an assay's overall accuracy. This dependence explains why the same numeric result can be suitable for exclusion in one patient while a high-probability presentation still warrants imaging.[1,12]

The most relevant safety subgroup for age adjustment consists of patients above the fixed cutoff but below the adjusted cutoff, since those below both thresholds would already avoid imaging. Examining only the entire negative group can dilute failures in that additional interval with a much larger group whose management was unchanged. ADJUST-PE, RELAX-PE, and the recent adaptive-threshold meta-analysis explicitly inform this interval, allowing the tradeoff between extra exclusion and missed events to be evaluated more directly.[6,7,13]

4.4 FROM DERIVATION TO PROSPECTIVE VALIDATION

Douma and colleagues examined data from 5132 patients across derivation and validation cohorts and proposed the age-times-ten threshold for patients older than 50 years. The proportion in whom pulmonary embolism could be excluded increased by approximately five to six percentage points in validation cohorts, with larger gains among patients older than 70 years. These findings established the rationale and suggested safety, but retrospective application could not fully reproduce management in which imaging is prospectively withheld on the basis of the adjusted result.[4]

Schouten and colleagues subsequently synthesized 13 cohorts comprising 12,497 patients with non-high probability of venous thromboembolism. In patients older than 80 years, specificity increased from 14.7% with the conventional cutoff to 35.2% with age adjustment, while sensitivity remained above 97% across age categories. Because the analysis concerned suspected venous thromboembolism rather than exclusively pulmonary embolism and reconstructed test performance, it supports diagnostic discrimination but should not be substituted for prospective pulmonary embolism management outcomes.[5]

4.5 THE ADJUST-PE MANAGEMENT STUDY

ADJUST-PE prospectively evaluated 3346 outpatients with suspected pulmonary embolism in 19 centers, using clinical probability, highly sensitive D-dimer testing, and CT pulmonary angiography when indicated. Among 2898 patients with non-high or unlikely clinical probability, 817 had D-dimer below 500 µg/L and another 337 had a value between 500 µg/L and the age-adjusted cutoff. Patients in the additional age-adjusted group did not undergo CT pulmonary angiography and were followed without anticoagulation for three months.[6]

Among 331 evaluable patients in that additional group, one thromboembolic event occurred, giving a failure rate of 0.3% with a 95% confidence interval of 0.1% to 1.7%. This is the most directly relevant safety estimate for patients whose management changes because the cutoff increases with age. Its confidence interval is essential: a small observed failure rate supports safety under the study conditions but does not demonstrate that the true risk is zero.[6]

The proportion below either the fixed or adjusted threshold increased from 28.2% to approximately 39.8% among the 2898 eligible patients. The additional 11.6 percentage points describe increased exclusion without imaging in the non-high-probability population, not an 11.6% reduction among every patient presenting with suspected pulmonary embolism. Keeping the denominator explicit prevents exaggerating the expected reduction in total departmental CT pulmonary angiography use.[6]

The largest benefit appeared in older participants: of 766 patients aged at least 75 years, 673 had non-high clinical probability and were eligible for the relevant comparison. The proportion in whom pulmonary embolism could be excluded using D-dimer increased from 43 of 673, or 6.4%, to 200 of 673, or 29.7%, without additional false-negative findings in that subgroup. The absolute gain was 23.3 percentage points, illustrating why age adjustment is especially useful when a fixed threshold otherwise yields very few negative results.[6]

4.6 VALIDATION IN ROUTINE CARE

RELAX-PE enrolled 1507 outpatients in whom pulmonary embolism was considered excluded by non-high probability and a negative age-adjusted D-dimer in routine care across ten hospitals. Of these, 301 had D-dimer at least 500 µg/L but below the age-adjusted cutoff, and no venous thromboembolism occurred among 269 evaluable untreated patients in this

interval over three months. The corresponding 95% confidence interval extended to 1.41%, supporting the management strategy while retaining uncertainty around rare failures.[7]

Across 1421 evaluable untreated participants, RELAX-PE observed one nonfatal pulmonary embolism, an overall three-month event rate of 0.07%. The cohort was assembled from patients already classified as having a negative age-adjusted result, so its incremental yield should not be interpreted as a population-wide reduction among all suspected cases. Loss to follow-up and anticoagulation for other indications also explain why the safety denominators differ from the total enrolled population.[7]

Together, ADJUST-PE and RELAX-PE provide prospective evidence that the clinically important interval between the fixed and adjusted cutoffs can be managed without imaging in selected outpatients. Neither study randomized all participants to fixed versus age-adjusted thresholds, so some comparative efficiency calculations remain based on what the conventional pathway would have required. Their strongest contribution is direct follow-up after withholding imaging and anticoagulation, which is more clinically informative than laboratory reclassification alone.[6,7]

4.7 META-ANALYSES AND VARIATION IN EFFICIENCY

An individual-patient meta-analysis of six prospective studies included 7268 patients evaluated with a dichotomized Wells rule and quantitative D-dimer. Applying age adjustment increased estimated efficiency from 28% to 33% overall, with a larger increase in older patients and an increase of only 2.6 percentage points in inpatients. The findings show that average imaging avoidance depends on case mix and cannot be predicted from the very elderly ADJUST-PE subgroup alone.[14]

A 2021 meta-analysis involving nine cohorts and 47,720 patients with non-high clinical probability found high sensitivity with both strategies and fewer false-positive results after age adjustment. A rapid systematic review likewise supported the strategy while emphasizing variation in study design and the need to use the specified probability and assay conditions. Accuracy syntheses and management studies converge in direction, but sensitivity estimates and three-month thromboembolic failure rates remain different measures.[15,16]

A 2026 meta-analysis of prospective management studies examined adaptive thresholds, including both age-adjusted and probability-adjusted strategies. Across six studies with 12,194 patients, the pooled failure rate within the adaptive interval above 500 ng/mL was 0.50%, with a 95% confidence interval of 0.20% to 1.11%. These data strengthen

confidence in validated adaptive algorithms collectively, but their mixed interventions and highly heterogeneous efficiency estimates do not provide an isolated pooled effect for age adjustment.[13]

4.8 WHAT FEWER CT PULMONARY ANGIOGRAMS MEANS

Avoiding a CT pulmonary angiogram removes an episode of radiation exposure, contrast administration, and scanner use for a patient whose pulmonary embolism can be excluded through a validated pathway. This can improve diagnostic efficiency, particularly when older adults would otherwise proceed to imaging because of a modestly elevated nonspecific D-dimer. However, the management studies establish exclusion and imaging avoidance more directly than they establish reductions in contrast-associated kidney injury, downstream treatment harm, or mortality.[6,7]

The number of scans potentially avoided is also influenced by whether clinicians order D-dimer in appropriate patients and follow the resulting pathway. In an observational audit of 573 CT pulmonary angiograms, age-adjusted interpretation was estimated to have prevented 26 scans without false negatives in that reviewed sample. Because patients had already undergone imaging and the analysis was retrospective, this estimate illustrates an implementation opportunity rather than a prospectively demonstrated change in institutional scan volume.[17]

A reduction in scan use should be accompanied by surveillance for subsequent venous thromboembolism and by documentation of the probability category and threshold used. Patients whose symptoms persist, evolve, or become more concerning require renewed clinical assessment even after an initially reassuring evaluation. Safe exclusion is a decision based on the presentation at the time of testing, not a guarantee against future thrombosis or an explanation for every symptom.[1,6]

4.9 DISTINGUISHING AGE ADJUSTMENT FROM YEARS AND PEGED

The original YEARS algorithm combines clinical signs of deep-vein thrombosis, hemoptysis, and the judgment that pulmonary embolism is the most likely diagnosis with two D-dimer thresholds. It uses 1000 ng/mL when no YEARS item is present and 500 ng/mL when at least one item is present, rather than calculating the threshold from age. In its prospective study, CT pulmonary angiography was not indicated in 48% of patients compared with an

estimated 34% under Wells plus a fixed cutoff, a comparison that should not be attributed to age adjustment.[18]

PEGeD similarly adapts the threshold to clinical probability, excluding pulmonary embolism with D-dimer below 1000 ng/mL in low-probability patients and below 500 ng/mL in moderate-probability patients. Among 1325 patients with low or moderate probability and a protocol-negative D-dimer, no venous thromboembolism occurred during follow-up, with an upper 95% confidence limit of 0.29%. The study's efficiency result concerns that specific probability-based pathway and cannot justify choosing the most permissive cutoff from several algorithms after seeing a test result.[19]

Freund and colleagues randomized emergency departments to a combined YEARS and age-adjusted strategy or to an age-adjusted control strategy in 1414 patients. In the intervention, patients without YEARS criteria used a 1000 ng/mL threshold, whereas those with criteria used the age-adjusted threshold, and the three-month outcome met the specified noninferiority criterion. Chest imaging occurred in 30.4% versus 40.0%, so the additional reduction reflects the combined strategy relative to age adjustment, rather than the effect of age adjustment relative to a fixed cutoff.[9]

These alternatives can all be clinically useful when implemented as complete validated pathways with the appropriate eligible population. Their rules should not be blended informally by applying a higher threshold whenever it avoids imaging, because such an improvised approach may no longer preserve the validation conditions. The distinction also matters in evidence summaries, where pooled adaptive strategies may conceal differences in both baseline risk and the patients reclassified as negative.[13,20]

4.10 CANCER AND OBESITY

Cancer raises the prevalence of venous thromboembolism and commonly elevates D-dimer, reducing the proportion of patients who can avoid imaging. In an ADJUST-PE post hoc analysis, age adjustment increased the proportion of cancer patients excluded by clinical probability and D-dimer from 6.3% to 12.6%, with no follow-up events but an upper confidence limit of 6.9%. The wide interval limits reassurance from that subgroup alone, although it does not support treating cancer as an automatic prohibition against a validated diagnostic algorithm.[21]

A 2026 individual-patient meta-analysis included 2258 cancer patients from 17 management studies and found comparable failure rates across categories with imaging

withheld or standard imaging performed. Its results support the applicability of established algorithms in cancer, while the reported subgroup confidence intervals and limited efficiency remain relevant to individual decisions. Probability assessment and adherence to the full pathway are especially important when the patient's symptoms, malignancy, or treatment make a low-probability classification less credible.[22]

A secondary analysis involving 1593 patients found that age adjustment increased exclusion without imaging among obese patients from 28% to 38%. No three-month failures were observed in obese patients left untreated after a negative adjusted result, although the upper 95% confidence limit was 2.9%. This supports using the validated strategy in appropriately selected patients with obesity without inventing an additional body-weight-based D-dimer threshold.[23]

4.11 HOSPITALIZATION AND HIGH PROBABILITY PRESENTATIONS

D-dimer is frequently elevated during acute medical illness, even when venous thromboembolism is not suspected. A prospective cohort of 995 hospitalized adults aged at least 60 years found elevated values in 74.4% using the fixed threshold and 62.2% using age adjustment. Because that study did not enroll a suspected-pulmonary-embolism diagnostic population, it demonstrates limited specificity in hospitalized illness rather than validating exclusion in every inpatient.[24]

Recent surgery and substantial inflammation can similarly reduce the efficiency of D-dimer testing, while hospitalization may bring higher baseline thromboembolic probability. Existing individual-patient analyses suggest that some suitable inpatients can be evaluated with established pathways, but average gains are smaller than in older outpatients and subgroup precision is limited. Clinical context should therefore guide whether D-dimer adds useful information instead of assuming that age adjustment corrects every cause of a positive value.[1,14]

A 2025 ancillary analysis included 651 high-probability patients, of whom 70 had D-dimer below the age-adjusted threshold and none had pulmonary embolism identified at presentation or follow-up. The upper 95% confidence limit for failure in that negative subgroup was 6.5%, leaving substantial uncertainty despite the absence of observed events. This study generates a research question but does not provide a sufficient basis to abandon guideline-directed imaging in high-probability patients.[2,12]

4.12 PREGNANCY AND ANTICOAGULANT EXPOSURE

The adult age-adjusted threshold should not be presented as a validated pregnancy-specific solution. Pregnancy-adapted YEARS prospectively evaluated a distinct algorithm with compression ultrasonography when deep-vein thrombosis symptoms were present and avoided CT pulmonary angiography in 39% of participants. That evidence supports the pregnancy-adapted pathway in appropriate settings and remains separate from the age-adjustment evidence discussed in older nonpregnant adults.[3,25]

Anticoagulant treatment can lower D-dimer and weaken the reliability of a negative result. An analysis of the effects of heparin estimated a mean decline of approximately 25% after 24 hours, with a modeled reduction in sensitivity, highlighting why a value obtained after treatment is not equivalent to a pretreatment test. When feasible within appropriate care, the diagnostic sample should precede anticoagulation, and a treated patient's negative result should not be interpreted by simply applying the usual outpatient exclusion rule.[26]

4.13 ASSAY VARIATION AND IMPLEMENTATION

A 2025 secondary analysis of ADJUST-PE compared five assays in 597 evaluable samples and found that classification under age adjustment differed between tests. Some assays classified more patients as negative, including patients with pulmonary embolism, despite low overall failure estimates. This result shows why nominally identical units do not eliminate assay-dependent differences and why evidence from one platform should be assessed before automatically transferring its threshold to another.[11]

A retrospective study of 1831 emergency-department patients tested with a DDU-based assay found greater specificity with an age-times-five cutoff than with its conventional 230 ng/mL threshold. The study enrolled patients who also underwent CT pulmonary angiography, so the selected sample and retrospective design do not establish prospective safety after withholding imaging. It supplies useful assay-specific information while reinforcing the need for validated local interpretation rather than a universal conversion formula.[10]

Implementation should identify the assay and units, calculate the threshold, and document the probability pathway before deciding about imaging. Audit should track eligibility, testing, actual imaging, protocol departures, and subsequent thromboembolism by age. These measures determine whether local practice reproduces the benefits of prospective management studies.[6,11,17]

Table 1

Principal evidence on diagnostic safety and imaging avoidance

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Douma et al. (2010) [4]	Retrospective derivation/validation across 5132 suspected-PE patients. Age-adjusted versus fixed cutoff.	Exclusion increased by 5–6 percentage points in validation cohorts, with greater gains in older patients.	Established the rationale; retrospective classification preceded prospective management validation.
Schouten et al. (2013) [5]	Meta-analysis; 13 cohorts, 12,497 non-high-probability patients with suspected VTE.	Above age 80, specificity 14.7% fixed versus 35.2% adjusted; sensitivity above 97% across age groups.	Improved specificity; mixed VTE accuracy evidence is distinct from PE management safety.
Righini et al. (2014) [6]	ADJUST-PE prospective management study; 3346 outpatients, including 2898 with non-high/unlikely probability.	Adaptive interval: 1/331 failures at three months, 0.3% (95% CI 0.1–1.7%). Eligible age ≥75: exclusion 6.4% to 29.7%.	Direct evidence for withholding CTPA in the age-adjusted interval; the older subgroup gained 23.3 percentage points.
Robert-Ebadi et al. (2021) [7]	RELAX-PE prospective routine-care study; 1507 outpatients already negative under a non-high-probability age-adjusted pathway.	Adaptive interval: 0/269 events at three months (95% CI 0–1.41%). Overall: 1/1421 untreated evaluable patients.	Confirms outpatient management safety; negative-only cohort cannot estimate all-suspected-patient imaging reduction.
Freund et al. (2021) [9]	Cluster crossover RCT; 1414 ED patients. Combined YEARS/age adjustment versus age-adjusted control.	Three-month VTE 0.15% versus 0.80% in primary per-protocol assessment; chest imaging 30.4% versus 40.0%.	Met prespecified noninferiority criterion; extra imaging reduction reflects the combined strategy.
Robert-Ebadi et al. (2025) [11]	Preplanned ADJUST-PE secondary analysis; 597 evaluable samples compared across five assays.	Failure estimates below 2%; two assays reclassified additional PE patients as age-adjusted negative.	Assay agreement and classification differ; units alone do not establish interchangeability.
Graziani et al. (2026) [13]	Meta-analysis; six prospective studies, 12,194 patients; age- and probability-adapted strategies.	Pooled adaptive-interval failure 0.50% (95% CI 0.20–1.11%); overall failure 0.12%.	Supports adaptive pathways collectively; mixed algorithms do not isolate age adjustment.
van Es et al. (2016) [14]	Individual-patient meta-analysis; six prospective studies, 7268 patients. Wells plus fixed or age-adjusted D-dimer.	Estimated efficiency 28% to 33%; gains larger in older patients and smaller in inpatients.	Average benefit depends on case mix; post hoc comparisons and subgroup precision limit interpretation.
Vrotniakaite-Bajerciene et al. (2026) [22]	Individual-patient meta-analysis; 2258 cancer patients from 17 prospective management studies; several decision rules.	Three-month VTE estimates after exclusion ranged from 0.52% to 2.83%; maximum diagnostic yield 26%.	Supports established algorithms in cancer, with limited efficiency and wide subgroup confidence intervals.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Gaugler et al. (2024) [23]	Secondary prospective-cohort analysis; 1593 suspected-PE patients, 22% obese.	In obese patients, exclusion without imaging 28% to 38%; three-month failure 0% (95% CI 0–2.9%).	Supports the validated pathway in selected obese patients; no weight-specific threshold was tested.

CI, confidence interval; CTPA, CT pulmonary angiography; ED, emergency department; PE, pulmonary embolism; VTE, venous thromboembolism. The adaptive interval is above the fixed cutoff but below the applicable adaptive threshold. Imaging efficiency denominators differ between studies.

5 LIMITATIONS OF THE EVIDENCE AND THIS REVIEW

Many studies apply alternative thresholds retrospectively, and meta-analyses combine assays, probability rules, and patient populations that differ in important ways. Rare follow-up events produce wide confidence intervals in special populations, while three-month events can include both initially missed disease and subsequent thrombosis. Imaging efficiency is also sensitive to the denominator, so results from all suspected patients, non-high-probability patients, and already-negative cohorts should not be compared as though they measured the same outcome.[7,13,14]

This review used a focused PubMed search with targeted supplementation and purposive selection, which may have omitted relevant studies. It did not perform a formal risk-of-bias assessment or calculate a new pooled estimate, and some recent findings were evaluated primarily through their PubMed abstracts. The synthesis therefore supports application of established algorithms under their validation conditions rather than providing a new threshold or an exhaustive estimate for every clinical subgroup.

6 CONCLUSION

Age-adjusted D-dimer safely increases exclusion without imaging in appropriately selected adults with non-high clinical probability of pulmonary embolism, with the largest efficiency gains generally occurring in older outpatients. Prospective ADJUST-PE and RELAX-PE data support withholding CT pulmonary angiography in patients whose values are above the fixed cutoff but below the validated age-adjusted threshold. These findings depend on the entire diagnostic pathway and should be communicated with the relevant denominators and confidence intervals.[6,7]

Clinical probability, hemodynamic stability, assay sensitivity, reporting units, and anticoagulant exposure determine whether the result can be used for exclusion. Age adjustment and probability-adapted strategies such as YEARS offer related but distinct

approaches, and their benefits should not be conflated or their thresholds combined informally. Reliable implementation can reduce unnecessary CT pulmonary angiography while preserving timely investigation of patients whose probability or presentation warrants imaging.[3,9,11]

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