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Normal D-dimer concentration in hospitalized patients with lung diseases

Częstość prawidłowego stężenia D-dimerów u pacjentów hospitalizowanych z chorobami płuc

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Abstract

Introduction: D-dimer testing is an established method in diagnostics of suspected pulmonary embolism (PE). However, in hospitalized patients, increased D-dimer concentration may be caused by comorbidities, which limits the applicability of this test in PE diagnostics. According to published data, calculating the index D-dimer/fibrinogen ratio can increase specificity of D-dimer testing in diagnostics of venous thromboembolism (VTE). The aim of the present study was: 1) to determine the frequency of normal D-dimer concentration in hospitalized patients with lung diseases in whom the differential diagnostics of PE can be particularly difficult; and 2) to evaluate the utility of D-dimer/fibrinogen ratio in subgroups of patients with acute VTE or with lung cancer.

Materials and methods: The study group included 619 consecutive patients aged 54.9 ($\pm$ 15.4) years, hospitalized in a pulmonology reference centre. Among them there were 96 (15%) patients with acute VTE, 65 (10%) with exacerbation of COPD, and 172 (27%) with lung cancer.

Results: Mean D-dimer concentration (Vidas D-dimer New) was 1956 $\pm$ 3691 ng/ml and median value was 842 (45–35 678) ng/ml. Normal D-dimer concentration ($<$ 500 ng/ml) was found in 225/523 (43%) patients without acute VTE. In 49% (32/65) patients with COPD and in 25% (43/172) patients with lung cancer, D-dimer concentration was below 500 ng/ml. D-dimer/fibrinogen ratio was significantly higher in acute VTE patients compared to lung cancer patients (808 $\pm$ 688 and 289 $\pm$ 260, respectively; $p <$ 0.001).

Conclusions: Normal D-dimer concentration was found in more than 40% of patients with lung diseases hospitalized in the reference pulmonology centre. This observation can suggest a better utility of D-dimer measurement for PE exclusion in such a population than that seen in previously published reports. D-dimer/fibrinogen ratio is significantly higher in acute VTE than in lung cancer, but the clinical value of this test requires further evaluation.

Key words: D-dimer, lung diseases, lung cancer, hospitalized patients

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Introduction

Introduction of D-dimer testing markedly improved diagnostics in venous thrombosis and pulmonary embolism (PE). Using this analysis, non high-risk PE cases (according to current nomenclature used in the recommendations of the European Society of Cardiology, ESC) can be safely excluded in almost one third of all patients [1]. The clinical probability of PE diagnosis must be first assessed before D-dimer measurement is performed [2]. If the clinical probability of PE is low, a normal result of D-dimer level measurement means that the risk of PE or venous thrombosis (VT) development in untreated patients is less than 1% under three-month-long follow-up [1]. The clinical value of D-dimer testing in PE diagnostics is limited to cases with normal levels of this marker. D-dimer testing methods of possible use in PE diagnostics must have a very high sensitivity and negative predictive value (NPV), so as to avoid false negative results [1]. This, however, reduces the specificity of the test. D-dimer is product of fibrin degradation, and its levels are increased not only in venous thromboembolism (VTE) but also in other conditions, including hospitalized patients with comorbidities [3, 4], in elderly persons [5–7], in patients with malignancies [8], and during pregnancy [9]. Studies concerning utility of D-dimer testing in PE diagnostics included mainly patients in non-hospital settings [10, 11]. In hospitalized patients with many ailments, however, this test has low specificity and the number-needed-to-test (NNT) is high, the latter describing the number of patients in whom D-dimers must be tested to exclude a single case of PE. The NNT value can be 10 times higher in hospitalized patients as compared to the general population (30 vs. 3.1) [4]. Utility of D-dimer testing in hospitalized patients is therefore debatable; however, it is still of value for exclusion of PE [3, 12]. Differential diagnostics of PE in hospitalized patients, especially those with concomitant lung diseases or malignancies, can be challenging; therefore, D-dimer testing could be helpful. Some authors suggested calculation of the D-dimer/fibrinogen ratio in diagnostics of VTE in order to increase the specificity of the test. The ratio is higher in acute PE as compared to patients not having VTE, and values of over 1,000 are very specific for PE, according to Kucher et al. [13]. Patients with malignancies often have high fibrinogen levels [14–16], and thus should have a lower D-dimer/fibrinogen ratio, which could be of value for diagnostics.

The aim of the present study was: 1. to evaluate the frequency of normal D-dimer levels in the patients with various lung diseases and 2. to compare D-dimer/fibrinogen ratios in patients with acute PE and in patients with lung malignancies.

Material and methods

The study group included 619 consecutive patients admitted to 3rd of Department of Lung Diseases and the Department of Chest Medicine, in whom D-dimer and fibrinogen levels were examined during hospitalization. Mean patients age was 54.9 years ($\pm$ 5.4). 172 patients (27%) had lung malignancy, including 26 patients with small cell lung cancer (SCLC), 142 patients with non-small cell lung cancer (NSCLC), and 4 patients with other types of tumours. Other causes of hospitalization included exacerbated chronic obstructive pulmonary disease (COPD; 65 patients, 10%), pneumonia (39 patients, 6%), systemic connective tissue disease with lung involvement (28 patients, 4%), acute VTE (96 patients, 15%), and previous episode of VTE (70 patients, 11%). Other diagnoses found in the study group are presented in table 1. In patients treated conservatively, no antithrombotic prophylaxis was routinely used during the hospitalization period. Pulmonary embolism was diagnosed based on imaging findings, including computed tomography with pulmonary artery angiography or lung perfusion scintigraphy. Venous thrombosis was diagnosed by ultrasound examination.

D-dimer and fibrinogen levels were evaluated on average after 4 ± 4 days of in-hospital stay, with

Table 1. Main diagnosis in the group of 619 hospitalized patients

Diagnosis	Number of patients (%)
Pulmonary malignancy	72 (27%)
Acute VTE	96 (15%)
History of VTE	70 (11%)
COPD	65 (10%)
Pneumonia	39 (6%)
Sarcoidosis or pulmonary fibrosis	30 (5%)
Systemic connective tissue disease	28 (4%)
ARDS	5 (0.8%)
Other	114 (18%)

COPD = chronic obstructive pulmonary disease; VTE = venous thromboembolism; ARDS = acute respiratory distress syndrome

analysis performed directly after sampling. Analyses were performed on the day of admission in some patients; however, all persons had samples taken when qualified for hospitalization.

Serum D-dimer concentration was evaluated by quick ELISA test (enzyme-linked immunosorbent assay; VIDAS D-dimer New, bioMérieux, France), using a quantitative automatic analyser. Threshold value for D-dimers was 500 ng/ml, according to the manufacturer's recommendations.

Fibrinogen concentration was assessed quantitatively by von Clauss method (system IL Coagulation System), with reference values of 2.2–4.9 g/l.

The percentage of normal results was assessed in the entire group of patients and separately for all patients not having acute VTE. Moreover, distribution of D-dimer values was assessed in patients in the following age groups (separated by quartiles): less than 45 years of age (118 patients), 45–58 years (112 patients), 59–67 years (120 patients), and more than 67 years (105 patients). Wilcoxon test for independent variables was used for comparisons between the groups. Spearman correlation test was used for assessment of correlations between D-dimer levels and patient age.

D-dimer concentration and D-dimer/fibrinogen ratio were expressed as mean values with standard deviation and median with range of values. For comparison of D-dimer levels and D-dimer/fibrinogen ratios between subgroups, Wilcoxon test for independent variables was applied. Statistical significance was assigned for $p < 0.05$. STATSOFT software was used for calculations.

Results

Mean D-dimer concentration in the studied patient group was markedly higher than the reference value given by the test manufacturer, i.e. 1956 ± 3691 ng/ml, with median value of 842 ng/ml (45–35 678 ng/ml). Normal values (< 500 ng/ml) were found in 226/619 patients (37%). When excluding patients with acute VTE, the proportion of patients with normal D-dimer values was 43% (225/523). There were no significant differences between various age groups, although a tendency for higher mean values was noted in patients of over 67 years of age ($p = 0.08$) (fig. 1). Abnormal D-dimer levels (over 500 ng/ml) occurred significantly more often in patients over 67 years old as compared to other age groups ($p = 0.03$).

No correlation was found between D-dimer concentration and duration of in-hospital stay.

No statistically significant differences in D-dimer concentrations were found between groups of patients with respective lung diseases; however, mean values in patients with COPD and sarcoidosis or idiopathic lung fibrosis were only slightly over 500 ng/ml, whereas patients with acute respiratory distress syndrome (ARDS) had levels up to 7,500 ng/ml (tab. 2, fig. 2). Median values were also compared, considering that some of the patient subgroups were very small (fig. 3). The highest median value of serum D-dimer concentration (2,884 ng/ml; $p < 0.001$) was noted in patients with acute VTE, of which one had more than 35,000 ng/ml. Very high levels (close to or more than 20,000 ng/ml) were found in some patients with lung tumours, pneumonia, or ARDS (Tab. 2). None of the

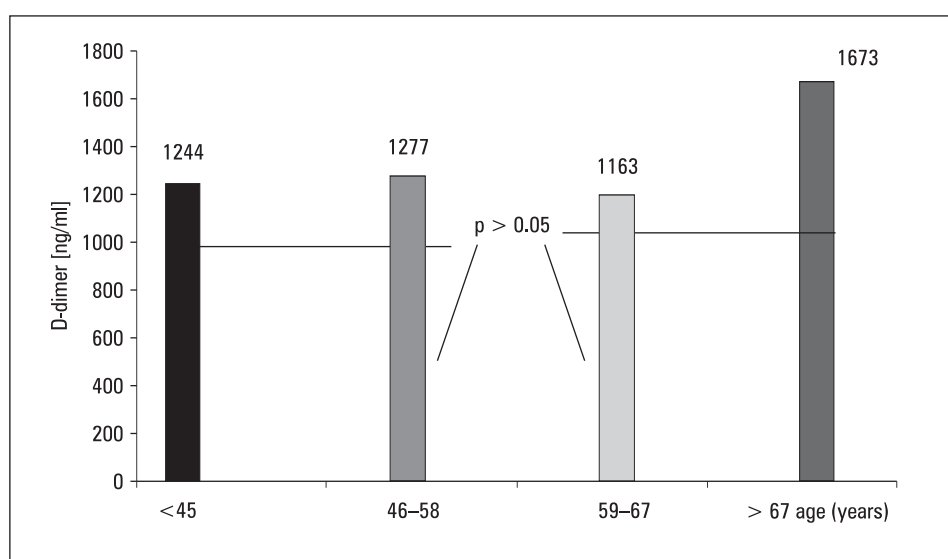
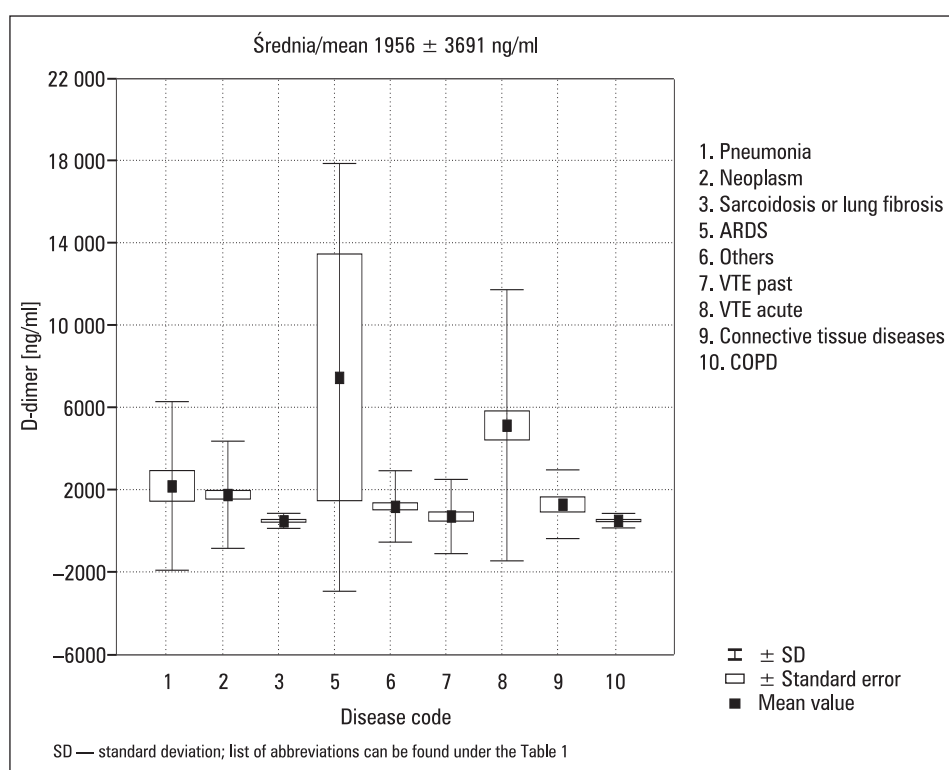


Figure 1. Mean D-dimer concentration by age in the group of 619 hospitalized patients with lung diseases

Table 2. Mean and median values of serum D-dimer concentration by diagnosis in 619 hospitalized patients

Diagnosis	Mean $\pm$ SD	Median (range) [ng/ml]
Pneumonia	2.214 $\pm$ 2.950	1.118 (99–23.133)
Lung malignancy	1.785 $\pm$ 1.990	941 (91–21.977)
Sarcoidosis or idiopathic pulmonary fibrosis	518 $\pm$ 884	512 (45–1.270)
ARDS	7491 $\pm$ 17.886	1.950 (1.041–19.483)
History of VTE	728 $\pm$ 2.532	305 (62–10.509)
Acute VTE	5.151 $\pm$ 5.867	2.884 (249–35.678)
Connective tissue disease	1.324 $\pm$ 1.689	880 (191–6.155)
COPD	527 $\pm$ 5.75	4.36 (70–1.559)
Other	1.218 $\pm$ 2.954	542 (50–9.711)

List of abbreviations can be found under the Table 1

**Figure 2.** Mean concentration of plasma D-dimer dependent on diagnosis in 619 patients with different lung diseases

ARDS patients had a normal D-dimer level. Normal levels were observed in 25% of patients with malignancy (43/172) and 28% of patients with pneumonia (11/39). Of note, only one of 26 SCLC patients (3%) had D-dimer concentration < 500 ng/ml. As for other lung disease groups, normal D-dimer concentrations were found in 28% of patients with connective tissue disease (8/28), 49% of patients with COPD (32/65), and 56% of patients with sarcoidosis or idiopathic lung fibrosis (17/30). As many as 74% of patients who previously had a VTE episode (52/70) had normal D-dimer concentrations.

One patient with acute VTE had a D-dimer level of 249 ng/ml. This patient had PE but the timing of his disease onset was difficult to estimate. The sensitivity of D-dimer measuring in acute VTE was therefore 99%.

The D-dimer/fibrinogen ratio was significantly higher in acute VTE than in lung cancer (808 ± 688 and 289 ± 260 , respectively; $p < 0.001$). Values over the threshold of 1,000, as suggested by Kucher et al. [13], were found in 29% of patients with acute VTE (28/96). All patients with lung malignancies had a ratio of less than 1,000.

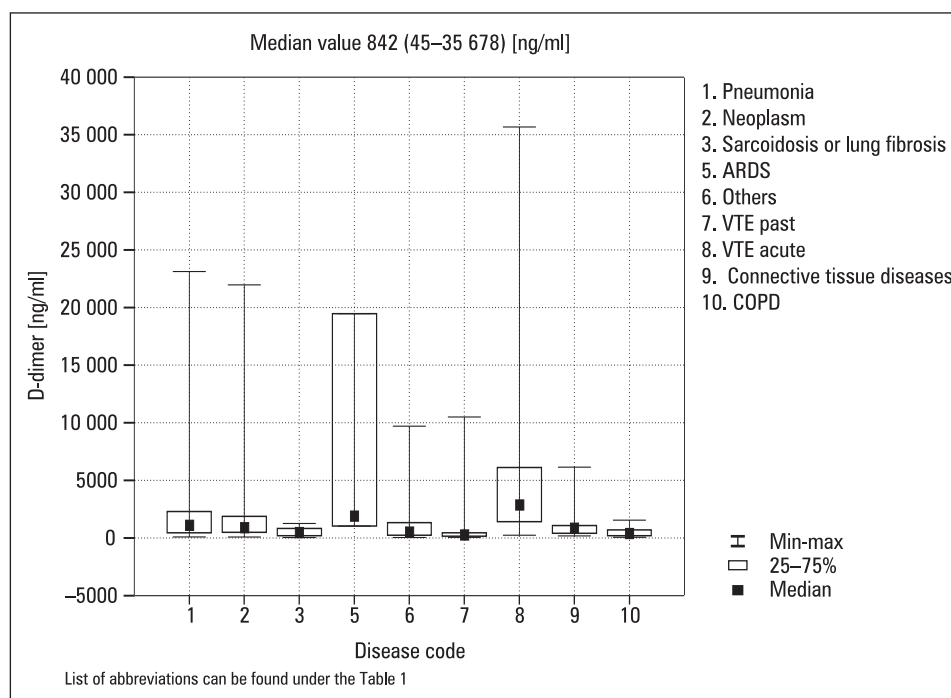


Figure 3. Median D-dimer concentration by lung disease diagnosis in 619 hospitalized patients

Discussion

In the described group of hospitalized patients with lung diseases, a relatively high proportion of them had normal values of D-dimer concentration. Two prospective studies concerning PE diagnostic strategy with assessment of clinical probability and D-dimer measurement in hospitalized patients supported the use of these procedures [17, 18]. During the three months after hospitalization and PE exclusion, no antithrombotic therapy was administered and no patient had a VTE episode (0% of cases, 95% CI [confidence interval] 0–4.9% and 0%, 95% CI 0–6.7%, in respective studies). However, only 10% and 3% with excluded PE in these studies had normal D-dimer concentrations. When comparing to the currently presented patient population, patients in the two cited studies were slightly older (54.9 vs. 61 years and 71 years), and in the first study, 19% of patients previously underwent a surgical procedure. The authors of the CHRISTOPER study evaluated PE diagnostic strategy including D-dimer measurement, and found normal D-dimer concentrations in various patient groups with a similar frequency (35%) as in the presented study. Mean patient age in the cited publication was 53 years, similarly to the currently described group; however, only 18% of patients were hospitalized [17].

High frequency of normal D-dimer concentrations in the mentioned reports can probably be

attributed to relatively young patient age. The age issue can possibly also explain the lack of significant correlation between D-dimer level and patient age in the presented study, where patients over 70 years of age made up almost 20% of the group. According to Harper et al., D-dimer testing specificity (using VIDAS) in VTE diagnostics decreases from 70.5% in patients under 40 years of age to 4.5% in patients older than 70 years [18]. Most patients had thus increased D-dimer levels due to reasons other than VTE. Mironi et al., in their study from Genève, described hospitalized patients with mean age of 74 years, of which only 7% had normal (< 500 ng/ml) D-dimer levels assessed by VIDAS [4].

In the presented study, abnormally high D-dimer levels were more likely related to the intensive inflammatory reaction than to older age. This conclusion can be supported by the fact that none of the ARDS patients had normal D-dimer levels, and few patients with pneumonia had normal values. The D-dimer increase in $\frac{3}{4}$ of lung cancer patients was possibly related to malignancy itself. Some reports in literature describe D-dimer measurement as a method of monitoring lung cancer progression. It cannot be excluded that very high D-dimer levels were related to development of disseminated intravascular coagulation (DIC) syndrome in some patients; however, no clinical DIC diagnosis was made. D-dimer concentration may also be

correlated to histopathological type of lung malignancy, since normal levels were found in only 3% of SCLC patients and in 30% of patients with NSCLC diagnosis.

The frequency of normal D-dimer concentrations in patient subgroups should be commented on here. Patients with COPD included in the CHRISTOPER study were half as likely to have normal D-dimer levels compared to the presented study group (26% vs. 49%) [17], which is difficult to explain. The patient population from the CHRISTOPER study might have different characteristics than our COPD patients with suspected PE. Moreover, authors of the Dutch study noted half as many patients with normal D-dimer levels and malignancies compared to the presented group (12% vs. 25%) [17]. However, Ten Wolde et al. observed normal D-dimer concentrations in 64 patients with malignancies (29%) in their report [19], which is a similar result to the presented study.

A very high incidence of normal D-dimer concentrations (75%) in patients with previous VTE episodes should be noted in the presented material. In the CHRISTOPER study, only 27% of patients with history of VTE had D-dimer levels within the normal range. Palareti et al. (PROLONG study) evaluated the efficacy of D-dimer measurements for the prediction of VTE recurrence, and found normal values in 64% of patients one month after cessation of antithrombotic therapy [20]. These authors state that the risk of VTE recurrence is significantly lower in patients with normal D-dimer concentrations. Thus, the high number of patients with past episodes of VTE who had normal D-dimer levels in our study may suggest a new indication for D-dimer testing, i.e. for assessing the risk of VTE recurrence when deciding on cessation of secondary antithrombotic prophylaxis [1, 21].

In the presented group of patients with in-hospital treated lung diseases there was a higher number of cases with normal D-dimer levels as compared to other published studies concerning hospitalized patients. This may suggest that a selected group of patients with lung diseases more often have normal D-dimer concentrations than the general population of hospitalized patients, particularly those with suspected VTE. This finding is interesting since data from literature concerning hospitalized patients show high NNT and low specificity of D-dimer measurement, but the sensitivity and negative predictive value of this test were still very high.

The high frequency of normal D-dimer concentration was not due to the low sensitivity of the test in the presented study. Analyses were performed

using VIDAS D-dimer test, which was also used in most other publications. Moreover, there were very few false negative results in patients with acute VTE. Lower D-dimer concentrations in the presented patient group cannot be explained by heparin administration, since no antithrombotic prophylaxis was routinely used in non-surgical patients hospitalized in our institution.

Calculation of the D-dimer/fibrinogen ratio can be an interesting alternative, aimed at increasing test specificity. In the presented study, the ratio was significantly higher in patients with acute VTE as compared to oncological patients. This finding is in accordance with reports from other authors, who also showed low fibrinogen levels in VTE as compared to D-dimer concentrations. This phenomenon can be explained by activation of the coagulation cascade and fibrinogen consumption, with high fibrinolytic activity marked by high D-dimer levels. High fibrinogen levels in patients with malignancies may be related to progression of the disease itself as well as extravascular fibrin generation, accompanied by high fibrinolytic activity [16]. Kucher et al. found that 25.7% of patients with acute VTE had D-dimer/fibrinogen ratio over the threshold value of 1,000 [13]. In the presented study, similar levels were found in 29% of patients, which means that more than 2/3 of patients with objectively confirmed VTE had ratio values below that threshold. The potential clinical applicability of this test is therefore doubtful.

In a selected population of hospitalized patients with respiratory tract diseases, measurement of D-dimer concentration for PE diagnostics can possibly be of value, and NNT can be markedly lower than in patients hospitalized in general profile institutions. Application of this test in PE diagnostics in patients with lung diseases can be beneficial if contrast media usage is contradicted, e.g. in patients with renal failure, but could also contribute to cost reduction. For that purpose, however, validation under prospective clinical studies would be necessary. This restriction also applies to the issue of D-dimer/fibrinogen ratio calculation and utility in differential diagnostics of acute PE, especially in patients with lung malignancies.

Conclusions

1. Normal D-dimer concentrations can be found in more than 40% of patients with lung diseases hospitalized in a pulmonology reference centre. This finding suggests that the test can potentially be of greater utility for PE exclusion than the current literature reports suggest.

2. D-dimer/fibrinogen ratio is significantly higher in patients with acute VTE than in patients with lung malignancy; however, the clinical impact of this parameter remains to be further studied.

Conflicts of interest

The authors declare no conflicts of interests.

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