

Prediction scores do not correlate with clinically adjudicated categories of pulmonary embolism in critically ill patients

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BACKGROUND: Prediction scores for pretest probability of pulmonary embolism (PE) validated in outpatient settings are occasionally used in the intensive care unit (ICU).

OBJECTIVE: To evaluate the correlation of Geneva and Wells scores with adjudicated categories of PE in ICU patients.

METHODS: In a randomized trial of thromboprophylaxis, patients with suspected PE were adjudicated as possible, probable or definite PE. Data were then retrospectively abstracted for the Geneva Diagnostic PE score, Wells, Modified Wells and Simplified Wells Diagnostic scores. The chance-corrected agreement between adjudicated categories and each score was calculated. ANOVA was used to compare values across the three adjudicated PE categories.

RESULTS: Among 70 patients with suspected PE, agreement was poor between adjudicated categories and Geneva pretest probabilities (kappa=0.01 [95% CI -0.0643 to 0.0941]) or Wells pretest probabilities (kappa=-0.03 [95% CI -0.1462 to 0.0914]). Among four possible, 16 probable and 50 definite PEs, there were no significant differences in Geneva scores (possible = 4.0, probable = 4.7, definite = 4.5; P=0.90), Wells scores (possible = 2.8, probable = 4.9, definite = 4.1; P=0.37), Modified Wells (possible = 2.0, probable = 3.4, definite = 2.9; P=0.34) or Simplified Wells (possible = 1.8, probable = 2.8, definite = 2.4; P=0.30).

CONCLUSIONS: Pretest probability scores developed outside the ICU do not correlate with adjudicated PE categories in critically ill patients. Research is needed to develop prediction scores for this population.

Key Words: Intensive care unit; Prediction models; Pulmonary embolism

Pulmonary embolism (PE) is a common complication in critical illness (1), with a mortality rate of up to 25% (2). Although PE has potentially serious consequences, it is often unrecognized in critically ill patients. Left undiagnosed, PE in critically ill patients who have impaired cardiopulmonary reserve may experience catastrophic consequences (3). In a 25-year longitudinal study, 9% of hospital patients had PE at autopsy and, in 84% of these, the diagnosis was missed

Les indices de prédiction ne sont pas corrélés avec les catégories cliniques d'embolie pulmonaire des patients gravement malades

HISTORIQUE : Les indices de prédiction d'embolie pulmonaire (EP) validés en consultations externes avant le test sont parfois utilisés à l'unité de soins intensifs (USI).

OBJECTIF : Évaluer la corrélation des indices de Geneva et de Wells avec des catégories d'EP attribuées aux patients de l'USI.

MÉTHODOLOGIE : Dans un essai aléatoire de thromboprophylaxie, les patients ayant une EP présumée ont été classés entre une EP possible, probable ou définitive. Les chercheurs ont ensuite rétrospectivement extrait les données pour déterminer l'indice diagnostique d'EP de Geneva et les indices diagnostiques de Wells, de Wells modifié et de Wells simplifié. Ils ont calculé le consensus corrigé en fonction du hasard entre les catégories et chaque indice. Ils ont utilisé l'analyse de variance pour comparer les valeurs entre les trois catégories d'EP.

RÉSULTATS : Chez les 70 patients ayant une EP présumée, on observait peu de consensus entre les catégories et les probabilités de Geneva avant le test (kappa=0,01 [95 % IC -0,0643 à 0,0941]) ou les probabilités de Wells avant le test (kappa=-0,03 [95 % IC -0,1462 à 0,0914]). Entre les quatre EP possibles, les 16 probables et les 50 définitives, les chercheurs n'ont remarqué aucune différence significative des indices de Geneva (possible = 4,0, probable = 4,7, définitive = 4,5; P=0,90), des indices de Wells (possible = 2,8, probable = 4,9, définitive = 4,1; P=0,37), de Wells modifié (possible = 2,0, probable = 3,4, définitive = 2,9; P=0,34) ou de Wells simplifié (possible = 1,8, probable = 2,8, définitive = 2,4; P=0,30).

CONCLUSION : Les indices de probabilité avant le test élaborés à l'extérieur de l'USI ne sont pas corrélés avec les catégories d'EP des patients gravement malades. Des recherches s'imposent pour élaborer des indices de prédiction au sein de cette population.

before death (4,5). Even in critically ill patients, PE remains one of the most common unsuspected autopsy findings (6).

PE is particularly difficult to diagnose in critically ill patients. Diagnosis requires a high index of clinical suspicion (7,8) because critically ill patients are usually unable to communicate their symptoms due to their underlying condition, pharmacotherapy and mechanical ventilation. In addition, signs and symptoms, such as dyspnea,

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tachycardia, hypoxemia and hypotension, which are suggestive of PE in nonintensive care unit (ICU) settings, are considerably more common in the ICU setting and attributable to many other factors. Tests that may be suggestive of physiological alterations compatible with PE (eg, decreased oxygen saturation, increased plasma troponin concentration) are often nonspecifically abnormal in critically ill patients.

Clinical decision rules (9-13) are used in medicine to provide pretest probabilities and guide decision making. Due to the silent nature of some PEs (14), simple, objective diagnostic scoring systems could be helpful in diagnosing PE. These prediction scores are often detailed in the chart or used in conversation with the ICU team because they are the only scores developed for PE. These scores have utility in patient populations in which they were developed and validated, in addition to other patient groups. Although these PE scores have been developed and tested in the emergency department, they have not been validated in the ICU setting. We aimed to establish whether these PE scores have discriminative power in the critically ill population. The objective of the present study was to evaluate whether two diagnostic PE scores – the Geneva and Wells scores – were useful in distinguishing critically ill patients who had possible, probable or definite PE according to clinical adjudication.

METHODS

The present preplanned study was conducted using the database from a recent international trial (Prophylaxis of Thromboembolism in Critical Care [PROTECT]; Clinicaltrials.gov number: NCT00182143) that compared the low-molecular weight heparin (LMWH) dalteparin, and unfractionated heparin (UFH) for thromboprophylaxis in 3746 medical-surgical ICU patients (15). The study was conceived as a project under the 'PE-METRICS' program, which was designed to use the infrastructure of the PROTECT trial to understand the methodology, epidemiology and treatment of PE in critically ill patients. The PE-METRICS grant was submitted while PROTECT was enrolling patients to conduct work related to PE after the main publication. This was a peer-review, funded research program. Ethics approval was obtained as part of the PROTECT publication.

In PROTECT, patients were routinely screened with twice-weekly compression ultrasound for proximal leg deep vein thrombosis (DVT). However, PE detection did not involve screening. Patients who developed suspected PE were investigated and managed by the local ICU team using a predetermined diagnostic algorithm. First, these patients underwent bilateral leg ultrasound. Then, chest computed tomography pulmonary angiogram was performed in the 70 patients who did not have contraindications to this procedure. Thereafter, four members of a central adjudication committee (DC, MM, SM and RH) each independently adjudicated, using trial forms and the patient's chart, all cases of suspected PE. Adjudicators resolved disagreements by consensus. PE events were adjudicated as possible, probable or definite, and are defined in Table 1. Definite PE was defined by a clearly positive test (such as characteristic intraluminal filling defect on chest computed tomography or high-probability ventilation-perfusion scan). Probable PE was defined by a high clinical suspicion (moderate or high pretest probability) and either a nondiagnostic test for PE or no test for PE. Possible PE was defined as low clinical suspicion (low pretest probability) and a nondiagnostic test for PE. 'No test for PE' is not part of the definition of a possible PE because the clinical concern had to be sufficient to order a test unless the patient was moribund or preterminal. 'No PE' was defined as either no test for PE or a clearly negative test for PE. A nondiagnostic test was defined as an inconclusive test for PE and did not include negative tests (15). In the present study, patients who had clinically suspected prevalent PE (diagnosed within 72 h of ICU admission) or incident PE (diagnosed >72 h following ICU admission) were included.

Geneva and Wells scores

Appendix Tables 1 to 4 summarize the four scoring systems (9-13) used in the present study. The maximum Geneva score of 16 corresponds to a pretest probability of 81%; a score of ≤ 4 corresponds to a pretest

TABLE 1
Definitions of pulmonary embolism (PE) adjudication categories

PE category	Definition
Possible	Possible PE was defined as low clinical suspicion (low pretest probability) and a nondiagnostic test for PE. 'No test for PE' is not part of the definition of a possible PE because the clinical concern had to be sufficient to order a test unless the patient was moribund or preterminal
Probable	Probable PE was defined by a high clinical suspicion (moderate or high pretest probability by the adjudication committee) and either a nondiagnostic test for PE or no test for PE
Definite	Definite PE was defined by a positive test (such as characteristic intraluminal filling defect on computed tomography pulmonary angiogram or high probability ventilation-perfusion scan)

PE adjudication categories used by adjudication committee defined in the Prophylaxis of Thromboembolism in Critical Care (PROTECT) Trial (15)

probability of 10.3% (9,11). The Wells PE Diagnostic score has a maximum score of 12.5, which corresponds to a pretest probability of 40.6%; a score of ≤ 4 corresponds to a pretest probability of <7.8% (10). The Modified Wells PE Diagnostic score (13) has a maximum score of 9; a score of ≤ 4 corresponds to a pretest probability of 6% and a score of >4 corresponds to a pretest probability of 78%. The Simplified Wells PE Diagnostic score (12) has a maximum score of 7, which corresponds to a pretest probability of 62%; the minimum score of 1 corresponds to a pretest probability of 12%.

Pilot exercise

A pilot exercise was conducted to examine and optimize interobserver rater agreement in preparation for the full study. In duplicate and independently, two research personnel (CK and MD) retrospectively abstracted data relevant to the scoring systems from medical records in a computerized ICU clinical information system (CareVue, Philips Inc, USA), written clinical notes, laboratory and other test results from the day that PE was suspected (within 12 h). Using pretested forms and an implementation manual, the two blinded raters abstracted data regarding signs and symptoms of PE, and data to calculate diagnostic score in a reliability and calibration exercise on one trial patient; subsequently, two blinded raters abstracted 18 items (six symptoms, eight signs, two tests and two scores) from the medical records of four trial patients. These individual variables were defined as per previous studies (16): six symptoms (dyspnea, pleuritic chest pain, substernal chest pain, cough, hemoptysis and syncope), eight signs (fever >38°C, tachypnea with respiratory rate >30 breaths/min, tachycardia [heart rate >100 beats/min], hypotension [systolic blood pressure <100 mmHg], central cyanosis, oxygen saturation <90%, physical signs of DVT such as calf pain, unilateral calf swelling or pain on flexion, and cardiopulmonary arrest) and two test results (arterial partial pressure of oxygen and echocardiographic findings of right heart strain). Data were also abstracted to calculate the Geneva Diagnostic score and the original Wells score. Chance-corrected agreement (using the original interpretation by Fleiss [17]) was calculated between two raters' measures of each dichotomous variable and each score.

Chance-corrected agreement values on the initial pilot exercise for symptoms were: dyspnea $\kappa=0.82$, pleuritic chest pain $\kappa=0.97$, substernal chest pain $\kappa=0.90$, cough $\kappa=0.85$, syncope $\kappa=0.85$; for signs: fever $\kappa=0.71$, tachypnea $\kappa=0.78$, tachycardia $\kappa=0.60$, hypotension $\kappa=0.95$, hemoptysis $\kappa=0.85$, cyanosis $\kappa=0.59$, desaturation $\kappa=0.91$, physical signs of DVT $\kappa=0.87$, cardiopulmonary arrest $\kappa=0.88$; and for test results: arterial blood gas PO_2 $\kappa=0.70$, echocardiographic signs of right heart strain $\kappa=0.90$. For PE diagnostic scores, agreement was: Geneva diagnostic score $\kappa=0.53$, original Wells score $\kappa=0.71$ (Table 2).

TABLE 2
Pilot study: Agreement scores

Symptom	κ	Signs	κ
Dyspnea	0.82	Fever >38°C	0.71
Pleuritic chest pain	0.97	Respiratory rate >30 breaths/min	0.78
Substernal chest pain	0.90	Heart rate >100 beats/min	0.60
Cough	0.85	Systolic blood pressure <100 mmHg	0.95
Syncope	0.85	Cyanosis	0.59
		Desaturation <90%	0.91
		Physical signs of deep vein thrombosis	0.87
		Cardiopulmonary arrest	0.88
		Hemoptysis	0.85
Test results	κ	Diagnostic models	κ
ABG PO ₂ criteria	0.70	Wells	0.71
Echo criteria	0.90	Geneva	0.53

Inter-rater agreement (between two raters) for signs, symptoms and test results for pulmonary embolism in five pilot study patients. Kappa values are presented, indicating chance-corrected agreement between two raters. ABG Arterial blood gas; Echo Echocardiography

Case report forms were distributed to research personnel in 67 centres that participated in the PROTECT trial (15). Blinded to study drug and PE adjudication status, research personnel (physicians or research coordinators) at each centre retrospectively abstracted data to calculate four scores: the Geneva score, original Wells score, Modified Wells score and Simplified Wells score. The research personnel who abstracted the data were asked to tabulate the points for each score based on interpreting the physicians' notes, nurses' notes, laboratory or other test values. The attempt was made to make assessments and assign numerical points as per clinical practice.

Analysis

To examine the relationship among the three adjudicated categories of possible, probable and definite PE, and each of the low, intermediate and high pretest probability categories of PE on the Geneva and Wells scores, respectively, chance-corrected agreement was calculated using kappa and its original interpretation by Fleiss (17). ANOVA was used to examine the association between clinically adjudicated categories of PE and values for each of the four diagnostic scores. $P < 0.05$ indicated that a diagnostic score was significantly different across three adjudicated categories of possible, probable and definite PE.

TABLE 3
Demographic and clinical characteristics of patients adjudicated for pulmonary embolism (PE)

Characteristic	Possible PE	Probable PE	Definite PE	P
Patients, n	4	16	50	–
Patient demographics				
Age, years, mean \pm SD	59.9 \pm 22.8	56.7 \pm 14.7	59.2 \pm 16.8	0.86
Female sex, n (%)	0 (0.0)	6 (37.5)	16 (32.0)	0.40
Body mass index, kg/m ² , mean \pm SD	22.9 \pm 4.0	34.4 \pm 10.7	29.8 \pm 8.5	0.05
Medical admission, n (%)	4 (100.0)	13 (81.3)	40 (80.0)	>0.99
APACHE II score, mean \pm SD	21.0 \pm 6.1	22.5 \pm 7.6	21.2 \pm 5.9	0.77
Comorbid illness at baseline, n (%)				
History of or current malignancy	1 (25.0)	0 (0.0)	4 (8.0)	0.22
Heart failure	0 (0.0)	0 (0.0)	2 (4.0)	>0.99
Personal history of venous thromboembolism	0 (0.0)	1 (6.3)	3 (6.0)	>0.99
Family history of venous thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)	–
End-stage renal disease (dialysis dependent)	0 (0.0)	0 (0.0)	0 (0.0)	–
Prevalent PE*	1 (25.0)	0 (0.0)	10 (20.0)	0.10
Baseline life support, n (%)				
Vasopressor dependent	1 (25.0)	8 (50.0)	27 (54.0)	0.65
Mechanically ventilated	4 (100.0)	16 (100.0)	49 (98.0)	>0.99

*Diagnosed before intensive care unit admission. APACHE Acute Physiology and Chronic Health Evaluation

TABLE 4
Pretest probability scores of published prediction models (Geneva, Wells, Modified Wells and Simplified Wells score) stratified according to PROTECT pulmonary embolism adjudication category

Prediction model	Pulmonary embolism			P
	Possible (n=4)	Probable (n=16)	Definite (n=50)	
Geneva score	4.0 \pm 3.5	4.7 \pm 2.8	4.5 \pm 2.8	0.90
Original Wells	2.8 \pm 1.0	4.9 \pm 3.4	4.1 \pm 2.8	0.37
Modified Wells	2.0 \pm 0.8	3.4 \pm 2.4	2.9 \pm 1.9	0.34
Simplified Wells	1.8 \pm 0.5	2.8 \pm 1.7	2.4 \pm 1.3	0.30

Data presented as mean \pm SD unless otherwise indicated. See Appendix Tables 1 to 4 for the prediction models. PROTECT Prophylaxis of Thromboembolism in Critical Care trial

RESULTS

There were 3746 patients included in the PROTECT trial. There were 70 patients in the final study including the five pilot patients, reflecting all 70 patients who were adjudicated for PE in the PROTECT trial; these patients were cared for in 30 of the 67 participating centres (Table 3). This yields an incidence of 1.9% (70 of 3746) of patients who were adjudicated for PE. Of the 70 PEs in the present study, 10 were prevalent and 60 were incident. Of 70 patients, four were adjudicated as 'possible PE', 16 as 'probable PE' and 50 as 'definite PE'. Agreement was poor between adjudicated categories of PE and both Geneva score pretest probabilities ($\kappa = 0.01$ [95% CI -0.0643 to 0.0941]) and Wells score pretest probabilities ($\kappa = -0.03$ [95% CI -0.1462 to 0.0914]). Across four patients who had possible, 16 patients who had probable and 50 patients who had definite PE, there were no significant differences in total Geneva scores (possible = 4.0, probable = 4.7, definite = 4.5; $P = 0.90$), total original Wells scores (possible = 2.8, probable = 4.9, definite = 4.1; $P = 0.37$), Modified Wells scores (possible = 2.0, probable = 3.4, definite = 2.9; $P = 0.34$) or Simplified Wells scores (possible = 1.8, probable = 2.8, definite = 2.4; $P = 0.30$) (Table 4).

DISCUSSION

Among 70 patients with a clinical suspicion of PE adjudicated in the PROTECT trial (15), agreement was poor among adjudicated categories of PE and each of the Geneva score and three Wells scores. Across

the three adjudicated categories of PE, there were no significant differences in total Geneva scores, Wells scores, Modified Wells scores or Simplified Wells scores. We conclude that many physiological variables used in these models, shown to be valuable in the ambulatory setting, are of questionable utility when applied to intubated, critically ill patients.

Two possible explanations for the poor agreement among adjudicated categories and prediction scores relate to the population we studied and the quality of information in the medical charts. Regarding the first explanation, some of the variables required to calculate these scores cannot be discerned in critically ill patients (eg, dyspnea) and are, therefore, nondiscriminatory. All patients in PROTECT were considered to be 'at risk for' DVT and PE. It is possible that the incidence of venous thromboembolism in this trial could be decreased as a consequence of universal prophylaxis with either UFH or LMWH. Furthermore, it is possible that patients receiving thromboprophylaxis may have different signs and symptoms of PE than patients not receiving prophylaxis, although, to our knowledge, this has not been studied. Bahia and Albert (13) demonstrated that these clinical scores accurately predict PE in prophylaxed hospitalized patients. There have been no studies in the literature that document the utility of these scores in thromboprophylaxed critically ill patients.

Regarding the issue of information quality, the original data for this substudy, and the original trial data collected by research coordinators on which the adjudication was based, were from patient medical records, which are known in both in paper and electronic formats to contain errors of over- (18) and under- (19) documentation on the part of nurses (20), trainees (21,22) and staff physicians (23). In other words, some components of the scoring systems may be too challenging to detect in ICU patients, whereas other predictor variables may be present or absent, but the information may not be recorded in the medical charts.

Strengths of the present study include the development, testing and refinement of data abstraction tools in a pilot exercise that documented excellent inter-rater reliability before starting the full study. To avoid ascertainment bias, data for the scoring systems were abstracted blinded to study drug, participating centre and adjudicated outcome. Similarly, the original PE events were adjudicated in quadruplicate, blinded to study drug, participating centre and other adjudicator assessments. Given the lack of previous evidence to evaluate well-known scoring systems for the diagnosis of PE in critically ill patients, we designed the present study a priori to examine the utility of these diagnostic scores in the ICU setting.

Limitations to the present study include the relatively small number of patients with PE. Because this thromboprophylaxis trial did not protocolize screening for PE, as per usual practice, not all patients underwent the same testing to diagnose PE (15). We did not compare scores in patients with suspected PE, but were subsequently proven not to have PE based on objective testing, or patients with no suspicion whatsoever of PE, thereby replicating practice. However, silent PE may be relatively common, as suggested in a recent study involving 176 medical-surgical ventilated ICU patients requiring thoracic computed tomography. In this cohort, 33 (18.7%) had PE, including 20 (61%) with no clinical suspicion (24). Unlike some patients studied in the original prediction score studies, ICU patients in the present study were all receiving either UFH or LMWH thromboprophylaxis and had poor cardiopulmonary reserve, which may have influenced the threshold of concerns when various signs or symptoms were found. The original prediction score studies were also not necessarily completed in thromboprophylaxed patients; however, they have been found to be discriminatory in this population (13).

Our findings may not be generalizable to all types of critically ill patients (eg, trauma, neurosurgery or cardiac surgery, who were not enrolled in the present study).

We did not apply the prediction scores to all patients, including those in whom PE was never considered as a clinical problem, as per the original score development process. We chose our methods to best

approximate the use of the prediction scores in some critical care practices, abstracting data for these scores in patients in whom the clinical suspicion of PE existed.

Developing PE scoring systems in the future would ideally incorporate other tests such as troponin, B-type natriuretic peptide values or echocardiographic findings. Specifically, elevated troponin levels predict short-term mortality as shown in a meta-analysis of 20 studies in general hospitalized patients with acute PE and normal blood pressure (OR 5.24 [95% CI 3.28 to 8.38]) (25). Another meta-analysis demonstrated higher risk of death associated with specific echocardiographic findings (OR 2.4 [95% CI 1.3 to 4.3]) and elevated B-type natriuretic peptide (OR 7.7 [95% CI 2.9 to 20]) in patients with hemodynamically stable PE (26).

CONCLUSION

Pretest probability models developed and validated outside the ICU setting do not correlate with clinically suspected PE in the ICU. Further clinical research is needed to identify features that help to reliably identify patients with PE in this setting, and to develop a practical clinical prediction rule for critically ill patients with suspected PE. Ideally, the latter would incorporate a complete spectrum of risk using readily available clinical, physiological and laboratory tests. Such new prediction models could be of great value to supplement clinical judgment, and aid in more timely identification and appropriate treatment of PE and, possibly, improved patient outcomes.

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APPENDIXES

**APPENDIX TABLE 1
Geneva Diagnostic score**

Clinical characteristic	Point value
Previous PE/DVT	2
Heart rate >100 beats/min	1
Recent surgery	3
Age, years	
60–79	1
>80	2
PaCO ₂ , mmHg	
<36	2
36–39	1
PaO ₂ , mmHg	
<48.7	4
48.7–59.9	3
60–71.2	2
71.3–83.4	1
Plate-like atelectasis on chest radiograph	1
Elevated hemidiaphragm on chest radiograph	1

DVT Deep vein thrombosis; PaCO₂ Partial pressure of carbon dioxide; PaO₂ Partial pressure of oxygen; PE Pulmonary embolism

**APPENDIX TABLE 2
Original Wells score**

Clinical characteristics	Point value
Clinical signs of DVT	3
Heart rate >100 beats/min	1.5
Recent surgery/immobilization	1.5
Previous PE/DVT	1.5
Hemoptysis	1
Active cancer	1
Alternative diagnosis less likely	3

DVT Deep vein thrombosis; PE Pulmonary embolism

**APPENDIX TABLE 3
Simplified Wells score**

Clinical characteristics	Point value
Clinical signs of DVT	1
Heart rate >100 beats/min	1
Recent surgery/immobilization	1
Hemoptysis	1
Previous PE/DVT	1
Cancer	1
Alternative diagnosis less likely	1

DVT Deep vein thrombosis; PE Pulmonary embolism

APPENDIX TABLE 4
Modified Wells score

Clinical characteristics	Point value
Clinical signs of DVT	3
Heart rate >100 beats/min	1.5
Recent surgery/immobilization	1.5
Previous PE/DVT	1.5
Hemoptysis	1
Active cancer	1
Alternative diagnosis less likely	3
≥4 PE likely	
<4 PE unlikely	

DVT Deep vein thrombosis; PE Pulmonary embolism

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