Diagnostic accuracy of D-dimer assay in suspected pulmonary embolism patients

Abdel Rahem I. Youssf a,1, Mohammed F.M. Ismail a, Reda ElGhamry a,*, Mahmoud R. Reyad b

a Chest Diseases, Zagazig University, Egypt
b Mansoura Chest Hospital, Egypt

Received 21 November 2013; accepted 19 December 2013
Available online 22 February 2014

Abstract  Background: Pulmonary embolism (PE) is a frequent and potentially severe disease. So objective testing is required to establish or exclude the presence of pulmonary embolism.
Aim: This study was carried out to evaluate the diagnostic accuracy of D-dimer test in suspected pulmonary embolism patients.
Patients and Methods: This study was carried out on 30 patients with clinical and radiological signs suspicious of PE. All cases were subjected to the following: evaluation of clinical probability by Revised Geneva Score, plain chest X-ray, CT pulmonary angiography (CTPA), electrocardiographic examination, arterial blood gases analysis, calculated alveolar arterial oxygen (PA-aO2) gradient, duplex ultrasonographic, D-dimer assay, and measurement of partial end tidal carbon dioxide (PetCO2).
Results: PE confirmed in 22 cases by CTPA, 20 cases of PE (91%) had positive D-dimer and 2 cases (9%) had negative D-dimer test. The sensitivity, specificity and accuracy of D-dimer in diagnosis of PE were (90%, 37.5%, and 26.6%) respectively. The sensitivity of D-dimer in evaluation of PE when clinical probability of PE low or intermediate was (100%), its specificity was (37.5%), its negative predictive value (NPV) was (100%) and its positive predictive value (PPV) was (67.7%), while in high clinical probability its sensitivity was (83.3%), specificity was (100%) and its PPV was (100%). There was statistically significant difference among the negative and positive PE cases as regards the PetCO2 result (P < 0.05). The sensitivity of PetCO2 in diagnosis of PE was (68%) its specificity was (87.5%), NPV was (50%) and its PPV was (93.7%).
Conclusion: D-dimer alone cannot exclude or confirm the presence of PE. The combination of D-dimer, PetCO2 ≤28.5 mmHg and the clinical probability could improve diagnostic accuracy in patients with suspected PE.
© 2014 Production and hosting by Elsevier B.V. on behalf of The Egyptian Society of Chest Diseases and Tuberculosis.
Introduction

Pulmonary embolism (PE) is a frequent and potentially severe disease, an accurate and rapid diagnosis of PE remains difficult in clinical practice because of non-specific clinical presentation also treatment carries significant potential side effects, so objective testing is required to establish or exclude the presence of pulmonary embolism. Although pulmonary angiography is being considered as the definitive diagnostic technique or “gold standard” in the diagnosis of acute pulmonary embolism, it suffers from limitation in its use as a result of being relatively expensive, time-consuming and involves radiation and contrast exposure [1].

In recent years, various combinations of non-invasive aids to diagnose, including the assessment of clinical probability, D-dimer testing, end tidal carbon dioxide (PetCO₂), venous compression ultrasonography of the legs (CUS) and ventilation perfusion lung scanning or CT pulmonary angiogram (CTPA), have been developed and validated to reduce the need for pulmonary angiography [2].

Pulmonary computed tomography angiography (CTPA) has become the preferred method to confirm or exclude PE. It has been shown to have high specificity, sensitivity, and negative predictive value for the diagnosis of acute PE [3].

D-dimer is a fibrin degradation product (FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross linked D fragments of the fibrinogen protein [4].

D-dimers are not normally present in human blood plasma, except when the coagulation system has been activated, as in the presence of thrombosis or disseminated intravascular coagulation. The D-dimer assay depends on the binding of a monoclonal antibody to a particular epitope on the D-dimer fragment. The binding of the antibody is then measured quantitatively by one of various laboratory methods [4].

D-dimer assays were characterized by having high sensitivity and negative predictive value, but poor specificity because elevated D-dimer may be present due to various causes as liver disease, high rheumatoid factor, inflammation, malignancy, trauma, pregnancy, recent surgery as well as advanced age [5].

The aim of this study is to evaluate the diagnostic accuracy of D-dimer assay in patients with suspected pulmonary embolism.

Patients and methods

Patients

This study was performed on 30 patients with clinical suspicion of pulmonary embolism admitted at the Chest Department and Respiratory Intensive Care Unit, Zagazig University Hospitals during the period from January 2010 to October 2011. There were 18 males and 12 females with mean age 49.1 ± 10.1 years. Patients were classified according to final diagnosis by CTPA into 22 cases positive for PE (73.3%) and 8 cases negative for PE (26.7%).

Inclusion criteria

The included patients were suspected to have pulmonary embolism according to:

1. Clinical history and symptoms suggestive of PE [1,2].
2. Clinical examination and signs that raise the suspicion of PE [1].

Exclusion criteria

Patients were excluded from the study if they: have renal insufficiency, patients refusing to do CTPA and those having hypersensitivity to IV contrast.

Methods

All the studied patients were subjected to the following:

1. Full medical history taking stressing on risk factors and symptoms suggestive for PE.
2. General and local chest examination for signs of PE and leg examination for signs of DVT.
3. Evaluation of clinical probability by Revised Geneva Score:
   Consisting of calculation of Revised Geneva Score and categorization of clinical probability of PE as low, intermediate, or high [6].
4. Plain chest X-ray (postero-anterior and lateral views) to detect radiological finding suggestive of PE [7].
5. Arterial blood gases analysis.
6. Alveolar–arterial oxygen Gradient: A–aO₂ gradient ≤20 mmHg was considered normal. While A–a gradient > 20 mmHg was considered abnormally wide [8].
7. Electrocardiography (ECG) was used to search for changes suggestive of PE [9].
8. Routine investigation: Complete blood picture, liver, kidney functions and bleeding profile.
9. D-Dimer assay.
10. Using the ELFA technique (Enzyme Linked Fluorescent Assay). The assay principle combines a two-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). The D-dimer cut off value ≥ 500 ng/ml was considered positive and results < 500 ng/ml were considered negative [10].
11. Lower limb duplex: Done by a Doppler ultrasound device (Toshiba sonolayer) with superficial probe (7.5) MHz, for the diagnosis of DVT according to Pezzullo et al. [11].
12. End tidal CO₂: Measurement by quantitative capnometry (patient monitor, medical industry, model M3, Borg El-Arab) using a nasal cannula. Cut off point was calculated by the Receiver operating characteristic curve (ROC curve) which equals 28.5 mmHg. PetCO₂ was considered positive if ≤28.5 mmHg.
13. Pulmonary CT angiography: Performed for all patients using (Dual slice Hi speed spiral CTPA). It is the gold standard for the final diagnosis of pulmonary embolism.

Statistical analysis

Data were entered and analyzed using the Microsoft Excel software. Data were summarized using the arithmetic mean (X), the standard deviation (SD), chi-square and student t-test.
Disaminative diagnostic values including, sensitivity, specificity, predictive value, and receiver operating characteristic (ROC) curve were assessed by medical tests. Significant was detected according to the $P$ value ($P < 0.05$).

**Results**

Our study included 30 cases suspected to have PE (18 males and 12 females). Their age ranged from 25 to 70 years, with a mean age (49.1 ± 10.1) years. Twenty-two cases (73.3%) proved to have PE by CTPA and eight cases (26.7%) were negative. The demographic data and results of diagnostic tests were used in the study (Table 1). The mean age of positive and negative PE cases was (49.6 ± 10.8 and 47.7 ± 8.4) respectively, with statistically non-significant difference among studied cases as regards to age and sex.

Also, hypoxemia and widening of alveolar arterial $O_2$ gradient were present in 20 cases (91%) with positive PE. While ten cases had negative PE. In 45.5% had DVT on duplex ultrasonography venous study and 12 cases (54.5%) had normal duplex.

Results of D-dimer test were positive in 20 cases (91%) of PE and were negative in 2 cases (9%).

Also, measurements of End tidal $CO_2$ showed that 68% of proved PE had Pet$CO_2$ ≤28.5 mmHg and 32% of them had Pet$CO_2$ > 28.5 mmHg.

Table 2 shows that the sensitivity of D-dimer test in diagnosis of PE was (90%) while its specificity was (37.5%) as well as its positive predictive value was (60%), while sensitivity of Pet$CO_2$ in diagnosis of PE was (68%), its specificity was (87.5%) and its NPV was (50%) while its PPV was (93.7%).

Table 3 shows all cases with low clinical probability had negative D-dimer test and negative PE. 15 cases while intermediate clinical probability had positive D-dimer, 10 cases of them had positive PE and the other 5 cases were negative for PE, on the other hand all cases with high clinical probability had PE, 10 cases of them had positive D-dimer and 2 cases had negative D-dimer result.

Table 4 shows that the sensitivity, specificity, NPV and PPV of D-dimer test in evaluation of pulmonary embolism when the clinical probability of pulmonary embolism is low or intermediate were (100%, 37.5%, 100% and 67.7%), respectively. While, the sensitivity, specificity and PPV of D-dimer test in cases of high clinical probability of PE were (83.3%, 100% and 100%) respectively.

Table 5 shows that the sensitivity of Pet$CO_2$ measurement in evaluation of PE when the clinical probability of pulmonary embolism was low or intermediate was (40%), its specificity was (87.5%), its NPV was (53.8%) and its PPV was (80%), while its sensitivity when the clinical probability of PE was high was (91.6%), specificity was (100%) as well as its positive predictive value was (100%).

**Discussion**

In recent years, various combinations of non-invasive aids to diagnose PE including the assessment of clinical probability, D-dimer testing, Pet$CO_2$, venous compression ultrasonography of the legs (CUS) and ventilation perfusion lung scanning or CTPA have been developed and validated to reduce the need for pulmonary angiography[2].

The D-dimer test is usually performed first because it can safely rule out PE and thus, reduce the need for further testing but relying on D-dimer testing alone carries an unacceptable risk if the clinical probability of PE is not taken into account because of its poor specificity, especially in elderly patients, patients with cancer, hospitalized patients and pregnant women, the D-dimer test excludes PE in only 30% of patients [12].

So this study was carried out to evaluate the diagnostic accuracy of D-dimer in suspected pulmonary embolism patients.

This study included 30 cases suspected to have PE; 22 cases (73.3%) were positive for PE by CTPA and the other 8 cases (26.7%) were negative for PE. The mean age of positive and negative PE cases was (49.6 ± 10.8, 47.7 ± 8.4), respectively.
These results are in agreement with Stein et al. [5] who found that the venous thrombo-embolism and pulmonary embolism are diseases associated with advancing age due to the cumulative effect of risk factors that patients acquire with aging such as immobility, trauma, surgery, hypertension and obesity.

The present study (Table 1) showed that 20 cases (91%) of the proved PE cases had hypoxemia and (PA-aO₂) gradient > 20 mmHg, while 2 cases (9%) had no hypoxemia and (PA-aO₂) gradient ≤ 20 mmHg. There was statistically significant difference among the studied cases as regards hypoxemia and (PA-aO₂) gradient (P < 0.05).

These results are in agreement with Adam et al. [1] who noted that; hypoxemia and wide (A-aO₂) gradient are the most common arterial blood gas abnormalities in patients with PE, but up to 20% of patients with PE can be normal.

In the current study ten cases (45.5%) of PE had DVT on duplex ultrasonography venous study and 12 cases (54.5%) of them had normal duplex. While all cases that were negative for PE had normal duplex study. There was statistically significant difference among the negative and positive PE cases as regards duplex ultrasonography examination (Table 1).

These results are in agreement with Fawzy [13], who also proved that; 53.8% of the patients proved to have PE have no evidence of acute DVT.

These results are also supported with Adam et al. [1] who mentioned that DVT is only found in approximately 30% to 50% of patients confirmed to have PE, and a normal ultrasonography exam of the leg veins does not rule out PE.

Regarding the final diagnosis (Table 1) among 22 cases who had PE by CTPA 20 cases (91%) had positive D-dimer and 2 cases (9%) had negative D-dimer. On the other hand, 8 cases were proved to be negative for PE, 5 cases (37.5%) of them had positive D-dimer and 3 cases (62.5%) had negative D-dimer result.

The recorded sensitivity, specificity, and accuracy of D-dimer test as regards the final diagnosis by CT pulmonary angiography were 90%, 37.5%, and 76.6% respectively (Table 2).

This is in accordance to the results of Patrick et al. [14] who reported that D-dimer assay was unsuitable to be used as a sole test to exclude or confirm VTE. The recorded sensitivity, specificity, negative predictive value and positive predictive value of D-dimer test as regards the final diagnosis by CT pulmonary angiography were (78%, 41%, 84%, and 34%) respectively.

In contrast, Kearon [15], concluded that enzyme-linked immunosorbenent assay (ELISA) D-dimer assays (cut-off of about 500 fibrinogen-equivalent units/mL) have a sensitivity for venous thromboembolism of about 98% or higher and their negative likelihood ratio is high enough to “rule out” pulmonary embolism in all patients and, consequently, these assays can be used as a “stand-alone” test for the exclusion of pulmonary embolism.

The present study (Table 3) showed that all 3 cases with low clinical probability had negative D-dimer and negative for PE by CTPA. On the other hand 15 cases with intermediate clinical probability that had positive D-dimer, 10 cases of them were positive for PE by CTPA while 5 cases were negative for PE.

Also, it was found that (Table 4) the sensitivity of D-dimer assay in evaluation of PE when clinical probability of PE was low or intermediate was (100%), its specificity was (37.5%), its NPV was (100%) and its PPV was (67.7%). Also the study showed that 5 cases with intermediate clinical probability had false positive D-dimer, this can be explained by the fact that D-dimer levels are sensitive but non-specific markers for thrombosis because Systemic D-dimer values are raised in a variety of clinical conditions such as; trauma, infection, malignancy, pregnancy, atrial fibrillation, disseminated intravascular coagulation, acute coronary syndromes and stroke [16].

Rapid quantitative ELISA assay has been proved to be safe to exclude PE when the pre-test clinical probability is non high (low or intermediate) [17].

All cases with high clinical probability were positive for PE by CTPA. 10 cases of them had positive D-dimer while the other 2 cases had negative D-dimer (Table 3).

Also the sensitivity of D-dimer assay in evaluation of PE when the clinical probability was high was (83.3%) while its specificity was (100%) as well as its positive predictive value was (100%) (Table 4).

Florence et al. [2] concluded that D-dimer assay in patients with high clinical probability was not suggested that clinicians should ignore a normal D-dimer concentration when the clinical probability is considered to be high [17].

From the previous results it was found that relying on D-dimer testing alone carries an unacceptable risk if the clinical probability of PE is not taken into account so, it is important to first examine the patient and assess the clinical probability, after which the d-dimer concentration can be taken into account, in order to prevent physicians from being influenced by a normal d-dimer test result when they evaluate the clinical probability of PE. Patients with a likely clinical probability

| Table 2 | Sensitivity and specificity of D-dimer test result and PetCO₂ in relation to final diagnosis by CTPA. |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| D-dimer | Sensitivity% | Specificity% | NPV% | PPV% | Accuracy% |
| 90 | 37.5 | 60 | 80 | 76.6 |
| PetCO₂ | 68 | 87.5 | 50 | 93.7 |

| Table 3 | Results of D-dimer test for cases with low, intermediate and high clinical probability in relation to final diagnosis by CTPA. |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| D-dimer test | Clinical probability | PE no PE | PE no PE | PE no PE |
| Low (3) | Intermediate (15) | High (12) |
| Positive (25) | 0 | 0 | 10 | 5 | 10 | 0 |
| Negative (5) | 0 | 3 | 0 | 0 | 2 | 0 |

| Table 4 | Sensitivity, specificity, NPV, and PPV of D-dimer test result in cases with clinical probability in relation to CTPA. |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| Clinical probability | Sensitivity% | Specificity% | NPV% | PPV% |
| Low & Intermediate | 100 | 37.5 | 100 | 67.7 |
| High | 83.3 | 100 | – | 100 |
should undergo further testing, regardless of the d-dimer test outcome [18].

The study showed that, 2 cases with high clinical probability had false negative D-dimer as an initial investigation (Table 5 and Figs. 1 and 2).

The first case was a female 45 years old proved to have systemic lupus erythematosus (SLE) as regards to positive anti nuclear anti bodies (ANA) and anti double strand DNA (Anti DS). The false negative D-dimer result in this patient was in agreement with Meesters et al. [19] who noted that the d-dimer values of patients with SLE may not be significantly different from those of age-matched controls, despite higher levels of plasma inflammatory markers in the blood.

The second case was a female 42 years old had past history of previous PE and DVT one year ago, already received anticoagulant therapy these can be explained by the fact that the use of agents with predominantly anti-Xa activity as low-molecular-weight heparin (LMWH) or agents with combined anti-Xa and antithrombin activity as unfractionated heparin (UFH), results in equivalent changes in fibrin formation and degradation after acute thrombosis [4].

These are also in agreement with Patrick et al. [14] who reported drops in mean plasma D-dimer of approximately 40% within 24 h in heparin-treated patients.

In the present study, the optimal cut off point for PetCO₂ equal to 28.5 mmHg which was calculated by ROC curve (Fig. 3).

Regarding the final diagnosis (Table 1); among 22 cases who had PE 15 cases (68%) of them had PetCO₂ ≤28.5 and 7 cases (32%) had PetCO₂ > 28.5. On the other hand, 8 cases were proved to be negative for PE, one case (12.5%) had PetCO₂ ≤28.5 and 7 cases (87.5%) had PetCO₂ > 28.5. There was

Table 5 Characteristics of the 2 patients with a confirmed PE and negative D-dimer.

| Age   | Sex | Past history of VTE | Risk factors for VTE | Clinical probability | D-dimer level | Duplex | CTPA |
|-------|-----|---------------------|----------------------|----------------------|---------------|--------|------|
| 45 Years | Female | Past history of PE and DVT | Contraceptive pills | High | 219 | +ve | +ve |
| 42 Years | Male | No | Thrombophilia (SLE) | High | 433 | −ve | +ve |

Figure 1 CTPA showing right pulmonary artery filling defect partially occluding its lumen and left main pulmonary artery filling defect occluding its lumen with evidence of bilateral pleural effusion more evident at left side.

Figure 2 CTPA showing small right and left pulmonary artery branches filling defect with left pleural effusion.

Figure 3 Diagonal segments are produced by ties. This curve shows the cutoff point of PetCO₂ among all the study participants for the prediction of cases of PE from the PetCO₂ result.
The positive PetCO\textsubscript{2} level less than or equal to cutoff = 28.5 mmHg statistically significant difference among the studied cases as regards PetCO\textsubscript{2} result. The PetCO\textsubscript{2} sensitivity, specificity, NPV, and PPV were (68%, 87.5%, 50%, and 93.7%) respectively.

These results are in agreement with those of Kline et al. [20] who calculated the sensitivity of PetCO\textsubscript{2} as 67.2% and specificity as 76.3%.

In contrast, Hogg et al. [21] recorded the sensitivity of PetCO\textsubscript{2} as 100% but a low specificity of 22.7%.

The study showed that Table 6); the sensitivity of PetCO\textsubscript{2} in patients with low or intermediate clinical probability for PE was (40%), its specificity was (87.5%), its NPV was (53.8%) and its PPV was (80%).

This result was in agreement with Tadeja et al. [22] who found that the combination of PetCO\textsubscript{2} of more than 28 mmHg and low clinical probability (PE unlikely) is a potentially safe method for excluding PE in patients with suspected PE and positive D-dimer in the pre hospital setting.

The sensitivity of PetCO\textsubscript{2} in patients with high clinical probability for the presence of PE was (91.6%), its specificity was (100%), and its PPV was (100%). All cases with high clinical probability had PetCO\textsubscript{2} < 28.5 mmHg (Table 6).

This result was in agreement with Tadeja et al. [22] who found that the combination of high clinical probability (PE likely) and a PetCO\textsubscript{2} of less than 28 mmHg had 93.2% specificity for the confirmation of PE (Table 7).

This can be explained by the fact that PE significantly decreases alveolar carbon dioxide (CO\textsubscript{2}) content. It obstructs blood flow to a normally ventilated area of lung, producing locally high ventilation, low perfusion relation, therefore increasing alveolar dead space. Gas exhaled from this unperfused lung unit contains little CO\textsubscript{2} and therefore reduces the partial pressure of end-tidal carbon dioxide (PetCO\textsubscript{2}) of the whole lung in relation to the partial pressure of arterial CO\textsubscript{2} (PaCO\textsubscript{2}) [23].

Table 7 ROC curve for the prediction of PE from PetCO\textsubscript{2} result levels.

| Diagnostic test | Sensitivity% | Specificity% |
|-----------------|--------------|--------------|
| Positive PetCO\textsubscript{2} level less than or equal to cutoff = 28.5 mmHg | 87.5 | 31.8 |

Conclusion

D-dimer alone cannot exclude or confirm the presence of PE. The combination of D-dimer, PetCO\textsubscript{2} < 28.5 mmHg and the clinical probability could improve diagnostic accuracy in patients with suspected PE.

Conflict of interest statement

None declared.

References

[1] T. Adam, P. Arnaud, K. Stavros, et al, Guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 29 (2008) 2276–2315.
[2] P. Florence, M. Sophie, M. Guy, et al, Diagnostic value of D-dimer in patients with suspected pulmonary embolism: results from a multicentre outcome study, Thromb. Res. 120 (2007) 195–200.
[3] Y. Fang, W. Thomas, D. Albert, Inappropriate use of D-dimer assay and pulmonary CT angiography in the evaluation of suspected acute pulmonary embolism, Am. J. Med. Qual. 27 (1) (2012) 74–79.
[4] S. Soheir, S. Nigel, S. Charles, D-dimer antigen: current concepts and future prospects, Blood 113 (2009) 2878–2887.
[5] P. Stein, R. Hull, K. Patel, et al, D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review, Ann. Intern. Med. 140 (2004) 589–602.
[6] G. Le Gal, M. Righini, P. Roy, Prediction of pulmonary embolism in the emergency department: the revised Geneva score, Ann. Intern. Med. 144 (2006) 165–171.
[7] C. Elliott, S. Goldhaber, L. Visani, et al, Chest radiographs in acute pulmonary embolism. Results of International Cooperative Pulmonary Embolism, Chest 118 (2000) 33–38.
[8] P. Stein, S. Goldhaber, J. Henry, Alveolar–arterial oxygen gradient in the assessment of acute pulmonary embolism, Chest 105 (1995) 598–603.
[9] A. Geibel, M. Zehender, W. Kasper, et al, Prognostic value of the ECG on admission in patients with acute major pulmonary embolism, Eur. Respir. J. 25 (2005) 843–848.
[10] D. Mountain, I. Jacobs, A. Haig, The VIDAS D-dimer test for venous thromboembolism: a prospective surveillance study shows maintenance of sensitivity and specificity when used in normal clinical practice, Am. J. Emerg. Med. 25 (2007) 464–471.
[11] J. Pezzullo, A. Perkins, J. Cronan, Symptomatic deep vein thrombosis: diagnosis with limited compression US, Radiology 198 (1996) 67–70.
[12] A. Perrier, P. Roy, D. Aujesky, et al, Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study, Am. J. Med. 116 (2004) 291–299.
[13] A. Fawzy, A. Ibrahim, M. Ragab, et al., Role of spiral volumetric computed tomography in the assessment of patients with clinical suspicion of pulmonary embolism (MD thesis), 2001.
[14] R. Patrick, B. Bensalem, B. Sophie, Referent D-dimer enzyme-linked immunosorbent assay testing is of limited value in the exclusion of thromboembolic disease: result of a practical study in an emergency department, Am. J. Emerg. Med. 24 (2006) 313–318.
[15] C. Kearon, Diagnosis of pulmonary embolism, Can Med Assoc J. 168 (2) (2003) 183–194.
[16] S. Siragusso, Plasma D-dimer test accuracy can be affected by heparin administration, Arch. Intern. Med. 163 (2003) 246.
[17] T. Rajan, K. Rajesh, J. Kevin, et al, D-Dimers and efficacy of clinical risk estimation algorithms: sensitivity in evaluation of acute pulmonary embolism, Am. J. Roentgenol. 198 (1996) 67–70.
[18] S. Nadine, S. Maaike, E. Victor, The importance of clinical probability assessment in interpreting a normal D-dimer in patients with suspected pulmonary embolism, Chest 134 (2008) 789–793.
[19] E. Meesters, H. Hansen, H. Spronk, The inflammation and coagulation cross-talk in patients with systemic lupus erythematosus, Blood Coagul. Fibrinolysis 18 (2007) 21–28.
[20] J. Kline, E. Israel, E. Michelson, et al, Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study, JAMA 285 (2001) 761–768.

[21] K. Hogg, D. Dawson, T. Tabor, et al, Respiratory dead space measurement in the investigation of pulmonary embolism in outpatients with pleuritic chest pain, Chest 128 (2005) 2195–2199.

[22] H. Tadeja, K. Miljenko, G. Štefek, Capnometry in suspected pulmonary embolism with positive D-dimer in the field, Crit. Care 12 (2009) 196–205.

[23] J. Kline, S. Meek, D. Boudrow, et al, Use of the alveolar dead space fraction (Vd/VT) and plasma D-dimers to exclude acute pulmonary embolism in ambulatory patients, Acad. Emerg. Med. 4 (1997) 856–863.