



D-dimer value in the diagnosis of pulmonary embolism – may it exclude only?

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Background: Pulmonary embolism (PE) is the third most common cause of death for cardiovascular diseases in Europe. Quick PE diagnosis is therefore crucial for prognosis improvement. It is critical to have suitable screening tests both to exclude PE as well to select patient with highest likelihood of PE occurrence. Currently D-dimer test is accepted as important tool useful to exclude PE in low risk patients. Our goal was to assess the D-dimer test positive prognostic value.

Methods: A retrospective study based on medical record analysis of consecutively admitted patients to 9 wards of The University Clinical Center in Katowice who were hospitalized during four consecutive years was performed. Three hundred and seventy patients met the inclusion criteria for the study, which involved the D-dimer tests and computed tomographic pulmonary angiography (CTPA) performed during hospitalization. Assessed patients were divided into two groups: PE confirmed and PE excluded by CTPA.

Results: We have found that patients with D-dimer levels higher than 2,152 ng/mL had significantly increased risk of PE [area under curve (AUC) of 0.69; 95% CI, 0.64–0.75; $P < 0.05$]. Positive predictive value (PPV) reached the level of 53%, whereas negative predictive value (NPV) reached 82%. We also found that patients with the history of neoplasm and at >65 years of age had D-dimer cut-off point moved to the level of 2,652 ng/mL (AUC of 0.67; 95% CI, 0.52–0.81; $P < 0.05$).

Conclusions: Whereas the NPV of the D-dimer test is generally accepted our results suggest that, in selected cases, an increased plasmatic D-dimer levels may have PPV in PE diagnosis. Patients with the history of neoplasm have higher cut-off D-dimer points above which we should consider increased PE likelihood. CTPA should be considered even for patients with low probability of PE when D-dimer values exceed four times the normal level.

Keywords: Pulmonary embolism (PE); D-dimer; prognostic value; neoplasm

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Introduction

PE usually results from an occlusion of the pulmonary artery or its branches by a thromboembolus (1). PE is usually one of clinical manifestations of venous thromboembolism disease (VTE) and is the third (after ischemic heart disease and cerebrovascular disease) most frequent cardiovascular disease with an incidence of 1–2% in the general population and 12–20% among hospitalized patients (2-4). Approximately 60% of all VTE cases are found in hospitalized patients. Among those, 5–10% suffer from PE (2,5,6). Clinicians are concerned about PE, because of its high risk of mortality (7-10).

If left untreated (most often because undiagnosed), acute PE has a lethality high as 59%, whereas adequately treated acute PE leads to death in only 7% of cases (11). The gold standard for the diagnosis of PE is computed tomographic pulmonary angiography (CTPA) (12). However, CTPA has certain disadvantages such as radiation exposure, the need for contrast medium administration, which may cause renal failure and the high cost of the test (13). Therefore, less invasive and less expensive diagnostic tools are desirable. One of currently unresolved question is whether plasma D-dimer assays may be considered as reliable test both for excluding PE and for screening for patients at the highest risk. Plasma D-dimers are cross-linked fibrin derivatives produced when fibrin is degraded by plasmin. Elevated D-dimer levels are found in many conditions that lead to activation of blood coagulation and fibrin formation (14). Since the 1980's, researchers have been trying to create algorithms useful for ruling out PE with plasma D-dimer assays (15-26). In almost all trials the cutoff point was established at the level of 500 ng/mL, but it was helpful only to rule out PE in patients with low and moderate clinical probability of PE. Thereafter plasma D-dimer assays have been studied in various aspects connected with VTE: the correlation of D-dimer levels with short-term or long-term mortality (27), the severity of the course of the disease (28), predicting disease relapse after stopping anticoagulant therapy (29), and correlation with radiological severity of PE (30). In addition, two studies reported the presence of correlation between increased D-dimer levels and the likelihood of PE diagnosis by CTPA (31,32). The aim of our study is to determine the practical plasma D-dimer level above which the risk of PE is sufficiently high that CTPA is mandatory.

Methods

Study population and data acquisition

We retrospectively analyzed medical history notes of patients at University Teaching Hospital (SP CSK im. Kornela Gibińskiego in Katowice, Poland). In the hospital database from January 2009 through December 2013 we selected all patients with both a D-dimer blood level test and CTPA performed. Our inclusion criteria fulfilled 370 patients from nine wards of the hospital (*Table 1*). We then divided the sample into two groups: patients with PE confirmed by CTPA and those without such a diagnosis.

Plasma D-dimer assay

Plasma D-dimer levels were measured used automated quantitative latex-based, immuno-agglutination assay (HemosIL D-Dimer HS 500) (33). We included D-dimer results obtained within 48 hours before CTPA was performed. Positive test result was defined as a D-dimer level of >500 ng/mL. A normal D-dimer range was defined as <500 ng/mL.

CTPA

PE had been diagnosed by CTPA in the presence of filling defects in pulmonary arteries or images suggesting pulmonary microembolism interpreted by certified experienced radiologists.

Statistical analysis

Analysis was performed using Statistica (<http://www.statistica.com/>) software version 10. Receiver operating characteristic (ROC) curve were built to determine the best cutoff value for the diagnosis of PE. We first included all records and second excluded patients from surgical wards. In addition, ROC curves were built for patients aged >65 and ≤65 with and without the history of neoplasm according to the most important risk factors of thromboembolism. Because of the retrospective design of the study important clinical characteristics such as neoplasm type were not recorded. Youden's index was calculated ($YI = \text{sensitivity} + \text{specificity} - 1$) for each coordinate point of the ROC curve to determine the cut-off value with the maximum sensitivity and specificity.

Table 1 Patient characteristics

Characteristics	All patients	Patients with PE	Patients without PE
N	370	134	236
Age (years)	63.52±16.94	65.95±15.49*	62.14±17.60
Male	189	76	113
Female	181	58	123
D-dimer (ng/mL)	3,693.79±5,896.28	5,055.81±6,705.96**	2,920.45±5,242.21
Pneumology (n)	116	38	78
Neurology (n)	107	53	54
Internal medicine and pharmacology (n)	58	21	37
Internal medicine and metabolic disease (n)	25	8	17
Surgery (n)	24	4	20
Gastroenterology (n)	19	6	13
Perinatology (n)	11	3	8
Gynecology (n)	8	1	7
Intensive care unit (n)	2	0	2

Comparisons between patients with and without PE: *, P<0.05; **, P<0.001. n, number; PE, pulmonary embolism.

Results

The study population included 189 men and 181 women. A total of 134 patients (36.2%) were diagnosed with PE and 236 patients (63.8%) were negative for PE. The mean plasma D-dimer level in the group with confirmed PE (5,056 ng/mL) was significantly higher than in the group of patients without PE diagnosis (2,920 ng/mL); P<0.05. The baseline characteristics of the study population are shown in *Table 1*. The relative frequency PE diagnosis by D-dimer range is shown in *Figure 1*.

Patients with positive D-dimer test

The construction of the ROC curve allowed us to determine the best cut-off point. Having D-dimer values above 2,152 ng/mL significantly increased the likelihood of a PE diagnosis [area under curve (AUC) of 0.69; 95% CI, 0.64–0.74; P<0.05] (*Figure 2*). Building a second ROC curve excluding patients from surgical wards (surgery, gynecology, perinatology, intensive care unit) provided similar results (the best cutoff point was 2,152 ng/mL with an AUC of 0.71; 95% CI, 0.65–0.77; P<0.05).

The sensitivity, specificity, PPV and negative predictive value (NPV) were calculated for different values of D-dimer

concentration. For the best cutoff point (2,152 ng/mL) determined in this study, the specificity was increased from 20.3% to 62.7% (in comparison to the results for the 500 ng/mL cutoff typically used), whereas its sensitivity was at 75.4%. Also, the PPV was raised by 13.1% (from 40.3% to 53.4%), while the NPV decreased only by 5.6% (from 87.3% to 81.8%).

The construction of another ROC curves allowed us to determine the best cut-off points of D-dimer levels in four group samples divided according to the patients age (>65 or ≤65) years of age and the history of neoplasm. In our study, 96 patients (25.9%) had malignancy. Patients with the history of neoplasm and aged >65 had significantly increased likelihood of PE diagnosis at the D-dimer level of 2,652 ng/mL with an AUC of 0.67; 95% CI, 0.52–0.81; P<0.05 (*Figure 3*), whereas in patients aged ≤65 the best cut-off point was 2,563 ng/mL with an AUC of 0.69; 95% CI, 0.5–0.86; P=0.05 (*Figure 4*). Patients who did not suffer from neoplasm and were more than 65 years old had D-dimer cut-off point determined at the level of 2,169 ng/mL with an AUC of 0.71; 95% CI, 0.62–0.79; P<0.05 (*Figure 5*), whereas in patients aged ≤65 the best cut-off point was 1,093 ng/mL with an AUC of 0.7; 95% CI, 0.61–0.79; P<0.05 (*Figure 6*).

We also assessed the accuracy of D-dimer test in excluding PE in patients with malignancy—sensitivity was

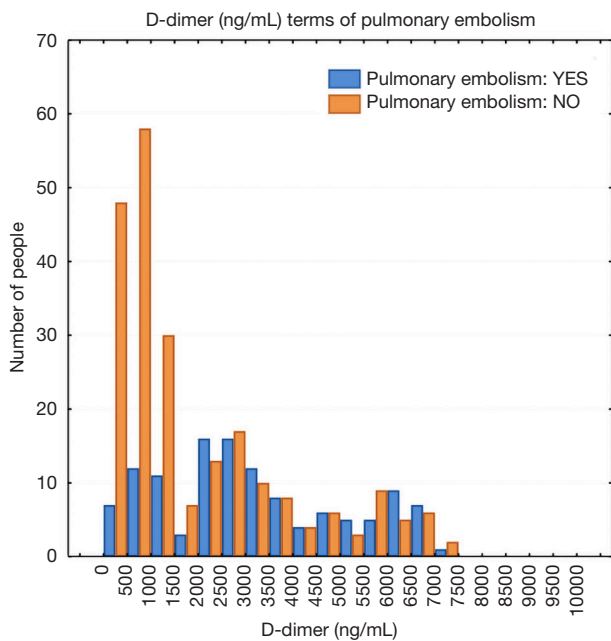


Figure 1 Relative frequency of PE diagnosis by D-dimer range (ng/mL). PE, pulmonary embolism.

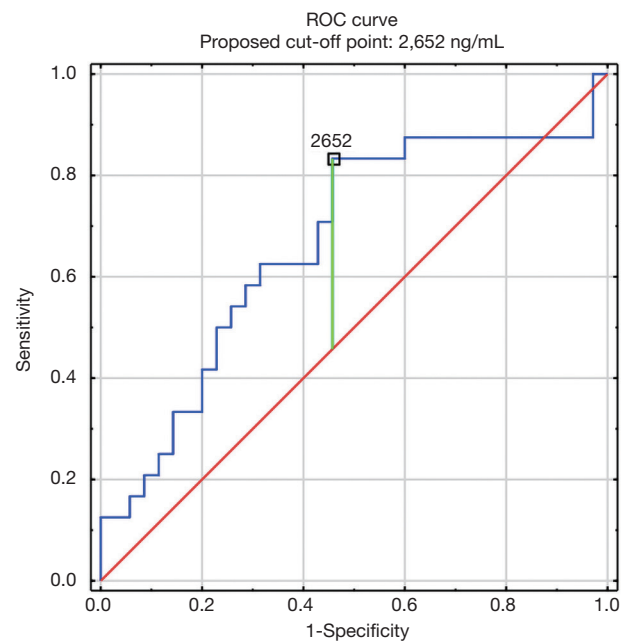


Figure 3 Receiver operating characteristic curve for PE diagnosis by D-dimer level (ng/mL). Patients with the history of neoplasm and aged >65 (n=59). PE, pulmonary embolism.

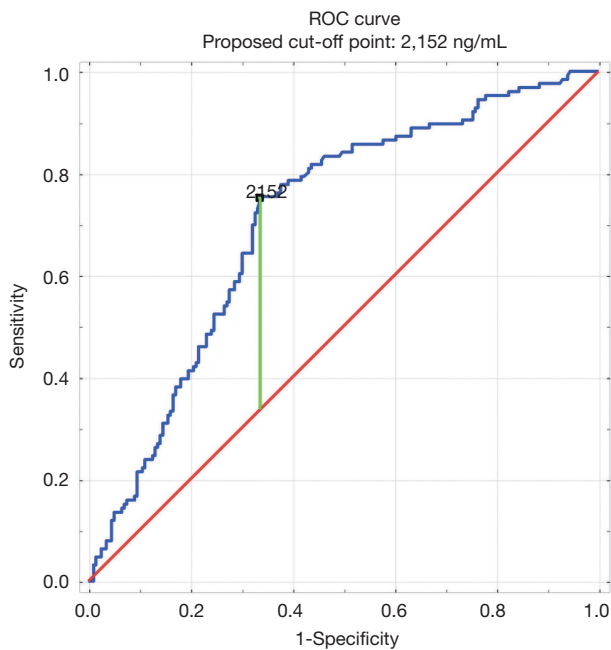


Figure 2 Receiver operating characteristic curve for PE diagnosis by D-dimer level (ng/mL). All patients included (n=370). PE, pulmonary embolism.

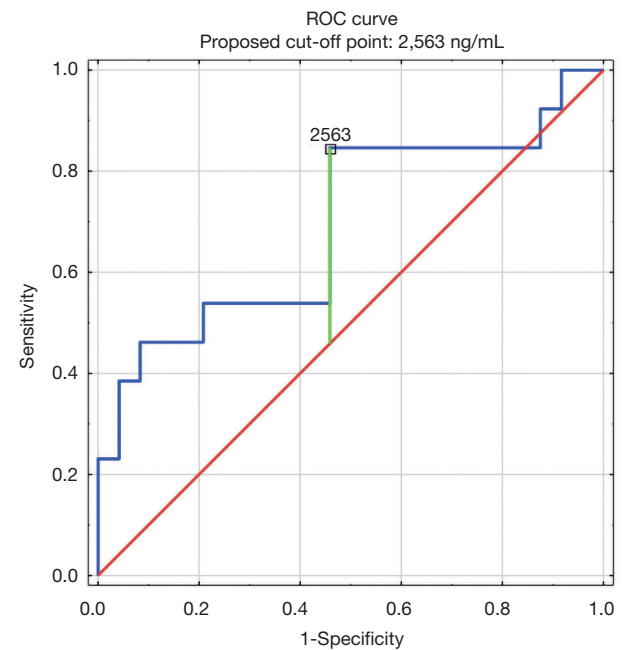


Figure 4 Receiver operating characteristic curve for PE diagnosis by D-dimer level (ng/mL). Patients with the history of neoplasm and aged ≤ 65 (n=37). PE, pulmonary embolism.

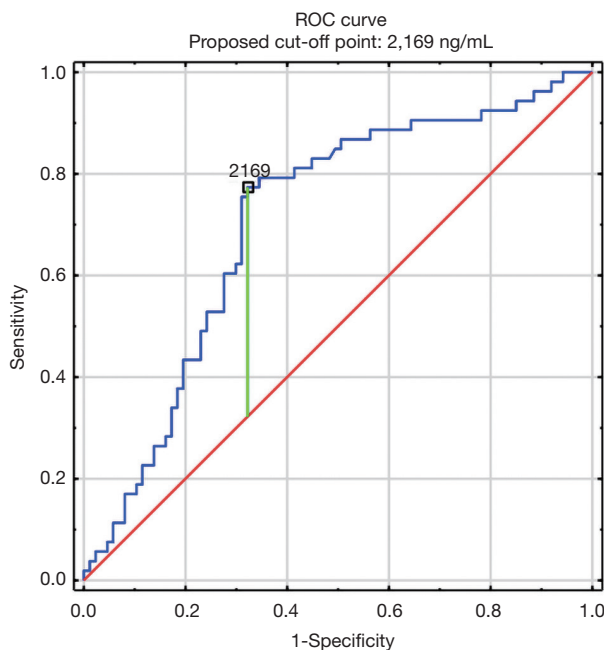


Figure 5 Receiver operating characteristic curve for PE diagnosis by D-dimer level (ng/mL). Patients without the history of neoplasm and aged >65 (n=140). PE, pulmonary embolism.

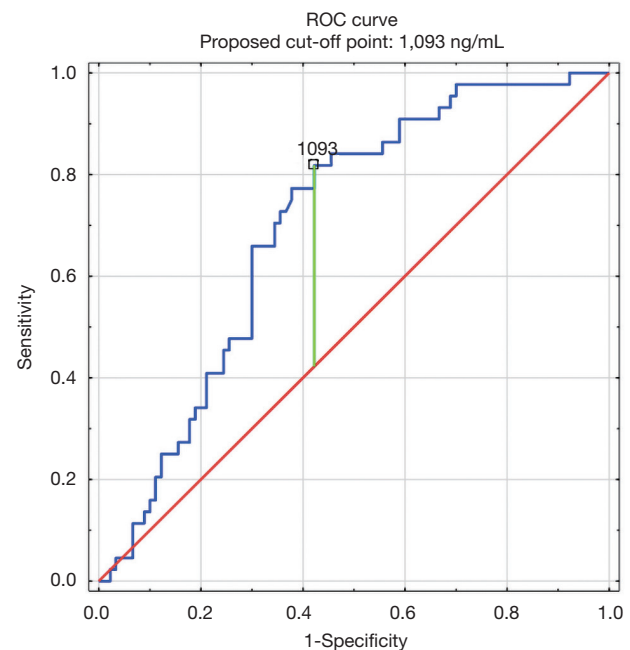


Figure 6 Receiver operating characteristic curve for PE diagnosis by D-dimer level (ng/mL). Patients without the history of neoplasm and aged ≤65 (n=134). PE, pulmonary embolism.

94.6%, specificity was 6.8%, PPV 38.9% and NPV 66.7%.

Patients with negative D-dimer test

In our study, 55 patients had negative D-dimer result (under 500 ng/mL) and 7 (12.7%) of them had PE confirmed by CTPA, of which 2 (28.6%) had subsegmental PE. We also checked why CTPA was performed despite normal D-dimer concentrations in these patients. Of the 55 patients, 48 (87.27%) had extended diagnostics because they had worrying clinical symptoms and/or PE risk factors, 2 (3.6%) had pneumonia after ineffective course of antibiotics, 2 (3.6%) had higher D-dimer test levels before they were admitted to the hospital, 2 (3.6%) had CTPA performed to exclude other diseases (e.g., vascular malformations) and 1 (1.8%) could not be explained.

Discussion

The most important result of our study is the finding that highly elevated plasma D-dimer values (in our laboratory—2,152 ng/mL) are associated with significantly higher risk of PE. Our value of 2,152 ng/mL is approximately four times higher than the normal plasma D-dimer cut-

off value. This finding has aroused researchers' interest in investigating the best D-dimer cut-off level for diagnostics of PE. One of the studies based on ROC curves, determined the best cut-off level to be 830 ng/mL (AUC 0.762; 95% CI, 0.653–0.850; $P < 0.05$), which is 1.5 times higher than the normal D-dimer concentration for that laboratory (500 ng/mL) (34). In another study, the best cut-off level based on ROC curve was determined to be 900 ng/mL (AUC 0.76; 95% CI, 0.69–0.82; $P < 0.001$), which also was 1.5 times higher than the normal D-dimer value (580 ng/mL for that laboratory) (31). Analysis of the ROC curve in our study showed that patients with D-dimer values >2,152 ng/mL have a 69% increased risk of developing PE. In comparison, the studies previously cited indicated that cut-off levels of 830 ng/mL or 900 ng/mL have ~76% increased risk of developing PE (31,34). However, these studies had relatively small study populations and only few patients with confirmed PE. The first study had only 58 patients with PE (31) and the second had only 40 (34), whereas in our study 134 patients had confirmed PE. In addition, we analyzed medical histories of patients from nine different wards of the hospital, including internal medicine wards and surgical wards, whereas the previous studies analyzed only patients from the department of internal diseases (34)

and the emergency department (31). The data on specificity and sensitivity in our study are in keeping with the conclusions of a systematic review of the literature: more sensitive is the assay less specific it becomes (35). There are large differences in proposed cut-off levels proposed for PE 1,5 times in the cited studies (31,33) which may result in a significant number of unnecessary CTPA. On the other hand, our results indicate that some patients with lower plasma D-dimer concentrations have acute PE. Therefore, prospective large scale, multicenter study should be conducted to obtain the best cut-off level.

According to the latest [2014] guidelines on the diagnosis and management of acute pulmonary embolism (PE), the PPV of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE and elevated D-dimer concentration has prognostic value only for short-term mortality (36). Our findings indicate otherwise. D-dimer levels may have important prognostic value in the diagnosis of PE therefore patients with low clinical probability of PE and D-dimer concentration four times exceeding normal value should be assessed carefully and considered for CTPA.

It is well known that plasma D-dimer levels may be elevated by many clinical conditions, such as postoperatively and during pregnancy (37). Therefore, we decided to exclude such cases and examine only non-surgical patients. By building another ROC curve with the exclusion of surgical patients (Surgery, Gynecology, Perinatology, and ICU), we arrived at the same cut-off point (2,152 ng/mL), with an AUC of 0.7 which indicates a comparable risk of developing PE as found using the full sample. This is the proof that our cut-off point isn't overestimated because of other, D-dimers related conditions.

After analyzing other PE risk factors, we have determined whether the presence of two other important risk factors from Revised Geneva Score alter the cut-off points at which the likelihood of PE rises (12). Patients with an history of neoplasm had a significantly increased D-dimer cut-off level, than patients without such history regardless of their age. At the opposite, age was a significant factor in the patients without history of neoplasm with a significantly increased D-dimer cut-off level in patients >65 years old compared with those ≤65 years old. The age-adjusted D-dimer cut off point is already a well-established method of ruling out PE (38), but we propose that a better way to determine the best cut-off point above which significantly increases the likelihood of PE diagnosis is to accept the patients age as in Revised Geneva Score compared with using age-adjusted D-dimer cut-off levels. To the best of

our knowledge our paper seems to be the first to describe the likelihood of PE in such groups of patients. There were only reports about importance of those two risk factors in ruling out the PE, especially using age-adjusted D-dimer cut-off levels (39).

Moreover, it is worth to mention that in our study population there were 96 (25.9%) patients with malignancy while in the Geneva score study (40) only 13% [138] of patients in their cohort had malignancy. Karamat *et al.* assessed the utility of D-dimer test in predicting PE in 104 cancer patients (41) and we had similar sensitivity (94.6% vs. 95.5%), lower specificity (6.8% vs. 28.2%), as well as the PPV (38.9 vs. 42.8) and the NPV (66.7% vs. 91.6%) was lower.

It should also be underlined that in our study a negative D-dimer test does not exclude the presence of acute PE 100% of the time, because 12.7% of the patients with normal plasma D-dimer levels had confirmed PE. Furthermore, among all patients with confirmed PE in our study, 7 of 134 (5.2%) had normal D-dimer concentrations. An earlier study reported an even higher percentage of PE patients with normal D-dimer values—26% (42). Whereas other studies, in agreement with our results, reported that 3.4% of 382 patients (43), 3.6% of 55 patients (44), and 4% of 725 patients (45) with PE had normal plasma D-dimer values, which is compatible with our results. Another study has shown that 2 of 5 (40%) patients with normal with plasma D-dimer levels had PE or DVT (46). These results are comparable with our results, where 3 of 7 (42.8%) patients with plasma D-dimer levels <500 ng/mL had acute PE. Another study also encourages physicians to search for acute PE in patients with normal D-dimer values, when symptoms can't be explained otherwise (can't be connected with another disease), in the presence of thromboembolism risk factors and when duration of symptoms is unnaturally long (45). We also considered what could explain negative D-dimer results on those patients. Most often false-negative results are caused by anticoagulation therapy (47)—all patients in our study were hospitalized so they could use antithrombotic prophylaxis and 3 of them were already treated because of DVT or stroke before PE diagnosis.

The 2014 European Society of Cardiology (ESC) guidelines on the diagnosis and management of acute PE state that a normal plasma D-dimer level renders acute PE or DVT unlikely but also that the quantitative latex-derived assays (used in our study) and a whole-blood agglutination assay have a diagnostic sensitivity <95% and are thus often referred to as moderately sensitive. In

outcome studies, those assays proved to be safe in ruling out PE in PE—unlikely patients as well as in patients with a low clinical probability. Their safety in ruling out PE has not been established in the intermediate clinical probability category (36). Our study in combination with previously cited studies (42,43,45,46) confirm results the guidelines, however we suggest, that clinicians should also include information about patients with normal plasma D-dimer level, especially if had previous PE or DVT, duration of symptoms is unnaturally long or when symptoms can't be explained otherwise.

Our study was based on the retrospective analysis of the medical notes of patients in a hospital database, which prevented us from checking reasons for ordering the plasma D-dimer test and the time frame from symptoms to CTPA. We also did not include cases in which PE was diagnosed without previous D-dimer tests and patients who were diagnosed with acute PE without using CTPA, because contraindicated. However, these cases were few, and it is unlikely that they would have changed the results of our study. Unfortunately, because of the retrospective design of our study we did not have the possibility to use the Geneva score or modified Wells criteria and not always the score of these scales was recorded in the medical notes of our patients, despite the 2014 ESC Guidelines on the diagnosis and management of acute PE recommend to assess the clinical probability of acute PE diagnosis (36). The value of this clinical evaluation has been confirmed in few clinical studies for example the prospective investigation on PE diagnosis (PIOPED) (48). The small number of patients included in our study does not allow to draw clear conclusions about utility risk factors like cancer, pregnancy or post-surgery to obtain different plasma D-dimer cut-off values for those patients and prospective studies in this area are needed.

Conclusions

In general population of patients with plasma D-dimer levels exceeding at least four times (in our study 2,152 ng/mL) its normal value, CTPA should be considered predictive even for patients with a low clinical probability of acute PE. However, the small number of patients included in our study does not allow us to draw clear conclusions about patients with cancer, pregnancy or post-surgery that are also often associated with increased plasma D-dimer levels. Also, the age >65 years and a history of neoplasm, should always be considered in suspecting acute PE, because may significantly

increase the plasma D-dimer cut-off level associated with an increased likelihood of acute PE.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The research was conducted according to the principles of the Declaration of Helsinki. And in Poland (according to the polish law) studies which are not experimental—including retrospective analyses or observational studies—do not require ethical committee approval.

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