A PaDd-informed, Assay-calibrated Diagnostic Pathway for Suspected Pulmonary Embolism in Older Adults: From Signal to Strategy

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To the Editor,

We commend Cohen et al. for introducing a pragmatic composite—Padua score × D-dimer (PaDd)—designed to refine pulmonary embolism (PE) exclusion in adults aged ≥65 years, a population often characterized by multimorbidity, physiological heterogeneity, and atypical presentations. Their single-center retrospective cohort (2021–2023) provides a compelling, hypothesis-generating signal: combining a validated venous thromboembolism risk score with D-dimer may enhance specificity without compromising safety.[1]

Context of Existing Evidence

Two decades of research confirm that adaptive D-dimer strategies consistently and safely reduce imaging utilization. Age-adjusted D-dimer (AADD) and clinical-probability-adapted models are now well established.[2] The two algorithms—Pulmonary

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Embolism Graduated D-dimer (PEGeD) and YEARS (based on three clinical criteria: signs of deep vein thrombosis, hemoptysis, and pulmonary embolism as the most likely diagnosis)—integrate pre-test probability with dynamic D-dimer thresholds, maintaining low miss-rates while significantly reducing CT pulmonary angiography (CTPA) exposure across emergency and primary-care settings.[3,4]

Against this backdrop, PaDd is appealing because it encodes comorbidity-driven thrombotic risk and leverages D-dimer's high sensitivity. However, transforming PaDd from a promising signal into an implementable diagnostic policy requires attention to four critical domains.

(1) Comparator-anchored validation: PaDd's performance must be benchmarked directly against AADD, YEARS, and PEGeD using identical reference standards and 3-month venous thromboembolism outcomes. External validation of PEGeD has already revealed contexts in which 1000-ng/mL thresholds may be insufficient, particularly above age-adjusted limits—highlighting gaps a PaDd-augmented model should proactively address.[3]

(2) Assay-specific calibration: D-dimer is not a single test, and assay heterogeneity meaningfully affects cutoff performance. Data from the ADJUST-PE study show wide inter-assay variability when AADD is applied.[5] A future PaDd rule must therefore be assay-calibrated, with outcomes stratified by reagent platform to ensure reproducibility and clinical safety.

(3) System-level and ethical considerations: In emergency-care systems worldwide, over-testing, under-testing, and mis-testing of suspected PE persist.[6] Reducing low-value CTPA is a clinical, economic, and ethical imperative. A PaDd pathway should be embedded within a de-implementation framework supported by decision-curve analysis, cost-effectiveness modeling, and equity metrics, especially in resource-constrained settings.

(4) Downstream management of subsegmental PE: Diagnostic parsimony should align with therapeutic parsimony. Structured surveillance without anticoagulation is safe for carefully selected patients with isolated subsegmental PE, yet remains underutilized.[7] A PaDd-based pathway should predefine subsegmental PE management contingencies to avoid inadvertently replacing imaging overuse with treatment overuse.

Proposed Validation Roadmap

We propose a four-part roadmap to strengthen the next stage of PaDd evaluation:

- Pre-test probability: Classification using YEARS or 4PEPS (4-Level Pulmonary Embolism Clinical Probability Score) where validated.[4,8,9]

- Assay-calibrated D-dimer: Application of assay-specific AADD or clinical-probability-adapted thresholds.[2,5]

- PaDd overlay for ≥65 years: Adjustment of D-dimer cutoffs upward for low comorbidity (low Padua score) and downward for high-risk profiles.[1]

- Equity and safety framework: Reporting calibration accuracy, safety margins, and failure rates stratified by age, estimated glomerular filtration rate (eGFR), cancer status, and assay type.[3,5] Integration of subsegmental PE management aligned with local follow-up capacity.[7,8]

Global Significance

If validated rigorously, assay-informed PaDd-augmented pathways could meaningfully reduce imaging in regions where scanners are scarce, contrast nephropathy is prevalent, or workforce capacity is limited. Evidence from primary-care YEARS already demonstrates feasibility; integrating PaDd for geriatric patients may further enhance diagnostic equity and safety.[4]

Cohen et al. have introduced a clinically relevant and geriatric-sensitive concept.[1] To ensure that PaDd becomes not only innovative but implementable, future studies must be multicenter, assay-calibrated, transparent, and anchored to comparator trials. Such rigor will help deliver a diagnostic pathway that is safer, scalable, and ethically aligned with global standards.

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