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Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism

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Summary. Overuse of the D-dimer to screen for possible pulmonary embolism (PE) can have negative consequences. This study derives and tests clinical criteria to justify not ordering a D-dimer. The test threshold was estimated at 1.8% using the method of Pauker and Kassirer. The PE rule-out criteria were derived from logistic regression analysis with stepwise backward elimination of 21 variables collected on 3148 emergency department patients evaluated for PE at 10 US hospitals. Eight variables were included in a block rule: Age < 50 years, pulse < 100 bpm, SaO_2 > 94%, no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no prior PE or DVT, no hormone use. The rule was then prospectively tested in a low-risk group (1427 patients from two hospitals initially tested for PE with a D-dimer) and a very low-risk group (convenience sample of 382 patients with chief complaint of dyspnea, PE not suspected). The prevalence of PE was 8% (95% confidence interval: 7–9%) in the low-risk group and 2% (1–4%) in the very low-risk group on longitudinal follow-up. Application of the rule in the low-risk and very low-risk populations yielded sensitivities of 96% and 100% and specificities of 27% and 15%, respectively. The prevalence of PE in those who met the rule criteria was 1.4% (0.5–3.0%) and 0% (0–6.2%), respectively. The derived eight-factor block rule reduced the pretest probability below the test threshold for D-dimer in two validation populations, but the rule's utility was limited by low specificity.

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Introduction

Over 110 million patients seek Emergency Department care annually in the United States, and approximately 10 million of these patients have complaints of dyspnea, chest pain, or both [1]. Pulmonary embolism is a common, frequently undiagnosed, and potentially fatal cause of either symptom [2–7]. Consequently, emergency medicine specialists often feel compelled to order a D-dimer in patients with dyspnea or pleuritic chest pain, even when the clinician recognizes a very low pretest probability. Overtesting for PE has long been recognized as a significant problem in the process of ruling out pulmonary embolism [8]. In particular, the D-dimer test frequently results in a false positive test result that demands expensive and time-consuming radiological imaging [9].

The purpose of this report was to provide criteria to rule-out pulmonary embolism at the bedside without additional ancillary testing, including the D-dimer. Accordingly, we performed a multicenter derivation and validation study of patients evaluated for possible pulmonary embolism in the emergency department. In the derivation phase of the investigation, we sought to produce a set of predictor variables from this population, that, when all absent, would confer a pretest probability of pulmonary embolism less than the test threshold [10]. The test threshold defines the point of equipoise in pretest

probability. When the pretest probability is lower than the test threshold, the probability that the patient will be harmed by further testing (including a screening test such as the D-dimer) exceeds the probability that the patient will benefit from further testing. We also constructed the rule to allow its use in patients with dyspnea or chest pain. In the validation phase, we test the derived rule in two populations of emergency department patients, one low-risk, and in a very low-risk group. The low risk group was studied primarily to test the sensitivity of the rule. The very low risk group was studied primarily to test the feasibility of the rule, i.e. whether the rule would be negative in a sufficient percentage of patients to make it useful.

We also compare the performance of the derived rule to a Canadian score < 2. Although the Canadian score was designed for use with D-dimer testing, one study found that only 1.3% of patients with a Canadian score < 2 were diagnosed with pulmonary embolism, suggesting utility for our purpose [11].

Methods

This research protocol was approved by the Institutional Review Board of Carolinas HealthCare System and the Human Research Committee of Partners HealthCare System. Derivation data for this study originated from 10 emergency departments in the United States (see acknowledgments). Each of 21 independent variables was collected from 3148 emergency department patients who underwent evaluation for possible pulmonary embolism (Table 1). During data collection, explicit definitions of each variable were used as described in the appendix. Patients were evaluated for pulmonary embolism based upon the unstructured threshold defined as 'enough clinical suspicion for pulmonary embolism that a board-certified emergency physician thought that a formal evaluation for pulmonary embolism was necessary.' All data were prospectively collected with the exception of four categorical variables that were collected retrospectively on 744 (23%) patients using structured chart review which included internal testing for interobserver reliability (kappa > 0.5 for all variables). All 21 variables were coded for all 3148 patients. Criterion standard for diagnosis included computerized tomography (CT) angiography in 196 patients, CT angiography with CT venography [12] in 1116 patients, ventilation-perfusion scintillation lung scanning in 1055 patients (372 followed by duplex ultrasound of the extremities), pulmonary angiography in 110 patients, and autopsy in 21 patients. Six hundred and fifty patients in the derivation study had pulmonary embolism ruled out without pulmonary vascular imaging using a structured protocol that included a D-dimer plus an alveolar deadspace measurement and 90-day follow-up as we have previously described [13]. Diagnosis of pulmonary embolism in the derivation study required the endpoint of treatment for either pulmonary vascular thrombosis or definite deep venous thrombosis or diagnosis of these entities at autopsy. To prospectively test for interobserver variability of the 21 variables, a convenience sample of 129 patients was examined by two independent physician observers who collected all 21 variables using a written data collection protocol and form. These observers performed their measurements 10 min apart on same subjects and were blinded to each other's results.

Table 1 Clinical characteristics and *P*-values from logistic regression in the derivation population ($N = 3148$)

Continuous variables	Mean	SD	*P* (full model)
Age (years)	48	17.9	< 0.0001
Pulse rate (beats min^{-1})	92	20.3	0.0001
Systolic blood pressure (mmHg)	137	24.8	0.0004
Room air pulse oximetry (%)	96	4.4	< 0.0001
Categorical variables	***N***	**%**	
VTE +	348	11.0	
Female gender	2162	68.6	0.033
Dyspnea	2262	71.8	0.0001
Cough	974	30.9	0.0415
Pleuritic chest pain	1584	50.3	0.3772
Substernal chest pain	1357	43.1	0.6577
Sudden onset of symptoms	1422	45.2	0.0327
Syncope	124	3.9	0.8203
Hemoptysis	107	3.4	0.0009
Unilateral leg swelling	298	9.5	< 0.0001
Asthma, COPD or active wheezing	490	15.6	0.0009
Current smoker	994	31.6	0.9066
Recent surgery	293	9.3	0.0017
Immobility	314	10.0	0.0193
Prior PE or DVT	389	12.4	< 0.0001
Prior or current malignancy	407	12.9	0.6322
Hormone use	330	10.4	0.0003
Pregnancy or post partum	116	3.7	0.2649

P-values from multivariate regression analysis.

The derived criteria were tested in a low-risk population and a very low-risk population. The low-risk population consisted of 1427 emergency department patients prospectively studied at Carolinas Medical Center ($N = 867$) and Brigham and Women's Hospital ($N = 560$) from 1 January 2001 through 30 June 2003. All low-risk validation patients were selected using the same broad, unstructured entry criterion as in the derivation study except that clinicians believed that patients were at low enough risk to justify exclusion of pulmonary embolism on the basis of a negative D-dimer. Throughout the study period, Carolinas Medical Center employed the SimpliFY assay (Agen Biomedical, Brisbane Australia) and Brigham and Women's hospital employed the VIDAS assay (< 500 FEU/mL, bio Merieux SA, Marcy-Etoile, France). The diagnostic utility of these assays in the emergency department setting has been reviewed [14]. CT angiography, CT angiography-venography or ventilation-perfusion lung scanning with selected use of venous ultrasonography was performed if D-dimer testing was abnormal. Using the same written definitions of terms, clinicians [physician assistants (4%), attending physicians (36%), and residents (60%)] prospectively completed a mandatory computerized data collection form that recorded all 21 variables on all low-risk patients prior to completion of diagnostic test results. In addition, patients were asked the questions necessary to compute the Canadian pulmonary embolism score [15]. Clinicians completing data entry were not provided with the

information required to compute the rule derived in this report nor to compute the Canadian score, although the method to compute the latter was published prior to the time of data collection. Upon discharge from the emergency department, all low-risk patients were told and received written instructions to return immediately to the emergency department if symptoms prompting the evaluation persisted or if other symptoms of pulmonary embolism occurred. Each low-risk patient was followed until 90 days after enrollment using the combination of telephone follow-up, examination of medical records and contact with the patient's personal physician. We considered a true positive outcome for any patient who received anticoagulation, vena caval interruption for venous thromboembolism, or who died from undiagnosed pulmonary embolism [13].

The very low-risk validation population consisted of a convenience sample of 382 prospectively studied adult emergency department patients at Carolinas Medical Center during 2003 who were evaluated for dyspnea, and who were not part of either the derivation or low-risk groups. Patients were identified by one research nurse who continuously surveyed adult patients (age $>$ 18 years) presenting to the emergency department during weekday hours, and who were identified by the triage nurse as having some type of breathing complaint. The research nurse approached each patient to determine eligibility. The enrollment criteria required: (i) The patient answered yes to the question 'was shortness of breath the most important or just as important as the main reason you came to the emergency department today?' and (ii) The emergency physician stated to the research nurse that pulmonary embolism was not the most likely diagnosis. While the very low-risk patients were physically in the emergency department, an experienced research nurse recorded 21 clinical variables on a standardized form. These variables were identical to that which had been collected previously for patients in the derivation phase of the study. Very low-risk patients then underwent diagnostic testing at the discretion of the attending physician. Admitted patients were followed each day while in the hospital and all very low risk patients were followed prospectively for 90 days in the same fashion as the low-risk group. The primary objective was to test the potential specificity of the derived pulmonary embolism rule-out criteria (hereafter termed the PERC rule) to determine how often the rule could assist the implicit decision to not order a D-dimer in this very low-risk group.

All statistical analyzes were performed using STATSDIRECT software (version 2.2.3) Continuous data are presented as means $\pm$ standard deviation or proportions and 95% confidence intervals (CIs) computed from the Clopper–Pearson method (Stats Direct© vs. 2.2.3). Means and proportions were compared with the 95% CI for differences [16]. The 21 variables in the derivation set were tested for significance ($P < 0.05$) using logistic regression analysis. Model fit was tested using the goodness of fit chi square and the Hosmer–Lemeshow statistic [17]. Variable selection was accomplished using a modified backward stepwise process. First, we excluded variables that did not have significance. Second, significant continuous variables (e.g. age) were dichotomized by receiver operating characteristic curve analysis to determine the cut-off corresponding to the lowest likelihood ratio negative. Third, we computed Cohen's κ for categorical and dichotomized variables and excluded any variables that had a lower limit 95% CI for κ less than 0.40 [18]. The logistic regression equation was performed using all remaining variables, and the equation was solved for the *P*-value (probability). For the PERC rule, we sought to produce a simple, all-negative rule-out criteria. We therefore excluded variables that were negatively associated with venous thromboembolism. We then tested the ability of the solved logistic regression equation, the negative PERC rule, and the Canadian score < 2 to reduce the pretest probability below the test threshold in the low and very low risk populations. The test threshold was estimated at 1.8%, using the method of Pauker and Kassirer as described in the appendix [10].

Results

Clinical characteristics of the derivation population are shown in Table 1. The prevalence of pulmonary embolism was 11% (95% CI: 10–12%). The 21 variables were reduced as illustrated in Fig. 1. First, logistic regression analysis found six variables to be non-significant: pleuritic chest pain, substernal chest pain, syncope, smoking status, malignancy and pregnancy or immediate postpartum status. The continuous variables were then dichotomized by receiver operating characteristic curve analysis (curves not shown). The rounded cutoffs that generated the lowest likelihood ratio negative were age $<$ 50 years, pulse rate $<$ 100 beats min^{-1}, systolic blood pressure $<$ 110 mmHg, and pulse oximetry reading $>$ 94%. Second, the variables immobility and sudden onset of symptoms were excluded due to low interobserver reliability [$\kappa = 0.30$ (95% CI: 0.12–0.48) and $\kappa = 0.48$ (0.30–0.66), respectively,]. Third,

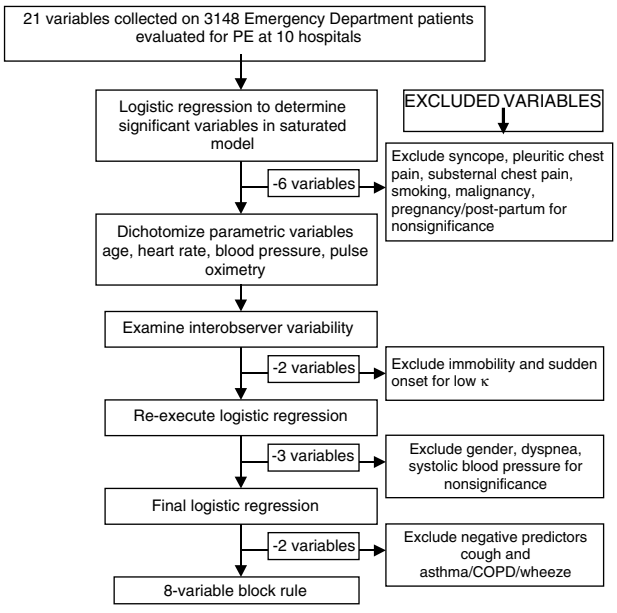

Fig. 1. Flow diagram showing the process used to derive the 8-factor block rule.

Table 2 Results of the final logistic regression model

Parameter	Coefficient	Standard error	*P*-value	Odds ratio	Bias corrected 95% CIs*
Constant	−3.1246	0.1257	$P < 0.0001$	0.1	NA
Age > 50	0.5449	0.1272	$P < 0.0001$	1.7	1.3–2.2
Pulse rate > 100	0.451	0.1253	$P = 0.0003$	1.6	1.2–2.0
SaO_2 < 95%	1.2049	0.1324	$P < 0.0001$	3.3	2.5–4.4
Cough	−0.3768	0.1417	$P = 0.0078$	0.6	0.5–0.9
Hemoptysis	1.0382	0.2678	$P = 0.0001$	2.8	1.6–4.8
Unilateral leg swelling	1.0844	0.1549	$P < 0.0001$	3.0	2.2–4.1
Asthma/COPD/wheeze	−0.6072	0.184	$P = 0.001$	0.5	0.4–0.8
Surgery or Trauma	0.6651	0.1702	$P < 0.0001$	1.9	1.3–2.7
Prior PE or DVT	0.6354	0.1586	$P < 0.0001$	1.9	1.3–2.6
Hormone use	0.5166	0.1818	$P = 0.0045$	1.7	1.2–2.4

SaO_2 pulse oximetry reading with the patient breathing room air; PE pulmonary embolism; DVT, deep venous thrombosis. *From 1000 Bootstrap iterations.

Model analysis: logit $P = -3.125 + 0.5445$ Age > 50 + 0.451 HR > 100 + 1.205 SaO_2 < 95% − 0.376 COUGH + 1.038 HEMOPTYSIS + 1.084 UNILAT_LEG_SWELLING − 0.607 AST_COPD_WHEEZE + 0.665 TRAUMA_SURGERY + 0.635 DVT_PE + 0.516 HRT_OCP; deviance (likelihood ratio) chi-squared = 276.8, d.f. = 10, $P < 0.0001$; Pseudo (McFadden) *R*-square = 0.421; Pseudo (likelihood ratio index) *R*-square = 0.126; Pearson chi-squared goodness of fit = 386.31, d.f. = 290, $P = 0.0001$. Deviance goodness of fit = 379.960, d.f. = 290, $P = 0.0003$; Hosmer–Lemeshow test = 5.23, d.f. = 7, $P = 0.630$.

the logistic regression equation was re-executed with 13 dependent variables; gender, dyspnea and systolic blood pressure were excluded for non-significance. The final logistic regression equation included 10 variables (Table 2). Model fit was adequate based upon the likelihood ratio chi-squared and the Hosmer–Lemeshow statistics. Lastly, to develop a straight, all negative block rule, we excluded two negative predictor variables, cough and asthma/chronic obstructive pulmonary disease/active wheezing. The final PERC rule negative required age < 50 years, pulse < 100, pulse oximetry > 94%, no unilateral leg swelling, no hemoptysis, no recent surgery, no prior pulmonary embolism or deep venous thrombosis, and no oral hormone use. The PERC rule was then tested in two populations drawn from the emergency department setting as illustrated in Fig. 2.

The clinical characteristics of the two validation populations are shown in Table 3. Ninety percent of low-risk patients had a complaint of dyspnea or chest pain or both. One hundred and fourteen low-risk patients 114/1427 or 8% (95% CI 6.6–9.5%) were diagnosed and treated for venous thromboembolism within 90 days. Seven hundred and ninety (55%) low-risk patients had venous thromboembolism excluded on the basis of D-dimer testing plus the absence of venous thromboembolism on 90-day follow-up (none lost to follow-up). In 637

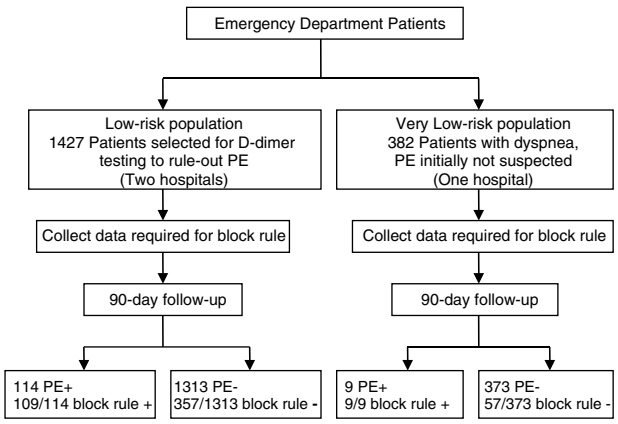

Fig. 2. Schematic overview of validation testing of the block rule.

Table 3 Clinical features of the two validation populations

	Low prevalence population ($N = 1427$)		Very low prevalence population ($N = 382$)	
Clinical feature	Mean	SD	Mean	SD
Age (years)	47	17	56	18
Pulse rate (beats min^{-1})	91	20	94	21
Systolic blood pressure (mmHg)	135	27	133	25
Room air pulse oximetry (%)	97	4	95	5
	N	%	*N*	%
VTE +	114	8	9	2
Female gender	852	60	214	56
Dyspnea	940	66	382	100
Cough	262	30	177	46
Pleuritic chest pain	698	49	55	15
Substernal chest pain	529	37	106	28
Sudden onset of symptoms	528	60	118	31
Syncope	61	7	7	2
Hemoptysis	36	3	15	4
Unilateral leg swelling	153	11	35	9
Asthma, COPD or active wheezing	311	22	135	35
Current smoker	554	39	140	37
Recent surgery	138	10	25	7
Immobility	65	6	67	18
Prior PE or DVT	169	12	32	8
Prior or current malignancy	176	12	39	10
Hormone use	143	10	17	4
Pregnancy or post partum	36	4	10	3
PE most likely diagnosis	655	46	0	0

Table 4 Diagnostic performance of the derived rule in the two validation populations

	Sensitivity (%)*	Specificity (%)*	False negative rate (%)*	% of total
Low-risk population ($N = 1427$)				
$P < 1.8\%$ from equation†	99 (95–100)	1 (0–2)	5.0 (1–25)	1
Block rule negative‡	96 (90–99)	27 (25–30)	1.4 (0.4–3.2)	25
Canadian score < 2§	76 (67–84)	44 (41–47)	4.5 (3.0–6.5)	42
Very low-risk population ($N = 382$)				
$P < 1.8\%$ from equation	100 (59–100)	2 (0–4)	0 (0–40)	2
Block rule negative	100 (59–100)	15 (11–18)	0 (0–6)	15
Canadian score < 2	78 (40–97)	77 (72–81)	0.7 (0–7)	75

*95% CIs shown in parenthesis. †$P = 1–1/(1 + \exp(-3.1246 + 0.5449 \times \text{Age} > 50 + 0.451 \times \text{HR} > 100 + 1.2049 \times \text{SaO}_2 < 95\% - 0.3768 \text{ COUGH} + 1.0382 \times \text{HEMOPTYSIS} + 1.0844 \times \text{UNILAT\_LEG\_SWELLING} - 0.6072 \times \text{AST\_COPD\_WHEEZE} + 0.6651 \times \text{TRAUMA\_SURGERY} + 0.6354 \times \text{DVT\_PE} + 0.5166 \times \text{HRT\_OCP})$. ‡Age < 50 years, pulse rate < 100 beats min^{-1}, pulse oximetry reading < 95%, no unilateral leg swelling, no hemoptysis, no recent surgery, no prior pulmonary embolism or deep venous thrombosis and no oral hormone use. §Computed according to the method described by Wells *et al.* [15]

low-risk patients, the D-dimer was positive but pulmonary embolism excluded on the basis of negative pulmonary vascular imaging [CT angiography-venography ($N = 215$), CT angiography ($N = 275$), scintillation lung scanning ($N = 126$), or pulmonary angiography ($N = 21$)] plus the absence of diagnosis of venous thromboembolism on 90-day follow-up.

In the very low-risk population, the most common initial diagnoses were rule out acute coronary syndrome (22%), congestive heart failure (21%), asthma exacerbation (15%), pneumonia (12%), chronic obstructive pulmonary disease (7%), upper respiratory infection or bronchitis (6%). In 52/382 (13%) patients, a D-dimer was ordered later in the emergency department and 37 others had a D-dimer ordered after admission to the hospital. The D-dimer was positive in 42/89 patients (47%). Sixty-five very low-risk patients underwent pulmonary vascular imaging, 28 others had venous ultrasonography. Almost all of this diagnostic testing (90%) was performed in the 193 (50%) very low-risk patients who were hospitalized at the time of enrollment. Nine of 382 (2.4%, 1.0–4.4%) very low-risk patients were ultimately diagnosed with venous thromboembolism within 90 days.

In Table 4, we compare the ability of three methods to exclude venous thromboembolism in the two validation populations. First, Table 4 shows the diagnostic utility of the 10-variable logit equation, solved for P (the probability estimate), where $P < 1.8\%$ was considered negative. Second, Table 4 presents the diagnostic utility of the PERC rule negative. Third, the Table shows the diagnostic utility of the Canadian score < 2. In the low-risk population, the solved logistic equation almost always output a probability above 1.8% in diseased patients (sensitivity 99%, 95–100%), but the equation rarely offered a pretest probability below 1.8% in patients without disease, resulting in a specificity of only 1%. As a result, the probability of venous thromboembolism in the small group with an equation-predicted probability < 1.8% was unacceptably high (one in 20). The PERC rule yielded a sensitivity of 96% (90–99%) and specificity of 27% (25–30%). One-quarter of the low-risk population had the PERC rule negative ($N = 362$), and five of these patients developed venous thromboembolism. Thus, the false negative rate was 1.4% (0.5–3.0%), which was below the test threshold estimate of 1.8%. The Canadian score < 2 had a sensitivity of 78% (67–84%) and a specificity of 44% (41–47%). Forty-two percent of low-risk patients had a Canadian score < 2, and the probability of venous thromboembolism in this group was 4.5% (3.0–6.5%).

In the very low-risk population, the estimation of a probability < 1.8% from the logistic equation again offered essentially no diagnostic utility owing to low specificity. The PERC rule detected all nine patients with venous thromboembolism (sensitivity 100%, 59–97.5%), but was negative in only 57 of 373 without disease, resulting in a specificity of 15% (11–18%). On the other hand, the Canadian score was < 2 resulted in a sensitivity of 78% (40–97%) and specificity of 76% (72–81%). In the very low-risk population, both the PERC rule and the Canadian score < 2 produced false negative rates below the test threshold [0% (0–7%) and 0.6% (0–2.5%) for the PERC rule and the Canadian score < 2, respectively].

Discussion

D-Dimer testing for pulmonary embolism imposes a Janus-face effect on the evaluation of pulmonary embolism in the emergency department setting [9,19,20]. On the beneficial side, the D-dimer can facilitate wider screening for pulmonary embolism and afford a higher rate of diagnosis of this potentially fatal disease. But the high false positive rate of the D-dimer can create the potential for a detrimental increase in pulmonary vascular imaging, increased patient length of stay in overcrowded emergency departments, and increased false positive diagnoses [14,20]. These concerns motivated us to develop the PERC rule.

We used rigorous methodology to derive and test this decision rule in accordance with recommendations of Stiell *et al.* [21] The derivation data were collected from emergency departments at 10 US hospitals with geographic, socioeconomic, and physician practice diversity. The derivation database contained no missing data on any of 21 variables for 3148 patients. These 21 variables include all objective predictors (excluding results of diagnostic tests) that have been found to

be significant in previous studies of outpatients [15,22,23]. To enhance the rule's sensibility, we aimed to derive a straight-shot decision rule comprised of objective variables that can be ascertained with acceptable interobserver reproducibility at the bedside. Although immobility was significantly associated with outcome of venous thromboembolism in the derivation population, this variable was excluded secondary to low interobserver agreement. Sudden onset of symptoms was similarly excluded. Curiously, sudden onset of symptoms was a significant negative predictor of venous thromboembolism in the derivation population. This finding contrasts to work by Miniati and colleagues that found sudden onset to be positively associate with presence of pulmonary embolism [22,24]. To allow a straight negative rule, we also excluded two variables that were negatively associated with the presence of venous thromboembolism. As opposed to more complex, variable-weighted scoring systems or mixed rules that contain positive and negative predictors, we believe the block rule conforms better to the clinical thinking process. We speculate that clinicians are more accustomed to the process of excluding risk factors (i.e. recognizing absence of advanced age, tachycardia, hypoxemia, etc.) rather than including negative predictors to justify not to initiating a diagnostic work up for PE.

To evaluate for possible bias or inaccuracy, we tested the rule in two validation populations (Fig. 2). The two validation populations had very different underlying probabilities of venous thromboembolism. The low-risk population represents the patient strata in which a D-dimer is often ordered: a patient at low risk for pulmonary embolism, but not low enough for the clinician to justify not ordering some type of objective test. In the low-risk group, the probability of an outcome of venous thromboembolism was low (in comparison to many published studies), even in patients when the clinicians thought pulmonary embolism was the most likely diagnosis (9%, 7–11%). A substantial number of low-risk patients had 'sudden onset of symptoms' with dyspnea or pleuritic chest pain, but without abnormal vital signs or risk factors. One interpretation of these findings is that clinicians feel compelled to order a D-dimer in younger patients with dyspnea or pleuritic pain because a good explanation is often lacking, and pulmonary embolism represents a lingering, unquantifiable threat to life. In contrast, the very low risk population was an older, heterogenous group of patients for whom clinicians initially felt certain had non-thromboembolic causes of dyspnea. Only 2% of these patients developed venous thromboembolism after 90 days of surveillance. We submit that most clinicians would prefer to not order a D-dimer in patients of this ilk, but without a defensible rationale, the decision to not test may cause self-doubt.

The PERC rule was negative in one quarter of low-risk patients, and within 90 days, 1.4% of these patients developed pulmonary embolism or deep venous thrombosis – a rate less than the computed test threshold of 1.8%. In comparison, a larger proportion of low-risk patients (42%) were characterized by having a Canadian score < 2, but the occurrence of venous thromboembolism was 4.5% in this group. This probability was significantly higher than 1.3% (0.5–2.7%) probability associated with a Canadian score < 2 in a multicenter validation study performed in an emergency department population with a 9.5% overall prevalence of venous thromboembolism [11]. However, in the very low-risk population, the Canadian score < 2 was helpful in as much as it was negative in 77% of patients, and the probability of venous thromboembolism in this group was 0.6%. The PERC rule was negative in only 15% of very low risk patients. Although no patient in the very low risk group with a negative PERC rule developed thromboembolism, this apparent 100% sensitivity must be interpreted with caution, given that the lower limit of the 95% CI was 59%, and the minority of very low-risk patients underwent pulmonary vascular imaging. This finding suggests that the Canadian score < 2 is calibrated more appropriately to rule-out pulmonary embolism in a very low-risk patient when a firm alternative diagnosis exists. The PERC rule required eight features to be absent, whereas the Canadian rule could allow any one of five risk features to be present and still yield a score < 2. Unfortunately, the Canadian score < 2 did not capture all of the patients who went on to be diagnosed with pulmonary embolism within 90 days. A pivotal point to the Canadian score lies in the question of whether all of the clinicians for the very low risk patients held a steadfast clinical viewpoint that pulmonary embolism was an unlikely diagnosis. This opinion may have changed with the influence of further testing and opinions of additional caregivers, given that one-third of very low-risk patients eventually were tested for venous thromboembolism, including five patients who underwent formal pulmonary angiography. Over 90% of these tests were performed during hospital stay immediately after enrollment.

We offer the PERC rule to compliment clinical judgement rather than replace it [25]. When Chagnon and colleagues applied the comprehensive scoring system developed by Wicki *et al.* the authors found that the addition of unstructured clinical suspicion of high risk complimented the Geneva score [23,26]. Kline *et al.* found a similar benefit to the addition of unstructured clinical suspicion of high risk added to a decision rule to determine when a patient is safe for a D-dimer based point of care protocol to rule out pulmonary embolism [13].

In any given patient, the derived block rule may be negative when a host of other factors not included in the rule may demand that the patient be tested further, such as known thrombophilia, a strong family history of thrombosis, or concurrent beta blocker use that could blunt reflex tachycardia. Likewise, clinical judgement has to be imposed for patients with borderline or indeterminate factors, such as patients with transient tachycardia, patients with amputations, massively obese patients in whom leg swelling cannot be reliably ascertained, or patients with baseline hypoxemia in whom a pulse oximetry reading $< 95\%$ is long-standing. Clearly, no decision rule is comprehensive and should not be used in isolation from other influences that make a clinician believe that pulmonary embolism is present.

We conclude that clinicians should pause before ordering a D-dimer on a patient under 50 years of age, and who has a

pulse < 100, a pulse oximetry $> 94\%$, no unilateral leg swelling, no hemoptysis, no recent surgery and no oral hormone use. When all eight factors are negative, the pretest probability of pulmonary embolism is likely to be so low that D-dimer testing for pulmonary embolism will not yield a favorable risk–benefit ratio.

Authors contributions

JAK, AMM, CK and DMC conceived the study. JAK, CK and DMC obtained study funding and supervised data collection including quality control. AMM and DMC contributed substantially to data collection, data entry and data analysis. JAK performed statistical analysis in consultation; JAK drafted the manuscript and all authors contributed substantially to its revision. JAK takes responsibility for the paper as a whole.

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Appendix

I. Dictionary of variables

Pulse rate (beats min^{-1})	Measured off of the pulse oximetry device or ECG monitor
Systolic blood pressure (mmHg)	Measured from cuff sphygmomanometry using the oscillimetric method on FDA approved devices
Room air pulse oximetry (%)	Oximetry derived from dual wavelength (680/805 nm) measurement; probe on the fingertip or earlobe
Categorical variables	
VTE +	Outcome of treated PE or DVT within 90 days of evaluation
Female gender	Biological sex
Dyspnea	Patient admission to any type of shortness of breath prompting hospital visit
Cough	Any cough in the past week
Pleuritic chest pain	Non substernal chest pain that increases with a deep inhalation
Substernal chest pain	Any substernal chest pain
Sudden onset of symptoms	Abrupt, non-gradual onset
Syncope	Any nontraumatic loss of consciousness prompting ED visit
Hemoptysis	Patient report of coughing up any blood in past week
Unilateral leg swelling	Asymmetrical calfs when the legs are raised by the heels off of the bed by the examiner
Asthma, COPD or active wheezing	Prior history of inhaler use for either asthma, or 'emphysema' or current wheezing ausculated on physical examination
Current smoker	Any cigarette use within last 2 weeks
Recent surgery or trauma	Either surgery or trauma requiring treatment with general anesthesia in the previous 4 weeks
Immobility	Generalized whole body immobility > 48 h or plaster or external fixator limb stabilization
Prior PE or DVT	Personal history of PE or DVT requiring treatment
Prior or current malignancy	Any history of malignancy raising the possibility of current hypercoagulability
Hormone use	Oral contraceptives, hormone replacement or estrogenic hormones use in males or female patients
Pregnancy or post partum	Post-partum = within 4 weeks of delivery

II. Computation of test threshold

The test threshold is computed using the CT angiogram as the diagnostic test [1]. The risk of CT angiography is primarily related to the incidence of life-threatening complications from receiving contrast media plus the small risk of cancer from radiation exposure. The risk of life-threatening anaphylactoid reaction or severe pulmonary edema requiring intubation, or need for hemodialysis after a 150 mL dye load is about 1 in 2000 ($R_t = 0.0005$). It has been estimated that the composite absolute increase in risk of malignancy induced by the radiation dose of CT angiography (2.4–3.0 mSv) is 1.5/15 000 [2,3]. Metaanalyses indicate that the sensitivity of CT angiography is approximately 85% ($P_{pos/d} = 0.85$), and approximately 10% of scans are false positives ($P_{pos/nd} = 0.1$) [4,5]. The only randomized controlled trial of anticoagulation vs. placebo performed demonstrated a 20% absolute reduction in the outcome of death [6]. After either 6 weeks or 6 months of anticoagulation, patients randomized to placebo have a 17–18% rate of composite outcome of death or recurrence of PE, vs. 7–9% in patients treated with continued low-dose warfarin [7,8]. Based upon these data sources, $B_{rx} = 0.15$. The risk of major hemorrhage with treatment with warfarin for six months is about 1.7% ($R_{rx} = 0.017$) [9].

$$T_t = (P_{pos/nd} \times R_{rx} + R_t)(P_{pos/nd} \times R_{rx} + P_{pos/d} + B_{rx})$$

$$T_t = (0.1 \times 0.017 + 0.00006)/(0.1 \times 0.017 + 0.85 \times 0.15) = 1.8\%$$

The interpretation of this number is that patients with a pretest probability below 1.8% should not undergo D-dimer testing, because a positive D-dimer result would mandate CT angiography, and the probability of harm will outweigh the probability of benefit in this patient. One immediate question that follows is whether the 1.8% estimate should then be increased to consider the fraction of patients in whom imaging could be avoided by a negative D-dimer test. However, this step would introduce the possibility of a false negative D-dimer and the attendant consequences of untreated venous thromboembolism. For purpose of computing a test threshold, the most valid way to eliminate this possibility is to set the D-dimer cutoff point to a concentration that would produce essentially no false negative results. Drawing from published data on quantitative D-dimer testing, where appropriate reference intervals or receiver operating characteristic curve data are presented, the threshold would have to be set below 100 FEU mL^{-1}, which would cause > 95% of D-dimer tests to be 'positive' with either the enzyme-linked immunoassay or immunoturbidimetric format [10–14]. Accordingly, the test threshold was not adjusted upward to consider the effect of interposing the D-dimer between clinical assessment and CT angiography.

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