

D-dimer for the diagnosis of acute venous thromboembolism in the emergency department: a Janus-face marker

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Venous thromboembolism (VTE) consists of two related conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). In the United States, VTE occurs for the first time in ~100 per 100 000 persons each year, with an exponential rise according to age (< 5 cases per 100 000 persons < 15 years to ~500 cases per 100 000 persons at age 80 years)¹. Data from the US National Hospital Discharge Survey² reported an incidence of DVT increased from 0.8% to 1.3% of admissions (slope 0.028%/year), whereas the incidence of PE was 0.4% of admissions and did not change over the considered period. Mortality remains high: at the end of 20th century, data from an international registry reported a mortality from PE to be slightly more than 7%³, with no significant difference compared to that estimated in the mid 1970s⁴. Thus, prevention of DVT and early and correct diagnosis of PE still remain the milestones to improve patient morbidity and mortality.

Data from the United States⁵ indicate that over 110 million patients seek emergency department care annually, and approximately 10 million of them complain of dyspnoea, chest pain, or both. Since all these symptoms may indicate the presence of PE, a potentially fatal disease, emergency medicine physicians often have to rule out VTE (and especially PE) in their diagnostic pathway. Thus, there is a crucial need for appropriate diagnostic tools that should be rapid, reliable, and possibly not much expensive. In fact, both underdiagnosis and overdiagnosis are associated with substantial morbidity and mortality rates.

Since it is evident that in Italy the emergency department has become the frontline of the majority of acute diseases (and not only emergencies), in this issue of *Internal and*

Emergency Medicine, Siragusa⁶ very appropriately and exhaustively focus on a widely used marker, the D-dimer (D-d), characterised by a Janus-face effect. On one hand, in fact, D-d testing can facilitate wider screening for PE and allow a higher rate of diagnosis. On the other, however, overuse or misuse of the D-d to screen for possible PE may have negative consequences, in terms of both burden for patients and healthcare costs. Despite clinical guidelines, in fact, inappropriate and unnecessary measurement of D-d values is a significant clinical problem⁷.

The antigen fibrin D-d is the primary enzymatic degradation product of cross-linked fibrin by plasmin, and systemic values of D-d are an index of fibrin turnover in the circulation. However, although these systemic D-d values aid diagnosis and might be a diagnostic indicator in a variability of emergency clinical conditions, a first important limitation comes from its low specificity in patients with several comorbidities (Table 1)⁷⁻³². However, D-d testing might be used in an emergency setting for diagnosing either DVT or PE.

Deep vein thrombosis

Typically, DVT has a marginal importance in the emergency department since it is, for most cases, a primary care disease. In this setting, D-d testing associated with the use of simple diagnostic indicators from patient history and physical examination (male gender, oral contraceptive use, presence of malignancy, recent surgery, absence of leg trauma, vein distension, calf difference) can safely rule out DVT in a large number of patients and reduce unnecessary healthcare costs³³. A combination of D-d testing and clinical probability score has been found to be effective in reducing (~23%) unnecessary venous duplex scanning in suspected symptomatic DVT in the low and moderate pretest clinical probability (PCP) score. In the low-risk PCP patients, D-d testing provided 100% sensitivity, 46% specificity, 4.8% positive predictive value, and 100% negative predictive value. In the moderate-risk PCP, the

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Table 1. Clinical conditions associated with D-dimer increase in addition to venous thromboembolism.

Non-pathological	
Age (healthy elderly) ⁸	
Black race ⁹	
Cigarette smoking ⁹	
Functional impairment ⁸	
Pregnancy ¹⁰	
Surgery ^{11,12}	
Pathological	
Acute coronary syndrome ¹³	
Acute upper gastrointestinal haemorrhage ^{14,15}	
Arterial thromboembolism ¹⁶	
Atrial fibrillation ¹⁷	
Cerebral sinus thrombosis ¹⁸	
Cirrhosis ^{19,20}	
Disseminated intravascular coagulation ²¹	
Heparin administration ²²	
Infection ^{23,24}	
Neoplasm ²⁵	
Portal venous thrombosis ²⁶	
Preeclampsia ^{27,28}	
Sickle cell disease ²⁹	
Stroke (ischaemic/haemorrhagic) ^{30,31}	
Trauma ³²	

From Wakai et al.⁷, modified.

D-d testing showed 100% sensitivity, 45% specificity, 49% positive predictive value, and 100% negative predictive value³⁴.

Wells et al.³⁵ recently reviewed studies (1990-2004) that prospectively enrolled consecutive, unselected outpatients with suspected DVT and applied clinical prediction rules before D-d testing or diagnostic imaging. Inclusion criteria were presence of sufficient information to allow the calculation of DVT prevalence for at least one out of three clinical probability estimates (low, moderate, high), and a minimum of 3-month follow-up period. The authors concluded that diagnostic accuracy for DVT was improved when clinical probability was estimated before diagnostic tests. Patients with low clinical probability on the predictive rule showed prevalence of DVT of less than 5%. In low-probability patients with negative D-d testing, DVT can be excluded without performing ultrasound examination, whereas in those with high clinical suspicion results should not affect clinical decision. Also in cancer patients with clinically suspected DVT, a negative D-d might be useful in excluding the diagnosis within the low or low-moderate clinical pretest probability³⁶.

Moreover, D-d testing is a useful tool to evaluate the risk of recurrence. In a prospective cohort of outpatients after oral anticoagulant therapy, suspension for a first idiopathic episode of DVT, abnormal D-d at 1 month after anticoagulant therapy withdrawal was found to be an independent risk factor for recurrent VTE³⁷.

Pulmonary embolism

As for PE, a disease often characterised by common and non-specific signs and symptoms³⁸, the need for diagnostic tools capable of addressing the diagnosis is particularly crucial in emergency settings. With the exception of patients with cancer, in whom a negative D-d assay can safely exclude the diagnosis of PE (due to low specificity, when testing 100 patients with suspected PE, a normal D-d concentration can safely rule out PE in 15 patients with cancer and in 43 patients without cancer)²⁵, D-d testing cannot be safely used alone. In fact, in their cohort of more than 400 patients presenting to the emergency department with pleuritic chest pain, Hogg et al.³⁹ found that the Simplify D-dimerTM was not sufficiently sensitive to exclude the diagnosis of PE.

Over the last years, several non-invasive diagnostic tests have been validated for patients with suspected PE⁴⁰. However, there is not a single non-invasive test always suitable when taken alone, and only the combination of clinical probability and one or more diagnostic tests may allow physicians to make differential diagnosis between PE and several other acute diseases. Thus, many studies have recently addressed this topic, searching for the optimal combination of instrumental and laboratory examination, and clinical evaluation.

A consecutive series of about 300 patients presenting to the emergency department in New Zealand with suspected PE were evaluated according to measurement of D-d, arterial oxygen pressure (PaO₂), and assessment for the presence of major clinical risk factors⁴¹. Patients with no risk factors, normal D-d testing, and PaO₂ ≥ 80 mmHg (group A) were discharged and followed up by telephone interviews, whereas patients with elevated D-d levels, PaO₂ < 80 mmHg, or one or more risk factors (group B) were managed according to hospital guidelines. No cases of PE were diagnosed over the 3-month follow-up period in group A against 37 cases (21%) in group B. Test accuracy for suspected PE varies greatly, and a systematic meta-analysis was aimed to assess the likelihood ratios of diagnostic strategies for PE and to determine their clinical application according to pretest probability⁴². Positive likelihood ratios for diagnostic tests were: high-probability ventilation perfusion lung scan 18.3 (95% confidence interval [CI] 10.3-32.5), spiral computed tomography (CT) 24.1 (95% CI 12.4-46.7), ultrasonography of leg veins 16.2 (95% CI 5.6-46.7). In patients with moderate or high pretest probability, these tests were associated with a greater than 85% post-test probability of PE. Negative likelihood ratios were: normal or near normal appearance on lung scan 0.05 (95% CI 0.03-0.10), a negative result on spiral CT along with a negative result on ultrasonography 0.04 (95% CI 0.03-0.06), and a D-d concentration < 500 µg/l measured by quantitative enzyme-linked immunosorbent assay

0.08 (95% CI 0.04-0.18). In patients with a low or moderate pretest probability, these findings were associated with a post-test probability of PE < 5%.

A study aimed to assess the clinical effectiveness of a simplified algorithm based on a dichotomised clinical decision rule, D-d testing, and CT in patients with suspected PE has recently been published⁴³. A prospective cohort of more than 3000 consecutive patients enrolled in 12 centres in the Netherlands was categorised as "PE unlikely" or "PE likely" on the basis of a dichotomised version of the Wells clinical decision rule. The group of patients classified as "PE unlikely" had D-d testing, and PE was excluded in the presence of a negative D-d testing. All other patients performed CT, and PE was ruled as confirmed/excluded based on the results. The diagnostic management strategy using a simple clinical decision rule, D-d testing, and CT resulted effective in the evaluation and management of patients with clinically suspected PE, and its use was associated with a low risk for subsequent fatal and non-fatal VTE. Excluding or confirming PE remains a diagnostic challenge especially in elderly patients, in whom PE is associated with substantial comorbidity. However, the combination of a non-high clinical decision rule probability and normal D-d result is a safe strategy to rule out PE in elderly outpatients as well⁴⁴.

Are we adhering to specific guidelines enough?

Even if international guidelines include several strategies for diagnosing PE with confidence, in everyday clinical practice the impression is that it is unlikely these guidelines are fully implemented. To address this question, the EMDEPU Study Group investigators performed a prospective cohort observational study in 117 emergency departments⁴⁵. The authors studied more than 1500 patients with suspected PE, and compared each patient's data and the treating physician's final diagnosis with pre-specified diagnostic criteria. Appropriateness of diagnostic criteria according to international guidelines, and incidence of thromboembolic events during follow-up were measured. Diagnostic management was inappropriate in 43% of patients: 8% of patients with confirmed PE and 57% of patients in whom PE was ruled out. Independent risk factors for inappropriate management are summarised in Table 2. As a consequence, among patients who did not receive anticoagulant treatment, a thromboembolic event during follow-up occurred in 1.2% of patients who received appropriate management and in 7.7% of patients who received inappropriate management ($p < 0.001$), and inappropriateness was independently associated with thromboembolism occurrence (adjusted odds ratio 4.29, 95% CI 1.45-12.70). The authors concluded their paper

Table 2. Independent risk factors for inappropriate management of pulmonary embolism⁴⁵.

Risk factors	Adjusted OR	95% CI
Current or recent pregnancy	5.92	1.81-19.30
Currently receiving anticoagulant treatment	4.57	2.51-8.31
Lack of a written diagnostic algorithm and clinical probability score	2.54	1.51-4.28
Age > 75 years	2.27	1.48-3.47
Known heart failure	1.53	1.11-2.12
Chronic lung disease	1.39	1.00-1.94

CI, confidence interval; OR, odds ratio.

stating that institutions should concentrate their efforts on establishing written diagnostic guidelines that include a clinical probability scoring system.

Thus, a crucial point is the simplification of scoring systems. In this respect, in recent years clinical probability assessment has gained growing importance for optimal diagnosis of PE⁴⁶⁻⁴⁸, and some prediction rules have been validated. The most widely used are the Wells score⁴⁹ and the Geneva score⁵⁰, which after comparison with implicit judgement, showed similar accuracy⁵¹. Both prediction scores had limitations. On one hand, in fact, the Wells score includes the clinician's judgement of whether an alternative diagnosis is more likely than a PE diagnosis, and this may not be standardised. On the other, the computation of the Geneva score requires arterial blood gas variables while breathing room air, and this variable was not available in 15% of patients in the external validation sample. Thus, a revised Geneva score is now available, easy to compute, entirely based on clinical variables and independent of physicians' implicit judgement (Table 3)⁵², and it should now be tested for clinical usefulness in specific outcome studies.

Conclusions

The great number of papers published on D-d over the last months show how "hot" is this topic, making rather impossible going step-by-step with the literature. New diagnostic tools and laboratory tests are being available. For example, soluble fibrin has been indicated as a useful marker for the diagnosis of DVT (sensitivity and specificity of D-d and soluble fibrin were 90 and 50%, and 77.6 and 88.3%, respectively), and it has been suggested that measurement of both D-d and soluble fibrin could increase the sensitivity and specificity for the diagnosis of DVT and PE⁵³. Again, recent data seem to support the hypothesis that standard C-reactive protein might be used to safely rule out PE as well, either as a sole test or combined with clinical probability assessment, but further prospective studies are needed⁵⁴.

Due to the reasons exhaustively put forward in the review article by Siragusa⁶, D-d testing "can be safely used in the

Table 3. The revised Geneva score⁵².

Variable	Points
Risk factors	
Age > 65 years	1
Surgery (under general anaesthesia) of fracture (lower limbs) within 1 month	3
Active malignant condition (solid or haematologic, currently cured or considered curative < 1 year)	2
Symptoms	
Unilateral lower limb pain	3
Haemoptysis	2
Clinical signs	
Heart rate	
75-94 bpm	3
≥ 95 bpm	5
Pain on lower limb deep venous palpation and unilateral oedema	4
Clinical probability	
Low	0-3 total
Intermediate	4-10 total
High	≥ 11 total

management of acute VTE in emergency medicine only in conjunction with pre-test clinical probability". Clinical decision rule still remains the cornerstone upon which building up the diagnosis of VTE, and the completeness of internist's knowledge is crucial.

Among the multitude of precious suggestions and teachings my "maestro", professor Carmelo Fersini, gave me going through 25 years of collaboration since the first day I attended his clinical ward as a young student, one is coming to my mind now: "Remember, Roberto – he was used to say – when you are in front of a discrepancy between clinical and laboratory or instrumental findings, clinical evaluation must go first". Thirty years after, even in a modern era taking advantage from randomised controlled trials, evidence-based medicine, and dramatic improvements in laboratory and diagnostic testing, I believe these words are still appropriate and to be dedicated to the younger generations of doctors.

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