Improving diagnostics of pulmonary embolism with clinical prediction models in a clinic of pulmonary diseases

Pomen algoritmov za izračun klinične verjetnosti pljučne embolije pri diagnosticiranju pljučne embolije v specializirani bolnišnici za pljučne bolezni

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Ključne besede:
predtestna klinična verjetnost, Wellsov algoritem, Ženevski sistem točkovanja

Key words:
Pre-test Clinical Probability, Wells Model, Geneva Scoring System

Citirajte kot/Cite as:
Zdrav Vestn 2010; 79: 698–706

Prispelo: 2. jan. 2010,
Sprejeto: 9. jun. 2010

Abstract

Purpose of the Study: Clinical prediction models have been developed to assess the pre-test probability for pulmonary embolism (PE). The Wells model and the revised Geneva score are the two most well studied. Our purpose was to compare the two prediction models, and indentify the frequent clinical findings of PE in patients admitted to the University Clinic of Pulmonary and Allergic Diseases Golnik.

Methods: In 100 random emergency department patients and hospital inpatients with suspected PE and performed pulmonary CT angiography (CTPA) as the gold standard, a retrospective assessment of the clinical probability of PE by the Wells rule and the revised Geneva score was made. ECG, D-dimer, NT-proBNP, arterial blood gas analysis, chest X-ray, CTPA and 13 other clinical findings were analysed as well.

Results: Average age was 65 years (SD 14.5), 39 % were male. The overall prevalence of PE was 33 %. The rates of PE in low, moderate, and high PE risk groups as determined according to the Wells model and the revised Geneva score were 3.7, 53,1, 100, and 14.3, 32.1, 83.3 %, respectively. ROC analysis showed that the Wells model was statistically more accurate than the Geneva score with the area under the curve (AUC) in Wells model 0.85 (95 % CI 0.762–0.936) and in Geneva score 0.73 (95 % CI 0.612–0.838). Sudden dyspnea, active malignancy, venous thromboembolism (VTE) history, estrogen therapy, deep vein thrombosis (DVT) signs, ECG changes and lower $PaCO_2$ were significantly more frequent in PE group. All patients with PE had an increased concentration of D-dimer, and no PE were diagnosed in the group of patients with normal D-dimer. CTPA was ordered in 17 % of patients with low pre-test probability of PE according to Wells criteria and normal D-dimer.

Conclusions: The Wells model is more accurate than the Geneva scoring system for the diagnosis of PE in patients admitted to a pulmonary clinic. Additional findings, such as sudden dyspnea, estrogen therapy, ECG changes and lower $PaCO_2$, should always be incorporated in clinical assessment of PE. Adding the Wells algorithm to the clinical pathway for PE management might slightly decrease the number of CTPA.

Izvleček

Izhodišča: Za izračun klinične verjetnosti za pljučno embolijo (PE) obstaja več algoritmov. Namen raziskave je bil primerjati natančnost Wellsovega algoritma z natančnostjo Ženevskega sistema točkovanja za izračun klinične verjetnosti za PE ter poiskati pomembne klinične kazalce za PE.

Metode: V retrospektivno raziskavo smo vključili 100 naključno izbranih ambulantnih in hospitaliziranih bolnikov Bolnišnice Golnik, ki smo jim zaradi suma na PE opravili pljučno angiografijo z računalniško tomografijo (CTA). Primerjali smo natančnost Wellsovega algoritma z Ženevskim sistemom točkovanja. Analizirali smo klinične in laboratorijske kazalce pri bolnikih s potrjeno PE in pri bolnikih, katerim PE nismo dokazali.

Rezultati: Povprečna starost bolnikov je bila 65 let (SD 14,5), moških je bilo 39 %. PE smo dokazali v 33 %. PE smo v skupinah z majhno, srednje veliko in veliko verjetnostjo za PE, določenih po Wellsovem algoritmu, beležili v 3,7 %, 53,1 % in 100 %, po Ženevskem algoritmu pa v 14,3 %, 32,1 % in 83,3 %. Z analizo ROC smo ugotovili, da je algoritem po Wellsu (AUC 0,85, 95 % CI 0,762–0,936) natančnejši od Ženevskega algoritma (AUC 0,73, 95 % CI 0,612–0,838). Za bolnike z dokazano PE so bili značilni nenadno nastala dispneja, aktivna maligna bolezen, prebolela globoka venska tromboza (GVT) ali PE, zdravljenje

z estrogenom, znaki za GVT, spremembe v EKG in nižji $PaCO_2$. Vsi bolniki z dokazano PE so imeli povišan D-dimer, pri bolnikih s koncentracijo D-dimera pod mejno vrednostjo nismo dokazali PE. CTA pljuč je bila opravljena pri 17 % bolnikov z majhno klinično verjetnostjo po Wellsovih merilih in normalnim D-dimerom.

Zaključek: Za bolnike, sprejete v bolnišnico za pljučne bolezni, je za izračun klinične verjetnosti za PE Wellsov algoritem natančnejši kot Ženevski sistem točkovanja. Pri bolnikih s sumom na PE moramo biti pozorni na nenadno nastalo dispnejo, spremembe na EKG, hipokapnijo ter estrogensko zdravljenje. Upoštevanje Wellsovega algoritma pri diagnostičnem algoritmu PE lahko zmanjša število opravljenih CTA pljuč.

Introduction

Early diagnosis and correct treatment of pulmonary embolism (PE) can reduce its mortality.[1,2] The clinical indicators, raising the suspicion of PE are neither sensitive nor specific.[3,4] The vast majority of patients with proven acute PE present with at least one of the following signs or symptoms: dyspnea, pleural chest pain, or tachypnea. However, the signs and symptoms of PE may frequently be seen in other conditions, including pneumonia, exacerbation of chronic obstructive lung disease, pneumothorax, myocardial infarction, heart failure, pericarditis, musculoskeletal pain or trauma, pleuritis, malignancy, and, occasionally, intra-abdominal processes, such as acute cholecystitis, among others.

Pulmonary computed tomographic angiography (CTA) is the clinical gold standard for the diagnosis of PE. Our decision when to use it is supported by clinical data indicating the probability of PE.

Several clinical prediction rules have been developed to assess the pre-test probability of PE. The Wells model is the most studied one (Table 1).[5] In this model, the clinical probability of PE has to be assessed first. If it is high, imaging studies follow, if moderate, D-dimer is measured: if low, the patient is not investigated further, if D-dimer is increased, imaging studies should follow.

The Geneva model is an alternative scoring system derived from patients presenting to the emergency room with dyspnea or chest pain (Table 2). This model uses eight independent predictors.[6] However, its clinical utility has not yet been prospectively studied.

The aim of our study was to compare the accuracy of the Wells model with revised Geneva scoring system in a clinic of pulmonary diseases. Secondly, we analysed the frequency and predictive value of clinical and laboratory findings for PE in our patients. Those clinical and laboratory findings are used in other clinical prediction rules: the Charlotte rule, which includes age, shock index, unexplained hypoxemia, unilateral leg swelling, recent surgery, hemoptysis;[7] the PISA-PED group rule, which includes echocardiography (ECG) and chest x-ray findings,[8] as well as the probability assessment

Table 1: Wells´ Simplified Clinical Prediction Model for Suspected PE (< 2 low, 2–6 moderate, > 6 high PE probability).[7]

Clinical Finding	Points
Clinical signs and symptoms of DVT (at least local lower extremity tenderness along deep venous system and swollen lower extremity)	3.0
No alternative diagnosis greater than or equal to the likelihood of PE	3.0
Heart rate > 100 beats/min	1.5
Immobilisation or surgery within the last 4 weeks	1.5
History of prior venous thromboembolism	1.5
Hemoptysis	1.0
Active malignancy (ongoing treatment, or within the last 6 months, or palliative)	1.0

Table 2: The Revised Geneva Scoring System for Suspected PE (Low 0–3, Moderate 4–11, or High >=11 Probability).

Clinical Finding	Points
Age > 65 years	1
History of prior venous thromboembolism	3
Surgery using general anesthesia or lower extremity fracture within the last 4 weeks	2
Active malignancy (in the last 12 months)	2
Hemoptysis	2
Unilateral lower extremity pain	3
Local lower extremity pain, tenderness along the deep venous system and swollen lower extremity	4
Heart rate 75–94 beats/min	3
Heart rate >=95 beats/min	5

by Hyers, which incorporates gas analysis of arterial blood into three clinical variables (unexplained hypoxemia, pleuritic pain and chest x-ray findings).[9] We studied all referral diagnoses of our patients.

Materials & methods

One hundred randomly chosen emergency department patients and hospital inpatients were included into this retrospective study in which CTA was performed with suspected PE. CTA was indicated by the presence of symptoms typical of PE, high concentration of D-dimer as well as the attending physicians' experience. No patient had echocardiography performed before CTA. The clinical probability of PE was retrospectively assessed using the Wells rule and the revised Geneva score.

Patients' records were analysed retrospectively for: sudden onset of dyspnea, chest pain, syncope, signs of deep vein thrombosis (DVT), cough, hemoptysis, smoking, immobilisation in last four weeks, surgery in the last four weeks, history of prior venous thromboembolism (VTE), active malignancy in last six months, estrogen therapy in the last three months and acute or chronic conditions causing dyspnea (bronchitis, pneumonia, asthma, COPD, interstitial lung disease, pulmonary hypertension, congestive heart failure, and other less frequent conditions). We checked all referral diagnoses. Laboratory findings were also perused: D-dimer, arterial blood gas analysis, NT-proBNP, ECG and imaging studies–chest x-ray and pulmonary CTA. D-dimer were determined turbidimetrically on Sysmex 560 coagulation analyser using D-dimer PLUS reagent kit produced by Dade Behring. NT-proBNP were analysed by electrochemiluminescence immunoassay (ECLIA) on Elecsys 2010 (Roche Diagnostics). Arterial blood gas analyses were performed with blood gas analyser ABL 800 (Radiometer Copenhagen). Lower extremity ultrasonography was performed with a 5 to 7.5 MHz probe. The diagnostic criteria for thrombosis were noncompressibility of the femoral vein and the popliteal vein.

Criteria for ECG abnormalities indicative of PE were: right axis (> 90°) or intermediate axis (180° to -90°) deviation; transient incomplete right bundle branch block with a positive T-wave in lead V1 or ST elevation in lead V1; S-wave in lead I, Q-wave in lead III, and inverted T-wave in lead III ($S_1Q_3T_3$); S-wave in lead I and aVL > 1.5 mm; T inversion in lead III and aVF but not in lead II; T inversion in lead III and aVF or lead V1 to V4; ST elevation mimicking acute myocardial infarction; and pathologic Q wave mimicking acute myocardial infarction.

Chest x-ray reports were reviewed for changes such as dilatation of pulmonary vessels with defects of the vascular network, pulmonary effusion, elevation of the diaphragm, and presence or absence of lung field infiltration.

Table 3: Number of Patients with PE with Low, Moderate and High Pre-test Clinical Probability in Wells Model and Geneva Model.

Clinical Probability	No. of patients with Wells Model	No. of positive (%) PE	Number of patients with Geneva Model	No. of positive (%) PE
Low probability	54	2 (3.7)	35	5 (14.3)
Moderate probability	32	17 (53.1)	53	17 (32.1)
High probability	14	14 (100)	12	10 (83.3)

Pulmonary CTAs were performed on 64-slice CT using a non-ionic contrast medium (Iomeron 400).

In our analysis we relied on the Wells´ Simplified Clinical Prediction Model (Table 1) for probability of PE and divided our patients into three groups, after scoring with low (< 2 points), moderate (2–6 points), and high (> 6 points) probability of PE. Also using the revised Geneva scoring system (Table 2), patients were divided into groups with low (0–3 points), moderate (4–11 points) and high (>=11 points) probability of PE.

The accuracy of the Wells model and the Geneva scoring system was tested with the area under the curve (AUC) in receiver operating characteristic (ROC) analysis by using SPSS software (SPSS for Windows 16.0, Inc. 1989–2007, Chicago, Illinois, USA). The difference in clinical predictors between patients with proven PE and those in whom PE was not proven was tested with t-test and chi-square test. P value less than 0.05 indicated statistical significance.

Results

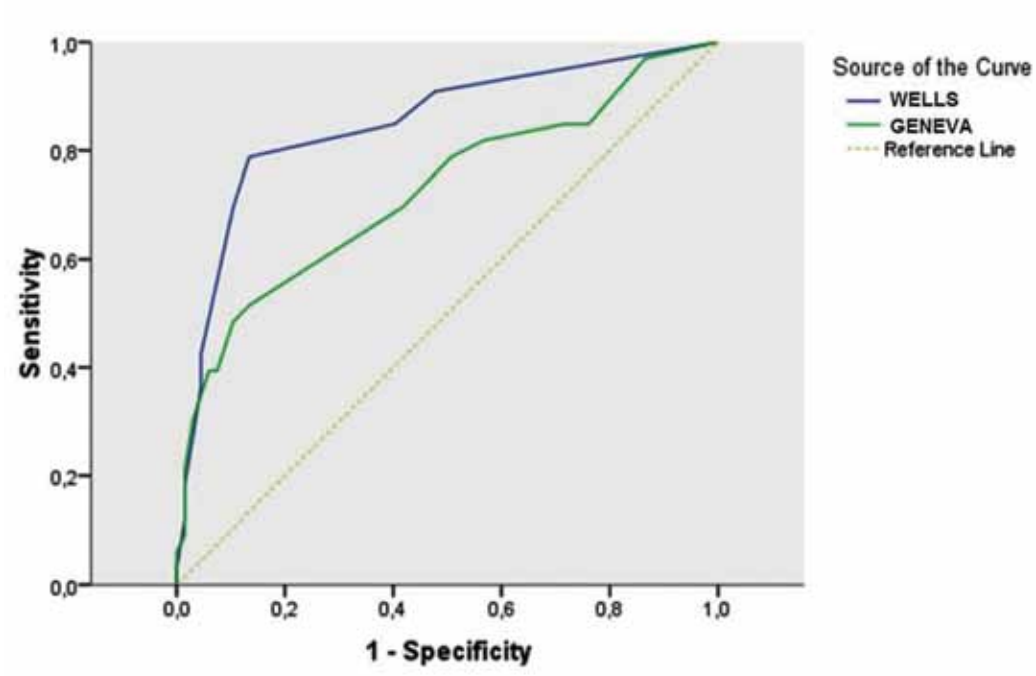
The study included 100 patients with suspected PE. 39 of our patients were men. Average age was 65 years (SD 14.6). A total of 33 of 100 patients were confirmed to have PE. PE was more frequent in men than in women (men/women ratio: 1.3). The frequency of PE in patients with low/medium/high probability according to the Wells model and the Geneva score are shown in Table 3.

ROC analysis showed that the Wells model gave more correct outcomes than the Geneva score. Area under the curve (AUC) in the Wells model was 0.85 (95 % CI 0.762–0.936) and in Geneva score 0.73 (95 % CI 0.612–0.838) (Figure 1).

All patients were than divided into two groups according to the CTA diagnosis of PE. The most frequent referral diagnoses in patients without PE were dyspnea (15/67), chest pain (9/67), pneumonia (7/67), hemoptysis (6/67), cough (6/67) and exacerbation of COPD (6/67). Dyspnea (12/33), cough (5/33), acute or previous DVT (5/33), acute or previous PE (4/33), exercise induced dyspnea (3/33) and chest pain (3/33) were the most frequent referral diagnosis in patients with proven PE.

Sudden dyspnea, a history of prior PE or prior DVT, active malignancy and, in females, estrogen therapy were significantly more often noted in the group with proven PE. In those patients also ECG abnormalities, low $PaCO_2$, evidence of DVT, and positive lower extremity compression ultrasound were more frequent (Table 4). The difference in laboratory findings between the PE positive and PE negative group are shown in Table 5.

Among the 54 patients with low probability of PE according to the Wells model, 23 had D-dimer concentration measured. Average D-dimer concentration in the group was 487µg/L (86–6473 µg/L). In four out of the 23 (17 %) patients in the low probability group the D-dimer concentration was below the reference value (below 130 µg/L) and all four patients had negative CTA. All patients with proven PE had a high concentration of D-dimer. There was no statistically significant difference in D-dimer values between the groups of patients with proven versus unproven PE. Neither have we found any differences in NT-proBNP concentrations (8 patients only), or in mortality (2/23 in



Picture 1: Wells Model and Revised Geneva Score System Compared by Area under the Curve of ROC Curves.

PE positive group, 4/67 in PE negative (P 0,986)).

Discussion

The diagnostic procedure in a patient with suspicion of PE starts with a thorough history and clinical examination. Our PE positive patients frequently presented with sudden dyspnea, a history of PE or DVT, active malignancy and estrogen therapy in women. Clinical indicators for PE, often confirmed by clinical or laboratory examinations, were evidence of DVT, ECG abnormalities, low $PaCO_2$ and positive compression ultrasound of the lower limbs. Same findings, with the exception of estrogen therapy and active malignancy, were also found as predictors in a large Swiss study on 1090 outpatients with suspected PE.[10] Their analysis of the influence of estrogen therapy is questionable, since it seems males were also included in the study of estrogen influence. The connection between estrogen therapy and PE was confirmed in a large study in 2008.[11] In the Swiss study, but not our study, additional characteristics of PE patients were: immobilization, post-operative state, chest pain, hemoptysis and tachycardia. Most probably the difference can be explained by different structure of the patients referred to our specialized pulmonary diseases hospital, compared to those referred to a general hospital. Namely, most patients who are referred to a specialized hospital for pulmonary diseases have dyspnea as the leading symptom while patients with leading symptoms and signs of deep venous thrombosis are primarily referred to a general hospital.

In 2005 we published a study on the frequency of pathological chest x-rays in PE patients.[12] Chest x-ray has a low sensitivity and specificity for PE and its role is in ruling out other conditions that can present with a similar clinical picture.[13,14] We did not prove PE in the majority of patients with specific x-ray changes, such as pneumonia, congestive heart failure, exacerbation of COPD and interstitial lung disease. PE was also rare in patients with acute bronchitis, asthma, pulmonary hypertension, Pickwick syndrome or anemia established at referral. We did not find differences in demographic characteristics of patients between our and similar studies.[10,15,16] The proportion of males and those over 60 was higher in the group with proven PE.[17]

The proportion of PE in our group was comparable with that in the Swiss study of 1090 patients in which, as in ours, models for assessing the clinical probability of PE were not used before pulmonary CTA.[10] In

Table 4: Clinical Findings in Patients with positive PE.

Clinical Finding	No. of patients with present clinical sign	Frequency of Clinical sign in PE positive group	Frequency of Clinical sign in PE negative group	Chi-Square Test
Sudden Dyspnea	51	67 % (22/33)	43 % (29/67)	0.028
Chest Pain	41	39 % (13/33)	42 % (28/67)	0.819
Syncope	9	3 % (1/33)	12 % (8/67)	0.143
Signs of DVT	18	45 % (15/33)	4 % (3/67)	< 0.001
Cough	41	30 % (10/33)	46 % (31/67)	0.127
Hemoptysis	9	9 % (3/33)	9 % (6/67)	0.982
Smoking	29	30 % (10/33)	28 % (19/67)	0.840
Immobilisation (< 4 weeks)	7	9 % (3/33)	6 % (4/67)	0.565
Surgery (< 4 weeks)	7	6 % (2/33)	7 % (5/67)	0.796
History of prior VTE	12	21 % (7/33)	7 % (5/67)	0.047
Active Malignancy	7	18 % (6/33)	1 % (1/67)	0.002
Estrogen Therapy **	8	15 % (5/18)	4 % (3/43)	0.028
Heart Rate > 100 beats/min	34	27 % (9/33)	37 % (25/67)	0.312
ECG Changes	40	55 % (18/33)	33 % (22/67)	0.053
Changes on Chest X-ray	40	39 % (13/33)	40 % (27/67)	0.931
Needed O_2 therapy	20	15 % (5/33)	22 % (15/67)	0.395
Positive Lower Extremity Compression Ultrasound	17	51 % (17/33)	0 % (0/67)	< 0.001
* Acute or Chronic Conditions causing Dyspnea	29	15 % (5/33)	36 % (24/67)	0.032

** Congestive heart failure 6 patients, Asthma 7 patients, COPD 8 patients , Pneumonia 3 patients, Pulmonary Hypertension 2 patients, Interstitial Lung Disease 2 patients, 1 patient: Anaemia, Chronic Bronchitis, Pickwick Syndrome, Asbestosis.*
*** Analysis of female Patients only*

a Dutch prospective study of 300 patients using Wells model the diagnosis of PE was twice less likely than in our study.[15]

The clinical approach to the detection of PE is presented in the diagnostic algorithms.[18,19] In our patients, the Wells model proved to be more accurate than the Geneva scoring system. The predictive accuracy in our population was comparable to the data from the original study and establishment of the Wells model.[5] Other studies showed the Wells model to be better or equally accurate as the Geneva scoring system.[15,20-23] Dutch study followed patients for three months and concluded that it seems safe to exclude PE in patients with the combination of a low or intermediate clinical probability by the Wells score and a normal D-dimer concentration.

Compared to the Wells model, the Geneva scoring system includes 4 additional criteria (age over 65, unilateral lower leg pain, 75–94 pulse rate, and 95 or higher pulse rate), however, those proved not to be helpful in assessing the risk of PE in our patients. Those 4 criteria are probably discriminatory in patients referred to the hospital with a suspicion of deep venous thrombosis and PE, but not in our patients, who had pulmonary or cardiovascular comorbidities and presented with an increased dyspnea. A study published in 2009 in our hospital showed that an exceptionally high proportion of our patients with indication for VTE

Table 5: Laboratory Results (NT-proBNP, Arterial Blood Gas Analysis) for PE positive and negative Patients

Observed Laboratory Findings		Average Values and Standard Deviation in PE positive group (n=33)	Average Values and Standard Deviation in PE negative group (n=67)	P Value
Breaths/min		24.5 (SD 4.0)	24.4 (SD 4.5)	0.878
Heart Beats/min		89.8 (SD 22.8)	90.0 (SD 22.3)	0.966
D-dimer µg/L*		680.6 (SD 635.1)	412.8 (SD 948.3)	0.285
NT-proBNP pg/L**		650.6	668.0	0.984
Arterial Blood Gas Analysis	pH	7.3 (SD 0.6)	7.4 (SD 0.1)	0.328
	pO_2	9.0 (SD 2.3)	8.7 (SD 3.8)	0.792
	pCO_2	4.3 (SD 1.2)	5.3 (SD 2.5)	0.053

** Reference value was 130µg/L.*
***Reference value was 149pg/mL.*

prophylaxis actually received low-molecular-weight heparin (94 %).[24]

Our study showed that all patients with deep vein thrombosis of the leg, proven by compression ultrasound, also had PE. In patients with proven deep venous thrombosis the possibility of simultaneous PE has to be kept in mind since it is of prognostic significance. Diagnostic chest imaging is indicated in those patients, because routine treatment of DVT with heparin might be inadequate in the case of massive PE where thrombolysis should be considered.

We were not able to find a statistically significant difference in the concentration of D-dimer between PE positive and PE negative patients. A study published in 1999 in our hospital showed that values of D-dimer concentration above the cutoff value are of no help in differential diagnosis in patients with dyspnea and suspected pulmonary embolism.[25] We have however confirmed its reliability when it is negative and the clinical probability of PE is low. In that case the diagnostic work-up can be discontinued without CTA.[26] In our analysis it is apparent that in at least 17 % of patients the diagnostic work-up could be safely discontinued without CTA. In a French study on 1528 patients with suspected PE, among 56 patients with high PE probability 21 had a negative D-dimer.[27] Another French study on 352 patients with suspected PE showed that five patients with confirmed PE had negative D-dimer (two patients with high pre-test clinical probability).[28] In American prospective study on 2302 patients with suspected PE 21 patients (1.3 %) had negative D-dimer and proven PE.[7] In another American study on 444 patients who had clinically suspected PE with nondiagnostic lung scan or negative helical CT scan of the chest only 11 % had negative D-dimer result.[29] All of our PE positive patients had a high concentration of D-dimer. It is to emphasize that the highest concentrations of D-dimer were found in patients without PE. Those were patients with malignancy, urinary tract infection, atrial fibrillation and pneumonia, respectively. D-dimer cannot replace the algorithm in suspected PE, since it has a low positive predictive value as an independent predictor. It is to emphasize that acute and chronic conditions are associated with fibrin generation and a high concentration of its breakdown product D-dimer. A negative D-dimer in a patient with PE can occur if the blood sample is taken either too early after thrombus formation or several days after. Additionally, the presence of anticoagulation can render the test negative because it prevents thrombus extension.[30]

Our study is limited by being retrospective. Some history data (e.g. the suddenness of dyspnea occurrence) and data on concomitant diseases are less reliable. The study would gain strength with a larger number of patients studied prospectively, with separate

analysis of hospitalized and ambulatory patients and with inclusion of other algorithms for assessing clinical probability of PE into the study.

Conclusion

Models for assessing the clinical probability of PE are helpful to the physician in charge of taking account of the diagnostic algorithms. In our study of patients referred to a specialized hospital for pulmonary diseases the Wells model proved to be more accurate than the Geneva scoring system. Adding the Wells algorithm to the clinical pathway for PE management might slightly decrease the number of CTA.

Disclosure of Conflict of Interests

The authors state they have no conflict of interests.

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