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ORIGINAL ARTICLE

European and American suspected and confirmed pulmonary embolism populations: comparison and analysis

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Summary. *Background:* If the prevalence of pulmonary embolism (PE) differs significantly between the US and Europe, this observation could reduce the generalizability of diagnostic protocols for PE derived in either location. *Objective:* To determine possible causes and potential clinical consequences of these PE prevalence differences. *Methods:* Secondary analysis of three prospectively collected multicenter samples (two French and one from the US) including 3174 European and 7940 American PE-suspected patients in Emergency departments (ED) (117 for Europe and 12 for US). Comparison of clinical features, resource use and outcomes of European- and US-suspected PE populations in ED. *Results:* European patients evaluated for PE were significantly older and had a higher clinical pretest probability (CPP) for PE. The final PE prevalence was significantly higher in Europe, in the overall sample (26.5% vs. 7.6%) and in each level of CPP. Suspected European patients categorized as low CPP had a higher posttest probability than US low CPP patients. Suspected US patients categorized as high CPP had a much lower posttest probability of PE than in Europe. The mean number of tests performed for one PE diagnosis was lower in Europe (7.4 vs. 21.6). Among patients diagnosed with PE, European patients had a higher mean severity of illness score and a higher PE-mortality rate (3.4% vs. 0.7%). *Conclusions:* Among patients suspected of a PE and those ultimately diagnosed with a PE, European patients had higher acuity, a higher pretest probability and worse outcome than US patients. The present study underscores the importance of disease prevalence for pretest probability scoring approaches and for significance interpretation of imaging tests.

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Introduction

Pulmonary embolism (PE) remains a diagnostic problem because of the frequency of occurrence and its presentation with non-specific clinical signs and symptoms that overlap with other common cardiopulmonary disorders. On one hand, the fear of missing a potentially mortal diagnosis drives the desire to test, but on the other hand, the wish to avoid unnecessary examinations and their harmful consequences drives the desire to not test. Some authors speculate that as many as one-half of emergency patients with a PE go unrecognized and untreated leading to a mortality rate as high as 30% [1,2].

The fear of misdiagnosis as well as the availability of several non-invasive diagnostic procedures have fueled an increase in diagnostic testing for PE, especially in emergency departments (ED). The introduction of computed tomographic pulmonary angiography (CTPA) has seen a slight increase in the diagnosis of PE in the US but the number of patients tested without a PE has increased even more [2–4]. In recent diagnostic studies in North America, PE prevalence was as low as 5% to 10%, and approximately one-third of patients were found to have undergone repeated CTPA scanning that was negative for PE [5–7]. Conversely, in European diagnostic studies, PE prevalence remains around 20% to 30% [8,9]. As predicted by Bayes' theorem, such differences in suspected PE populations may have important consequences for medical practices because the predictive value of diagnostic test results varies with disease prevalence. To our knowledge, no previous study has directly compared the clinical features and outcomes of European and U.S. patients with a suspected PE. We hypothesized that comparison of two large, multicenter samples from Western Europe and the U.S. would reveal significant and clinically important differences in pretest probability, acuity and outcomes.

Methods

We analyzed three prospective collected databases from patients suspected of a PE.

The compilation of the first two samples represents the 'European-suspected population', and the third sample represents the 'US-suspected population'. The first European sample was a prospective cohort designed to measure the appropriateness of diagnostic criteria used in routine practice to rule in or rule out a PE in 117 EDs from France and Belgium ($n = 1529$) [10]. The second European sample was the intervention phase of a cluster-randomized trial measuring the effectiveness of a hand-held clinical decision support system to improve the diagnostic work-up for PE suspicion in 20 French EDs ($n = 1645$) [11]. The US sample was a prospective observational study of patients undergoing testing for a possible PE in 12 EDs from the US ($n = 7940$) [12]. In all three studies, a standardized form was prospectively completed reporting patient characteristics. Before any diagnostic testing, physicians were invited to give their gestalt assessment of the pretest probability of a PE (as low, intermediate or high for European studies and as $< 15\%$, 15%–40% and $> 40\%$ for the US study, considered low, intermediate and high, respectively). All three studies had a follow-up period (3 months in the European studies and 45 days in the US study). The patients, relatives or general practitioner were interviewed at the end of a follow-up period about the possible occurrence of a venous thromboembolic event or bleeding complication. Moreover in the US study, in absence of telephone follow-up, the patient's medical record and social security death index were searched. The diagnosis of a thromboembolic event was confirmed according to predefined criteria that included definitive findings on imaging followed by a clinical plan to treat [10–12]. Sudden deaths with no obvious cause were adjudicated as possibly related to PE. In the present study, to standardize reporting, only events occurring in the first 45 days of follow-up were used for outcome designation. Patients were excluded in the three studies if the diagnosis of thromboembolic disease was documented before admission. In European studies, patients were also excluded if (i) a PE was suspected during a hospital stay of more than 2 days duration; or (ii) diagnostic testing was cancelled for ethical reasons, because of rapid death, or because the patient decided to leave the hospital against medical advice or declined testing. In the US study, patients were also excluded before enrollment if (i) the patient indicated that the enrollment hospital was not his or her hospital system of choice for follow-up or (ii) any circumstance suggested that the patient would be lost to follow-up. We considered as a final diagnosis of PE: (i) a PE or a deep vein thrombosis (DVT) diagnosis ruled in at the end of the initial diagnostic work-up; (ii) a thromboembolic event (PE or DVT) occurring during the follow-up period, among patients in whom the diagnosis of PE was initially ruled out or (iii) death adjudicated as related or possibly related to PE. We collected the clinical gestalt assessment prospectively documented and retrospectively calculated the Wells' score. The subjective criterion about the likelihood of an alternative diagnosis was prospectively collected in the standardized form. As the criterion 'unilateral lower limb pain' was not collected in the US database, we calculated the Revised Geneva score (RGS) assuming this criterion was absent. The primary variables related to pretest probability assessment included the proportion of patients categorized in each clinical probability group (low, moderate and high) and the accuracy of categorization compared with observed outcome rate of a PE. The primary patient outcome variables included the overall rate of PE diagnosis, and the Pulmonary Embolism Severity Index (PESI) [13], overall mortality, PE-related mortality and bleeding complications. As previously it has been shown that the majority of PE-related deaths occurred within 2 weeks of the initial work-up [14], we also calculated PE-related mortality in the first 2 weeks of follow-up. As the 'altered mental status' was not available in the overall sample, we calculated the PESI assuming this criterion was absent.

We calculated the mean number of tests performed in all European and US patients for each new PE diagnosis as being the ratio of the total number of tests done in all suspected patients divided by total number of new PE diagnoses.

All statistical analyzes were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). A chi-square test (for categorical variables) or Mann–Whitney *U*-test (for continuous variables) was used to compare characteristics between European and US samples. A multivariate logistic regression was performed in order to determine the relationship between mortality and patient's origin, D-dimer use, CTPA use or severity (PESI).

Results

Table 1 reveals multiple differences in baseline characteristics of European (3174 patients) compared with US (7940 patients) PE-suspected populations. PE-suspected European patients were older, had a higher mean respiratory rate, lower oxygen saturation, higher frequency of syncope and hemoptysis, but a lower frequency of chest pain or dyspnea. Compared with US-suspected PE patients, European patients had a higher frequency of a personal history of VTE, congestive heart failure and active cancer. Conversely, patients in the US sample had more chronic respiratory disease, recent surgery and a higher frequency of pregnancy or postpartum status. At the time of diagnostic evaluation, the treating clinicians in Europe considered a PE as the most likely diagnosis significantly more often (34.5% vs. 16.8% $P < 0.001$). Regardless of the method used, clinical probability assessment categorized a significantly higher proportion of European patients as having a moderate or high pretest probability of PE. Clinicians in Europe ordered significantly more D-dimer tests, ventilation/perfusion (V/Q) scan and leg ultrasonography but fewer CTPA. In Europe, when a D-dimer test was performed, the assay format was more likely to be a high sensitivity quantitative test (98% vs. 73.9%; $P < 0.001$). The percentage of positive exams for each investigation was higher among the European samples. During the follow-up period, 298 patients were lost in Europe, none in the US.

Table 1 Characteristics of suspected pulmonary embolism (PE) populations

Suspected populations	European population $n = 3174$		US population $n = 7940$		*P*-value
	Data (missing/collected)	Mean or *n* (SD or %)	Data (missing/collected)	Mean or *n* (SD or %)	
Demographic characteristics					
Mean age, years	0/3174	62.4 (0.3)	6/7934	49.0 (0.2)	< 0.001
Gender, female	0/3174	1867 (58.8)	0/7940	5328 (67.1)	< 0.001
Clinical characteristics					
Mean SBP, mmHg	46/3128	141.2 (0.5)	26/7914	131.0 (0.3)	< 0.001
Mean heart rate, bpm	4/3170	89.9 (0.4)	22/7918	92.2 (0.2)	< 0.001
Mean respiratory rate, rpm	760/2414	21.7 (0.1)	62/7878	20.8 (0.1)	< 0.001
Mean O_2 saturation	186/2988	94.5 (0.1)	24/7916	96.5 (0.0)	< 0.001
Sign or symptom					
Chest pain	12/3162	1867 (59.0)	0/7940	5767 (72.6)	< 0.001
Dyspnea	17/3157	2061 (65.3)	0/7940	5587 (70.4)	< 0.001
Syncope or dizziness	22/3152	666 (21.1)	0/7940	479 (6.0)	< 0.001
Hemoptysis	0/3174	128 (4.0)	0/7940	228 (2.9)	0.002
Palpation pain and lower limb oedema	2/3172	426 (13.4)	0/7940	710 (8.9)	< 0.001
Personal history VTE	0/3174	605 (19.1)	0/7940	858 (10.8)	< 0.001
Known congestive heart failure	15/3159	439 (13.9)	0/7940	581 (7.3)	< 0.001
Chronic respiratory disease	1/3173	401 (12.6)	0/7940	1711 (21.5)	< 0.001
Stroke	9/3165	139 (4.4)	0/7940	300 (3.8)	0.134
Cancer	0/3174	242 (7.6)	0/7940	489 (6.2)	0.005
Past surgery < 1 month	0/3174	155 (4.9)	0/7940	520 (6.5)	0.001
Fracture	0/3174	67 (2.1)	0/7940	149 (1.9)	0.419
Current pregnancy	6/3168	25 (0.8)	0/7940	147 (1.9)	< 0.001
Postpartum < 4 weeks	7/3167	10 (0.3)	0/7940	141 (1.8)	< 0.001
Current anticoagulant treatment	10/3164	211 (6.7)	0/7940	520 (6.5)	0.818
PE is the most likely diagnosis	4/3170	1095 (34.5)	0/7940	1336 (16.8)	< 0.001
Clinical probability classification					
Gestalt assessment					
Low	1142/2032	766 (37.7)	8/7932	5357 (67.5)	< 0.001
Moderate		848 (41.7)		2087 (26.3)	
High		418 (20.6)		488 (6.2)	
Wells score					
Low	2/3172	1740 (54.9)	0/7940	5482 (69.0)	< 0.001
Moderate		1222 (38.5)		2201 (27.7)	
High		210 (6.6)		257 (3.2)	
RGS					
Low	5/3169	1027 (32.4)	28/7912	3292 (41.6)	< 0.001
Moderate		2011 (63.5)		4421 (55.9)	
High		131 (4.1)		199 (2.5)	
Examinations performed					
D-dimer test	0/3174	2838 (89.4)	0/7940	5907 (74.4)	
Quantitative D-dimer test	0/2838	2783 (98.0)	0/5907	4363 (73.9)	
CTPA	0/3174	1161 (36.6)	0/7940	4237 (53.4)	
V/Q scan	3/3171	484 (15.3)	0/7940	468 (5.9)	
Leg Ultrasonography	0/3174	1137 (35.8)	0/7940	987 (12.4)	
Angiography	0/3174	3 (0.09)	0/7940	499 (6.3)	
Positive Exams					
D-dimer test	0/2838	1825 (64.3)	0/5907	2242 (38.0)	
Quantitative D-dimer test	0/2783	1775 (63.8)	0/4363	1908 (43.7)	
CTPA	0/1161	415 (35.7)	0/4237	450 (10.6)	
V/Q scan*	0/484	157 (32.4)	0/468	39 (8.3)	
Leg Ultrasonography	0/1137	371 (32.6)	0/987	155 (15.7)	
Angiography	0/3	2 (66.7)	0/499	22 (4.4)	
Diagnosis					
VTE during emergency work-up	0/3174	733 (23.1)	0/7940	544 (6.9)	< 0.001
VTE during FU	298/2876	22 (0.7)	0/7940	16 (0.2)	0.002
All VTE = final PE diagnosis	298/2876	763 (26.5)	0/7940	561 (7.1)	< 0.001
Final PE prevalence according to pretest probability					
Gestalt					
Low	110/656	51 (7.8)	0/5357	167 (3.1)	< 0.001
Moderate	75/773	201 (26.0)	0/2087	223 (10.7)	

Table 1 Continued

Suspected populations	European population $n = 3174$ Data (missing/collected)	Mean or n (SD or %)	US population $n = 7940$ Data (missing/collected)	Mean or n (SD or %)	P-value
High	14/404	263 (65.1)	0/488	171 (35.0)	
Total	199/1833	515 (28.1)	0/7932	561 (7.1)	
Wells score					
Low	217/1523	151 (9.9)	0/5482	172 (3.1)	< 0.001
Moderate	74/1148	470 (40.9)	0/2201	294 (13.4)	
High	7/203	134 (66.0)	0/257	95 (37.0)	
Total	298/2874	755 (26.3)	0/7940	561 (7.1)	
RGS					
Low	133/894	91 (10.2)	0/3292	93 (2.8)	< 0.001
Moderate	160/1851	585 (31.6)	0/4421	401 (9.1)	
High	5/126	78 (61.9)	0/199	63 (31.7)	
Total	298/2871	754 (26.3)	0/7912	557 (7.0)	

VTE, venous thromboembolism; SBP, systolic blood pressure; RGS, Revised Geneva score; CTPA. computed tomographic pulmonary angiography; V/Q, ventilation/perfusion.
*Positive V/Q scan means exam with a high probability of a PE.

The overall final PE prevalence was significantly higher in Europe (26.5% final PE diagnosed in Europe vs. 7.1% final PE diagnosed in the US, 95% confidence interval [CI] for the difference of 19% = 17.8% to 21.2%). At each strata of the pretest probability, the PE prevalence was approximately two-fold higher in Europe vs. the US, regardless of the method of assessment used (gestalt, Well's score or RGS) (Table 1). The mean number of tests performed in all patients for each new PE diagnosis was 7.4 in Europe and 21.0 in the US ($P < 0.001$).

The severity of PE assessed by PESI was significantly higher in Europe 55.8% vs. 44.6% patients with a PESI > 85 ($P < 0.001$) (Table 2). Significantly more patients had a PE diagnosed using CTPA scanning in the US compared with Europe. PE-related mortality was significantly higher in the European population (3.4% vs. 0.7%, 95% CI for difference = 1.2% to 4.2%) whereas overall mortality and bleeding complications were similar. In the first 2 weeks, the results of PE-related mortality were similar (Table 2).

We used a multivariate logistic regression analysis to test if the independent variables country of origin, CTPA (performed or not), PESI (classes I and II vs. III, IV and V) and D-dimer (performed or not) were significant predictors of mortality. This analysis found that only the continent of origin was a significant predictor of mortality (Table 3).

Table 4 shows the hypothetical posttest probabilities that could be expected in each country, using published estimates of likelihood ratios for CTPA [15,16]. The primary findings of importance are the relatively high posttest probability for PE (6.9%–25.1%) after a negative CTPA in high pretest probability patients in Europe and the relatively low posttest probability (40.8%–45.8%) after a positive CTPA in low pretest probability patients in the US. Posttest probabilities

Table 2 Characteristics of patients with a final pulmonary embolism (PE) diagnosis

Patients with final VTE diagnosis	European population $n = 763$ Data (missing/collected)	Mean or n (SD or %)	US population $n = 561$ Data (missing/collected)	Mean or n (SD or %)	P-value
Demographic characteristics					
Mean age, years	0/763	69.0 (0.6)	1/560	55.6 (0.8)	< 0.001
Gender, female	0/763	462 (60.6)	0/561	305 (54.4)	0.024
Severity assessment – PESI					
≤65 (Class I)	179/584	98 (16.8)	7/554	198 (35.7)	< 0.001
66–85 (Class II)		160 (27.4)		109 (19.7)	
86–105 (Class III)		142 (24.3)		117 (21.1)	
106–125 (Class IV)		99 (16.9)		63 (11.4)	
> 125 (Class V)		85 (14.6)		67 (12.1)	
Exams					
CT performed	0/763	482 (62.3)	0/561	479 (85.4)	< 0.001
Complications					
Overall death	0/763	45 (6.7)	0/561	32 (5.7)	0.62
PE-related death	0/763	26 (3.3)	0/561	4 (0.7)	0.003
PE-related mortality in the first 2 weeks	0/763	18 (2.4)	0/561	2 (0.4)	0.006
Bleeding	0/763	37 (4.5)	0/561	25 (4.5)	0.840

VTE, venous thromboembolism; PESI, Pulmonary Embolism Severity Index [13]; CTPA, computed tomography pulmonary angiography.

Table 3 Mortality multivariate logistic regression analysis in patients with a pulmonary embolism (PE)

	Dependent variable: mortality	
Co-variables	*P*-value	OR (95% CI)
Continent origin (US vs. Europe)	0.004	0.39 (0.20–0.73)
Quantitative D-dimer performed	0.106	0.47 (0.19–1.17)
CTPA performed	0.888	1.07 (0.42–2.74)
PESI (classes I and II vs. III, IV and V)	0.073	2.56 (0.92–7.14)

CTPA, computed tomography pulmonary angiography. Equation: Mortality = −2.65 − 0.972 Origin + 0.83 CTPA + 0.958 PESI II − 0.773 D-dimer. Pearson's chi-square goodness of fit: 5.368. Hosmer–Lemeshow *P*-value: 0.615.

were similar when calculated using the RGS and the original Well's score (data not shown). We also calculated the posttest probabilities using the second-level Well's score categorizing patients as unlikely or likely as having a PE (Table 4).

Discussion

The present study confirms the presence of major differences in PE prevalence in patients tested, clinical characteristics and the diagnostic management between European- and US-suspected PE populations. Additionally, the data show significant differences in the severity of PE after diagnosis. Our results suggest some causes and consequences of these discrepancies.

Differences in clinical patients' characteristics suggest that at the time of diagnostic evaluation in the ED setting, European patients had a higher acuity than US patients: they were older, had a higher mean respiratory rate, a lower mean O_2 saturation and more frequently had syncope and a serious comorbidity such as cancer and heart failure. Even if all differences were statistically significant, some of them were clinically moderate. Nevertheless, an overall analysis suggests this higher acuity at ED admission of European patients. Dyspnea and chest pain were found more frequently in the US-suspected population, suggesting that these general classic symptoms were more often the reason that diagnostic testing was initiated in the US. Because the prevalence of PE was very low in the US, as a consequence, the number of tests ordered in all patients needed to achieve one PE diagnosis was near three-fold more in the US than in Europe.

Differences were also observed in clinical probability assessment. Regardless of the method used, the proportion of patients who were classified as low pre-test probability was much lower in Europe than in the US. Moreover, PE prevalence was around two-fold higher in each level of clinical probability in Europe. These findings have important clinical consequences in terms of estimating posttest probability of diagnostic strategies using a Bayesian approach. The risk of inappropriately ruling out PE on a negative CTPA scan in high clinical probability patients may be as high as 25% in Europe. Conversely, the risk of overdiagnosis of PE with a positive CT scan may reach 64% in US low clinical probability patients suspected of a PE (Table 4). This underscores the classic teaching that posttest probability, what clinicians and more importantly patients are most concerned about, is highly dependant on the baseline prevalence of disease among all those who are tested. Indeed, the risk is the highest when the clinical probability evaluation and the test result are discordant, for example low clinical probability and positive CTPA or high clinical probability and negative CTPA. As a consequence of very low prevalence in the US low clinical probability and the relatively high prevalence in the Europe high clinical probability, the problem is crucial in US low clinical probability with positive CTPA, as it is in Europe in high clinical probability with negative CTPA. In our sample, 135 American patients had low pretest probability and positive CTPA; on the other hand, 93 European patients had high pretest probability and negative CTPA. These figures mean that in 30% (135/450) of all positive CTPA in the US there is a potential risk of false-positive CTPA; and that in 13% (93/709) of all negative CTPA there is a potential risk of a false-negative, suggesting adaptation of our practices. There are no evidence-based recommendations, but first we suggest considering a second reading of the examination focusing on the quality of the test and the reliability of the result; a second evaluation of the CTPA performed by an expert CTPA radiologist would probably be effective to decrease the CTPA evaluation error [17–19]. In the case of suboptimal CTPA (and/or discordance between radiologists), consider performing another CTPA optimizing parameters or a V/Q scan in young patients without previous a PE or chest disease. In the case of a confirmed negative CTPA and high clinical probability in Europe, consider lower limb deep vein analysis [15,16,20]. A proximal

Table 4 Calculation of posttest probability for computed tomography pulmonary angiography (CTPA) results

Pretest probability	PE prevalence in Europe	PE prevalence in the US	Posttest probability in Europe if negative*	Posttest probability in the US if negative*	Posttest probability in Europe if positive†	Posttest probability in the US if positive†
Gestalt						
Low	7.8	3.4	0.3–1.5	0.1–0.6	62.4–67.1	40.8–45.8
Moderate	26.0	11.4	1.4–5.9	0.5–2.3	87.3–89.4	71.6–75.5
High	65.1	36.0	6.9–25.1	2.2–9.2	97.3–97.8	91.7–93.2
Wells						
Likely (≤4)	16.3	3.9	0.8–3.5	0.1–0.6	77.2–80.6	44.3–49.4
Likely (>4)	52.7	23.8	4.3–16.7	0.5–2.3	95.2–96.1	86–88.3

*Assuming a negative likelihood ratio of 0.04 or 0.18 [15,16].
†Assuming a positive likelihood ratio of 19.6 or 24.1 [15,16].
PE, pulmonary embolism.

lower limb or pelvic deep venous thrombosis means a false-negative CT and justified anticoagulant treatment. Conversely, if both are negative, clinically relevant venous thrombosis disease can be ruled out and anticoagulant can be withheld with confidence. In the case of a confirmed positive CTPA and low clinical probability, especially in the US, consider the level of pulmonary arteries involved. In the case of subsegmental PE, performing an ultrasonography or CT venography and withholding anticoagulant treatment in the absence of thrombosis seems appropriate [16,21,22].

These data show important differences between European and US patients diagnosed with PE in the ED. Severity and PE-related mortality were significantly lower in US PE patients. PESI classes I and II have been demonstrated to identify patients with a very low risk mortality which could benefit from out of hospital treatment [23]. Our results infer the possibility that a larger proportion of patients in the US could be considered for outpatient treatment compared with Europe.

Several explanations could be hypothesized to explain these differences in PE patients. The wide availability of D-dimer tests is associated with an increase of tested patients [2,24]. Multidetector CT may allow detection of smaller emboli than other diagnostic strategies such as V/Q scanning, and may increase the number of diagnosed PE without impacting mortality [4,17,25]. However, more D-dimer testing was performed in European patients and the multivariate regression analysis shows that the rate of PE-related mortality was significantly higher in European PE patients unrelated to CTPA use.

We speculate that European PE patients are more severely ill and have a higher PE mortality because European clinicians suspect PE in patients with more serious symptoms and/or a worse health condition than American physicians: PE patients are more serious because suspected PE patients are more serious. This may reflect a lower suspicion threshold in the US than in Europe. European practice seems to be not to suspect PE and not to order further tests in patients with mild symptoms. That may increase the risk of missed diagnosis by under-investigation. Conversely in the US, clinicians seem to suspect PE and initiate a diagnostic process at a very low level of suspicion (clinical probability) in patients with fewer serious symptoms and a better health condition. This may lead to over investigations and to possible over-diagnosis in the US. This lower suspicion threshold could be a consequence of medical teaching and practices more based on recommendations and standardized protocols in the US than in Europe, probably owing to the fear of legal procedures. Conversely, the medical and economic consequences of possibly unnecessary exams such as CTPA seem to be emphasized in Europe and, combined with difficulties in radiologic test access, may lead to under-investigation. Another explanation would be differences in populations evaluated in EDs and health care organization in the US vs. Europe. In Europe, as access to primary health care is easy; patients in emergency departments are often referred there by their general practitioner. In contrast, a larger proportion of patients in the US may have limited or no access to primary care physicians, and therefore must rely on the ED as their only portal of access to health care. Thus, it can be inferred that more young and healthy persons with chest pain or dyspnea may first visit a general practitioner in Europe, whereas these patients must to go to an ED in the US. In order to confirm these hypotheses, a prospective study with patient's inclusion based on classic PE symptoms (dyspnea or chest pain) and not on clinician's suspicion would be necessary. Such a study, including American and European patients, could allow us to derive a first step rule able to standardize the PE suspicion threshold.

The present study has some limitations. It was a secondary analysis of three prospective studies and the period of the European and the US studies were not exactly the same. Secondly, while no patient was lost during follow-up probably because of the US enrollment criteria, some European patients were lost during follow-up and could have had thromboembolic events or PE-related death. However, European lost to follow-up patient populations were similar than the analyzed population (data not shown), decreasing the likelihood of such a bias. Two extreme situations could have been possible: (i) no thromboembolic event was diagnosed among these patients, the overall PE prevalence would be in this case of 24.0% which do not change our results; or (ii) all lost of follow-up patients had a thromboembolic event leading the overall PE prevalence to 33.4% which only would further increase the PE prevalence difference between the two continents. Finally, similar to most existing studies of PE diagnosis, our investigation concerned only PE suspected patients in the ED, not allowing our results to be extrapolated to inpatients and general medicine practice. However, our results were obtained from unselected PE suspected patients from a large number of EDs (117 in Europe and 12 in the US.) and patients were managed as in daily practice. Therefore, our results are highly likely to provide an accurate sample of European and American prevalence and practice-pattern differences between the two continents.

Conclusion

Suspected PE populations in ED in Europe and the US have several clinically important differences in acuity and outcome. Patients in Europe who were judged to be low risk by clinicians had a higher posttest probability of disease than US low-risk patients. Patients tested in the US who were considered to be high risk had a much lower post-test probability of PE than in Europe. The present study underscores the importance of considering prevalence of disease when applying pre-test probability scoring approaches and when interpreting the significance of imaging tests.

Addendum

A. Penaloza and P.-M. Roy had full access to all data study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A. Penaloza, J. Kline, F. Verschuren, P.-M. Roy. Analysis and interpretation of data: A. Penaloza, J. Kline, F. Verschuren,

D.M. Courtney, F. Zech, B. Derrien, B. Vielle, F. Thys, P.-M. Roy. Drafting of the manuscript: A. Penaloza, J. Kline, F. Verschuren, D.M. Courtney, P.-M. Roy. Critical revision of the manuscript for important intellectual content: F. Zech, B. Vielle, B. Derrien, A. Armand-Perroux, F. Thys. Statistical analysis: A. Penaloza, F. Zech, B. Vielle. Study supervision: A. Penaloza, J. Kline, F. Verschuren, D.M. Courtney, B. Derrien, A. Armand-Perroux, F. Thys, P.-M. Roy.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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