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Incidence of Pulmonary Embolism in an Emergency Department Cohort Evaluated with a Simple Symptom-based Diagnostic Algorithm

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Abstract. *Background: Although complex scores were recommended for diagnosis of pulmonary embolism (PE), acceptance in clinical practice is limited. In our Emergency Department a symptom-based algorithm for patients with suspected PE including computed tomographic pulmonary angiography (CTPA) and D-dimer testing was implemented. Patients and Methods: The cases of 492 patients presenting with either chest pain, dyspnea or syncope for whom this algorithm was applied, were retrospectively analyzed with respect to the incidence of PE, D-dimer and high-sensitive troponin levels. Results: Our algorithm detected PE in 59 out of 492 patients. D-Dimer levels were significantly higher in the PE group than in the patients without PE ($p<0.0001$). High-sensitive troponin was significantly increased in patients with central PE compared to other patients ($p<0.01$). Conclusion: Our data demonstrate the utility and practicability of our symptom-based algorithm in combination with D-dimer testing and the use of CTPA in patients with suspected PE.*

Reliable detection of pulmonary embolism (PE) is considered a major challenge for emergency facilities. Previous studies have demonstrated that approximately two-thirds of all cases of PE are not detected, and that approximately 30% of these patients subsequently die due to consequences of overlooked PE (1-4). These data demonstrate an uncertainty in the detection of PE which has lasted for decades. Plasma D-dimer as an indicator of acute coagulatory activation, has been widely recognized as being useful in the diagnostic work-up of PE (5-11). D-Dimers are highly sensitive for PE in patients at low and moderate clinical risk, but are of very low specificity (6, 8, 9, 11-17). In current PE guidelines, the recommendation for D-dimer testing is based on its highly negative predictive value in stable patients suspected of having PE and is, therefore, well-suited for ruling-out PE (7, 10, 18-21). Troponin is another important prognostic biomarker in the risk assessment of patients suspected of having PE and indicates myocardial damage with a high sensitivity and, thus, early identifies patients at an increased risk of mortality (22-24). New generations of highly-sensitive troponin (hs-troponin) assays are of particular interest for the management of acute coronary syndromes (25-28), but high-evidence data on their value for PE risk assessment are still rare (29, 30). Computed tomographic pulmonary angiography (CTPA) has become the diagnostic gold standard for the detection and safe exclusion of PE (31, 32). Thus, the 2008 European Society of Cardiology (ESC) guidelines for PE recommend early integration of CTPA in the diagnostic work-up of PE (33). However, for risk stratification prior to CTPA, complex scoring systems such as the Wells score and the Geneva score are currently recommended (34-36). Yet these scores are controversially discussed since they include rather subjective statements such as "PE is more likely than an alternative diagnosis". The complexity of these scores and the aforementioned vaguely-defined criteria limit their acceptance and application in the daily clinical routine. Thus, a simple symptom-based algorithm for the detection of PE was implemented at the Emergency Department of the University Medical Center Mannheim, Germany, which has abandoned scoring systems. The aim of this study was the evaluation of this algorithm. The initial criterion for this diagnostic algorithm is the presence or absence of one of the cardinal symptoms of chest pain, dyspnea or syncope, proven

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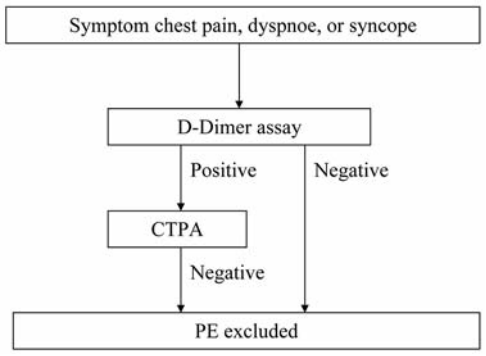

Figure 1. *Diagnostic algorithm for haemodynamically-stable patients with suspected acute Pulmonary embolism. CTPA: Computed tomographic pulmonary angiography.*

to occur particularly frequently in PE (37-41). This study focuses on the incidence of PE overall, as well as central, segmental and sub-segmental PE, and on D-dimer levels in the patient cohort. Another aspect of our work concerns the role of hs-troponin in PE risk assessment.

Patients and Methods

Diagnostic approach. We retrospectively reviewed the medical records of stable patients with suspected PE who had consecutively presented with suspected PE and positive D-dimer test to the Emergency Department of the University Medical Centre Mannheim, Germany, between 04/2010 and 07/2011. Institutional Review Board approval from the *Klinisches Ethik-Komitee, Klinikum Mannheim GmbH*, was obtained with no informed consent required for this retrospective analysis. The algorithm used for the diagnostics of PE is shown in Figure 1. The study comprises of haemodynamically-stable patients with at least one of the cardinal symptoms of chest pain, dyspnea or syncope. Patients in cardiogenic shock (systolic blood pressure <90 mmHg) or resuscitated patients were excluded from this study. The standard algorithm includes anamnesis of risk factors, physical examination and a 12-lead ECG. D-Dimers as a parameter of simultaneous activation of coagulation and fibrinolysis and hs-troponin as a marker of myocardial damage were routinely determined. If at least one of the mentioned symptoms was present and D-dimer testing yielded positive results, CTPA was performed. CTPA was considered contraindicated in cases of pregnancy, contrast medium allergy, high-grade renal insufficiency (creatinine >1.5 mg/dl), hyperthyroidism, and current metformin therapy. Determination of D-dimers (Tina-Quant D-dimer assay; Roche Diagnostics, Mannheim, Germany) was based on a reference range of 0-0.5 mg/l. D-Dimer levels >0.5 mg/l were considered pathological. Determination of hs-troponin (Vista; Siemens Healthcare Diagnostics, Eschborn, Germany) was based on a reference range of 0-0.045 ng/ml. Thus, hs-troponin levels >0.045 ng/ml were considered pathological.

Statistical analysis. Statistical analysis was performed using JMP 8.0 (SAS Institute, Cary, NC, USA) and MedCalc 12.3.0 (MedCalc Software bvba, Mariakerke, Belgium). Categorical variables were reported as counts (percentages). Continuous variables were expressed as the mean±standard deviation, median (25th to 75th percentile) and range. For each continuous variable, the Shapiro–Wilk test was performed to investigate the normality of the distribution of the data. Possible differences in the assessed study parameters between different patient subgroups were estimated with Fisher's exact test and Chi^2 test for categorical variables, and with one-way analysis of variance (ANOVA) for continuous variables; for normally-distributed variables, Student's *t*-test for independent samples was applied, for non-parametric variables the Wilcoxon/Kruskal–Wallis rank sum test and normal approximation was applied. All analyses were performed as two-tailed and a *p*-value of ≤0.05 was considered statistically significant.

Table I. *Patients' baseline characteristics (n=492).*

Age, years	
Mean±SD	68±17
Range	19 to 105
Gender, n (%)	
Male	218 (44)
Female	274 (56)
Symptoms, n (%)	
Chest pain	257 (52)
Dyspnoea	281 (57)
Syncope	81 (16)
Heart rate, beats/min	
Mean±SD	86±22
Range	49 to 175
Systolic blood pressure, mmHg	
Mean±SD	147±29
Range	90 to 290
Diastolic blood pressure, mmHg	
Mean±SD	80±15
Range	40 to 150
Oxygen saturation, %	
Mean±SD	96±4
Range	70 to 100

SD: Standard deviation.

Table II. *Results of electrocardiogram (ECG) and computed tomographic pulmonary angiography CTPA (n=492).*

ECG, n (%)	
Atrial fibrillation	43 (9)
Left bundle branch block	21 (4)
Right bundle branch block	61 (12)
ST-Segment depression	20 (4)
T-Wave inversion	67 (14)
CTPA, n (%)	
PE overall	59 (12)
Central PE	19 (4)
Segmental PE	34 (7)
Sub-segmental PE	6 (1)

PE: Pulmonary embolism.

Table III. *Results of laboratory values (n=492).*

	Median (25th to 75th percentile)	Range	*p*-Value
D-Dimer values (mg/l)			
Patients without PE (n=433)	1.26 (0.89 to 3.06)	0.51 to 35.00	-
Patients with PE overall (n=59)	3.77 (2.25 to 9.95)	0.53 to 32.00	<0.0001*
Patients with central PE (n=19)	10.90 (5.40 to 18.01)	1.36 to 29.00	<0.0001*
Patients with segmental PE (n=34)	2.87 (1.27 to 4.28)	0.53 to 32.00	<0.01*
Patients with subsegmental PE (n=6)	3.12 (1.12 to 4.74)	1.06 to 8.30	0.13
Hs-troponin values (ng/ml)			
Patients without PE (n=433)	0.02 (0.02 to 0.02)	0.01 to 8.30	-
Patients with PE overall (n=59)	0.02 (0.02 to 0.04)	0.02 to 3.12	>0.05
Patients with central PE (n=19)	0.02 (0.12 to 0.29)	0.02 to 3.12	<0.01*
Patients with segmental PE (n=34)	0.02 (0.02 to 0.02)	0.02 to 0.64	>0.05
Patients with subsegmental PE (n=6)	0.02 (0.02 to 0.04)	0.02 to 0.02	>0.05

*Values significantly higher compared to patients without PE. SD: Standard deviation; PE: pulmonary embolism; Hs-troponin: highly-sensitive troponin.

Results

Baseline characteristics. Our cohort consisted of 492 hemodynamically stable patients that suffered from at least one of the three following symptoms: chest pain, dyspnea, or syncope, and who underwent CTPA after positive D-dimer testing. Baseline characteristics are shown in Table I. The proportion of women (n=274; 56%) was slightly higher than that of men (n=220; 44%). Most frequent cardinal symptoms were dyspnea (n=281; 57%) and chest pain (n=257; 52%); syncope (n=81; 16%) was significantly less frequent.

Technical diagnostics. Table II shows the results of electrocardiogram (ECG) and CTPA. In ECG, T-wave inversion was the most common pathological finding (n=67; 14%). CTPA detected PE in a total of 59 (12%) out of the 492 investigated patients. Segmental PE (n=34; 7%) was the most common finding followed by central PE (n=19; 4%). Isolated subsegmental PE (n=6; 1%) was rare.

Laboratory diagnostics. Table III summarizes the laboratory findings. D-Dimer concentrations were significantly increased in patients with PE compared to patients without PE ($p<0.0001$). Concerning the subgroups, significantly higher D-dimer levels were only found in patients with central PE ($p<0.0001$) and segmental PE ($p<0.01$) compared to patients without PE. In patients with subsegmental PE, D-dimer levels did not differ significantly from those of patients without PE ($p=0.13$).

Regarding hs-troponin, significantly higher concentrations were only found in the central PE subgroup compared to patients without PE ($p<0.01$). In patients with segmental ($p=0.35$) or sub-segmental PE ($p=0.14$) and in the overall PE group ($p=0.62$) no significant differences in the hs-troponin levels were detected compared to patients without PE.

Discussion

Emergency facilities are in need of straightforward strategies for the diagnosis of PE that take into account all the relevant risk parameters, leave-out the unnecessary ones and are easy to implement in daily practice. The main therapeutic aim is the start of an anti-coagulation treatment as early as possible (42). In our study, haemodynamically-instable patients were excluded. According to the guidelines, in these patients echocardiography is a useful diagnostic tool. However, the vast majority of patients with suspected PE are haemodynamically-stable. Our algorithm was applied to stable patients with positive D-dimers. PE was detected in 12% of our patient cohort, in 88% PE was ruled-out. For these patients a simple algorithm with D-dimer testing routinely followed by CTPA seems to be most useful approach given the known diagnostic uncertainties associated with exclusion of PE in D-dimer-positive patients.

Determination of D-dimer levels plays a crucial role in patients with suspected PE. Normal D-dimer levels can be interpreted to safely rule-out PE in patients with low or moderate probability of PE (33). In our study, D-dimer levels in the patients who were later found to have PE, and especially in the subgroups with central and segmental PE, were significantly increased compared to the patients where PE was finally ruled out. To date, conflicting results have been published on the correlation between D-dimer levels and right ventricle dysfunction, but consensus exists regarding the association between an elevated D-dimer level and the burden of PE as assessed by CTPA (5). It has yet to be considered that individual cases of PE with a negative D-dimer test have been described, although such occurence has never been confirmed in systematic clinical trials (43-45). Patients with negative D-dimer findings were excluded from our retrospective study, but in principle, CTPA may yet be expedient in individual patients

with negative D-dimer test results if the probability of diagnosing PE is particularly high. This affects for example patients with a history of deep vein thrombosis or PE.

Another focus of our work is on hs-troponin. The reason for the release of troponin in a subset of patients with acute PE is still unclear (24). However, an explanation might be the existence of hypoxaemia due to perfusion-ventilation mismatch, hypoperfusion as a consequence of low output and reduced coronary blood flow, as well as cell injury caused by acute dilatation of the right ventricle, or a combination of these factors (2, 24). Data on hs-troponin in PE patients are scarce (29, 30). A verified, definite prognostic cut-off value is still lacking. Our data demonstrate significantly increased hs-troponin values in patients with a central PE, suggesting a higher risk for an adverse outcome. This might identify patients who would benefit from intensified monitoring even in cases of haemodynamic stability. In our study, no significant differences regarding hs-troponin concentrations were found in the overall PE group nor in the subgroups of segmental and sub-segmental PE compared to patients without PE. This is understandable because the overall PE group consisted predominantly of patients with segmental and sub-segmental PE and these two subgroups of PE are usually not associated with right ventricular dysfunction.

Overall, our algorithm consists of three simple work-up steps to PE diagnosis and abandons any complex scores. Low-threshold CTPA is the basic imaging method in accordance with the 2008 ESC guidelines. Nevertheless, the risk of missing a patient with PE presenting with atypical symptoms lacking presence of either of the three described cardinal symptoms remains. Residual uncertainties in the context of PE diagnostics will never be completely eliminated, but emphasize the particular importance of a comprehensive evaluation of all relevant clinical, technical and laboratory parameters. These always include a detailed history of the risk factors documented for PE to assess pre-test probability (46-49).

Conclusion

Although scores are recommended in current guidelines for diagnosis of PE, acceptance of their use in clinical practice is limited. We implemented a simple symptom-based algorithm for the detection of PE which abandons all scoring systems. In this retrospective analysis, we demonstrated the utility and practicability of this symptom-based algorithm in combination with D-dimer testing and the routine use of CTPA in Emergency Department patients with suspected PE.

References

1 Bell WR and Simon TL: Current status of pulmonary thromboembolic disease: Pathophysiology, diagnosis, prevention, and treatment. Am Heart J *103*: 239-262, 1982.

2 Horlander KT, Mannino DM and Leeper KV: Pulmonary embolism mortality in the United States, 1979-1998: An analysis using multiple-cause mortality data. Arch Intern Med *163*: 1711-1717, 2003.

3 Goldhaber SZ: Pulmonary embolism. Lancet *363*: 1295-1305, 2004.

4 Kline JA, Hernandez-Nino J, Jones AE, Rose GA, Norton HJ and Camargo CA Jr: Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. Acad Emerg Med *14*: 592-598, 2007.

5 Becattini C, Lignani A, Masotti L, Forte MB and Agnelli G: D-Dimer for risk stratification in patients with acute pulmonary embolism. J Thromb Thrombolysis *33*: 48-57, 2012.

6 Goldhaber SZ, Simons GR, Elliott CG, Haire WD, Toltzis R, Blacklow SC, Doolittle MH and Weinberg DS: Quantitative plasma d-dimer levels among patients undergoing pulmonary angiography for suspected pulmonary embolism. JAMA *270*: 2819-2822, 1993.

7 Abcarian PW, Sweet JD, Watabe JT and Yoon HC: Role of a quantitative D-dimer assay in determining the need for CT angiography of acute pulmonary embolism. Am J Roentgenol *182*: 1377-1381, 2004.

8 Kabrhel C, Mark Courtney D, Camargo CA Jr., Plewa MC, Nordenholz KE, Moore CL, Richman PB, Smithline HA, Beam DM and Kline JA: Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. Acad Emerg Med *17*: 589-597, 2010.

9 Kearon C, Ginsberg JS, Douketis J, Turpie AG, Bates SM, Lee AY, Crowther MA, Weitz JI, Brill-Edwards P, Wels P, Anderson DR, Kovacs MJ, Linkins LA, Julian JA, Bonilla LR and Gent R: An evaluation of D-dimer in the diagnosis of pulmonary embolism: A randomized trial. Ann Intern Med *144*: 812-21, 2006.

10 Righini M, Perrier A, De Moerloose P and Bounameaux H: D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost *6*: 1059-1071, 2008.

11 Yin F, Wilson T, Della Fave A, Larsen M, Yoon J, Nugusie B, Freelang H and Chow RD: Inappropriate use of D-dimer assay and pulmonary CT angiography in the evaluation of suspected acute pulmonary embolism. Am J Med Qual *27*: 74-79, 2012.

12 Ginsberg JS, Brill-Edwards PA, Demers C, Donovan D and Panju A: D-Dimer in patients with clinically suspected pulmonary embolism. Chest *104*: 1679-1684, 1993.

13 Kline JA, Nelson RD, Jackson RE and Courtney DM: Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: A multicenter US study. Ann Emerg Med *39*: 144-152, 2002.

14 Kline JA, Runyon MS, Webb WB, Jones AE and Mitchell AM: Prospective study of the diagnostic accuracy of the simplify D-dimer assay for pulmonary embolism in emergency department patients. Chest *129*: 1417-1423, 2006.

15 Orak M, Ustundag M, Guloglu C, Alyan O and Sayhan MB: The role of serum D-dimer level in the diagnosis of patients admitted to the emergency department complaining of chest pain. J Int Med Res *38*: 1772-1779, 2010.

16 Parent F, Maitre S, Meyer G, Raherison C, Mal H, Lancar R, Couturaut F, Mottier D, Girard P, Simonneau G and Leroyer C: Diagnostic value of D-dimer in patients with suspected pulmonary embolism: Results from a multicentre outcome study. Thromb Res *120*: 195-200, 2007.

17 Becattini C and Agnelli G: Acute pulmonary embolism: Risk stratification in the emergency department. Intern Emerg Med *2*: 119-129, 2007.
18 Brown MD, Vance SJ and Kline JA: An emergency department guideline for the diagnosis of pulmonary embolism: An outcome study. Acad Emerg Med *12*: 20-25, 2005.
19 Gupta RT, Kakarla RK, Kirshenbaum KJ and Tapson VF: D-Dimers and efficacy of clinical risk estimation algorithms: Sensitivity in evaluation of acute pulmonary embolism. Am J Roentgenol *193*: 425-430, 2009.
20 Kabrhel C: Outcomes of high pre-test probability patients undergoing D-dimer testing for pulmonary embolism: A pilot study. J Emerg Med *35*: 373-377, 2008.
21 Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Perrier A and Bounameaux H: Value of D-dimer testing for the exclusion of pulmonary embolism in patients with previous venous thromboembolism. Arch Intern Med *166*: 176-180, 2006.
22 Becattini C, Vedovati MC and Agnelli G: Prognostic value of troponins in acute pulmonary embolism: A meta-analysis. Circulation *116*: 427-433, 2007.
23 Becattini C, Vedovati MC and Agnelli G: Diagnosis and prognosis of acute pulmonary embolism: Focus on serum troponins. Expert Rev Mol Diagn *8*: 339-349, 2008.
24 Janata KM, Leitner JM, Holzer-Richling N, Janata A, Laggner AN and Jilma B: Troponin T predicts in-hospital and 1-year mortality in patients with pulmonary embolism. Eur Respir J *34*: 1357-1363, 2009.
25 Aldous SJ, Florkowski CM, Crozier IG, Elliott J, George P, Lainchbury JG, Mackay RJ, Than M, Flaws DF and Borowsky J: Comparison of high sensitivity and contemporary troponin assays for the early detection of acute myocardial infarction in the emergency department. Ann Clin Biochem *48*: 241-248, 2011.
26 Freund Y, Chenevier-Gobeaux C, Bonnet P, Claessens YE, Allo JC, Doumenc B, Leumani F, Cosson C, Riou B and Ray P: High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. Crit Care *15*: R147, 2011.
27 Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Fröhlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Münzel TF and Blankenberg S: Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med *361*: 868-877, 2009.
28 Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R and Mueller C: Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med *361*: 858-867, 2009.
29 Ferrari E, Moceri P, Crouzet C, Doyen D and Cerboni P: Timing of troponin I measurement in pulmonary embolism. Heart *98*: 732-735, 2012.
30 Lankeit M, Jimenez D, Kostrubiec M, Dellas C, Hasenfuss G, Pruszczyk P and Konstantinides S: Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: A prospective validation study. Circulation *124*: 2716-2724, 2011.
31 Mullins MD, Becker DM, Hagspiel KD and Philbrick JT: The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. Arch Intern Med *160*: 293-298, 2000.
32 Perrier A, Howarth N, Didier D, Loubeyre P, Unger PF, de Moerloose P, Slosman D, Junod A and Bounameaux H: Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. Ann Intern Med *135*: 88-97, 2001.
33 Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, Bengel F, Brady AJB, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M and Bassand JP: Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J *29*: 2276-2315, 2008.
34 Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, van Houten AA, Hofstee HM, Klok FA, ten Cate H, Ullmann EF, Bueller HR, Kamphuisen PW and Huisman MV: Performance of four clinical decision rules in the diagnostic management of acute pulmonary embolism: A prospective cohort study. Ann Intern Med *154*: 709-718, 2011.
35 Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H and Perrier A: Prediction of pulmonary embolism in the emergency department: The revised Geneva score. Ann Intern Med *144*: 165-171, 2006.
36 Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, Turpie AG, Bormanis J, Weitz J, Chamberlain M, Bowie D, Barnes D and Hirsh J: Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: Increasing the models utility with the simpliRED D-dimer. Thromb Haemost *83*: 416-420, 2000.
37 Calvo-Romero JM, Perez-Miranda M and Bureo-Dacal P: Syncope in acute pulmonary embolism. Eur J Emerg Med *11*: 208-209, 2004.
38 Castelli R, Tarsia P, Tantardini C, Pantaleo G, Guariglia A and Porro F: Syncope in patients with pulmonary embolism: Comparison between patients with syncope as the presenting symptom of pulmonary embolism and patients with pulmonary embolism without syncope. Vasc Med *8*: 257-261, 2003.
39 Koutkia P and Wachtel TJ: Pulmonary embolism presenting as syncope: Case report and review of the literature. Heart Lung *28*: 342-347, 1999.
40 Miniati M, Prediletto R, Formichi B, Marini C, Di Ricco G, Tonelli L, Allescia G and Pistolesi M: Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med *159*: 864-871, 1999.
41 Wolfe TR and Allen TL: Syncope as an emergency department presentation of pulmonary embolism. J Emerg Med *16*: 27-31, 1998.
42 Pollack CV, Schreiber D, Goldhaber SZ, Slattery D, Fanikos J, O'Neil BJ, Thompson JR, Hiestand B, Briese BA, Pendleton RC, Miller CD and Kline JA: Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: Initial report of EMPEROR (multicenter emergency medicine pulmonary embolism in the real world registry). J Am Coll Cardiol *57*: 700-706, 2011.
43 Breen ME, Dorfman M and Chan SB: Pulmonary embolism despite negative ELISA D-dimer: A case report. J Emerg Med *37*: 290-292, 2009.
44 Di Grande A, Tomaselli V, Massarelli L, Narbone G, Sabbia CM, Noto P, Amico S, Nigro F and Di Mauro A: Submassive acute pulmonary thromboembolism with normal D-dimer. A case report. Minerva Cardioangiol *54*: 277-284, 2006.

45 Dunn KL, Wolf JP, Dorfman DM, Fitzpatrick P, Baker JL and Goldhaber SZ: Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. J Am Coll Cardiol *40*: 1475-1478, 2002.

46 Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Willet WC and Hennekens CH: A prospective study of risk factors for pulmonary embolism in women. JAMA *277*: 642-645, 1997.

47 Kline JA and Miller DW: Risk stratification for acute pulmonary embolism. J Natl Compr Canc Netw *9*: 800-810, 2011.

48 Lauque D, Mazieres J, Rouzaud P, Sie P, Chamontin B, Carrie D, Hermant C, Tubery M and Carles P: Pulmonary embolism in patients using estrogen-progestagen contraceptives. Presse Med *27*: 1566-1569, 1998.

49 Lehmann R, Suess C, Leus M, Luxembourg B, Miesbach W, Lindhoff-Last E, Zeiher AM and Spyridopoulos I: Incidence, clinical characteristics, and long-term prognosis of travel-associated pulmonary embolism. Eur Heart J *30*: 233-241, 2009.

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