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META-ANALYSIS
Thrombosis and antithrombotic treatment

Diagnostic management of acute pulmonary embolism: a prediction model based on a patient data meta-analysis

Nick van Es [1,2*†], Toshihiko Takada[3,4†], Noémie Kraaijpoel[1,2], Frederikus A. Klok[5], Milou A. M. Stals[5], Harry R. Büller[1,2], D. Mark Courtney[6], Yonathan Freund[7], Javier Galipienzo[8], Grégoire Le Gal[9], Waleed Ghanima[10,11], Menno V. Huisman[5], Jeffrey A. Kline[12], Karel G.M. Moons[3], Sameer Parpia[13,14], Arnaud Perrier[15], Marc Righini[15], Helia Robert-Ebadi[15], Pierre-Marie Roy [16], Phil S. Wells[9], Kerstin de Wit[17,18,19], Maarten van Smeden [3‡], and Geert-Jan Geersing[3‡]

Background

- The diagnostic management of pulmonary embolism (PE) is a challenge faced by physicians in emergency rooms, outpatient clinics, and hospital wards, because signs and symptoms of PE are non-specific.
- The use of a diagnostic algorithm based on a clinical decision rule, consisting of medical history and physical examination findings, combined with D-dimer testing is recommended in patients with clinically suspected PE to exclude the disease and thereby reduce the need for CT scans.
- Nonetheless, up to 50% to 70% of patients with suspected PE with non-low clinical probability and elevated D-dimer levels are referred for imaging, and PE is not diagnosed in about 70% of them.

AIM of the study

To develop a clinical prediction model that provides an individualized, accurate probability estimate for the presence of acute PE in patients with suspected disease based on readily available clinical items and D-dimer concentrations.

Methods

- An individual patient data meta-analysis was performed based on sixteen cross-sectional or prospective studies with data from 28305 adult patients with clinically suspected PE from various clinical settings, including primary care, emergency care, hospitalized and nursing home patients.
- The outcome for the prediction model was a diagnosis of PE confirmed by imaging at baseline or venous thromboembolism during 30 to 90 day follow-up.
- Deaths adjudicated as fatal PE during the follow-up period in the original studies were also included in the outcome.

Results (I)

- Candidate diagnostic predictors were selected *a priori* based on their previously established associations with PE presence or absence in the literature.
- The following variables measured at baseline, without knowledge of the outcome, were considered as candidate predictors:

  - age (in years)
  - sex
  - previous VTE
  - recent surgery or immobilization
  - haemoptysis
  - cancer
  - clinical signs of DVT
  - inpatient status
  - D-dimer level (in μg/L).

Results (II)

- Since D-dimer levels are known to have a lower specificity in elderly patients, an interaction term for age and D-dimer was included as a candidate predictor.
- A web calculator of the model is available online (https://pred model.shinyapps.io/App_IPD_PE).
- The model consistently showed discrimination performance across all validation studies with a pooled c-statistic of 0.87 (95% CI, 0.85–0.89; 95% PI, 0.77–0.93). Overall calibration performance was also excellent.
- Individualized probability estimates of the present model were comparable to safety and efficiency of the currently used algorithms.
- Among patients where PE was considered excluded based upon the existing algorithms, the proportion of patients with an estimated (conditional) probability ≥2% based on the new model was 28% in the group in whom PE was considered excluded based on age-adjusted D-dimer testing and 44% among those in whom PE was considered excluded based clinical probability-adjusted D-dimer testing.

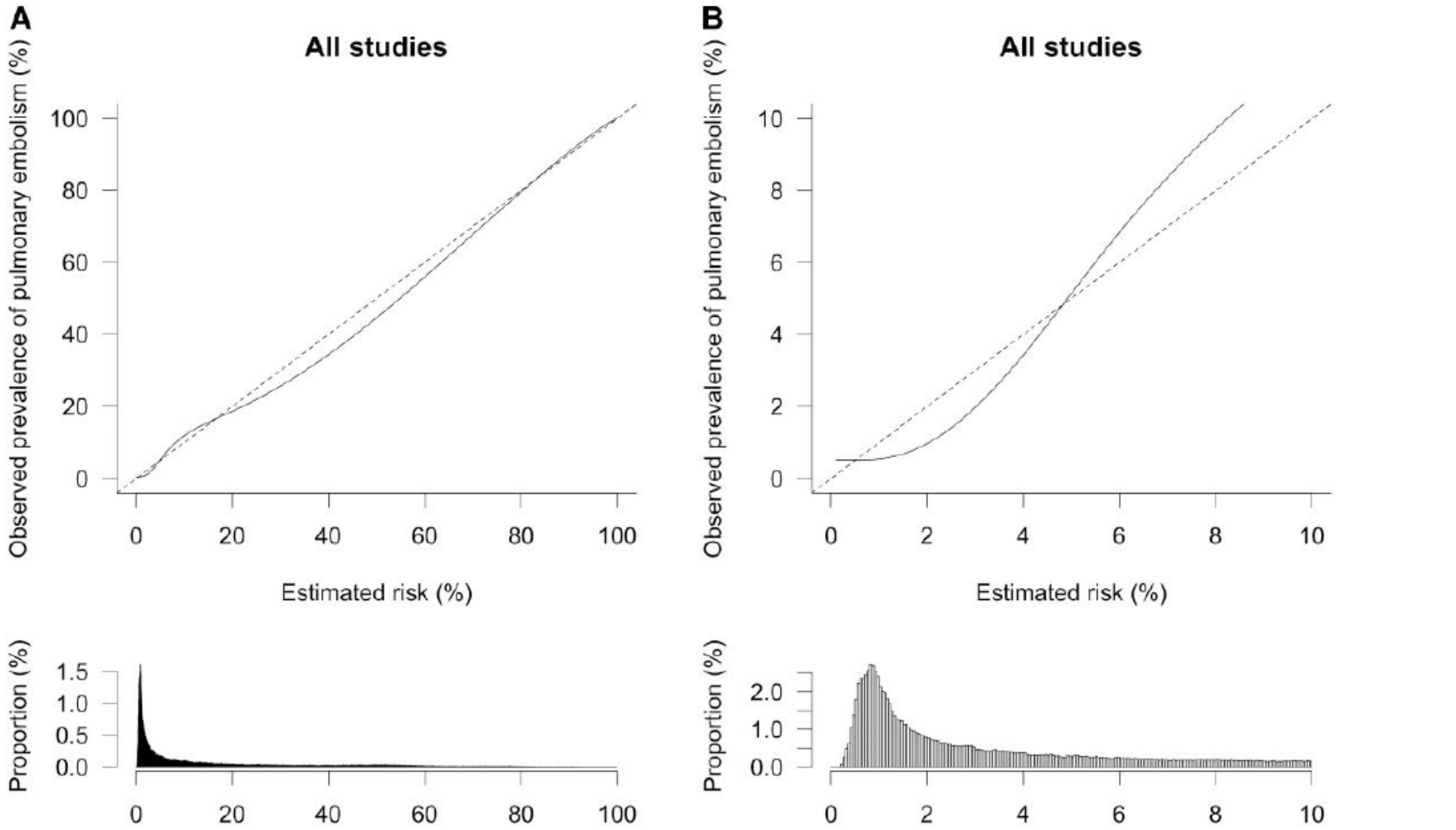

Figure 1 (*A*) Overall calibration of the new model. The dashed line indicates a situation of perfect calibration. The solid line reflects the actual correlation between estimated probabilities and observed prevalence of pulmonary embolism. The histogram below the plot shows the distribution of estimated probabilities in the study population. (*B*) Overall calibration of the new model for estimated risks between 0–10%. The dashed line indicates a situation of perfect calibration. The solid line reflects the actual correlation between estimated probabilities and observed prevalence of pulmonary embolism. Histogram below the plot shows distribution of estimated probabilities in the study population.

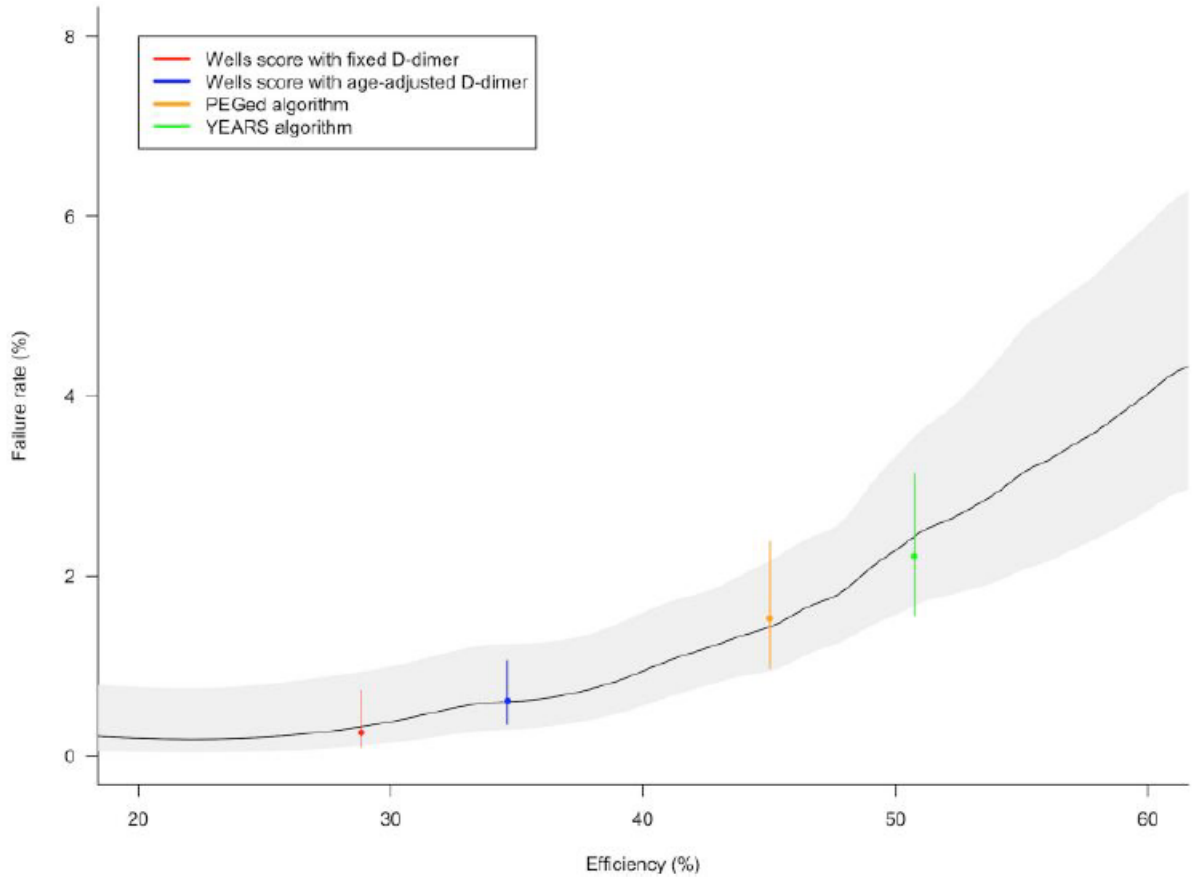

Figure 2 Efficiency and safety of currently used algorithms compared with the new model. Efficiency (x-axis) and failure rate (y-axis) of current diagnostic algorithms are plotted with 95% confidence intervals (dots with bars). The solid line shows the potential efficiency and safety of the new model based over the range of estimated probabilities, with the shaded area showing the 95% confidence intervals.

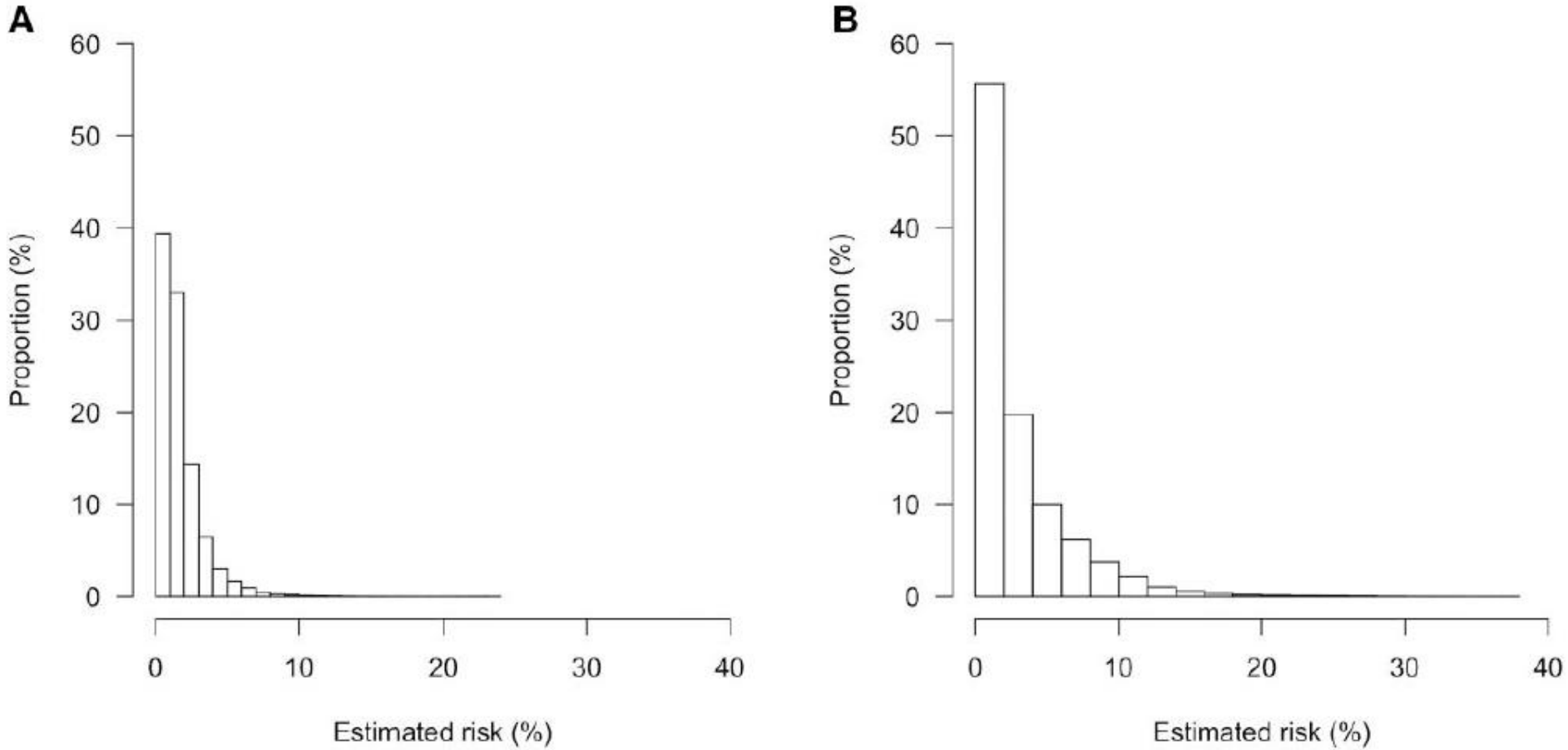

Figure 3 Distribution of risk estimated by the new model in patients categorized as 'pulmonary embolism excluded' based on the Wells score with D-dimer testing using the age-adjusted threshold (*panel A*) or a threshold based on clinical pretest probability (*panel B*).

Conclusions (I)

- The present model provides an absolute, individualized probability of PE presence in a broad population of patients with suspected PE, with very good discrimination and calibration.
- The new model identifies a substantial proportion of patients with a high individual PE probability (above the currently accepted ‘safe’ 2%) among patients classified as ‘imaging not indicated’ by current diagnostic algorithms.
- The new model does not include any subjective clinical items, incorporates D-dimer concentration as continuous variable (which is more informative than a dichotomized test result), and may perform better across subgroups and healthcare settings, possibly in part due to the interaction term age and D-dimer.

Conclusions (II)

- The new model allows for flexible probability estimation by varying the safety probability threshold, which permits physicians to tailor the interpretation of the model to their own clinical setting.
- This diagnostic clinical prediction model provides an individualized probability of pulmonary embolism in patients with suspected disease, which can be used as an alternative to traditional algorithms to guide decision about the need for imaging.
- Before it can be adopted in practice, its clinical utility should be evaluated in a prospective management study in which imaging is withheld based on the probability estimated by the model.