ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

Correlation of Pulmonary Embolism with D-dimer Level and Determination of Cut-off Values According to Age

Pulmoner Emboli ile D-dimer Düzeyinin Korelasyonu ve Yaşa Göre Eşik Değerlerinin Belirlenmesi

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ABSTRACT

Aim: This study was conducted to determine the D-dimer threshold levels according to age in patients diagnosed with pulmonary embolism (PE) by pulmonary computed tomography (CT) angiography.

Material and Methods: Patients who had pulmonary CT angiography performed and whose D-dimer test was obtained with the suspicion of pulmonary embolism (PE) in the emergency department of a tertiary university hospital between January 01, 2015, and December 30, 2019, were included in the study. The demographic characteristics of the patients, imaging reports, and 1-month mortality were evaluated retrospectively by examining the hospital information management system and patient files. Patients with missing records and patients who had diagnostic examinations other than the preliminary diagnosis of PE were excluded from the study.

Results: Among the 6240 patients included in the study, 58.1% were female. The mean age of the patients was 43±17 years. Of the 1,507 patients who had a pulmonary CT angiogram, 9.8% were diagnosed with PE. When we looked at the 1-month mortality of 6240 patients, whose D-dimer assay was analyzed with the preliminary diagnosis of PE, we found that 0.3% of patients died. The monthly mortality rate was 0.7% in patients with high D-dimer levels while the mortality rate in patients with normal D-dimer levels was 0.1%. A positive and statistically significant correlation was found between the location of the pulmonary embolism in pulmonary CT angiography and the D-dimer level (spearman's rho= 0.251, p<0.001). The cut-off D-dimer value in predicting the presence of PE in all age groups was calculated as 1.34 mg/L. The cut-off values of D-dimer to predict the presence of PE according to age ranges was calculated as 1.18 mg/L (<50 years), 1.19 mg/L (50-60 years), 1.58 mg/L (60-70 years) 1.79 mg/L (70-80 years), 2.83 mg/L (>80 years) respectively.

Conclusion: As age increases, the D-dimer cut-off value for the diagnosis of PE also increases. There is a positive and significant relationship between D-dimer level and pulmonary embolism severity.

Keywords: Pulmonary embolism, D-dimer for age, pulmonary angiography CT

ÖZ

Amaç: Bu çalışma pulmoner bilgisayarlı tomografi (BT) anjiyografi ile pulmoner emboli (PE) tanısı konan hastalarda yaşa göre D-dimer eşik düzeylerinin belirlenmesi amacıyla yapılmıştır.

Gereç ve Yöntemler: 01 Ocak 2015-30 Aralık 2019 tarihleri arasında üçüncü basamak bir üniversite hastanesinin acil servisinde pulmoner emboli (PE) şüphesi ile pulmoner BT anjiyografi yapılan ve D-dimer testi tetkik edilen hastalar çalışmaya dahil edildi. Retrospektif olarak hastane bilgi yönetim sistemi ve hasta dosyaları incelenerek, hastaların demografik özellikleri, görüntüleme raporları, hastaların 1 aylık mortalitesi değerlendirildi. Kayıtları eksik olan ve PE ön tanısı dışında tanısal tetkikleri olan hastalar çalışma dışı bırakıldı.

Bulgular: Çalışmaya alınan 6240 hastanın %58,1'i kadındı. Hastaların yaş ortalaması 43±17 olarak saptandı. Pulmoner BT anjiyografisi yapılan 1.507 hastanın %9,8'ine PE tanısı kondu. PE ön tanısı ile D-dimer testi çalışılan 6240 hastanın 1 aylık mortalitesi incelendiğinde %0,3 hastanın öldüğü saptandı. D-dimer testi yüksek olan hastalarda aylık mortalite oranı %0,7, D-dimer testi normal olan hastalardaki mortalite oranı ise %0,1'idi. Pulmoner BT anjiyografideki pulmoner embolinin lokalizasyonu ile D-dimer seviyesi arasında pozitif ve istatistiksel anlamlı bir korelasyon saptanmıştır (spearman's rho= 0.251, p<0.001). D-dimer değerinin tüm yaş gruplarından PE varlığını öngörmedeki eşik değeri 1,34 mg/L olarak hesaplandı. D-dimer değerinin yaş aralıklarına göre PE varlığını öngörmedeki eşik değerleri sırasıyla 1.18 mg/L (<50 yaş), 1.19 mg/L (50-60 yaş), 1.58 mg/L (60-70 yaş), 1.79 mg/L (70-80 yaş), 2.83 mg/L (>80 yaş) olarak hesaplandı.

Sonuç: Yaş arttıkça PE tanısı için D-dimer eşik değeri de artmaktadır. D-dimer düzeyi ile pulmoner emboli şiddeti arasında pozitif ve anlamlı ilişki bulunmaktadır.

Anahtar Kelimeler: Pulmoner emboli, yaşa göre D-dimer, pulmoner BT anjiyografi

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Introduction

Patients with pulmonary embolism (PE), which causes mortality if not diagnosed and treated early in the emergency department, frequently present with chest pain, dyspnea, tachypnea, and syncope (1).

In clinical settings with many atypical complaints and intensive patient admissions, such as the emergency department, the diagnosis of pulmonary embolism can sometimes be overlooked, or some of the patients are subjected to unnecessary investigations (2).

Clinical decision-making algorithms (such as Wells, PERC) have been developed for patients with suspected PE, thereby limiting the request for examination (3,4). It is recommended to perform direct pulmonary CT angiography in patients with medium and high Wells scores, measure D-dimer levels first in patients with low Wells scores, and then pulmonary CT angiography if the result is above the threshold value (5). Many studies suggest that the D-dimer level changes with the patient's age and that different cut-off values should be used according to age groups (6,7).

Few studies concurrently examine the age-related D-dimer threshold and the relationship between D-dimer level and embolism severity in patients with pulmonary embolism. The study's primary aim was to determine the D-dimer cut-off levels according to age in patients diagnosed with pulmonary embolism by pulmonary CT angiography. The study's secondary objective was to determine the relationship between D-dimer level and radiographically determined pulmonary embolism severity.

Material and Methods:

This study is a retrospective observational study, including patients admitted to a tertiary university hospital between January 01, 2015, and December 30, 2019, with a preliminary diagnosis of PE, who underwent pulmonary CT angiography and whose D-dimer assay was analyzed. The tertiary university hospital's Clinical Research Ethics Committee approval of "there is no scientific and ethical inconvenience in conducting the study" was obtained (Dated 05.02.2020/ number KAEK-98).

Inclusion Criteria

Patients aged 18 years or older, who underwent pulmonary CT angiography with a pre-diagnosis of PE and whose D-dimer was studied for a pre-diagnosis of PE, at the emergency department of a tertiary university hospital.

Exclusion Criteria

Patients whose D-dimer levels were not requested or who did not undergo pulmonary CT angiography, and patients under 18 years of age.

Data Collection

The hospital information management system was used to collect the data. Short history and discharge notes of the patients were obtained from the hospital information management system and evaluated.

The patients' gender, age, triage category, Wells score, D-dimer level, high sensitive trop-T level, pulmonary CT angiography results, 1-month mortality, and whether the patient applied to the emergency service with the same complaints within 30 days were recorded in the study form. Wells score of 0-1 was considered low clinical probability, a score of 2-6 as moderate clinical probability, and a score of 6 and above as high clinical probability. Patients with high clinical probability were not included in the study. A D-dimer level above 0.55 mg/L and a highly sensitive troponin T level above 0.06 ng/L are considered significant, and then radiological imaging studies are performed in our hospital.

Pulmonary CT angiography was performed on a 128-slice Siemens SOMATOM Definition Edge (Siemens, Erlangen, Germany) CT device. Radiologists interpreted the images.

Data analysis

All data obtained from the study were recorded in the SPSS-20.0 program and analyzed. Mean, standard deviation, and median values were used when presenting descriptive analyzes. The Chi-square test and Student's t-test were used for group comparisons. A p-value of <0.05 was considered significant for statistical significance.

Receiver Operating Curve (ROC) analysis was performed while determining the overall cut-off value of D-dimer and the cut-off value according to age. ROC analysis was performed while determining the cut-off value of troponin and D-dimer in predicting the presence of pulmonary embolism and mortality. Descriptive analyzes and Spearman's correlation analysis were used when investigating the correlation of the amount of occlusion in the pulmonary arteries, that is, the severity of pulmonary embolism, with the D-dimer level of the patient.

Results

Within the scope of the study, the records of 6240 patients who applied to the emergency department and whose D-dimer was studied with a preliminary diagnosis of PE were examined. Pulmonary CT angiography was performed in 1507 (24.2%) of these patients since the D-dimer level was higher than the standard cut-off level in the hospital. While PE was detected in 147 (9.8%) of 1507 patients who underwent pulmonary CT angiography, PE was not detected in 1360 (90.2%) (Figure 1). Among the 6240 patients in the study, 3628 (58.1%) were female. The mean age of the patients was 43±17 years.

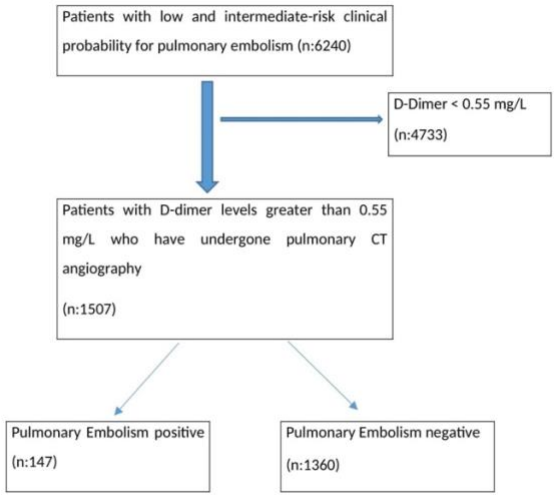

Figure 1. Patient Flow in the Study

Considering the 1-month mortality of 6240 patients with a preliminary diagnosis of PE at the emergency department admission, we found that 20 (0.3%) patients died. The monthly mortality rate in patients with high levels of D-dimer was 0.7% (17 patients), while the mortality rate in patients with normal D-dimer test results was 0.1% (3 patients) (p value<0.001). The average level of D-dimers in deceased patients was 5.20±7.04, whereas the average level of D-dimers in survivors was 1.03±2.72 (p value=0.016).

Whereas the mortality rate was 2% for patients with high troponin values, it was 0.2% for patients with normal troponin test results (p value<0.001).

The troponin value was found to have a weak significance in predicting pulmonary embolism by calculating the AUC (Area Under The Curve) value of 0.585. In contrast, with an AUC value of 0.738, the D-dimer value was found to have a higher agreement in predicting PE (Table1, Figure 2).

Test	AUC (%95)	Cut-off	p	Sensitivity (%)	Specificity (%)
Troponin	0,585 (0,530-0,639)	0,01 ng/L	0,001	37	75
D-dimer	0,738 (0,693-0,782)	1,34 mg/L	:0,001	68	68

Table 1. The cut-off value of troponin and D-dimer value in ROC analysis to predict pulmonary embolism

At first D-dimer cut-off value and AUC value were determined from the D-dimer results of all the patients, regardless of age category. Than, the D-dimer cut-offs of the patients were calculated separately for patients under 50 years old, 50-59 years old, 60-69 years old, 70-79 years old, and 80 years old and above. We observed that the cut-off values gradually increased depending on age.

The cut-off D-dimer value in predicting the presence of PE in all age groups was calculated as 1.34 mg/L. The cut-off values of D-dimer value to indicate the presence of PE according to age ranges respectively: 1.18 mg/L (<50 years), 1.19 mg/L (50-60 years), 1.58 mg/L (60-70 years), 1.79 mg/L (70-80 years), 2.83 mg/L (>80 years) (Table 2, figure 3).

It was observed that the mean D-dimer of the patients increased proportionally as the level of pulmonary artery stenosis went from the peripheral arteries to the central arteries (Table 3).

A positive and statistically significant correlation was found between the location of the pulmonary embolism in pulmonary CT angiography and the D-dimer level (spearman's rho= 0.251, p<0.001). Spearman's correlation analysis is shown in figure 4.

Discussion

PE is a recurrent, preventable disease with high mortality and morbidity. Early recognition and prompt treatment of patients with suspected PE will reduce mortality and morbidity rates. Therefore, a great responsibility falls on the physician who first evaluates the patient. There is still no definitive diagnostic laboratory marker. Pulmonary CT angiography, a widely used imaging method as a definitive diagnosis, requires a contrast agent and radiation to the patient. It may be challenging for the physician to make an imaging decision, particularly in patients with impaired kidney function. In addition, the radiation dose to be given in younger patients may increase the risk of developing malignancies in the rest of the patient's life. This study tried to find the cut-off value of the D-dimer test used for diagnosis according to age and determine whether there is a correlation between the D-dimer value and the severity of pulmonary embolism.

The female gender was observed to be higher in the study patients. The medical literature demonstrates variability concerning the gender distribution of patients diagnosed with PE. While the number of female patients (58.1%) was higher in the study conducted by Keller et al., male patients (53.2%) were the majority in a retrospective study of Doğan et al. in which they evaluated PE cases (8,9).

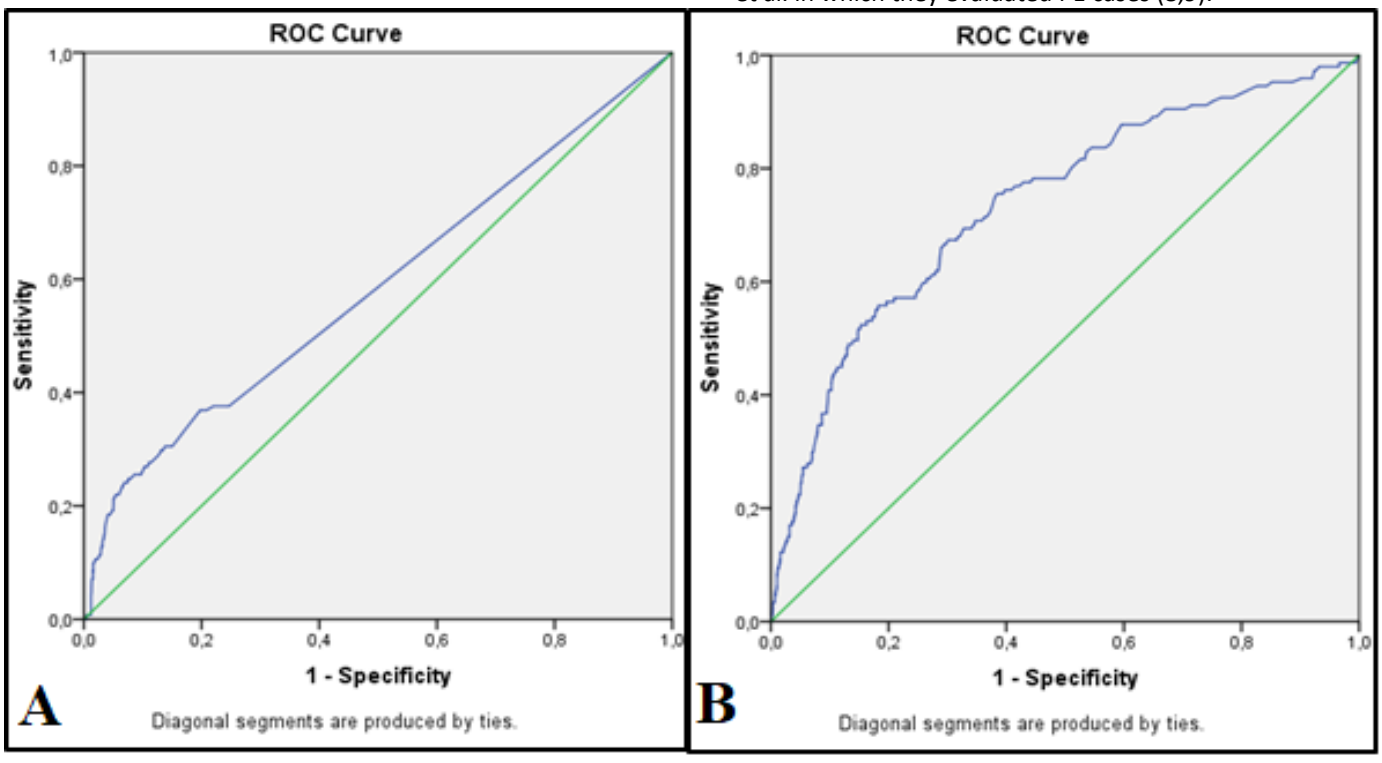

Figure 2- ROC analysis of troponin (A) and D-dimer (B) value in predicting pulmonary embolism

D-dimer	AUC (%95)	Cut-off (mg/L)	p	Sensitivity (%)	Specificity (%)
All age group	0,738 (0,693-0,782)	1,34	<0.001	68	68
<50 years	0,736 (0,667-0,806)	1,18	<0.001	71	71
50-59 years	0,699 (0,591-0,806)	1,19	0,002	63	64
60-69 years	0,782 (0,682-0,883)	1,58	<0.001	69	69
70-79 years	0,664 (0,507-0,820)	1,79	0,033	62	62
≥80 years	0,723 (0,588-0,857)	2,83	0,009	64	68

Table 2. Cut-off values of D-dimer value according to age group and age ranges in the whole ROC analysis to predict pulmonary embolism.

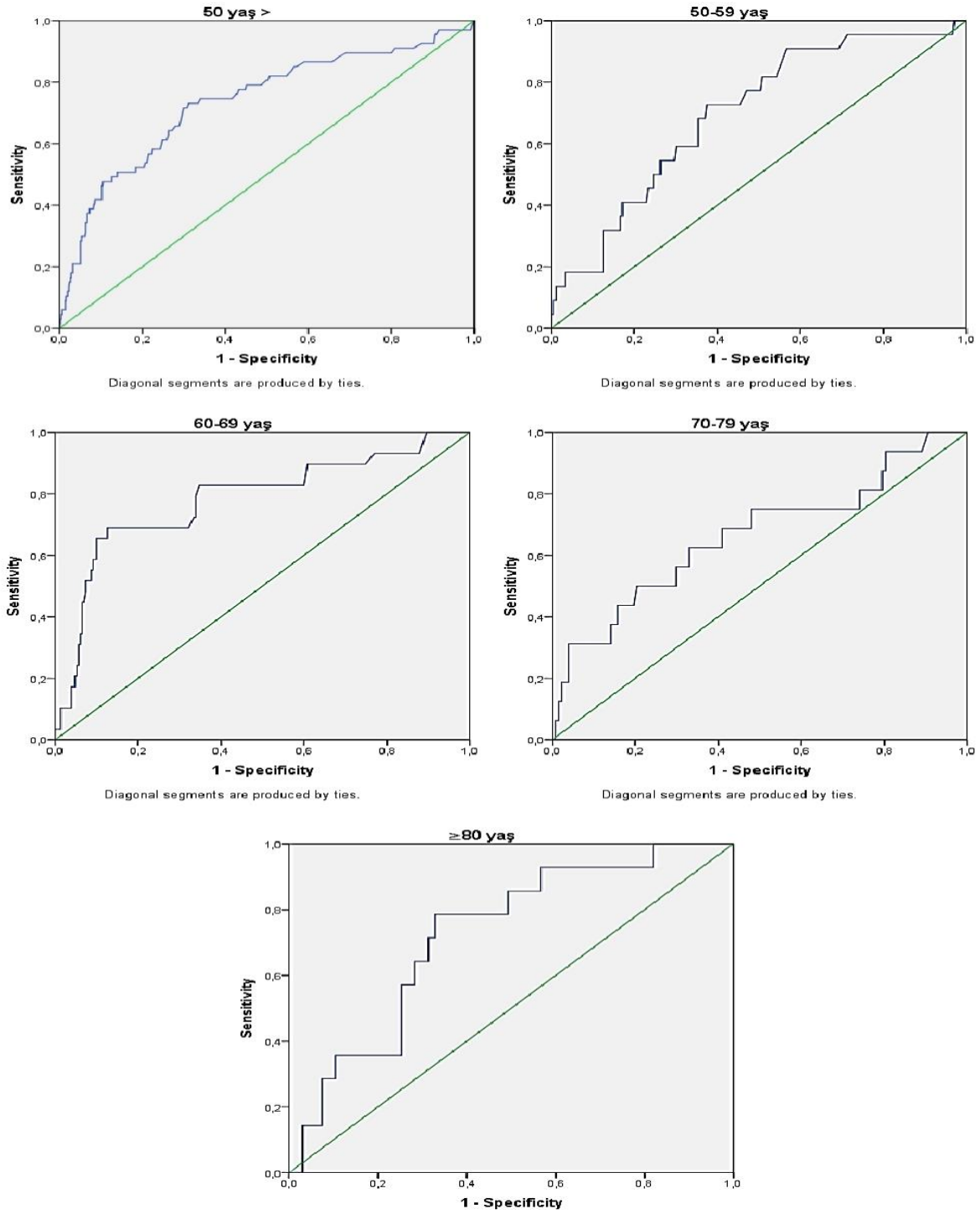

Figure 3. ROC analysis of age-related D-dimer values to predict pulmonary embolism

Pulmonary Embolism Localization	D-dimer (mg/L), Average (min-max)	D-dimer (mg/L), Standard deviation	Number of patients
No pulmonary embolism	1,67 (0,17-37,53)	2,64	1360
Subsegmental	1,94 (0,17-6,52)	1,62	33
Segmental	3,30 (0,28-34,56)	4,78	68
Lobar	3,24 (0,54-8,96)	2,47	16
The main pulmonary artery	6,53 (3,51-11,98)	2,61	10
Massive	10,73 (2,72-35,11)	9,27	20

Table 3: Distribution of patients according to presence and localization of pulmonary embolism

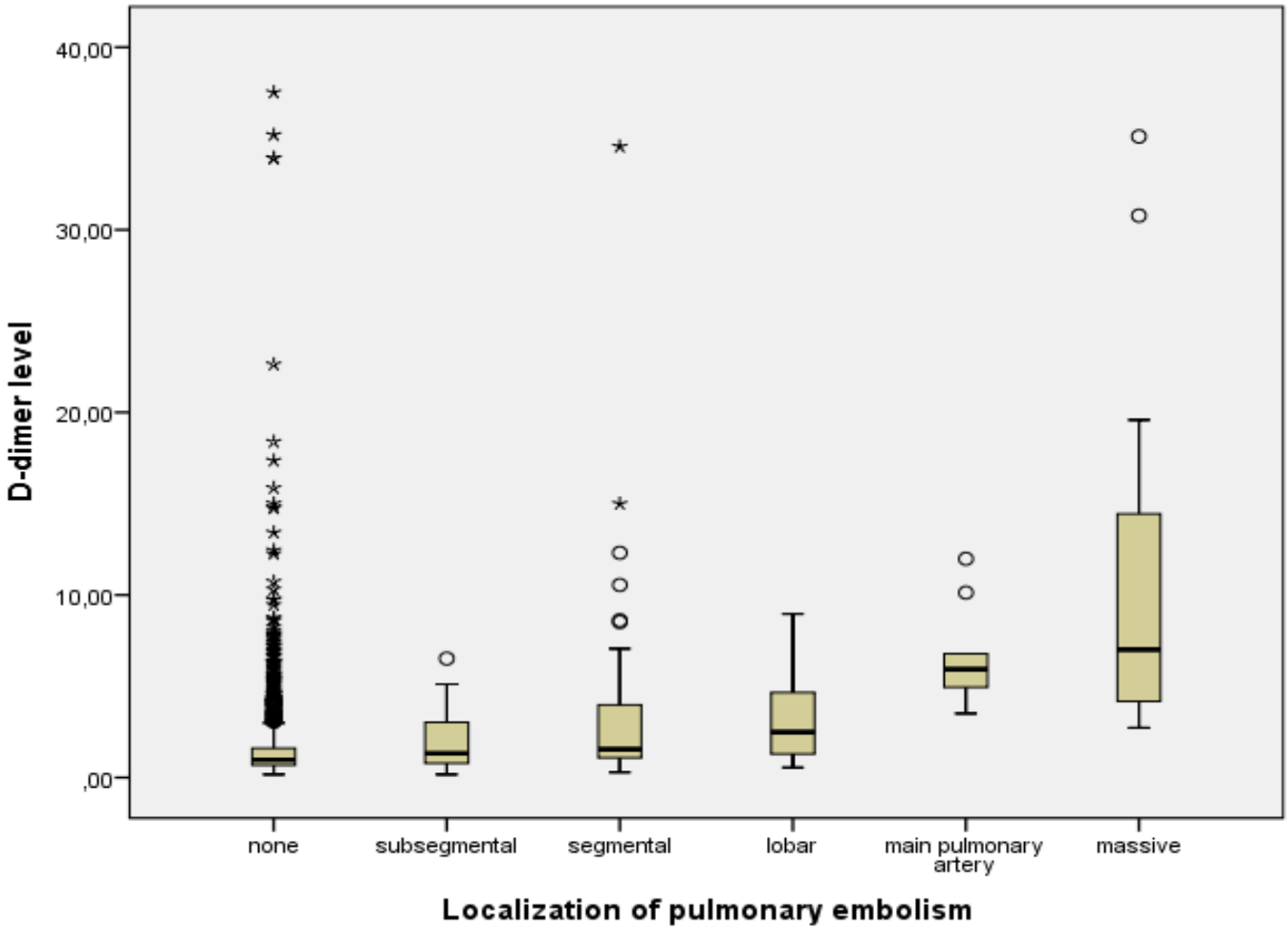

Figure 4. Localization of pulmonary embolism and D-dimer value correlation analysis

In the study conducted by Hakemi et al., the mean age of PE patients was found to be 56.2±13.5 years (10). In the study of Huynh et al., 838 patients with deep vein thrombosis (DVT) were diagnosed, and 271 patients developed PE in these patients; the mean age was 65 years (11). According to the literature, the mean age of patients with PE was lower in our study.

PE was found in 9.8% of the patients included in our study who underwent pulmonary CT angiography. When we look at the literature in general, it is seen that the prevalence of PE varies between 5% and 50% due to the age and comorbidity differences of the patients included in the study (12).

In our study, mortality was 1.4% in patients with PE; while Hacievliyagil et al. found 3.1%, Kadıoğlu et al. found 5.8% and Tanabe et al found 6.1% mortality (13-15). The mortality rate in our study was below the literature. It is not possible to compare the mortality rates with healthy ones due to the low number of patients who died and the heterogeneity of the patients included in the studies. Troponin T and I are heart-specific enzymes. Especially the presence of PE that can cause acute right heart failure (massive embolism), can

cause increases in the oxygen requirement by causing right ventricular dilatation, thus decreasing the coronary circulation. Micro-infarctions occur, and the troponin level increases (16). In many meta-analyses, patients with normal troponin values have lower mortality rates than those with high troponin values (17). In our study, the troponin value had a strong significance in predicting 1-month mortality. In the study conducted by Liu et al. to see early mortality in patients with saddle pulmonary embolism, the cardiac troponin I cut-off value was calculated as 0.18 ng/L, sensitivity 88.89%, specificity 67.14%, and AUC value 0.888±0.035 in predicting mortality (18). We think the reason for the lower troponin cut-off value (0.027ng/L) in predicting mortality in our study was that we conducted the study in a population with less morbidity.

In our study, the D-dimer value was found to have a strong statistical significance in terms of predicting mortality (p:0.002 AUC (95%): 0.869 (0.798-0.940)). In the mortality and D-dimer study conducted by Grau et al. it was observed that the mortality rate of patients with over 5000 ng/ml was high (19). In the study of Klok et al. on its relationship with high D-dimer and 15-day and 3-month mortality, a 3,000 ng/ml D-dimer level was determined as a predictive value for mortality (20). In the study of Coskun et al. to evaluate the usability of D-dimer levels in estimating the prognosis in terms of 28-day mortality, the cut-off value was found to be 2.50 mg/L. The AUC of the study was 0.792, the sensitivity was 86%, and the specificity was 65% (21). D-dimer cut-off value (2.07mg/L), which we determined as a mortality predictor in our study, was slightly lower than in the literature, but its specificity (78%) was higher.

Our study observed that the D-dimer cut-off values of the patients increased gradually depending on age. In the study conducted by Righini et al. while the D-dimer cut-off value was 500 µg/L was normal, the cut-off value was calculated by increasing the age x10 µg/L in individuals over 50 years of age, PE was excluded in patients below the cut-off value, and the patients were followed without treatment for three months. During these follow-ups, pulmonary embolism was diagnosed in only 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%]). In contrast, the proportion of patients in whom PE could be excluded increased from 43 of 673 (%6,4 [%95 CI, %4,8-%8,5]) to 200 of 673 (%29,7 [%95 CI, %26,4-%33,3]) patients (7). In the study of Cini et al., the conventional D-dimer (230 ng/mL) cut-off value and modified cut-off value (376 ng/mL if ≥60 years old) and age-adjusted cut-off value (age years × five ng/mL, >50 years) to exclude venous thromboembolism (VTE) compared. It was concluded that more patients were safely excluded for VTE with both cut-offs changed (22). In their study, Nagel et al. analyzed four age groups (<50, 50-64, 65-74, and ≥75 years) using pulmonary CT angiography as a diagnostic reference. As a result of the study, the optimum cut-off value was calculated as 1900, 2300, 2800, and 2800 µg/L, respectively (23). The results of our study also show parallelism with the literature data.

In their study examining 30 patients with suspected pulmonary embolism and high D-dimer levels, Rawat et al found that the D-dimer level was proportional to both the presence of pulmonary embolism and the size of the emboli (24). Kubak et al. divided pulmonary embolism patients into peripheral lobar and central groups. D-dimer values correlated significantly with the location of the pulmonary embolism, Spearman's rho: 0.43, P <0.01 (25). In our study, the presence and localization of pulmonary embolism were classified according to its location in the pulmonary arteries. It was observed that the mean D-dimer of the patients increased proportionally as the pulmonary artery stenosis level increased from the peripheral arteries to the central arteries.

Limitations

There are some limitations to our study. Since this study is retrospective, some patients were excluded from the study because the data of some patients within the study dates were incompletely recorded in the system. Patients whose pulmonary angiography CT and D-dimer were both studied were included in the study. However, patients diagnosed with PE by other imaging methods due to kidney failure and contrast allergy were excluded from the study.

Conclusion

As age increases, the D-dimer cut-off for the diagnosis of PE also increases. There is a positive and significant relationship between D-dimer level and pulmonary embolism severity.

Conflict of Interest: The authors declare no conflict of interest regarding this study.

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Authors' Contribution: Conceptualization; Nafis VURAL (NV), Yıldıray CETE (YC), Murat DUYAN (MD); Data curation;NV,YC MD; Formal analysis; NV,YC MD; Funding acquisition; NV,YC MD; Investigation; NV,YC MD; Methodology; NV,YC MD; Project administration; NV,YC MD; Resources; NV,YC MD; Software; NV,YC MD; Supervision; NV,YC MD; Validation; NV,YC MD; Visualization; NV,YC MD; Roles/Writing - original draft; NV,YC MD; Writing - review & editing; NV,YC MD

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