



D-Dimer: a Role in Ruling out Pulmonary Embolism in an Emergency Care Department

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Abstract

Background/Aim: Pulmonary embolism (PE) is a diagnostic challenge, particularly in prehospital care. The aim of this study was to determine to what extent the evaluation of D-dimer value helps physicians with differentiation of PE and whether D-dimer values are in correlation with the values of revised Geneva score.

Methods: Data have been collected for the patients whose D-dimer has been evaluated at the Emergency Care Department of the City of Banja Luka in 2018. Gender, age, symptoms, working diagnosis and D-dimer value have all been recorded and also the fact whether the patient was referred to hospital treatment or not. For each patient the revised Geneva score was determined.

Results: Sixty-eight tests were done in 2018. Out of 68 tests, 41 were negative (60.3 %). D-dimer results helped in making decisions about referring patients to the hospital or not ($\chi^2 = 36.32$, $p < 0.001$). Patients with elevated D-dimer levels, especially where the values were four times higher than the reference ones typically were referred to hospital treatment, whereas 67.5% patients with negative D-dimer results were sent home after giving a treatment and advice. In the elderly patients D-dimer was statistically more positive ($F = 10.82$, $p < 0.001$). Values of D-dimer were not significantly different regarding gender ($\chi^2 = 2.19$, $p = 0.33$). According to the results of the revised Geneva score, 5.1 % of patients had high risk of PTE, while moderate and low risk had 47.5 % each. Although it has been found that the values of D-dimer were slightly more elevated at higher values of the revised Geneva score and that the difference was not statistically significant ($\chi^2 = 7.71$, $p = 0.10$).

Conclusion: Values of D-dimer considerably helped in differentiation of PE in the Emergency Care Department. D-dimer has a high negative predictive value and should be used to exclude PE diagnosis for patients with low clinical probability of PE.

Key words: D-dimer, pulmonary embolism, revised Geneva score, emergency care department.

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Introduction

Pulmonary embolism (PE) is one of the most difficult conditions to diagnose, particularly in the prehospital care. It represents the most serious clinical manifestation of venous thromboembolism (VTE), which represents the third most common cardiovascular disease.¹⁻⁴ The main cause of PE-related deaths is the undiagnosed PE during lifetime (59 %), followed by sudden

fatal PE (34 %). It is estimated that only 7 % of patients who died from PE had PE diagnosed on time.⁵⁻⁷ Frequency of PE is hard to determine because it can sometimes remain asymptomatic and therefore go unsuspected, while on the other hand PE is often accidentally diagnosed as an incidental finding.⁸

PE is one of the most urgent conditions in medicine. The success of treatment largely depends on timely diagnosis. PE primarily needs to be thought of, and early diagnosis and treatment of patients is possible if PE is suspected on the basis of detailed anamnestic data. Many risk factors can raise suspicion about PE, however it can happen without any of the predisposing factors (up to 30 %).⁹ Clinical manifestation of PE is also nonspecific, so dyspnoea, as the most common symptom/sign of PE, occurs in only 50 % of the clinically confirmed PEs.^{10, 11} A clinical probability for PE is estimated on the basis of clinical presentation by using the Wells clinical decision rule or the revised Geneva score.¹²⁻¹⁶

The electrocardiographic (ECG) changes are miscellaneous and usually nonspecific (most common is sinus tachycardia, followed by the right bundle branch block - RBBB, turning of heart axis to the right, SI QIII TIII, P pulmonale, simultaneous inversion of T waves in inferior and right precordial leads), but in 18 % of patients ECG is normal.^{17, 18} Nonspecific changes or lack of them can also be found during the physical check-up, chest X-ray and laboratory tests.^{7, 19, 20} Gold standard for the diagnosis of PE is computed tomography (CT)-pulmonary angiography and/or ventilation-perfusion (VQ) scan.^{21, 22}

D-dimer is a fibrin degradation product, a small protein fragment present in the blood after fibrinolysis. Role of D-dimer is to exclude the PE diagnosis.²³⁻²⁵ D-dimer plasma levels are elevated in patients with acute thrombosis because of the simultaneous activation of coagulation and fibrinolysis.²⁶ Negative predictive D-dimer value is high (95-98 %) and PE with normal values of D-dimer is unlikely. On the other hand, fibrin is produced in other conditions including cancer, inflammation, bleeding, trauma, necrosis and surgical intervention.²⁷⁻²⁹ Therefore, positive predictive D-dimer value is low and elevated D-dimer levels are not useful in confirmation of PE.^{30, 31} This implies recommendations that the patients with highly suspected PE should immediately undergo CT-pulmonary angiography and skip the D-dimer testing.^{9, 32, 33}

The aim of this study was to determine to what extent D-dimer values help to differentiate PE in emergency care departments and therefore help in making a decision to transfer patients to a higher referential level or not. Furthermore, the aim was to determine whether the D-dimer values correlated with the values of revised Geneva score.

Methods

The protocol of the study was approved by the Ethics Committee of the Primary Medical Centre Banja Luka and all the efforts were undertaken in order to keep the anonymity of the included patients.

Following the protocol of the Emergency Care Department of the City of Banja Luka, data were found for all the patients in whom the D-dimer was tested in 2018. Gender has been recorded (female/male), age, symptoms, D-dimer level (mg/L), working diagnosis, and data whether the patient was referred to the hospital treatment or not. Patients' anonymity was preserved, while only gender and age were recorded, excluding other personal data.

The D-dimer values have been analysed by a quantitative, latex-enhanced immunoturbidimetric immunoassay on Cobas h-232 system. Although D-dimer has only one cut-off value, the authors were interested in finding to what extent a D-dimer value affected the physician's decision, ie, if there was a difference whether a D-dimer value was slightly elevated or if it was four times or more higher than referential value. Therefore, a value of D-dimer was recorded in two ways, as a numeric value and as a value in one of three categories: < 0.5 mg/L, ≥ 0.5-2 mg/L and ≥ 2 mg/L.

Table 1. Geneva score: clinical prediction rules for pulmonary embolism

Variable	Points
RISK FACTORS	
Age 65 or over	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
SYMPTOMS	
Unilateral lower limb pain	3
Haemoptysis	2
CLINICAL SIGNS	
Heart rate: 75-94/min	3
≥ 95/min	5
Pain on deep palpation of lower limb and unilateral edema	4
CLINICAL PROBABILITY	
Low	0-3
Intermediate	4 - 10
High	≥ 10

Using the anamnestic data, symptoms, clinical signs, age and gender of the patient, for each patient the revised Geneva score was calculated. The parameters set for Geneva score are listed in

Table 1.¹⁴ Based on the values of Geneva score, patients were allocated into one of three categories: with low, intermediate or high clinical probability for PE.

Results were processed by using IBM SPSS 21.0 software. Categorical data were analysed by Chi-square test and age, after distribution uniformity was verified, by one-way analysis of variance (ANOVA). The average D-dimer values were distributed by the Man-Whitney U test, or the Kruskal-Wallis test.

Results

Sixty-eight tests were done in the Emergency Care Department of the City of Banja Luka in 2018. Of 68 tests, 41 were negative (60.29 %), meaning that it was less than 0.5 mg/L; from 0.5 up to 2 mg/L there were 19 tests (13.23 %), and over 2 mg/L there were 8 tests (11.76 %). Patients' characteristics are shown in Table 2.

The mean age of the patients was 60.3 (\pm 17.4) years, with 45.5 % patients being older than 65. Levels of D-dimer were statistically significantly higher in elderly people (Kruskal-Wallis test: $\chi^2 = 12.96$, $p = 0.002$). Also, by analysing the ratio of positive and negative values of the

Table 2. Distribution of gender, age and D-dimer values

Variable	N (%)	D-dimer		Test	p-value
		Mean (SD)	95 % CI		
GENDER					
Male	30 (44.12 %)	0.77 (0.99)	0.40-1.14	U = 479.50*	0.264
Female	38 (55.88 %)	0.80 (0.93)	0.49-1.10		
AGE (years)					
< 40	12 (17.65 %)	0.47 (0.93)	0.11-1.06	$\chi^2 = 12.96^{**}$	0.002
41-65	25 (36.76 %)	0.55 (0.59)	0.32-0.79		
> 65	31 (45.59 %)	1.21 (1.14)	0.75-1.66		
TOTAL	68 (100.00 %)	0.79 (0.95)	0.55-1.02		

*Man-Whitney U test;

**Kruskal-Wallis test showed general statistical significance; further post-hoc analysis showed statistical significance for all groups.

D-dimer, the frequent D-dimer was significantly more positive in elderly people (One-way ANOVA: $F = 10.82$, $p < 0.001$).

There were 30 men (44.12 %) and 38 women (55.88 %). The ratio of positive and negative results of the D-dimer tests was without significant difference with respect to gender (Chi square test: $\chi^2 = 2.19$, $p = 0.33$), as was the average value of the D-dimer itself (Man-Whitney U test: $U = 479.50$, $p = 0.264$).

The most common symptoms/signs in patients for whom D-dimer level were determined were: dyspnoea (37.3 %), chest pain (25.4 %), heart rate over 90 per minute (20.39 %), cough (15.25 %), pain and leg oedema (15.25 %), nausea (11.86 %), fever (11.86 %) and syncope (10.17 %). Anamnestically, 3.36 % of patients had previous surgeries and 3.36 % of patients had deep vein thrombosis or pulmonary embolism.

According to the Geneva score, 5.08 % of patients were at high risk of PTE and 47.46 % at intermediate or low risk each. Although the D-dimer values were found slightly higher at the higher Geneva score values, the difference was

Table 3. Correlation between the revised Geneva score and D-dimer values

D-dimer (mg/L)	Revised Geneva score-Clinical probability			Total N (%)
	Low - N (%)	Interm. - N (%)	High - N (%)	
< 0.5	21 (75.00 %)	13 (46.43 %)	1 (33.33 %)	35 (59.32 %)
0.5 - 2	6 (21.43 %)	10 (35.71 %)	2 (66.67 %)	18 (30.51 %)
≥ 2	1 (3.57 %)	5 (17.86 %)	0 (0.00 %)	6 (10.17 %)
TOTAL	28 (47.46 %)	28 (47.46 %)	3 (5.08 %)	59 (100.00 %)

* Chi-square test showed no statistical significance between groups ($\chi^2 = 7.71$, $p = 0.10$)

not statistically significant ($\chi^2 = 7.71$, $p = 0.10$) (Table 3).

Half of the patients analysed for the D-dimer were not referred for further hospital treatment (48.48 %). On suspicion of PE, 27.27 % of patients were referred for further hospital treatment and other patients were referred, but under a different diagnosis. The D-dimer values helped in making the decision whether to refer a patient to hospital treatment or not ($\chi^2 = 36.32$, $p < 0.001$).

Table 4. Effect of D-dimer on decision to refer for further hospital treatment

D-dimer (mg/L)	Referred to the hospital			Total
	No	Yes	Yes, diff. Dg*	
< 0.5	27 (67.50 %)	2 (5.00 %)	11 (27.50 %)	40 (60.60 %)
0.5-2	5 (27.78 %)	8 (44.44 %)	5 (27.78 %)	18 (27.27 %)
≥ 2	0 (00.00 %)	8 (100.00 %)	0 (00.00 %)	8 (12.12 %)
TOTAL	32 (48.48 %)	18 (27.27 %)	16 (24.24 %)	66 (100.00 %)

* Patients referred for hospital treatment but under another diagnosis (pulmonary embolism excluded)

Patients who were found to have high D-dimer values, especially where they were four times more the cut-off values, were generally referred for hospital treatment, while 67.50 % of patients with negative D-dimer values were returned home after receiving treatment and advice (Table 4).

Discussion

In 2018, 68 D-dimer analyses were performed at the Emergency Care Department of the City of Banja Luka. The assumption is that the need for analyses was greater, but unfortunately analyses are not continuously available. For this reason, it was decided to analyse only patients who had done the D-dimer test, because if all patients who were suspected on PE or with dyspnoea had been analysed, an unrealistically low percentage of patients in whom D-dimer was determined would have been obtained.

Two thirds of the tests were negative (< 0.5 mg/L). A high percentage of patients who are D-dimer-negative is logical, since the D-dimer is primarily used to rule out the diagnosis of PE and deep vein thrombosis.³⁰ The D-dimer was significantly higher in elderly patients, which is in accordance with the results of other studies. There are also recommendations to adjust the cut-off value of the D-dimer according to age by adding 0.1 to 0.5 mg/L for every 10 years of age for people over 50.³⁴⁻³⁶ This is thought to increase the specificity of the D-dimer in the elderly.³⁷⁻³⁹

Clinical studies indicate that the D-dimer values are slightly higher in women, which is in accordance with the results of this study. As was the case with the results of other researchers, the difference was not significant in the present study either. The difference in D-dimer values in men and women is considered to be of no clinical significance and it is not recommended to correct the cut-off values based on gender.³⁹ However, some researchers believe that D-dimer values should be adjusted for both gender and age, with multiple cut-off values, in order to significantly improve the specificity of D-dimer testing.⁴⁰ In contrast to the D-dimer values, PE itself is slightly more common in men.⁴¹ The results of this study show that women were slightly more frequently diagnosed with PE (30 % : 20 % of patients), which could be explained by the fact that no cut-off corrections were made for women and therefore there was a higher percentage of false-positive tests in female patients.

The Wells score and the Geneva score were introduced in an attempt to adequately suspect or exclude PE based on history, symptoms and clinical presentation.⁴² Clinical trials indicate that the significance of the revised Geneva score is

primarily in the exclusion of PE combined with low D-dimer values.^{43, 44} The results of this study indicate that the revised Geneva score values did not influence physicians' decision not to refer such patients for further treatment, but only the D-dimer values. Analysis from other studies also implies underuse of clinical decision rules.⁴⁵ There was a correlation between the revised Geneva score and the D-dimer, but it was not statistically significant. However, given a relatively small sample, it would be assumed that with a sufficiently large sample statistical significance would be reached. It is also the authors' belief that when deciding whether to refer a patient for further hospital treatment or not, physicians should consider the revised Geneva score, especially if its value is < 3 .^{46, 47} Intermediate-risk PE patients present a diagnostic and therapeutic dilemma.⁴⁸ Besides, research results indicate that in older, high-risk patients, the Wells scores are more in correlation with the diagnosis of PE than the revised Geneva score.⁴⁹⁻⁵¹

The D-dimer values significantly aided the physicians' decision to refer the patient to further hospital treatment under the diagnosis of PE. When D-dimer values were < 0.5 mg/L, two-thirds of patients were not referred for further hospital treatment and the others were referred under some other diagnosis. Two patients, despite the negative D-dimer values, were referred under the diagnosis of PE and this is, in fact, an example of poor clinical practice. The reason is that if the low D-dimer value does not alter the physician's opinion that it is PE or not, the D-dimer should not be tested at all. On the other hand, half of the patients with D-dimer values > 0.5 and all patients with values > 2 mg/L were referred for further treatment and diagnosis.

Conclusion

The very purpose of the D-dimer and revised Geneva score is to exclude PE and reduce unnecessary imaging diagnostic procedures, such as CT-pulmonary angiography and similar. The fact that the test results are available after 20 minutes should also not be overlooked, given that the speed of diagnosis and patient treatment is one of the key factors in working in an emergency care department.

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Conflict of interest

None.

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