Critical Review Form
Meta-analysis

Tamariz LJ, et al. Usefulness of Clinical Prediction Rules for the Diagnosis of Venous Thromboembolism: A Systematic Review. Am J Med 2004; 117: 676-684.

Objective: To review the available evidence regarding the diagnostic accuracy of clinical prediction rules in the diagnosis of deep venous thrombosis and pulmonary embolism. (p. 676).

Methods: Using the key words sensitivity, specificity, deep venous thrombosis, pulmonary embolism, and clinical, the authors searched the medical literature using MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Controlled Trials registry through January 2003. In addition, the retrieved articles' reference lists were reviewed and content experts were queried to identify additional literature. Articles were retrieved if they were in English, reported original data, and had the venous thromboembolism confirmed by appropriate reference standards. Additionally, the sample had to exceed 30 subjects and the CDR had to have been prospectively validated. Two authors reviewed the abstracts for inclusion criteria. Utilizing non-validated quality assessment forms modeled after the User's Guide to the Medical Literature, one author graded each study's overall quality, while a second confirmed the accuracy of the information transposed onto the data abstraction forms. 72 articles were identified and 23 met eligibility criteria. Of the 17 studies (representing 7122 patients) using CDR for DVT, 15 utilized Well's criteria.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes, to review the available evidence regarding the diagnostic accuracy of clinical prediction rules in the diagnosis of deep venous thrombosis and pulmonary embolism. (p. 676)
2.	Was the search for relevant studies details and exhaustive?	No. EMBASE, Science Citation Index, industry-sponsored trials, and annual meetings were all excluded as were all non-English articles.
3.	Were the primary studies of high methodological quality?	Using a User's Guide format which was not studied for internal or external validity or reproducibility, the evidence was assessed according to 5 criteria: study sample representativeness, bias or confounding variables, description of the prediction rule, test interpretation, and statistical quality. The studies, as graded by a single author, appeared to be of high quality by this grading method with overall means of studies across these 5 categories ranging from 63-93% (Table 3, p. 682).
4.	Were the assessments of the included studies reproducible?	No Kappa analysis was reported, so intra-rater and inter-rater reproducibility remains unknown. "Differences regarding either quality or content abstraction were resolved at face-to-face meetings." (p. 677)

II.	***What are the results?***	
1.	What are the overall results of the study?	The vast majority of high-quality studies using DVT clinical prediction rules use Well's model. The median LR+ for high pre-test probability patients was 6.62 (95% CI, 1.9-17.6—Table 1 p. 679-680). LR+ NOT useful for moderate or low probability patients. LR – not reported and unable to compute with given data. Area under the curve (AUC) better for proximal DVT and the summary model is 0.78. The AUC refers to the area under the receiver operator curve (ROC). The ROC is a plot of the true positives of a test (sensitivity on the y-axis) against the probability of a false positive result (1-specificity on the x-axis). The point where the curve is closest to the upper left corner (where it begins to slope off) represents the point where sensitivity and specificity are simultaneously optimized (and helps one chose a cut-off point for a test like Troponin < 0.1 of D-dimer < 0.22). Additionally, different tests can be compared to one another by AUC with the larger AUC representing the better test because it more reliably identifies the "true value".
2.	How precise are the results?	Likelihood ratio confidence intervals not very precise, but AUC CI's seem fairly tight.
3.	Were the results similar from study to study?	The majority of studies have LR+ 3-7 and LR-0.1-0.3 with similar AUC (0.74-0.87). The populations studied appear similar with incidence of DVT stratified by pre-test probability: High: 7-15% Moderate: 4-9% Low: 2-3% Of note, the documentation of confounding variables (DVT risk factors) is variable and poor.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	By recognizing that the best-evidence currently available supports the use of Well's criteria in assigning risk to a patient where DVT is a clinical possibility. While a low probability patient has 2-3% incidence of DVT and probably does not need further testing, a high probability patient has 7-15% incidence. Moderate and high probability patients probably merit further testing. A negative ELISA or new whole blood agglutination latex D-dimer may further decrease the LR- (and post-test probability).

2.	Were all patient important outcomes considered?	Most studies did not perform the Gold standard on ALL patients and some (Egermeyer) would argue that clinical follow-up alone is insufficient.
3.	Are the benefits worth the costs and potential risks?	Recognizing the limitations noted below, yes, use of Well's DVT clinical decision rule is better than empiric judgment alone.

Limitations

1. Most studies were conducted outside of the United States, but this should not limit their applicability.
2. Results of this systematic review cannot be extrapolated to high-risk populations (hypercoaguable disorder, malignancy, etc.), as these were not documented in various studies.
3. The article review forms utilized were not validated.
4. Search strategy reproducibility uncertain (no Kappa analysis).
5. Possible spectrum bias (most studies recruited patients referred for further evaluation).
6. "Most studies did not have two independent observers applying the clinical prediction rules to the study subjects, lacked blinded interpretations of the reference test, or lacked independent observers interpreting the reference test." (p. 678)

Bottom Line

For the first-time diagnosis of DVT in the general population, use of Well's criteria provides a standardized, validated method to estimate the pre-test probability of DVT in a variety of clinical settings. Well's CDR is more meaningful if negative and performs better for proximal DVT than for distal DVT. D-dimer assays may enhance the negative predictive value of a low-risk subject by Well's criteria.