Alternative diagnoses in patients in whom the GP considered the diagnosis of pulmonary embolism

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Abstract

Introduction. Pulmonary embolism (PE) often presents with nonspecific symptoms and may be an easily missed diagnosis. When the differential diagnosis includes PE, an empirical list of frequently occurring alternative diagnoses could support the GP in diagnostic decision making.

Objectives. To identify common alternative diagnoses in patients in whom the GP suspected PE but in whom PE could be ruled out. To investigate how the Wells clinical decision rule for PE combined with a point-of-care d-dimer test is associated with these alternative diagnoses.

Methods. Secondary analysis of the Amsterdam Maastricht Utrecht Study on thrombo-Embolism (Amuse-2) study, which validated the Wells PE rule combined with point-of-care d-dimer testing in primary care. All 598 patients had been referred to and diagnosed in secondary care. All diagnostic information was retrieved from the GPs’ medical records.

Results. In 516 patients without PE, the most frequent alternative diagnoses were nonspecific thoracic pain/dyspnoea (42.6%), pneumonia (13.0%), myalgia (11.8%), asthma/chronic obstructive pulmonary disease (4.8%), panic disorder/hyperventilation (4.1%) and respiratory tract infection (2.3%). Pneumonia occurred almost as frequent as PE. Patients without PE with either a positive Wells rule (>4) or a positive d-dimer test, were more often (odds ratio = 2.1) diagnosed with a clinically relevant disease than patients with a negative Wells rule and negative d-dimer test.

Conclusion. In primary care patients suspected of PE, the most common clinically relevant diagnosis other than PE was pneumonia. A positive Wells rule or a positive d-dimer test are not only positively associated with PE, but also with a high probability of other clinically relevant disease.

Key words: Bacterial pneumonia, chest pain/dyspnoea, diagnostic decision making, differential diagnoses, primary care, pulmonary embolism.
Alternative diagnosis of pulmonary embolism

Introduction

In patients presenting with unexplained or deteriorating dyspnoea, pain on inspiration or unexplained cough symptoms, GPs have to differentiate between common but less clinically relevant diagnoses such as myalgia, and less common but more relevant diagnoses such as pulmonary embolism (PE) or pneumonia. Several clinical decision rules (CDRs) have been proposed and validated to exclude PE (1). One of the most validated and most used CDR is the Wells rule (2). The Amsterdam Maastricht Utrecht Study on thrombo-Embolism (Amuse-2) demonstrated the safety of the use of the Wells rule for PE combined with point-of-care D-dimer testing in primary care (3).

The Wells rule (Table 1) combines seven items into a score and is recommended to be combined with D-dimer testing to estimate the pre-test probability of PE. Plasma D-dimers are cross-linked fibrin derivatives produced when fibrin is degraded by plasmin. A positive D-dimer test result—occurring when the D-dimer level exceeds a certain value—increases the clinical probability of venous thromboembolism (2).

The Wells CDR includes the attending physician’s subjective judgement of the relative (un)likelihood of an alternative diagnosis that could explain the symptoms. The subjective character of this specific criterion and its moderate reproducibility are the main points of criticism to the Wells rule (4). However, clinical judgement has been shown to improve the accuracy of the Geneva score, which is a CDR consisting of only objective items (5). Furthermore, in secondary care it was shown that the subjective criterion of the Wells rule had a high predictive value in comparison to the other variables of the Wells rule (6).

Yet, a GP only sees a few patients suspected of PE yearly. Therefore, it may be difficult to compare the probabilities of PE and various alternative diagnoses. An empirical list of alternative diagnoses for the primary care setting could facilitate the differential diagnostic process before as well as after application of the Wells CDR and point-of-care D-dimer test. The spectrum of patients seen in primary care is by definition non-selected and more heterogeneous as compared to secondary care. GPs might therefore need a different list of alternative diagnoses than specialists in secondary care (7). Even when PE can be safely excluded, the GP may still want to refer patients to secondary care for other clinically relevant conditions, which need more than pain management and supportive care.

There is little evidence-based data on pre-hospital differential diagnoses at the end of a GP consultation. As such, alternative diagnoses of PE as seen in primary care have not been investigated. We aimed to identify the most common alternative diagnoses in patients in whom the GP also considered the diagnosis of PE. Additionally, we investigated whether the Wells PE rule combined with a point-of-care D-dimer test was associated with other relevant diagnoses as well.

Methods

Study design and population

The current study is a planned subanalysis of the Amuse-2 dataset. Amuse-2 was a prospective cohort study, performed in the Netherlands between July 2007 and December 2010. It evaluated the safety of the diagnostic strategy of the Wells PE rule and a point-of-care D-dimer test in ruling out PE. Patients in whom the GP considered that PE might be present, were invited to participate and to give informed consent. Suspicion of PE was based on the presence of at least one of the following symptoms: unexplained (sudden) dyspnoea, deterioration of existing dyspnoea, pain on inspiration or unexplained cough. All patients were referred to the hospital for further diagnostic work-up. GPs enrolled 662 primary care patients. Predefined exclusion criteria were met in 64 patients, leaving a study population of 598 patients. The study protocol was approved of by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands. Detailed information on Amuse-2 has been published elsewhere (3).

Data collection

Using a standard form, the GP recorded the patient’s history, physical examination and the items of the Wells CDR for PE. Subsequently, a point-of-care D-dimer test (Clearview; Inverness Medical, Bedford, UK) was performed. GPs were asked to refer all patients to secondary care for further diagnostic work-up regardless of the outcome of the Wells rule and the point-of-care D-dimer test. In secondary care, the diagnostic strategy was based on current guidelines and routine care protocols.

Information on all diagnostic investigations, including hospital discharge letters, was retrieved from the GPs’ medical records. In addition, all patients were followed up for 3 months. After 3 months, GPs were asked to document the final diagnosis of each patient by completing a case record form. The GP could choose one or more of the following predefined diagnoses: PE, deep vein thrombosis (DVT), pneumonia, (exacerbation of) chronic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
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<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)</td>
<td>3.0</td>
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<tr>
<td>PE more likely than an alternative diagnosis</td>
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<tr>
<td>Heart rate &gt;100/minute</td>
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<td>Immobilization (&gt;3 days) or surgery in the previous 4 weeks</td>
<td>1.5</td>
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<tr>
<td>Previous PE or DVT</td>
<td>1.5</td>
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<tr>
<td>Haemoptysis</td>
<td>1.0</td>
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<tr>
<td>Malignancy (receiving treatment, treated in the last 6 months or palliative)</td>
<td>1.0</td>
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obstructive pulmonary disease (COPD), coronary insufficiency, aortic aneurysm, thoracic trauma, malignancy, pneumothorax, myalgia, panic disorder, non-specific thoracic pain/dyspnoea or ‘other’. When ‘other’ was chosen, the GP was asked to further specify this final diagnosis. No specific criteria for the clinical diagnoses were provided; they reflected the way in which patients were actually managed in clinical care. If more than one final diagnosis had been reported, the main diagnosis explaining the signs and symptoms that originally resulted in PE suspicion was included in the current analyses by the research team. For example, in a patient with pain on inspiration diagnosed with atrial fibrillation and pneumonia, we included the diagnosis pneumonia.

Outcomes

The primary outcome of the current analysis is the frequency of alternative diagnoses in primary care patients suspected of PE after PE had been excluded.

To analyse the association between the results of the pre-hospital Wells score and D-dimer test, and the final diagnoses, we divided the alternative diagnoses in two categories:

1. ‘Clinically relevant diagnoses’, i.e. disease diagnosed by a doctor and confirmed with one of the following methods:
   a. Pneumonia: infiltrate on chest radiograph or computed tomography scan (8)
   b. Asthma/COPD: (i) newly diagnosed on the basis of patient history and physical examination and/or lung function test and prescribed bronchodilator or corticosteroid medication; (ii) exacerbation: deterioration in symptoms in known asthma/COPD patient and deterioration in lung function or change in medication (oral corticosteroids, inhalation beta2-agonists or antibiotics) (9)
   c. Pericarditis: a pericardial rub with auscultation or pericardial effusion with echocardiography or typical electrocardiography changes
   d. Heart failure: increased natriuretic peptides [brain natriuretic peptide (BNP) or NT-proBNP] and abnormalities with echocardiography as seen in heart failure (10)
   e. Lung cancer: confirmed with histopathology
   f. Respiratory tract infection: a diagnosis of respiratory tract infection treated with antibiotics but without an infiltrate on the chest radiograph was included in this category
   g. Other clinical relevant diagnoses: as assessed by the study investigators.

2. ‘Clinical less relevant diagnoses’, i.e. not leading to any treatment other than supportive care (e.g. analgesics in case of musculoskeletal pain), included: non-specific thoracic pain/dyspnoea, myalgia and panic disorder/hyperventilation.

Two investigators independently assessed the hospital discharge letters and 3 months follow-up forms completed by the GP, before assigning patients to one of these two categories. In case of disagreement, a third investigator was involved and disagreements were resolved by discussion (11).

Statistical analysis

Statistical analyses were performed by using IBM Statistical Package for the Social Sciences software (version 19; SPSS, Chicago, IL). Patients with PE (73/598; 12.2%) or a missing final diagnosis (9/598; 1.5%) were excluded from the analyses.

Descriptive statistics were used to describe the baseline characteristics and to report the frequency of the alternative diagnoses. Corresponding 95% confidence intervals (95% CI) were calculated for each alternative diagnosis by using Fisher’s exact test.

To investigate the association between the pre-hospital Wells score and D-dimer test, and type and severity of the alternative diagnosis, we performed subgroup analyses for patients with a Wells score >4 or a positive point-of-care D-dimer test vs. patients with a Wells score ≤4 and a negative point-of-care D-dimer test. The threshold of 4 was based on previous studies showing a high efficiency and safety at this cut-off point for excluding PE (2,3,11). Odds ratios (OR) and corresponding 95% CI for the alternative diagnoses by pre-hospital results for Wells rule and D-dimer were calculated by Mantel–Haenszel common OR. Furthermore, to summarize the diagnostic accuracy of the Wells rule, point-of-care D-dimer test and several baseline characteristics, we calculated the positive and negative likelihood ratios (LR) with corresponding 95% CI.

Missing values on items of the Wells PE rule or point-of-care D-dimer test results were observed in 24 (4.0%) patients. Missing data was not completely at random and therefore deletion of the subjects with missing values would not only lead to a loss of statistical power but also to biased results (12). To minimize the effect of selective missing, we imputed missing values using multiple imputation techniques. Imputation techniques are based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects (13).

Results

PE (and/or DVT) was present in 73/598 patients (12%), a clinically relevant diagnosis was present in 149/598 patients (25%), of which 67 had pneumonia (11%). A clinically less relevant disease was present in 367/598 patients (61%). Since a clear final diagnosis was missing in 9/598 patients (1.5%), a total of 516 patients were included in the analyses for the current study on alternative diagnoses (Fig. 1).
Baseline characteristics are shown in Table 2. The mean age was 47 years and 72% was female. Patients with a clinically less relevant diagnosis were younger than patients with a clinically relevant diagnosis.

Signs and symptoms

Patients diagnosed with a clinically relevant disease were more likely to have presented with a heart rate of >100 beats per minute (BPM) (OR = 5.1), haemoptysis (OR = 3.3), unexplained cough (OR = 2.0) or an unexplained (sudden) onset of dyspnoea (OR = 1.6). Furthermore, patients with a clinically relevant diagnosis were more likely to have a Wells risk score of >4 points (OR = 1.6) or a positive point-of-care d-dimer test (OR = 2.0) than patients with a clinically less relevant diagnosis.

The LRs in Table 2 show that the judgement of the GP that PE is the most likely diagnosis (positive LR = 6.46) as well as a heart rate of >100 BPM (positive LR = 3.69) are associated with moderate increase in the likelihood of having a clinically relevant disease (Table 2).

Common alternative diagnoses

The most common alternative diagnoses after excluding PE were nonspecific thoracic pain/dyspnoea (42.6%; 95% CI: 38.3–47.0%), pneumonia (13.0%; 95% CI: 10.2–16.2%), myalgia (11.8%; 95% CI: 9.2–15.0%), (exacerbation of) asthma/COPD (4.8%; 95% CI: 3.2–7.1%), panic disorder/hyperventilation (4.1%; 95% CI: 2.5–6.2%), respiratory tract infection (2.3%; 95% CI: 1.2–4.0%), heart failure (1.4%; 95% CI: 0.5–2.8%), pericarditis (1.2%; 95% CI: 0.4–2.5%) and lung cancer (1.0%; 95% CI: 0.3–2.2%). Pneumonia was the most common clinically relevant diagnosis, occurring almost as frequently as PE. Other, less frequent alternative diagnoses are presented in Figure 1.

Alternative diagnoses and pre-hospital Wells score and d-dimer test

There was a significant association (P = 0.001) between pre-hospital results of Wells score and d-dimer test and clinical relevance of the alternative diagnoses. Patients with a Wells score >4 or a positive point-of-care d-dimer test were more likely to have a clinically relevant diagnosis than patients with a Wells score of ≤4 and a negative point-of-care d-dimer test (OR = 2.1; 95% CI: 1.4–3.1). Sixty-two percent (n = 93) of the 149 patients with a clinically relevant diagnosis had a Wells score of >4 or a positive d-dimer test. An overall positive LR of 1.42 (95% CI: 1.20–1.69) also indicates that there is a small increase in the likelihood of having a clinically relevant disease if the Wells score is >4 or the patient has a positive d-dimer test.
In particular ‘pneumonia’ was strongly associated with a Wells score of >4 or a positive point-of-care d-dimer test (OR = 2.7; 95% CI: 1.6–4.8, \( P = 0.001 \)). Similarly, the individual positive LR of pneumonia (LR = 1.52, 95% CI: 1.26–1.83) shows that Wells >4 or a positive d-dimer is moderate predictive of a diagnosis of pneumonia. Forty out of the 67 (59.7%) patients with pneumonia had a positive d-dimer test. Although 123 of the 262 (46.9%) patients with a low score on the Wells PE rule combined with a negative d-dimer result were diagnosed with nonspecific thoracic pain/dyspnoea or myalgia, 56 (21.4%) of these 262 patients were diagnosed with a clinically relevant disease (Table 3).

**Discussion**

**Main findings**

In this analysis of a large prospective study performed in primary care including 598 patients in whom the GP considered the diagnosis of PE, we found that the most common alternative diagnoses were nonspecific thoracic pain/dyspnoea (43%), myalgia (12%) and pneumonia (13%). We showed that patients with either a positive Wells rule (>4) or a positive d-dimer test, in whom the diagnosis of PE had been excluded, were more often diagnosed with a clinically relevant disease (OR = 2.1). More than 60% of the 149 patients with a clinically relevant diagnosis had a Wells score >4 or a positive point-of-care d-dimer test. Yet, around 20% of patients with a low Wells score (<4) and negative point-of-care d-dimer result were diagnosed with a clinically relevant condition. Furthermore, we found that patients who presented with a heart rate >100 BPM, haemoptysis, unexplained cough or an unexplained (sudden) onset of dyspnoea, were more likely to have a clinically relevant diagnosis.

**Strengths and limitations**

To our knowledge, this is the first empirical study from primary care, presenting alternative diagnoses in patients in whom the GP considered the diagnosis PE but in whom PE could be excluded. It was a large prospective study, with a relatively complete data set, in which we minimized the possible effect of selective missing by using multiple imputation techniques.

Although GPs were instructed to refer all patients to secondary care, 17% of all (598) patients were not sent to the hospital for further diagnostic work-up. No referral to secondary care usually means less systematic diagnostic work-up. Nevertheless, all patients were followed-up in primary care for 3 months and the reported final diagnosis according to the GP for these patients was included in the present analysis. For 1.5% (9/598) patients no alternative diagnosis was reported. All these patients had a follow-up without venous thrombo-embolism.
Table 3. ORs and LRs for alternative diagnoses by result of Wells score and point-of-care d-dimer test

<table>
<thead>
<tr>
<th>Clinically relevant diagnoses</th>
<th>Clinically less relevant diagnoses</th>
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<td>Pneumonia</td>
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<tr>
<td>Asthma/ COPD</td>
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<tr>
<td>Respiratory tract infection</td>
<td>Panic disorder/ hyper-ventilation</td>
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<tr>
<td>Other clinically relevant diagnosis</td>
<td>Other clinically less relevant diagnosis</td>
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<tr>
<th>Wells &gt;4 or positive d-dimer; N = 254</th>
<th>N (%; 95% CI)</th>
<th>10 (3.9; 0.9–5.1)</th>
<th>30 (11.8; 8.36–16.4)</th>
<th>97 (38.2; 32.2–44.5)</th>
<th>23 (9.1; 5.8–13.3)</th>
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<th>33 (13.0; 9.1–17.8)</th>
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<tr>
<td>Pneumonia</td>
<td>N (95% CI)</td>
<td>47 (18.5; 13.9–23.8)</td>
<td>6 (2.4; 1.9–7.1)</td>
<td>30 (11.8; 8.36–16.4)</td>
<td>97 (38.2; 32.2–44.5)</td>
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<td>Myalgia</td>
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<tr>
<th>Wells ≤4 and negative d-dimer; N = 262</th>
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<th>10 (3.9; 0.9–5.1)</th>
<th>30 (11.8; 8.36–16.4)</th>
<th>97 (38.2; 32.2–44.5)</th>
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<tr>
<td>Pneumonia</td>
<td>N (95% CI)</td>
<td>20 (7.6; 4.7–11.5)</td>
<td>6 (2.3; 3.2–9.3)</td>
<td>15 (5.7; 3.2–9.3)</td>
<td>123 (46.9; 40.8–53.2)</td>
<td>38 (14.5; 10.5–19.4)</td>
<td>13 (5.0; 32 (12.2; 8.5–16.8)</td>
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<tr>
<td>Asthma/ COPD</td>
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<td>15 (5.7; 3.2–9.3)</td>
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<tr>
<th>Wells d-dimer; N = 516</th>
<th>OR (95% CI)</th>
<th>2.7 (1.6–4.8)</th>
<th>1.0 (0.3–1.5)</th>
<th>2.2 (1.2–4.2)</th>
<th>0.7 (0.3–1.0)</th>
<th>0.6 (0.3–1.5)</th>
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LR pos, positive LR; LR neg, negative LR. The boldface values present the statistically significant results.

*aOther clinically less relevant diagnoses: other diagnoses (e.g. bronchial hyperactivity, collaps n.o.s., trauma thorax, influenza, sinusitis) made by a GP or hospital physician not leading to any treatment other than supportive care (e.g. analgesic).

*bOther clinically relevant diagnoses in patients with a Wells score >4 or positive d-dimer: heart failure (n = 5), pericarditis (n = 4), lung cancer (n = 4), coronary insufficiency (n = 3), atrial fibrillation (n = 2), obstructive sleep apnoea syndrome (n = 2), pleuritis (n = 1), pneumothorax (n = 1), metastatic colon carcinoma (n = 1), endocarditis (n = 1), diabetes mellitus de novo (n = 1), sarcoidosis (n = 1), acute aortic dissection (n = 1), systemic lupus erythematosus (n = 1), Langerhans cell histiocytosis (n = 1), atelectasis (n = 1),

*cOther clinically relevant diagnoses in patients with a Wells score ≤4 and negative d-dimer: pleuritis (n = 2), rib fracture (n = 2), heart failure (n = 2), pericarditis (n = 2), atrial fibrillation (n = 1), pneumothorax (n = 1), atelectasis (n = 1), lymphadenopathy n.o.s. (n = 1), urosepsis diabetes (n = 1), lung cancer (n = 1), multiple myeloma (n = 1).
In 30% (44/149) of the patients without a confirmed PE but with a clinically relevant alternative diagnosis (such as pneumonia, pleuritis, pericarditis and exacerbation COPD), it was not clear whether objective testing had been performed to establish these diagnoses. This also occurs in daily clinical practice, and our study represents that reality. Excluding these patients would have led to selection bias and have diminished the generalizability of our findings.

The original study was designed to validate the diagnostic strategy of excluding PE in primary care by using the Wells CDR for PE and a point-of-care d-dimer test. Therefore, not all potentially relevant characteristics of the alternative diagnoses may have been recorded (e.g. body temperature).

**Interpretation**

The most common alternative diagnoses of PE found in this study among patients from primary care, correspond largely to reported alternative diagnoses in secondary care (Fig. 1). Bernard Bagattini et al. (7), in a large diagnostic study in secondary care patients suspected of PE, reported that the most frequent discharge diagnoses in emergency ward patients in whom PE was ruled out were nonspecific chest pain, bronchopneumonia and heart failure.

Furthermore, our results correspond to studies showing a high proportion of patients with clinically relevant diagnoses in patients with a positive Wells rule or a positive d-dimer test result (14,15).

The association in the current study between a high pre-hospital score of the Wells rule and positive d-dimer result and clinical relevance of the final diagnosis may be partly explained by high d-dimer levels. It is known from literature that pneumonia (16), malignancy (14,17), coronary syndromes and vascular disorders (18,19) and heart failure (20) are associated with high d-dimer levels. Our finding of an increased proportion of pneumonia in patients with a positive d-dimer test result is in line with these studies.

Additional to the d-dimer test, also the signs ‘heart rate > 100 BPM’ and ‘haemoptysis’ of the Wells CDR have contributed to the association with clinical relevance of the alternative diagnosis.

However, the LRs of the Wells rule combined with d-dimer testing are small and indicate that the association between Wells >4 or a positive d-dimer and the presence of a clinically relevant disease is moderate. It would be valuable if future studies would investigate the added value and LRs of potential risk factors (e.g. smoking, medical history), signs and symptoms (e.g. body temperature) and additional diagnostic tests [e.g. C-reactive protein (CRP) testing] specific for the most common clinically relevant alternative diagnoses of PE such as pneumonia, asthma/COPD and respiratory tract infection. By predefining objective testing to establish the alternative diagnosis uncertainty about the accuracy of a diagnosis will be prevented.

**Clinical implications**

For a GP, seeing just a few patients in a year in whom PE might be present, it may be difficult to judge whether an alternative diagnosis is less or more likely than PE. Our study revealed that the most common alternative diagnoses to consider in patients in whom PE might be present, are nonspecific thoracic pain/dyspnoea, myalgia and pneumonia. The latter diagnosis is the most common clinical relevant alternative diagnosis, occurring almost as often as PE.

Our description of alternative diagnoses can support the GP’s diagnostic process before and after the application of the Wells CDR for PE and d-dimer testing.

This study showed that the probability of a clinically relevant diagnosis is higher in patients with a Wells score >4 or a positive d-dimer test result. However, ~20% of patients with a negative Wells rule (≤4) and a negative d-dimer test were diagnosed with a clinically relevant disease. As always, the GP will need to take all available clinical data into account to make a likely diagnosis. Of the clinical variables investigated in this study, a heart rate >100 BPM, haemoptysis, unexplained cough or an unexplained (sudden) onset of dyspnoea, were indicative of a clinically relevant diagnosis.

Performing a point-of-care CRP test might be another option to consider. Additional analyses in our study cohort showed that a CRP value <10 mg/l might reduce the risk of having a clinically relevant alternative diagnosis (11).

**Conclusion**

In primary care, the most common alternative diagnoses in patients in whom PE was suspected but could be ruled out, were nonspecific thoracic pain/dyspnoea, myalgia and pneumonia. A positive Wells rule or a positive d-dimer test are not only positively associated with PE, but also with a high probability of other clinically relevant disease.

**Declaration**

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