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Systematic Review of Screening Prediction Diagnostic Models of Deep Venous Thrombosis and Pulmonary Embolism in Family Practice

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Abstract: **The occurrence of VTE is generally triggered by a confluence of environmental and constitutional risk factors. Environmental risk factors for thrombosis include trauma, surgery, or immobility. Therefore the early diagnosis of this condition is very important in primary care.**
Objective: to assess the possibility of the diagnostic tests used for suspected pulmonary embolism, DVT in Primary care.
Method: We searched literature-indexing systems to identify the articles relevant to our review, including MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews through the period of July 2016.
Conclusion: The accuracy of tests for suspected deep venous thrombosis and pulmonary embolism varies greatly, but it is possible to estimate the range of pretest probabilities over which each test or strategy can confirm or rule out pulmonary embolism.

Keywords: **VTE, MEDLINE, EMBASE, Environmental risk factors.**

1. INTRODUCTION

Pulmonary embolismis a major global public health concern, with an estimated 900,000 venous thromboembolic events occurring annually in the United States alone (1). Incidence rates for venous thromboembolism are higher in men, African-Americans, and increase substantially with age. It is critical to treat deep venous thrombosis at an early stage to avoid development of further complications, such as pulmonary embolism or recurrent deep venous thrombosis (2).

Pulmonary embolism can be classified depending on degree of pulmonary vasculature obstructed by burden of blood clots. While classifying pulmonary embolism, it is reasonable to consider not only size of the embolus but also the underlying cardiopulmonary reserve. Therefore, the best way to classify pulmonary embolism depends on the hemodynamic consequences (3).

The occurrence of VTE is generally triggered by a confluence of environmental and constitutional risk factors. Environmental risk factors for thrombosis include trauma, surgery, or immobility. Constitutional risk factors for thrombosis may be genetic or acquired. Genetic risk factors include deficiencies of endogenous anticoagulant proteins (such as antithrombin III, protein C or protein S); excessive function of procoagulant proteins, or elevated levels of factors VIII, IX and XI (6). Although disturbances of normal fibrinolytic function (e.g., tissue plasminogen activator (TPA) deficiency, excessive levels of plasminogen activator inhibitor 1 (PAI-1), or factor XII deficiency would be expected to contribute to a hypercoaguable state, clinical evidence of such is lacking (7).

In many countries, general practitioners are the first physicians to encounter patients with symptoms suggestive of pulmonary embolism. Risk stratification is valuable in deciding which patients to refer. All diagnostic models for safe exclusion of pulmonary embolism have been developed and validated in hospital or acute care settings. However, diagnostic prediction models developed in a particular setting often perform less well when applied in another setting. Therefore, models derived in hospital or acute care settings cannot simply be implemented in primary care [8,9,10,11,12,13,14]. Reasons for this poorer performance include differences in the case mix and the prevalence of pulmonary embolism due to the unselected population, as well as differences in physicians' experience of patients with suspected pulmonary embolism [9,10,15,16]. Hence, when transferring diagnostic models or strategies across healthcare settings, evaluation of their

performance in this other setting is necessary first. This form of external validation is referred to as domain or setting validation [8, 10,17] or as quantification of the transportability of prediction models [13,18] The incidence rate of pulmonary embolism is challenging to quantify, however, as it is often not diagnosed without autopsy. Possibly up to 30% of patients with DVT develop symptomatic pulmonary embolism, and another 40% have asymptomatic pulmonary embolism, which can be found with radiological tests (19). Pulmonary embolism dramatically reduces short- and long-term survival among patients with VTE (20). Despite anticoagulant therapy, VTE recurs frequently in the first few months after the initial event (21). Expedient diagnosis is crucial for prompt initiation of treatment, which improves patient outcomes (22).

All diagnostic tests involve a trade-off between sensitivity and specificity. Highly sensitive tests reduce harm by limiting false-negative results and allowing a patient to promptly begin treatment. Highly specific tests reduce harm by limiting unnecessary and perhaps risky confirmatory tests, as well as incorrect treatment. Diagnosis of VTE requires a test with high sensitivity, as a missed DVT diagnosis can result in a deadly pulmonary embolus or, at a minimum, postthrombotic syndrome in the leg. In contrast, a test with low specificity cannot be tolerated, as a false-positive result commits a patient to anticoagulation with its attendant risks (23).

Objectives:

We carried out a systematic review to assess the possibility of the diagnostic tests used for suspected pulmonary embolism, DVT in Primary care. For clinical purposes, we estimated the range of pretest probabilities over which each test can accurately confirm or exclude pulmonary embolism.

2. METHODOLOGY

Design:

This paper conducted as systematic review study following the steps of including and excluded criteria of review.

Study identification:

We searched literature-indexing systems to identify the articles relevant to our review, including MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews through the period of July 2016. To ensure identification of all relevant articles, we examined the reference lists from material identified through the electronic searching and from discussion with experts, and reviewed the tables of contents of recent issues of the most relevant journals. Search terms ((pulmonary emboli, or pulmonary thromboembol, Deep venous thrombosis, diagnosis or diagnostic, family medicine , primary care)), including all studies that matches our search criteria of such meta-analyses; clinical trials; and randomized, controlled trials.

Two authors independently reviewed the titles and abstracts of the references identified to determine suitability for inclusion and they extracted the data. If disagreement arose all three authors conferred to reach consensus.

3. RESULTS

Family practice perspectives for diagnosis of PE AND DVT:

according to *American Academy of Family Physicians and the American College of Physicians*, [24] good quality evidence supports the use of clinical prediction rules to establish pretest probability of disease [24]. The Wells prediction rules for DVT and for pulmonary embolism (Tables 1 and 2) have been validated and are frequently used to estimate the probability of VTE before performing more definitive testing on patients. The Wells prediction rule performs better in younger patients without comorbidities or a history of VTE than it does in other patients. Physicians should use their clinical judgment in cases where a patient is older or presents with comorbidities[24].

Table.1: Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of Pulmonary Embolism[35]

Clinical Characteristic	Score
Previous pulmonary embolism or deep vein thrombosis	+1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of deep vein thrombosis	+3
Alternative diagnosis less likely than pulmonary embolism	+3

Clinical Characteristic	Score
Hemoptysis	+1
Cancer	+1

Note: Clinical probability of pulmonary embolism: low 0–1; intermediate 2–6; high ≥ 7.

Table.2: Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of Pulmonary Embolism[35]

Clinical Characteristic	Score
Previous pulmonary embolism or deep vein thrombosis	+1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of deep vein thrombosis	+3
Alternative diagnosis less likely than pulmonary embolism	+3
Hemoptysis	+1
Cancer	+1

Note: Clinical probability of pulmonary embolism: low 0–1; intermediate 2–6; high ≥ 7.

We identified one systematic review[33]that demonstrated several strategies for pretests to exclusion of PE, for each strategy they calculated the post-test probability as a function of the pretest probability (fig.1 and fig.2). . For each diagnostic strategy they have express the accuracy of diagnostic decisions as a function of the pretest probability[33]

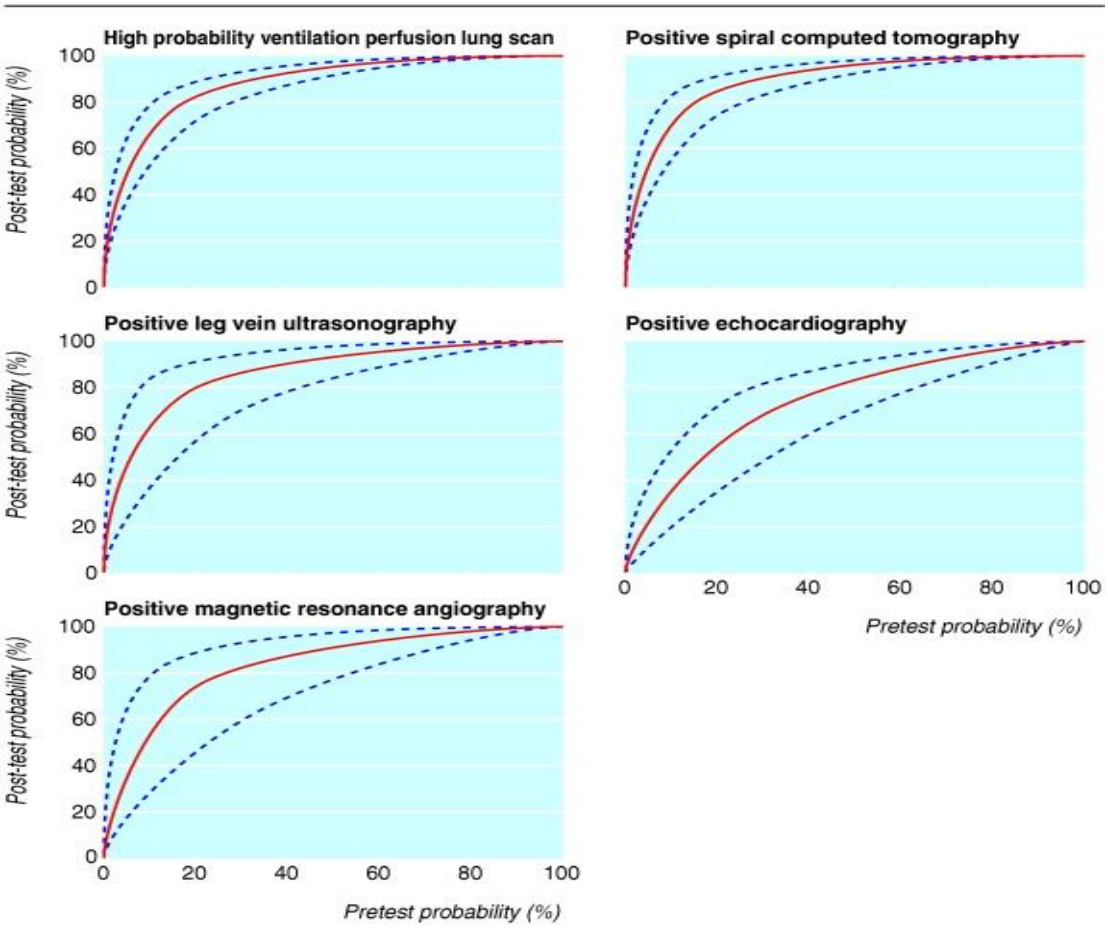

fig.1 Post-test probability according to pre-test probability and pooled values (solid line) or limits of 95% confidence intervals (broken lines) of the positive likelihood ratio[33]

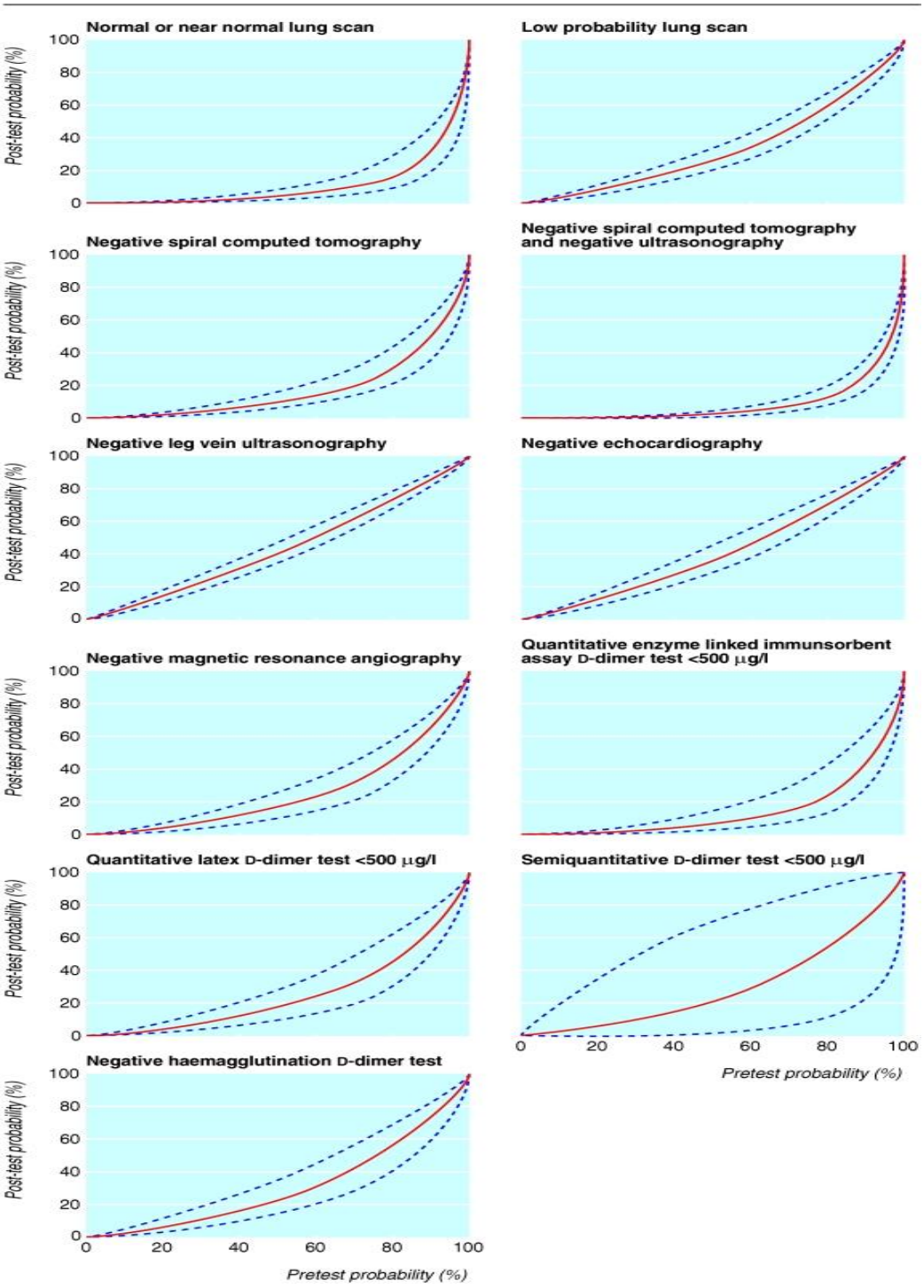

fig.2: Post-test probability according to pre-test probability and pooled values (solid line) or limit of 95% confidence intervals (broken lines) of the negative likelihood ratio[33]

Test D-Dimer assays for fast diagnosis of venous thromboembolism and pulmonary emoblism:

We identified four systematic reviews[24] evaluated the use of D-dimer testing alone (ie, without concomitant use of a clinical prediction rule) for diagnosis or exclusion of VTE. One of the systematic reviews included 11 studies evaluating enzyme-linked immunosorbent assays (ELISA) in 2,126 patients,[26] and the other included 9 studies evaluating latex turbidimetric assays in 1,901patients.[25] The methods in the 2 meta-analyses were similar, with inclusion of only studies that used defined reference standards to reduce reference standard bias. The authors pooled the results using random effects models, and plotted summary ROC curves. For both analyses, the authors used the test results as reported in the primary literature at a D-dimer cutoff of 500 ng/mL. The pooled sensitivity of the ELISA assays for diagnosing

pulmonary embolism was 95% (95% confidence interval [CI], 90%–98%) and the specificity was 45% (95% CI, 38%–52%). Latex turbidimetric assay results were similar with a sensitivity of 93% and specificity of 51%. The authors' ability to comment on subgroups was limited by having few studies. The D-dimer ELISA had higher specificity in patients without comorbidity than patients with comorbidity, but was less sensitive in that subgroup.

Two of these studies examined the use of D-dimer testing for excluding pulmonary embolism. These studies showed that both enzyme-linked immunosorbent assays (ELISA) and latex turbidimetric assays had a high sensitivity and a high negative predictive value for pulmonary embolism in patients with a low to moderate clinical probability of the disease (using a D-dimer cutoff of 500 ng/mL) [25,26]. Specificity decreased, however, for patients with associated comorbidity, older age, and longer duration of symptoms. Stein et al's meta-analysis of D-dimer assays for diagnosis of DVT or pulmonary embolism using ELISA found pooled specificities ranged from 40% to 50% [27].

We summarized this evidence that suggests a negative highly sensitive D-dimer test can help exclude the diagnosis of proximal DVT and pulmonary embolism in relatively healthy younger patients with short duration of symptoms that have a low pretest probability of VTE. There is variation in the sensitivity of D-dimer assays, however, and clinicians should be informed about the type of D-dimer assay used in their clinical setting relative to the population being tested and type of assay being used.

Helical Computed Axial tomography for diagnosis of Pulmunary emobolism:

The systematic reviews for use of helical CT in diagnosis of pulmonary embolism reported a wide range of summary sensitivities (66% to 93%) but a narrow range of summary specificities (89% to 98%) [29]. Inclusion criteria and reference standards varied across the different reviews, and heterogeneity was high across individual studies. Segal and colleagues performed their own systematic review including only prospective studies and those that uniformly applied pulmonary arteriography as the reference standard, and they confirmed the finding of wide variation in sensitivity (45% to 100%) and specificity (78% to 100%) [24].

Interpretation of this evidence is controversial because of such factors as substantial referral bias associated with the published evidence. More importantly, the literature has lagged behind rapid recent advances in CT technology. The authors of the EPC report estimate that for diagnosis of pulmonary embolism, helical CT has at best a sensitivity of 90% and specificity of 95% compared with conventional pulmonary arteriography. Data published after the EPC review was completed suggest that current-generation multidetector CT technology may offer significantly higher sensitivity and similar specificity to the technology assessed in the EPC review [30]. Even so, 2 recent systematic reviews conclude that helical CT alone may not be sufficiently sensitive to exclude pulmonary embolism in patients who have relatively high pretest probability [31,32].

4. CONCLUSION

Multiple studies have evaluated the diagnostic performance of the five diagnostic prediction models under study in a secondary (or tertiary) care setting. The failure rates observed in our validation study in primary care are largely in line with the previous studies regarding the performance of the Wells rules in combination with D-dimer testing. Moreover The accuracy of tests for suspected deep venous thrombosis and pulmonary embolism varies greatly, but it is possible to estimate the range of pretest probabilities over which each test or strategy can confirm or rule out pulmonary embolism.

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