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Full Length Article

Is D-dimer used according to clinical algorithms in the diagnostic work-up of patients with suspicion of venous thromboembolism? A study in six European countries

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ABSTRACT

Introduction: Clinical algorithms consisting of pre-test probability estimation and D-dimer testing are recommended in diagnostic work-up for suspected venous thromboembolism (VTE). The aim of this study was to explore how physicians working in emergency departments investigated patients suspected to have VTE.
Materials and methods: A questionnaire with two case histories related to the diagnosis of suspected pulmonary embolism (PE) (Case A) and deep venous thrombosis (DVT) (Case B) were sent to physicians in six European countries. The physicians were asked to estimate pre-test probability of VTE, and indicate their clinical actions.
Results: In total, 487 physicians were included. Sixty percent assessed pre-test probability of PE to be high in Case A, but 7% would still request only D-dimer and 11% would exclude PE if D-dimer was negative, which could be hazardous. Besides imaging, a D-dimer test was requested by 41%, which is a "waste of resources" (extra costs and efforts, no clinical benefit). For Case B, 92% assessed pre-test probability of DVT to be low. Correctly, only D-dimer was requested by 66% of the physicians, while 26% requested imaging, alone or in addition to D-dimer, which is a "waste of resources".
Conclusions: These results should encourage scientific societies to improve the dissemination and knowledge of the current recommendations for the diagnosis of VTE.

1. Introduction

When reviewing a patient with suspected venous thromboembolism (VTE), i.e. pulmonary embolism (PE) or deep venous thromboembolism (DVT), it is recommended first to estimate the pre-test probability of PE/DVT by means of clinical signs and symptoms [1–6]. This pre-test probability can be assessed either by using clinical experience or by calculating the probability based on scores i.e. clinical decision rules like the Wells scores for PE or DVT [5]. The rationale behind estimating the probability of VTE before further testing is to be able to select a safe and efficient diagnostic work-up based upon the recommended clinical algorithm [1–8]. In patients with a low to moderate pre-test probability, a negative D-dimer is sufficient to exclude VTE, while in a patient with a higher pre-test probability, a negative D-dimer cannot exclude VTE, and the patient has to be referred to radiologic imaging to be able to exclude or confirm VTE. Patients with low to

Abbreviations: VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CTPA, computer tomography pulmonary angiography.

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moderate pre-test probability and a positive D-dimer result, should also be referred to imaging [1–8]. By using pre-test probability scores followed by the clinical algorithm described above, studies have shown that VTE can be ruled out without imaging in 30–40% of the patients where VTE is suspected [1,3–5,7–10]. However, recent studies suggest that such pre-test probability scores and the clinical algorithm are not implemented in the routine diagnostic work-up of VTE in some countries [11–17]. The aim of this study was to explore how clinicians from several countries working in emergency departments investigate patients with suspected VTE in relation to their own estimated pre-test probabilities of VTE, and to compare this practice with the recommended clinical algorithm.

2. Methods

Two case histories followed by a questionnaire were developed by the members of the Working Group on Postanalytical Phase (WG-POST) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and the European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM), and were piloted by 1–5 physicians in Italy, Turkey, Norway, Hungary and Croatia. The case histories were slightly modified after the results from the pilot. During the summer of 2012, invitation letters (emails) with a link to the web-based questionnaire, using an online survey tool (SurveyMonkey [18]), were sent to physicians working in emergency departments, in these European countries. In addition, in France, the questionnaire was sent by regular mail. A reminder was sent after a couple of weeks. Most of the physicians were contacted through societies of internal medicine or emergency physicians, while the questionnaire was spread by using the project-coordinator's professional contacts with eligible physicians in France.

Some of the included countries do not have specialists in emergency medicine, and therefore physicians working within internal medicine were also asked to participate in those countries. All participants who included their email address received a feedback report including recommendations for the diagnostic work-up of VTE addressed in the case histories.

2.1. Case histories

The first patient had clinical symptoms and signs compatible with PE (Fig. 1, Case A), and the next patient had suspected DVT (Fig. 1, Case B). According to the pre-test probability scores with two levels e.g. Wells score and the revised Geneva score for PE, which categorise patients into likely or unlikely PE [10], Case A was most likely suffering from PE. However, if using the three-level scores, categorising patients into low, moderate or high probability for PE [9], patient A could have either moderate or high probability for PE depending upon the interpretation of the subjective criteria in the Wells score ("Alternative diagnosis less likely than PE") or a moderate probability according to the revised Geneva score. In Case B, DVT was unlikely or the pre-test probability was low using the two-level or the three-level scores, respectively [19,20].

In the first part of the questionnaire, the physicians were presented with Case A and B and an initial question about the probability of PE (Fig. 1, A1) and DVT (Fig. 1, B1), respectively, based on the symptoms and signs presented to them in the case histories. Further, they were asked about their preferred clinical actions for each patient based upon 1) the clinical information, 2) after a D-dimer below the cut-off value for VTE (negative) and 3) after a D-dimer above the cut-off value (positive). The physicians who decided to exclude DVT, based on a negative D-dimer in Case B, were asked to state the D-dimer concentration, which would indicate them to request imaging (Fig 1).

In the second part of the questionnaire, the physicians were asked about background information, as well as their use of pre-test probability scores in clinical practice and in this particular questionnaire (Table 1).

Case A: Slightly overweight 48-year-old female smoker with acute dyspnoea, tachycardia and chest pain has been admitted to the Emergency Unit.
The patient has no known comorbidity, takes no medication regularly and has no previous surgery or immobilisation. At physical examination her blood pressure is slightly elevated 145/85 mm/Hg and her heart rate is 102/min. Her left lower extremity is slightly swollen and slightly tender on palpation. Arterial blood gas analysis showed PaO2 of 10.1 kPa (reference 11 – 13 kPa), otherwise the blood gas analyes are normal. Chest X-ray was normal and acute coronary infarction was excluded by ECG and cardiac biomarkers.

A1. Do you think she has pulmonary embolism based on the information in the case history?
❑ No, it is unlikely ❑ Yes, it is likely ❑ She has low probability ❑ She has intermediate/moderate probability
❑ She has high probability

A2. What would you do first in this situation?
❑ Request only D-dimer ❑ Request only radiologic imaging ❑ Request both D-dimer and radiologic imaging
❑ Other action, please specify _____ ❑ I do not know

Your colleague had already requested a D-dimer, and you receive the result before you have ordered any diagnostic tests: D-dimer concentration 0.45 mg/L (cut-off 0.5 mg/L).

A3. What would you do after receiving the normal D-dimer result?
❑ No further diagnostics, pulmonary embolism can be excluded
❑ Request radiologic imaging to confirm or exclude pulmonary embolism
❑ Other action, please specify _____ ❑ I do not know

Case B: A 19-year-old woman is admitted to the emergency unit and complains about pain in her left leg. The pain started when she was out running the morning before. The pain is worse today. She mentions that her 75-year-old grandmother has had a deep venous thrombosis recently, and she is afraid she also has a deep venous thrombosis (DVT). She has not heard of any other family members suffering from venous thromboembolism. She is a non-smoker, and she does not use oral contraceptives. On clinical examination you find a slight tenderness when pressing deeply right below the popliteal area, otherwise your clinical examination is normal.

B1: Do you think she has a DVT based on the information in the case history?
❑ No, it is unlikely ❑ Yes, it is likely ❑ She has low probability ❑ She has intermediate/moderate probability
❑ She has high probability

B2. What would you do to exclude or confirm DVT in this situation?
❑ Request only D-dimer ❑Request only radiologic imaging ❑Request both D-dimer and radiologic imaging
❑ Other action, please specify _____ ❑ I do not know

D-dimer was already requested by your colleague, and the D-dimer concentration was 0.31 mg/L (cut-off 0.5 mg/L).

B3. What would you do after receiving the normal D-dimer result?
❑ DVT can be excluded based on a normal D-dimer result, no further diagnostics needed
❑ Request radiologic imaging to confirm or exclude DVT
❑ Other action, please specify _____ ❑ I do not know

B4. If you excluded DVT in the question above, how high should the D-dimer concentration be for you to request radiologic imaging? (cut-off 0.5 mg/L) _____

In a similar patient, the D-dimer concentration was 1.85 mg/L (cut-off 0.5 mg/L).

B5. What would you do after receiving the pathological D-dimer result?
❑ No further diagnostics, DVT can be excluded based on the clinical presentation
❑No further diagnostics, DVT can be diagnosed based on the clinical presentation and the D-dimer result.
❑ Request radiologic imaging to confirm or exclude DVT.
❑ Other action, please specify _____ ❑ I do not know

Fig. 1. Case histories and questionnaire.

2.2. Clinical actions based on the physicians' pre-test probability estimates

For the data analysis, the physicians' responses on the probabilities of having VTE (Fig. 1, A1 and B1) were divided into two groups; 1) "high probability"; consisting of high probability and likely VTE and 2) "non-high probability"; consisting of moderate and low probability and unlikely VTE. These groups were created based on the recommended clinical algorithm, where high probability or likely VTE, should lead directly to imaging without analysing D-dimer, and where moderate and low probability or unlikely VTE should lead to initial D-dimer analysis, and imaging indicated only if D-dimer is positive [2,3,5–7].

Further, the case histories were divided into Part I: clinical actions after the information in the case histories, Part II: clinical actions after a negative D-dimer and Part III: clinical actions after a positive D-dimer (only Case B). Clinical actions stated by the physicians in both high and non-high pre-test probability groups in each of the parts, were categorized into "correct, "waste of resources" or "hazardous" (Table 2).

2.3. Statistics

Data was analysed by simple descriptive statistics. Logistic regression was used to evaluate the probability for answering 1) "correct" clinical action or 2) "waste of resources" or "hazardous" when belonging