Cover Page

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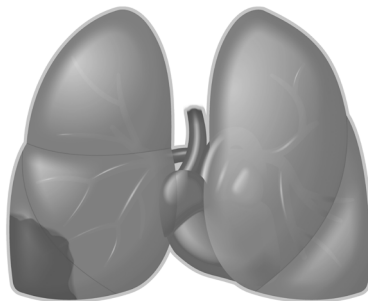**Title**: A more granular view on pulmonary embolism
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Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism

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ABSTRACT

Introduction

The simplified revised Geneva score is a fully standardized clinical decision rule (CDR) in the diagnostic work-up of patients with suspected pulmonary embolism (PE). The individual weights of the CDR variables are difficult to memorize and could lead to miscalculations in an acute setting. We have validated a simplified version of the revised Geneva score.

Methods

Patients from 2 large prospective diagnostic trials were analyzed. The simplified CDR was constructed by awarding one point for all items of the original CDR. Diagnostic accuracy of the simplified CDR was compared to the original CDR by comparing the AUC of ROC analysis. Further, clinical utility of the simplified CDR was studied by assessing the safety of ruling out PE on the basis of either a low-, intermediate- (in case of trichotomized outcome), or an unlikely (in case of dichotomized outcome) clinical probability in combination with a normal highly sensitive D-dimer test.

Results

The diagnostic accuracy between the two CDR's did not differ (AUC 0.75 {95%CI 0.71-0.78} vs 0.74 {0.70-0.77}). After 3 months of follow-up, no patients with a combination of either a low- (0%; 95%CI 0.0-1.6), intermediate- (0%; 0.0-2.6), or an unlikely (0%; 0.0-1.1) clinical probability using the simplified score and a normal D-dimer test was diagnosed with VTE.

Conclusions

This study shows that simplification of the revised Geneva score does not lead to a decrease in diagnostic accuracy and clinical utility. Prospective outcome studies are needed to confirm these findings.

INTRODUCTION

A clinical decision rule (CDR) can be defined as a clinical tool containing variables obtained from history, physical examination and simple diagnostic tests quantifying likelihood for diagnosis, prognosis or likely response to treatment in an individual patient.[1] Pulmonary embolism (PE) is clinically suspected in many patients with respiratory or chest complaints because of the non-specific nature of the presenting signs and symptoms. Nevertheless, the prevalence of PE in this population is relatively low. Several CDR's to assist the clinician diagnostic decision making have been developed.[2] Correct implementation of CDR's in diagnostic strategies have been proved to decrease the need for expensive, time consuming and invasive diagnostic imaging procedures, whereas the venous thromboembolism failure rate in patients in whom anticoagulant treatment is withheld, is acceptably low.[3-5]

   Although two CDR's for the pretest probability of PE have been extensively validated, i.e. the Wells rule and the Geneva score,[6,7] both have practical limitations.[7-10] A fully standardized rule, the revised Geneva score, has been developed and validated recently.[9,10] The revised Geneva score is independent from physicians' implicit judgment, which makes this CDR objective and easily reproducible.[10] The score consists of 9 different variables with diverse individual weights (Table 1). It could be reasoned that these diverse individual weights of the variables in the CDR's are difficult to memorize and this could lead to miscalculations in acute patient care. Therefore, we hypothesized that we could simplify the revised Geneva score by awarding one point for all variables (Table 1) in two large patients cohorts in which the revised Geneva score was assessed.[3,4] Subsequently, we compared diagnostic accuracy and clinical utility of the simplified revised Geneva score and the original revised Geneva score.

Table 1. Simplification of the revised Geneva score.

Variable	Original	Simplified
Age >65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within 1 month	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate 74-94 beats/min	3	1
Heart rate ≥95 beats/min*	5	1
Pain on lower limb deep vein palpation and unilateral edema	4	1

*By the original score, patients are awarded 0 points (heart beat <74 beats/min), 3 points (heart rate 74-94 beats/min) or 5 points (heart rate ≥95 beats/min); by the simplified score, patients are awarded 1 point if the heart rate exceeds 73 beats/min and one additional point (2 points in total) if the heart rate exceeds 94 beats/min. DVT: deep vein thrombosis, PE: pulmonary embolism.

MATERIAL AND METHODS

Patients

Data of two large prospective diagnostic trials were used and combined for the validation of the simplified revised Geneva score.[3,4] In the first trial consecutive patients with suspected PE, presented to the emergency department of 3 teaching hospitals (Geneva University Hospital; Angers University Hospital; and Hôpital Européen Georges-Pompidou, Paris, France) between September 2002 and October 2003, were eligible for inclusion.[3] Further we will refer to this as study A. In all patients, the Geneva score[7] was assessed. In patients with either a low or intermediate probability, plasma D-dimer levels (VIDAS, Biomerieux) were measured. Pulmonary embolism was ruled out in patients with a level below the cutoff value of 500 ng/l. Patients with a D-dimer level >500 ng/l with high clinical probability underwent proximal venous-compression ultrasonography of the lower limbs and multidetector-row computed tomography (CT). Patients with a CT that was positive for pulmonary embolism or ultrasonography that showed a deep venous thrombosis received anticoagulant treatment, where such therapy was withheld in patients in whom both tests were negative.

In the second study, the clinical effectiveness of a simplified algorithm using the dichotomized Wells rule, D-dimer testing, and CT in patients with suspected pulmonary embolism was evaluated.[4] A random set of patients referred to the Leiden Medical University Hospital (Netherlands) were taken for the present study. We will refer to this as study B. If the diagnosis of PE was unlikely (Wells score ≤ 4) in combination with a normal quantitative (VIDAS) D-dimer test result, PE was considered to be excluded. When the Wells score was 4 or less in combination with increased D-dimer (> 500 ng/l) or when the diagnosis of PE was likely (Wells score > 4), then the diagnosis of PE was confirmed with multi-detector spiral CT-scanning.

Patients of both studies were followed up for 3 months. Both studies were approved by the ethics committees of all participating hospitals and all patients provided written informed consent before they were enrolled.

In study A, D-dimer testing was part of the diagnostic work-up of all patients with either a low or intermediate probability with the Geneva Score.[7] In study B, D-dimer tests were only performed in patients with a Wells rule of 4 points or less. This resulted in missing D-dimer data for 69 patients in the low- and intermediate probability and for 29 patients in the unlikely clinical probability group as assessed by the simplified revised Geneva score.

Assessment of the revised Geneva score

In study A[3], the data collection form was identical to that used in the derivation study of the revised Geneva score, allowing retrospective calculation of the simplified revised Geneva score for each patient. In study B,[4] the Wells rule was used for assessing clinical

probability. The revised Geneva score comprises four variables not included in the Wells rule: age over 65 years, unilateral lower-limb pain, heart rate 75-94 beats per minute or more than 94 beats per minute, and pain on lower-limb deep venous palpation and unilateral edema. These items were abstracted from the patient charts after masking the final diagnosis. Values for each item were scored on the day of inclusion.[10]

In the simplified revised Geneva score, all variables were given one point if present (Table 1). In addition, contrary to the original score, where scores of either 0, 3 or 5 points for heart rate were given, in the simplified score 0 points was awarded to a heart rate under 75 beats per minute, one point was awarded to patients with a heart rate with 75 beats or more and one additional point was awarded to all patients with a heart rate of more than 94 beats per minute.

Data analysis

Patient characteristics and study outcomes of both studies were combined in one database. Optimal cut-off points (both dichotomized and trichotomized) of the simplified revised Geneva score scores were calculated by comparing the area under curve (AUC) in ROC analyses. Accuracy of the simplified revised Geneva score and the revised Geneva score was compared by comparison of the AUC in ROC analyses. We studied the clinical course of patients with a normal D-dimer result in different clinical probability categories using the simplified revised Geneva score. Statistical analysis was performed by using SPSS software (SPSS for windows 14.0.2, Inc. 1989-2005). P-values of <0.05 were considered statistically significant.

RESULTS

Study A comprised of 756 patients. They had a mean (±SD) age of 60±19 years, 60 percent were female. All patients were outpatients. The overall prevalence of pulmonary embolism in this cohort was 26%. However, due to missing values mainly for heart rate, the revised Geneva score could not be computed in seven patients, leaving 749 for the present analysis. Three hundred patients of study B with suspected PE were included in the present study. These patients were 47±16 years old at time of diagnosis, 60% were female and 96% were outpatients. The overall prevalence of PE was 16%. Taken as a whole, the complete validation population of the simplified revised Geneva score consisted of 1049 patients.

The optimal margin of low-, intermediate and high probability groups was set at 0-1, 2-4 and 5-9 points (Table 2, Figure 1). Using these cut-off points, 378 patients were assigned to the low clinical probability (0-1 points, 36% of total population, 7.7% PE {95% confidence interval 5.2-11%}), 629 patients to the intermediate clinical probability (2-4 points, 60% of total population, 29% PE {95% CI 26-33%}) and 42 patients to the

Table 2. Score application in the study population, percentage with PE, and proportions of the population in the 3-level and 2-level clinical probability categories.

	Three-level scheme			Two-level scheme	
	Low	Intermediate	High	PE unlikely	PE likely
Number	378	629	42	681	368
% population	36	60	4.0	65	35
% PE	7.7	29	64	13	42

PE: pulmonary embolism.

high clinical probability category (5-9 points, 4% of total population, 64% PE {95% CI 48-78%}). The optimal margin for dichotomization of the rule was set at 0-2 and 3-9 points (Table 2); 681 patients were designated PE unlikely (0-2 points, 65% of total population, 13% PE {95% CI 11-16}) and 368 patients were designated PE likely (3-9 points, 35% of total population, 42% PE {95% CI 36-47}). Flowcharts of both dichotomized and the trichotomized study outcome are shown in Figure 2 and 3.

We compared the AUC in the ROC curve for the revised Geneva score and simplified revised Geneva score (Figure 1a and b). The AUC of the continuous prediction rules was 0.75 (95%CI 0.71-0.78) for the revised Geneva score and 0.74 (95%CI 0.70-0.77) for the simplified revised Geneva score. The AUC of the categorized rules was 0.70 (95%CI 0.66-0.74) for the revised Geneva score and 0.68 (95%CI 0.64-0.72) for the simplified revised Geneva score.

Finally, we studied the clinical utility of the simplified revised Geneva score. After 3-month follow up in the combined patient population, no patient with a low (0%; 95%CI 0.0-1.6) or intermediate (0%; 95%CI 0.0-2.6) clinical probability score by the simplified revised Geneva score and a normal D-dimer result at inclusion was subsequently diagnosed with venous thromboembolism (Figure 2). Even so, in case of dichotomous outcome, no patient with an unlikely clinical probability (0%; 95%CI 0.0-1.1) was subsequently diagnosed with venous thromboembolism after the 3-month follow-up period (Figure 3).
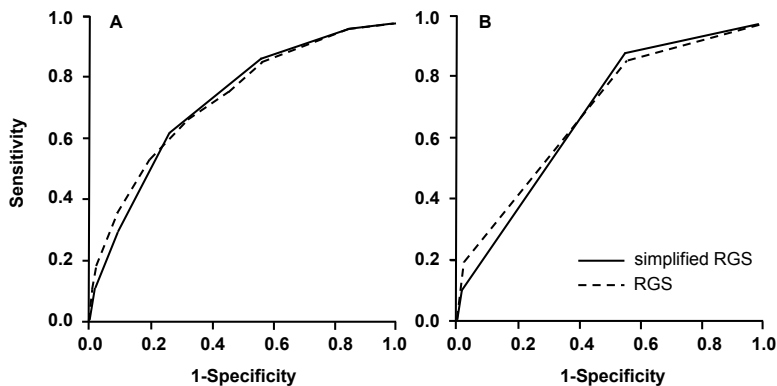
Figure 1A and 1B. Receiver operating characteristic curves of the continuous revised Geneva score (RGS) and simplified RGS (A) and 3-level categorized RGS and simplified RGS (B).
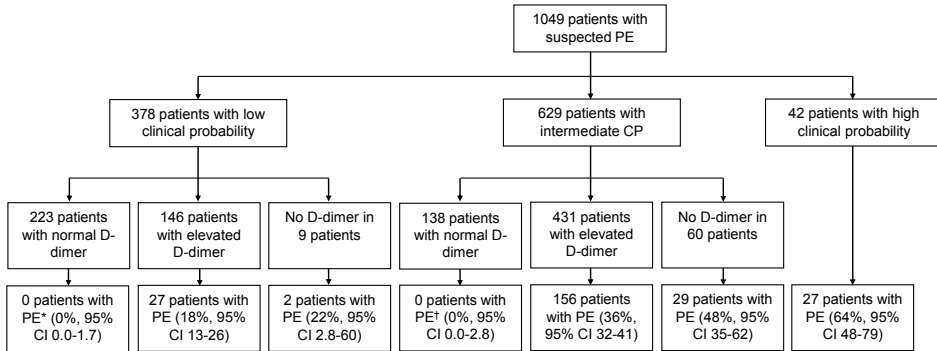
Figure 2. Flowchart of patients showing outcomes by 3-level simplified revised Geneva score. †One patient was lost to follow-up and 3 patients were treated with anticoagulant therapy for other reasons than pulmonary embolism (PE). §One patient was lost to follow-up and 7 patients were treated with anticoagulant therapy for other reasons than PE. CI: confidence interval; CP: clinical probability.
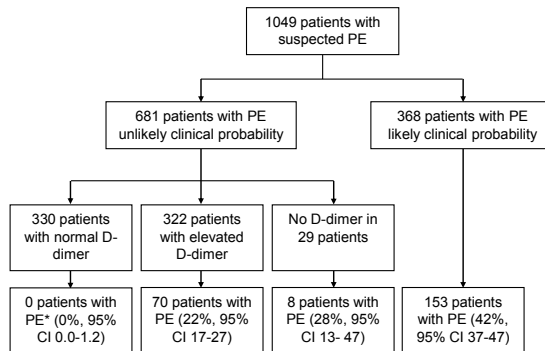

Figure 3. Flowchart of patients showing outcomes with dichotomous use of simplified revised Geneva score. †Two patients were lost to follow-up and 10 patients were treated with anticoagulant therapy for other reasons than pulmonary embolism (PE). CI: confidence interval.

DISCUSSION

This study shows that a simplification of the revised Geneva score doesn't decrease the diagnostic accuracy of the rule The distribution of the patient proportions by the simplified revised Geneva score in both trichotomized and dichotomized categories and the prevalence of PE in these categories were well comparable to those of the original revised Geneva score[9] as well as to two other validated and widely used CDR's, the Wells rule[4,6] and the Geneva score.[7] The simplified revised Geneva score remained to have great clinical utility because a combination of a low, intermediate or unlikely clinical probability with a normal D-dimer test result had low venous thromboembolism failure rates. Moreover, this simplified score has two potential advantages over the original revised Geneva score, i.e. clinicians will have less trouble memorizing and remembering the score and the final sum of the score is easier to calculate.

Several studies have shown D-dimer assays to have a high negative predictive value and to be a sensitive but nonspecific marker of PE.[14] However, different sensitivity for several D-dimer assays has been described in the literature.[2,14-16] In case of decreased sensitivity, the negative predictive value will be reduced. Also, the negative predictive value of a combined low clinical probability and a normal D-dimer test diminishes as disease prevalence rises.[14] Consequently, the sub-population of patients with suspected PE in which D-dimer testing is safe to exclude PE, is dependent on prevalence of disease and sensitivity of the D-dimer assay. In the present study, a highly sensitive quantitative D-dimer assay with a reported sensitivity of 95-98% was used.[2] For this reason, the dichotomized outcome of this CDR could be used safely. When a physician using the simplified revised Geneva score to assess pretest probability in patients with suspected PE has only availability over a D-dimer assay with a lower sensibility, he could decide to use the trichotomized outcome and perform D-dimer tests only in case of low clinical pretest probability to exclude PE.

Simplification of the score did not decrease the AUC of the ROC. One rationale for this could be differences in tested patient populations.[12] This phenomenon could also have been caused by statistical instability and overfitting of the multivariate Model.[12,13] Instability of multivariate models is caused by dependency of the variables selected as predictors in a clinical model on what other variables are used.[12] Overfitting is a concept related to regression to the mean.[13]

This study requires several comments. First, we performed a retrospective analysis. Nonetheless, consecutive patients were included and they were followed prospectively. In addition, both study A and B report a minimal loss to follow-up, being respectively 0.5 and 0.1%. In all study patients, the simplified revised Geneva score was easily calculated and our study organization could not have lead to selective inclusion of patients. Second, data of patients of two large trials were combined for this analysis. There were some differences in general characteristics between both study populations, i.e. mean age and prevalence of PE. However, the prevalence of PE according to the number of points in the simplified revised Geneva score was similar in the two groups (data not shown). For this reason, we don't believe that the differences in patient characteristics have influenced our conclusions. Finally, by study design, D-dimer results were not available for all patients. Data were missing in 9 (2.4%) patients with low, in 60 (9.5%) patients with intermediate and in 29 (4.3%) patients with unlikely clinical probability.

In summary, we have shown that simplification of the revised Geneva score doesn't decrease the score's diagnostic accuracy and clinical utility. Prospective outcome studies are however needed to confirm our findings.

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