SUPPLEMENTARY MATERIAL

This appendix has been provided by the authors for the benefit of readers

Supplement to Response to Letter to the Editor: Prospective Validation of PaDd—A Roadmap

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In This Supplement

PROPOSED VALIDATION ROADMAP

We propose a pragmatic, registry-embedded prospective cohort with the following features:

1. **Multicenter enrollment** (≥5 sites across diverse healthcare systems).
2. **Age ≥65 years**; care pathway stratification (Emergency department [ED]-discharge, ED-admit, direct-admit).
3. **Novel Oral Anticoagulant (NOAC)/heparin sensitivity analysis (or exclusion)**.
4. **Standardized mobility assessment** using pilot-tested templates.
5. **Assay-stratified reporting** with optional split-sample sub-study.
6. **Co-primary endpoints**:
    - Proportion of patients below PaDd threshold (efficiency).
    - 90-day venous thromboembolism incidence in PaDd-negative patients (safety).
7. **Pre-specified sub-analyses**: Age, sex, malignancy, infection, renal function, assay type, anti-antiaggregant treatment, Padua score with several templates of mobility reduction, exclusion of patients less than 70 years old, ED-discharge/admit, by center, D-dimer × Geneva Risk Score, PaDd ± YEARS versus AADD ± YEARS, exclusion if PaDd=0, exclusion if received NOAC/heparin, exclusion if patient has low platelets (need to define).

OPERATIONALIZING "REDUCED MOBILITY" IN THE PADUA SCORE: EVIDENCE-BASED TEMPLATE PROPOSALS

Background: The Problem with Current Padua Definitions

The Padua Prediction Score assigns **3 points** for "reduced mobility ≥3 days," but the original definition is vague:

> "Bed rest with bathroom privileges (apart from bathroom needs) due to patient limitations or on physician's order for at least 3 days."

Key Problems:

1. **"Bathroom privileges"** is ambiguous (walking 5 meters? wheelchair transfer?)
2. **"Patient limitations"** versus **"physician's order"** creates different assessment contexts
3. **No validated assessment tool** exists for retrospective chart review
4. **Inter-rater reliability unknown** in real-world settings

PROPOSED TEMPLATES FOR PROSPECTIVE VALIDATION

Five templates spanning quantitative, functional, objective, structured, and hybrid approaches. Each should be pilot-tested in a nested substudy to determine which best predicts pulmonary embolism (PE) risk.

TEMPLATE 1: Percentage-Based Mobility Reduction (Quantitative)

Assessment Question: *"Compared to the patient's baseline mobility 2 weeks ago, their current mobility is reduced by:"*

Category	Definition	Padua Points
0%	Unchanged from baseline	0
1%-24%	Slightly reduced (can walk but less than usual)	0
25%-49%	Moderately reduced (mostly walking short distances)	**3**
50%-74%	Severely reduced (mostly chair-bound, walks <10 meters/day)	**3**
75%-100%	Bedbound (cannot walk, transfers only to chair/toilet)	**3**

Advantages:

- Intuitive for clinicians
- Captures graded severity

Disadvantages:

- Requires baseline knowledge (may be unavailable in acute settings)
- Subjective percentage estimation

Validation Method: Compare against actigraphy (step count) in subsample

TEMPLATE 2: Functional Activity Scale (3-Day Recall)

Assessment Question: *"Over the past 3 days, the patient has been:"*

Level	Description	Examples	Padua Points
Level 0	Normal activity	Walking >500 m/day, shopping, household tasks	0
Level 1	Limited activity	Walking 100-500 m/day, sitting most of day but mobile	0
Level 2	Chair-dependent	Sitting >20 hours/day, walking only to bathroom (<50 m/day)	**3**
Level 3	Bed-dependent	Lying >20 hours/day, transfers only with assistance	**3**
Level 4	Fully bedbound	Cannot transfer without mechanical lift	**3**

Advantages:

- Clear behavioral anchors
- Aligns with WHO Performance Status concepts
- Easy to document in nursing notes

Disadvantages:

- Requires reliable patient/caregiver recall

Validation Method: Concordance with nurse-reported mobility documentation

TEMPLATE 3: Objective Measurement (Wearable Device)

Assessment Method: *Step count measured via wearable accelerometer (Fitbit, Apple Watch, hospital-issued device) over 72 hours*

Step Count (3-day average)	Interpretation	Padua Points
>3,000 steps/day	Adequate mobility	0
1,000-3,000 steps/day	Reduced but not severely	0
<1,000 steps/day	Severely reduced mobility	**3**

Advantages:

- Objective, reproducible
- No recall bias

Disadvantages:

- Requires technology infrastructure
- May not capture bed-to-chair transfers (underestimates immobility)
- Unsuitable for intensive care unit (ICU) patients

Validation Method: Gold standard for Template 1 and 2 comparisons

TEMPLATE 4: Structured Clinical Observation (Nurse-Rated)

Assessment Tool: Adapted from Johns Hopkins Highest Level of Mobility (JH-HLM) Scale

Nurse rates the highest level of mobility achieved in past 3 days:

Mobility Level	Description	Padua Points
1	Walking without assistance (>50 meters)	0
2	Walking with/without assistance (10-50 meters)	0
3	Transfer to chair, no walking	**3**
4	Sitting at edge of bed, no standing	**3**
5	Lying in bed, passive range of motion only	**3**

Advantages:

- Already used in hospital quality metrics
- High inter-rater reliability (validated in ICU/ward settings)
- Real-time documentation

Disadvantages:

- Requires nursing staff training

Validation Method: Correlation with 90-day venous thromboembolism (VTE) incidence

TEMPLATE 5: Hybrid Template (Clinical Judgment + Objective Trigger)

Two-Step Assessment:

STEP 1 (Screening Question): *"Has the patient been out of bed for <1 hour total per day (excluding bathroom) for ≥3 days?"*

- **YES** → Proceed to Step 2
- **NO** → Assign 0 points

STEP 2 (Objective Confirmation): *Document one of the following:*

- Physician order for bed rest
- Nursing note: "Patient bedbound" or "Chair-bound, no ambulation"
- Physical therapy note: "Unable to ambulate"
- Step count <500/day (if available)

If any criterion met → **Assign 3 points**

Advantages:

- Combines subjective and objective data
- Minimizes false positives (screening question filters out borderline cases)

Disadvantages:

- Two-step process may reduce compliance

RECOMMENDED PILOT STUDY DESIGN

Phase 1: Template Comparison Study (n=200 patients)

Objective: Determine which template best predicts PE risk

Methods:

1. Enroll 200 consecutive patients aged ≥65 with suspected PE
2. Apply **all 5 templates** to each patient (blinded assessors)
3. Record:
    - Final PE diagnosis (reference standard)
    - Inter-rater reliability (2 independent assessors per template)
    - Time to complete each assessment
4. Primary outcome: **Area under ROC curve** for PE prediction
5. Secondary outcomes:
    - Inter-rater reliability (Cohen's kappa)
    - Feasibility (% missing data)
    - Clinician preference survey

Phase 2: Prospective PaDd Validation (n=1,000 patients)

Objective: Validate PaDd using best-performing template from Phase 1

Methods:

1. Use the selected template to calculate Padua score
2. Compute PaDd (Padua × D-dimer)
3. Compare diagnostic accuracy versus age-adjusted D-dimer alone
4. Report outcomes stratified by mobility template threshold

Anticipated Results by Template

Template	Predicted Strength	Predicted Weakness	Best Use Case
Template 1	Captures gradations	Subjective estimation	Retrospective studies
Template 2	Clear definitions	Recall bias	Prospective cohorts
Template 3	Objective	Technology barrier	Research hospitals
Template 4	Already validated	Requires training	Pragmatic trials
Template 5	Balances rigor/feasibility	Two-step complexity	Clinical implementation

Recommendation:

Templates 2, 4, and 5 are identified as the most feasible options for immediate prospective validation, while **Template 3** may serve as an optional objective comparator in well-resourced sites where additional analytical rigor or benchmarking against established approaches is desired.