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Original Contribution

The DAGMAR Score: D-dimer assay-guided moderation of adjusted risk. Improving specificity of the D-dimer for pulmonary embolism

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ABSTRACT

We generated a novel scoring system to improve the test characteristics of D-dimer in patients with suspected PE (pulmonary emboli).

Electronic Medical Record data were retrospectively reviewed on Emergency Department (ED) patients 18 years or older for whom a D-dimer and imaging were ordered between June 4, 2012 and March 30, 2016. Symptoms (dyspnea, unilateral leg swelling, hemoptysis), age, vital signs, medical history (cancer, recent surgery, medications, history of deep vein thrombosis or PE, COPD, smoking), laboratory values (quantitative D-dimer, platelets, and mean platelet volume (MPV)), and imaging results (CT, VQ) were collected.

Points were designated to factors that were significant in two multiple regression analyses, for PE or positive D-dimer. Points predictive of PE were designated positive values and points predictive of positive D-dimer, irrespective of presence of PE, were designated negative values.

The DAGMAR (D-dimer Assay-Guided Moderation of Adjusted Risk) score was developed using age and platelet adjustment and points for factors associated with PE and elevated D-dimer.

Of 8486 visits reviewed, 3523 were unique visits with imaging, yielding 2253 (26.5%) positive D-dimers. 3501 CT scans and 156 VQ scans were completed, detecting 198 PE.

In our cohort, a DAGMAR Score < 2 equated to overall PE risk < 1.2%. Specificity improved (38% to 59%) without compromising sensitivity (94% to 96%). Use of the DAGMAR Score would have reduced CT scans from 2253 to 1556 and lead to fewer false negative results.

By considering factors that affect D-dimer and also PE, we improved specificity without compromising sensitivity.

1. Introduction

1.1. Background

Pulmonary emboli (PE) cause significant morbidity and mortality every year. PEs lead to about 80,000 deaths in the United States each year [1]. They can lead to prolonged hospitalization, pulmonary hypertension [2], and postthrombotic syndrome [3-5].

The most common confirmatory test for a PE is the computed tomography (CT) pulmonary angiogram, but the test is potentially carcinogenic, expensive, and time consuming, and carries the potential for adverse contrast reactions. In 20 year-old females, it is estimated that one of every 330 patients undergoing CT chest would develop a malignancy related to that diagnostic test [6]. The cost of a CTA thorax ranges from $505–$1736.90 in our hospital system, and requires long wait times for often negative results.

PEs can present with variable symptoms, which may include dyspnea, chest pain, hemoptysis, palpitations, syncope, or back pain [7]. There are many decision rules guiding evaluation and risk management for patients with PEs. Many include subjective factors such as clinical gestalt. Others help identify low risk patients but have not been validated to risk stratify PE in those patients who are moderate or high risk.

The Pulmonary Embolism Rule Out Criteria (PERC) studied 8,138 patients to help clinicians risk stratify patients for PEs with posttest

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probability <2% on clinical factors alone [8]. However, this finding was only validated in patients with a low pretest probability, and may not be sufficient for risk stratification in moderate or high-risk patients without further testing [9].

The Wells score and Revised Geneva score both attempt to risk-stratify patients based on history and clinical presentation [10] [11]. However, their utility is limited by test characteristics [12]. In their dichotomized versions, they both stratify patients into low to moderate *versus* high risk for PE. For Wells, lower risk patients have a PE rate of 12.1% and for Geneva, this rate is 7–9% [12]. Thus for both, the scores help reduce CT burden, but still suggest further testing with a D-dimer assay in the low risk groups.

1.2. Importance

An alternative or adjunctive approach to clinical decision rules is the use of the D-dimer, a fibrin degradation product elevated during active clot remodeling, as occurs in acute PEs. The advent of high sensitivity D-dimer testing allows for the assessment of PEs in moderate and high-risk patients, as classified by clinical prediction rules [13]. However, the lack of specificity limits its utility. When a D-dimer test is non-negative and clinical suspicion is high, additional testing (usually with CT pulmonary angiogram) is usually sought. Therefore, improving the test characteristics for serum testing and performing risk stratification may decrease the need for this expensive and potentially harmful test.

Many patients fall into an intermediate or high-risk category as assessed by the criteria outlined above. Historically, the D-dimer has only been applied to low-risk patients [14]. As the sensitivity of D-dimer has improved with newer tests, it has been validated in moderate and high-risk patients as well [15]. It is frequently applied to those patients in the lower bracket of the dichotomous Geneva and Wells scores.

The Emergency Departments (EDs) in this study used a high sensitivity HemosIL D-dimer, which has been validated on low, moderate, and high-risk patients with 100% (95% CI 69.2% - 100%) sensitivity [15]. That level of sensitivity is in fact better than the sensitivity of CT scan for detecting PEs [16]. This validation was performed in a prospective multi-center trial, in which all moderate and high-risk patients were imaged and followed up at 3 months [15]. However, the HemosIL D-dimer still has low specificity, which limits its utility in many patients. Furthermore, some physicians question results in high-risk patients because of a large confidence interval around the sensitivity, thus many patients continue to receive CT scans despite negative D-dimer testing.

This study is an important attempt to create a novel scoring system that addresses the challenges of assessing for PE given the variable clinical presentations, limitations of the low specificity of the D-dimer, and risks of excessive imaging.

It was further important in the validation of age-adjustment in the HemosIL assay and the recognition of the relationship of D-dimer and platelets. To our knowledge, this is the first recognition of that relationship. It is unclear the etiology behind the association, but is unsurprising given their mutual presence in the coagulation pathway.

1.3. Goals of this investigation

Our goal was to generate a novel scoring system including age and platelet adjustment with a point system to improve the specificity of the D-dimer assay, while simultaneously maintaining sensitivity.

2. Methods

2.1. Study design and setting

Electronic medical record data were recorded on Emergency Department (ED) patients 18 years or older on whom a D-dimer and imaging were ordered between June 4, 2012 and March 30, 2016. Data were collected from two EDs in an academic hospital system, with combined annual census of 65,000. Symptoms (dyspnea, unilateral leg swelling, hemoptysis), age, vital signs, medical history (cancer, recent surgery, medications, history of deep vein thrombosis or PE, COPD, smoking), laboratory values (quantitative D-dimer, platelets, and mean platelet volume (MPV)), and imaging results (CT, VQ) were collected.

2.2. Selection of participants

Cases were included if they visited the ED, age 18 years old or greater, and had a D-dimer and imaging (CT pulmonary angiography or VQ scan) completed. Patients >89 years old were all recorded as ">89" to maintain confidentiality as required by the IRB. Patients <18 years old, or those who did not have a D-dimer with imaging were excluded. These inclusion and exclusion criteria were defined prior to data collection.

2.3. Measurements

Laboratory values and age were collected through automated query. Other data were collected by abstracters trained in uniform fashion and recorded in a uniform abstraction form. Abstractors were blinded to the hypothesis being tested. Four abstracters were emergency medicine residents, one was a medical student, and one was a research assistant in the ED. The trainer met with the abstractors periodically and monitored the data collection to ensure consistent technique throughout the abstracters, and Cohen's Kappa was performed for 10% of charts demonstrating that all variables were ≥80%.

Variables were defined by positive D-dimer (≥240 ng/mL) or negative D-dimer (<240 ng/mL), based on the local lab reference standard. A VQ scan of moderate or high probability was considered positive for PEs. CT scan was interpreted as either positive or negative for acute PE based on the attending radiologist's final interpretation.

Any data not found by abstracters was entered "NR" in the database. For statistical analysis, if past medical history, past surgical history and medications were documented, then it was assumed that recent surgery, active cancer, history of PE, DVT, or COPD, exogenous estrogen, and pregnancy were not present in the patient if they were "NR." Signs and symptoms, such as syncope, cough, hemoptysis, shortness of breath or unilateral leg swelling that were not recorded were not assumed to have positive or negative values for those factors and those that were "NR" were left out of subsequent statistical analysis. If there were two D-dimers ordered for the same patient visit, the lower value was used.

Surgeries were included if they were major surgeries requiring anesthesia. Otherwise they were excluded. However, different types of surgery were not separated out in analysis.

p-Values < .05 were considered significant. Further Bonferroni correction was not pursued after multivariable logistic analysis as it was thought to be too selective and would have precluded factors generally accepted to predict presence of PE or elevated D-dimer.

2.4. Outcomes

The primary objective was the generation of a novel scoring system (named the DAGMAR Score) to improve the specificity of the D-dimer assay without sacrificing sensitivity.

We secondarily determined false negative D-dimer results with and without use of the DAGMAR Score and projected imaging that could have been safely avoided by using the DAGMAR Score.

We further compared the sensitivity and specificity of the D-dimer as used at our institution against previously published values on the assay [15].

2.5. Data analysis

In our analysis, we closely followed the methodology laid out in the development of the Wells Score [10]. Just as Wells et al. did, we performed a multivariable logistic regression analysis to determine factors predictive of PE. We then assigned points based on a designated standard.

However, unlike Wells et al., we performed two, not one, multivariable logistic regression analyses. First, we analyzed how the factors predicted likelihood of PE. Next, we analyzed how the factors predicted likelihood of elevated D-dimer (≥240 ng/mL), regardless of whether or not a PE was found. Variables in the multivariable logistic regression analysis with p values < .05 for either or both of the factors (PE or D-dimer positive) were considered significant. It should be noted that none of those variables overlapped the null value (*e.g.* OR = 1).

We observed that, like age, many factors that increased the risk of PE increased the risk of elevated D-dimer disproportionately. Thus, by performing two multivariable logistic regression analyses, we were able to create two sets of points. One accounted for increased risk of PE, yielding similar results to Wells et al. The second was created to balance the first, with negative points assigned to factors that predicted an elevated D-dimer. By merging the two, we accounted for factors (similar to age) that while increasing the risk of PE, also independently increased the risk of elevated D-dimer.

Again, following the methodology put forward by Wells et al., a threshold for the score was determined from a receiver operating characteristic (ROC) from 80% of the study population, randomly sampled [10]. That cutoff led to no further loss of sensitivity than using the D-dimer alone and led to improved specificity. The rule was confirmed on the remaining 20% validation sample with consistent results.

Previous investigation has suggested an age-adjusted D-dimer with the Vidas D-dimer, measured in Fibrinogen Equivalent Units [17-19]. There is an approximate 2 to 1 conversion ratio between the two D-dimer assays [20]. The age adjustment for the Vidas assay suggests that any patient over the age of 50 can have an adjusted D-dimer cutoff of the age of the patient multiplied by ten. Hypothetical application of this model to the HemosIL assay would suggest that the same formula could then be divided by two, but that model has not yet been tested on the HemosIL assay. We proceeded to test this age-adjustment and its effects on sensitivity and specificity. Thus, patients aged 50 years or more had an increased D-dimer cutoff determined by age multiplied by 5. For example, a 60-year-old patient had a HemosIL D-dimer cutoff of $60 \times 5 = 300$.

Finally, we evaluated the association between platelets and D-dimer results with a Spearman's Rank correlation to analyze the difference between platelets in those patients with a PE and those without a PE. The results suggested a further D-dimer adjustment that could be made for platelet results. That adjustment was created based on ROC results and confirmed on a 20% validation sample.

The final clinical prediction rule, including age and platelet adjustment, and a cutoff of ≥2, was then applied to the remaining 20% of the study population (the validation set). For both the point system and platelet adjustment, the entire database was divided into 80% for creation and 20% for validation, but that was done randomly and performed twice, once for the point system and again for the platelet adjustment. Thus, both the point system and the platelet adjustment were created and validated on the same database in its entirety, but on different randomly selected samples. Sensitivity and specificity for the DAGMAR Score with 95% confidence intervals were calculated for the entire population.

Odds ratios, 95% confidence intervals, univariate analysis, multiple regression analysis and p-values were calculated using the IBM SPSS Statistics 19.0 software package (SPSS, Inc., Chicago, IL).

3. Results

3.1. Characteristics of study subjects

D-dimer was ordered on 8486 patients who visited the ED in the designated time period. Of those, 170 (2%) results were excluded as they were duplicate D-dimer assays ordered on the same patient during the same ED visit. An additional 4793 were excluded as they were D-dimers (positive or negative) without associated imaging. Of the remaining 3523 patients, 2253 (64.0%) had a positive D-dimer and 1270 (36.0%) had a negative D-dimer. Of the positive D-dimers, 198 PE were detected by imaging (8.8%). Of the negative D-dimers, 9 PE were detected by imaging (Fig. 1).

All factors, except those in the table listed below had quite low values for "NR" (not recorded), <1% missing from data collection. Below are included those factors that were significant in their missing values (Table 1).

3.2. Main results

Multiple regression analysis showed factors that predicted PE (highlighted in bold in Table 2) and D-dimer (Table 3).

A positive D-dimer result was assigned five points as a reference standard. For each other significant variable, points for the clinical

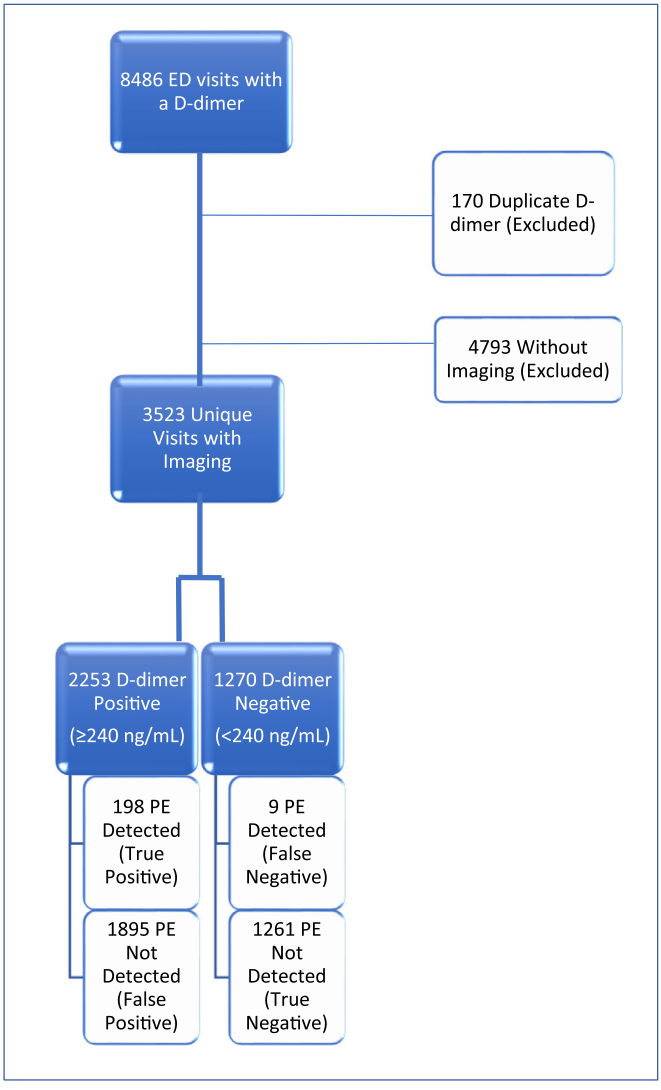

Fig. 1. Patient flow diagram - PE detected after D-dimer results.

Table 1
Factors with significant missing values in chart review.

	N	%
Hemoptysis	1450	41.2
Recent cancer	51	1.4
History of PE/DVT	45	1.3
COPD	53	1.5
Recent Surgery	654	18.6
Exogenous estrogen	472	13.4
Unilateral leg swelling	454	12.9
Smoking	480	13.6

prediction rule were assigned by calculating the combined odds ratio (effect on both PE and D-dimer) as a factor of D-dimer odds ratio predicting PE (10.635). For example, the odds ratio for a given factor, such as history of DVT/PE was divided by the odds ratio for D-dimer predicting PE, 10.635, the standard. In this example the odds radio for history of DVT/PE predicting PE is 1.746. That value was divided by 10.635 for the result of 0.162. We arbitrarily set our standard to be equal to 5 points. Thus, 0.162 was then multiplied by 5 to achieve a result of 0.821. Because this factor predicts PE, not elevated D-dimer, the factor was given a positive value. For factors that predict a PE and also an elevated D-dimer, the former was given a positive value and the latter was given a negative value. The results were summed to provide the net value. Then, each result was rounded to the nearest 0.5. Thus, if the factor increased the odds of PE more than it increased D-dimer, it incurred positive points as the odd's ratio for that factor divided by 10.635. If the factor increased the odds of a positive D-dimer result more than PE, it incurred negative points.

Age was excluded from the point system because of inclusion in the DAGMAR Score as an age-adjusted D-dimer result. Gender was excluded given variability of gender effect on presence of PE and elevated D-dimer, recurrence of PE, and signs and symptoms of PE [21-23]. It was thought to be an over simplification to include gender as one factor regardless of the different cohorts represented. DVT described patients with acute DVT found on the patient visit. Those patients were excluded from the DAGMAR Score so as not to add a confounding variable. Patients with DVTs were more likely to have an elevated D-dimer and were at an increased risk for PE. However, some patients found to have a DVT were treated empirically without further search for a PE. Most did not show signs or symptoms of a PE. Finally, we did not want to mandate an ultrasound in order to utilize the score as that would make the score more time consuming and less efficacious. Otherwise, only factors with OR > 1 and p-value < .05 were included (Tables 4a, 4b, and 4c). Those points that had a non-zero value were included in the DAGMAR Score (Table 5).

Table 2
Multiple logistic regression analysis for factors predicting PE.

	Omnibus test			Nagelkerke
	Chi-square	p-Value		R-square
Model	297.1	<.001		0.230
			95% CI	
Variables	p-Value	OR	Low	High
Age ≥ 50	.731	0.941	0.664	1.333
Cancer	**.005**	**0.470**	0.276	0.799
History of PE	**.015**	**1.746**	1.112	2.742
Shortness of breath	.000	**2.468**	1.733	3.515
Surgery in past 4 weeks	**.006**	**2.163**	1.250	3.743
Fever	.207	0.618	0.293	1.305
Cough	**.037**	**0.648**	0.431	0.973
COPD	.656	0.883	0.510	1.528
Current smoker	.698	1.083	0.724	1.618
Hemoptysis	.591	1.317	0.482	3.604
Unilateral leg swelling	.966	1.013	0.562	1.826
Syncope	.430	1.340	0.648	2.772
DVT	.000	**12.863**	8.000	20.681
Initial heart rate ≥ 100	**.035**	**1.423**	1.024	1.976
Initial respiratory rate ≥ 19	.795	1.046	0.744	1.471
Initial oxygen saturation < 95	**.050**	**1.467**	1.000	2.152
D-dimer > 240	.000	**10.635**	5.495	20.583

Table 3
Multiple logistic regression analysis for factors predicting elevated D-dimer.

	Omnibus test			Nagelkerke
	Chi-square	p-Value		R-square
Model	419.6	<.001		0.154
			95% CI	
Variables	p-Value	OR	Low	High
Age ≥ 50	.000	**2.293**	1.963	2.679
Cancer	**.000**	**2.545**	1.893	3.423
History of PE	.380	0.888	0.681	1.158
Shortness of breath	.411	0.938	0.805	1.093
Surgery in past 4 weeks	**.000**	**5.788**	3.381	9.909
Fever	**.000**	**2.777**	1.773	4.348
Cough	.248	0.897	0.745	1.079
COPD	.995	0.999	0.760	1.313
Current smoker	.343	0.913	0.756	1.102
Hemoptysis	.992	1.003	0.585	1.717
Unilateral leg swelling	.586	0.917	0.673	1.251
Syncope	.101	1.332	0.946	1.875
DVT	.001	**2.530**	1.475	4.341
Initial heart rate ≥ 100	**.000**	**1.797**	1.518	2.127
Initial respiratory rate ≥ 19	**.000**	**1.393**	1.172	1.656
Initial oxygen saturation < 95	**.000**	**1.711**	1.358	2.154

With that Score, a cutoff of ≥2 was used based on the ROC curves generated. With this cutoff, we were able to simultaneously improve sensitivity and specificity (Fig. 2).

When we age-adjusted the D-dimer threshold, according to the suggested model, it did improve specificity while maintaining sensitivity in our cohort.

The mean platelet number in those patients who had a PE was 220 ($1000/mm^3$), *versus* 230 ($1000/mm^3$) in those who did not have a PE. That corresponded with the significant Spearman's Rank correlation that we observed between D-dimer and platelet on preliminary analysis, $p < .01$. This suggested a further D-dimer adjustment could be made for platelet results. We performed the analysis on 80% of the population and set a D-dimer cutoff of 280 μg/L in those patients with platelets above 300 ($1000/mm^3$) to maintain sensitivity based on ROC results (Fig. 3).

After applying the DAGMAR Score, including age and platelet adjustment, specificity of the D-dimer assay improved while simultaneously maintaining sensitivity (Table 6). This lead to a negative likelihood ratio of 0.068, compared to 0.145 without the DAGMAR Score. If clinicians had not ordered CT scans on patients with negative D-dimers, 2253 total CT scans would have been ordered instead of 3501. If the DAGMAR Score were applied, 1556 total CT scans would have been ordered in the study period described.

Nine PE were diagnosed on CT on patients who had a negative D-dimer. Two had a new finding of a PE and were started on anticoagulation. Six were already on anticoagulation and management did not change with the discovery of a PE. One patient was already on anticoagulation

Table 4a
Factors giving positive points, adjusted to D-dimer at +5.

Factors predicting PE	Positive points, D-dimer set to 5
Positive D-dimer	5
History of PE/DVT	0.82
Shortness of breath	1.16
Surgery	1
Initial heart rate ≥ 100	0.67
Initial O_2 sat < 95	0.67

Table 4b
Factors giving negative points, adjusted to D-dimer at +5.

Factors predicting elevated D-dimer	Negative points, D-dimer set to 5
Cancer	−1.19
Fever	−1.3
Surgery	−2.72
Initial heart rate ≥ 100	−0.85
Initial O_2 sat < 95	−0.8
Initial respiratory rate ≥19	−0.65

and was changed to a different agent. Two were documented to be incidental findings. Therefore, of the 1250 CT scans performed with a negative D-dimer, 4 resulted in a change in management (0.4%), which is below the threshold for testing established by Kline et al. [8].

4. Discussion

Pulmonary emboli may pose a diagnostic dilemma for the Emergency physician, balancing the risk of testing with the risk of missing the benefits of treatment. There are well-recognized "classic" risk factors for PE, such as recent surgery or exogenous estrogen, but most patients who had surgery recently or take birth control pills will not suffer a PE.

Clinical decision rules can help mitigate the burden of diagnostic testing, and several such guidelines have been developed for pulmonary embolism (*e.g.* PERC, Wells, and Geneva) [10,24,25]. These rules may be sufficient to risk stratify patients with concern for PE, but may not apply to all patients. The recently published YEARS study demonstrated a novel score to improve specificity in determining presence of PE in order to reduce the burden of CT scans [26]. That study reduced CTPA by 14% (as compared to use of Wells and D-dimer to risk stratify) [26]. Similar to the YEARS study, our study further focuses on incorporating the D-dimer into the decision algorithm, but the DAGMAR Score encompasses many clinical factors found to be predictive by other algorithms and not included in the YEARS study.

Our study presents several important findings. First, it suggests that many of the factors that may cause the patient to present to the ED with a clinical picture concerning for a PE may cause elevation of the D-dimer, independent of the diagnosis of a PE. We propose a score to adjust the D-dimer result for those factors, thus significantly improving the specificity of the test without sacrificing the high sensitivity critical to a screening test.

We also acknowledge that the DAGMAR Score is somewhat counter-intuitive given conventional approaches to assessing a patient who may have a PE. This is true for several reasons. First, it is unconventional to suggest a scoring system that incorporates into in the D-dimer result. We suggest the DAGMAR Score be applied to all patients who cannot be fully evaluated with PERC. Thus, this is the patient population on whom a D-dimer would be conventionally ordered, but instead of using Wells or Geneva to risk stratify a patient, thus generating a percentage likelihood that a patient does or does not have a PE, we suggest a score that incorporates the D-dimer, thereby further reducing the number of patients on whom CT scans are unnecessarily ordered. Although unconventional in the merging of the D-dimer into the score, we believe this score will be powerful in its ability to further reduce unnecessary testing, further than what can be safely accomplished by the current purely clinical decision-making tools.

Next, it is unconventional to attribute negative points to factors that have historically been demonstrated to be risk factors for developing PE. This can be understood by realizing that those factors, such as recent surgery, cancer, or tachypnea are associated with PE, but are more strongly associated with a positive D-dimer, regardless of whether or not a PE is present. Thus, the net negative points reflect both the strength of association with PE and also the strength of association with an elevated D-dimer. It may be counter-intuitive to consider a patient with a positive D-dimer, tachypnea, cancer, recent surgery and fever to be low risk for PE. However, this scoring system suggests that the patient is more likely to be suffering an alternate etiology of those symptoms. Likely that patient would receive a CT scan to further evaluate, but it would probably not reveal a PE. However, this would need to be further validated in prospective study and inclusion of definite high-risk patients.

We accomplished a significant improvement in specificity without compromise of sensitivity by generating a score that accounted for factors known to increase the D-dimer. For example, many studies have demonstrated success behind age adjustment – leading to improved specificity of the D-dimer assay in patients who are elderly and are also more prone to have a PE [17-19]. However, the same strategy was used here in a novel fashion to consider the effect of surgery and cancer. Those factors are both well known to increase the risk of PE, but they also both inflate the D-dimer result excessively, just as an elderly person is likely to have an elevated D-dimer even in the absence of a PE. In the DAGMAR Score, we successfully quantified that dichotomy to improve specificity in a population where sensitivity is critical.

Table 4c
Factors summed and rounded to the nearest 0.5.

	Sum of positive and negative points	Sum rounded to the nearest 0.5
Positive D-dimer	5	5
History of PE/DVT	0.8	1
Shortness of breath	1.2	1
Surgery	−1.7	−2
Initial heart rate ≥ 100	−0.2	0
Initial O_2 sat < 95	−0.1	0
Cancer	−1.19	−1
Fever	−1.3	−1.5
Initial respiratory rate ≥19	−0.65	−0.5

Table 5
Points assigned to the DAGMAR Score. DAGMAR Score < 2 equates to a low overall PE risk < 1.2%.

DAGMAR Score	Points
Positive D-dimer	5
Shortness of breath	1
History of PE/DVT	1
Surgery	−2
Fever	−1.5
Cancer	−1
Initial respiration rate ≥ 19	−0.5

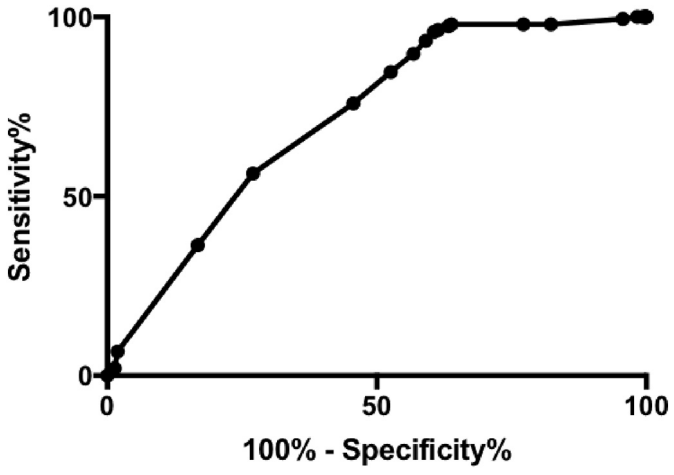

Fig. 2. ROC curve selecting the cutoff for DAGMAR Score. Area under the curve (AUC) 0.7182, p < .001 (95% CI 0.69–0.75) indicating discriminative ability.

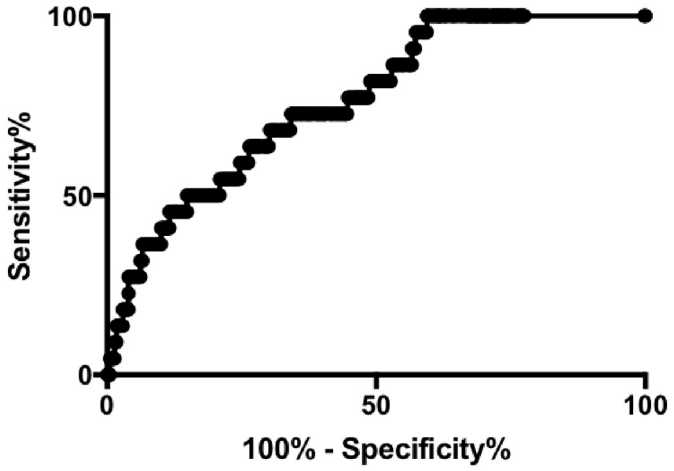

Fig. 3. ROC curve selecting the cutoff for platelets > 300. AUC 0.7639, p < .001 (95% CI 0.68–0.85).

We further validated the age-adjustment that has previously been proposed. To our knowledge, this is the first application to the HemosIL D-dimer assay with different units and a different cutoff (240 ng/mL D-dimer units as opposed to the 500 μg/L FEU units of the Vidas assay).

Although the safe cutoff threshold is largely mandated by the manufacturer, and in the United States by the Food and Drug Administration (FDA), many physicians have adopted the use of an age-adjusted cutoff based on the above-mentioned studies. Similarly, the DAGMAR Score allows for safe adjustment of the cutoff based on other factors that may artificially elevated the level of the D-dimer, irrespective of the presence of a PE. One could argue that the cutoff be lowered in a population that is extremely low risk for PE. We would argue that this population be defined by the PERC score and no D-dimer be ordered on those patients. In patients who were not PERC negative, we were unable to safely further lower the D-dimer cutoff beyond the current manufacturer standard.

Next, we are the first to suggest an adjustment for D-dimer based on total platelet number. Platelets were lower in patients with a PE and higher in those without, which may be the result of consumption developing the pulmonary thrombus, although this is not established by the current study. There was also an independent correlation between platelet result and D-dimer result. The exact interaction of this relationship within the clotting cascade, or how it may be affected by different physiological or pathological states bears further investigation and validation by examining in other, larger databases with diverse patient populations the relationship between D-dimer and platelets.

It is important to acknowledge the PEs that were unrecognized by both the HemosIL D-dimer assay alone and in combination with the DAGMAR Score. Based on previous recommendations, a testing threshold of 2% is not only acceptable, but desirable given the harm of testing for and treating PE [25]. Among those PEs missed by the DAGMAR Score and HemosIL D-dimer, there were clearly two PEs that were discovered and treated despite negative results (1%). However, two of the other PEs were determined to be incidental findings, which by current CHEST guidelines should not be treated [27-29]. The others were already on anticoagulation, although one patient did change type of anticoagulation.

Table 6
Sensitivity and specificity of the D-dimer assay with and without the DAGMAR Score.

	D-dimer without adjustment	DAGMAR Score
Sensitivity	94.45% (91–98)	95.98% (92–98)
Specificity	38.38% (36–40)	58.86% (57–61)

*95% CI in parenthesis.

It is interesting that the majority of the false negative D-dimers were found on patients on anticoagulation. That bears further investigation on the sensitivity and specificity of the HemosIL D-dimer for patients on different types of anticoagulation but could also be a result of the retrospective nature of the study. It may be that CT scans demonstrated acute PE on patients who in fact had subacute or chronic PE, thus accounting for a positive result but negative D-dimer.

Given the small confidence intervals and the high sensitivity in our study, this supports use of the HemosIL D-dimer for patients who are both low and moderate risk by Wells. If one accepts the possibility that only two PEs were missed in a way that would change outcome, then this further supports the suggestion that this highly sensitive D-dimer could potentially be used in combination with the DAGMAR Score on low, moderate, and high-risk patients as assessed by Wells.

These findings require further prospective validation. In addition, owing to its retrospective nature, many factors such as hemoptysis, were not recorded with enough frequency to be included in our analysis. It would also be interesting to apply the methodology used to create the DAGMAR Score on other databases that include other factors and follow-up imaging to determine if we could improve the utility of the DAGMAR Score by including more factors that may predict presence of PE or elevated D-dimer.

It would be further useful to use this methodology to develop a calculator that does not only provide a dichotomized result – a patient requiring further evaluation with imaging or one who has low likelihood of PE – but also a prediction of the likelihood of PE based on all results. However, in the clinical setting, many physicians rely on dichotomized results accepted in general practice to guide patients on the value of further work-up. Thus, we believe the DAGMAR Score will likely be useful in the clinical practice, even if future prediction scores give a precise likelihood of the presence of a PE.

4.1. Limitations

This study was limited by its retrospective nature, the inherent limitations of using a single hospital system with the same physicians, and the focus on factors found to be noteworthy by other clinical decision-making tools.

The most significant limitation is the exclusion of patients without imaging and lack of follow up on the patients with imaging. As this was a retrospective study, we focused entirely on those patients for whom we had imaging results and a D-dimer. This likely did not include many patients with a PE on whom a D-dimer was not sent as they were deemed to be high risk. It is also possible that patients went on to develop a PE shortly after being seen in the ED, and this data was not captured due to lack of follow up. Patients were likely also precluded from the population if they were particularly low risk, or those who were PERC negative and no D-dimer was ordered. Thus, we introduced bias by using only this population. That bias is reflected with our relatively high positive D-dimer rate (64%).

Also due to the retrospective nature, many factors were not documented. For example, hemoptysis was frequently not documented and thus was not sufficiently present to contribute significantly in our analysis. That may lead to selection bias in our analysis. Similarly, because many factors included in the Wells and PERC Scores were often not documented, it was difficult to compare rate of CT ordering with utilization of the DAGMAR Score as opposed to conventionally described clinical decision making. We sufficed by calculating sensitivity and specificity in our cohort and demonstrated the change with DAGMAR, but those values should not be interpreted as absolute sensitivity and specificity given the nature of the study.

Similarly, all VQ scans that were moderate and high-probability were considered positive for PE. Our aim was to be conservative, but it is possible that some of the VQ scans that showed moderate risk for PE were not actual PE.

5. Conclusions

With further prospective validation, the DAGMAR risk stratification tool in combination with D-dimer testing could improve current methods of non-invasive PE risk stratification in the Emergency Department, with potential improvements to sensitivity and specificity, and may ultimately decrease wait times, cost, and harmful side effects of imaging studies.

Meetings

Data presented at ACEP in Washington, DC, October 2017. Detailed platelet data presented at AAEM in San Diego, CA, April 2018 – second place award.

Conflicts of interest

We have no conflicts of interest to disclose.

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