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The impact of using different age-adjusted cutoffs of D-dimer in the diagnosis of pulmonary thromboembolism

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ABSTRACT

Background
This study was conducted to evaluate the relationship of age-adjusted D-dimer value with different coefficients in diagnosis of pulmonary embolism (PE) in geriatric patients.
Methods
The emergency admissions of the patients aged 65 and over with suspected PE during 2018 were reviewed retrospectively. The demographic characteristics, laboratory tests and radiologic findings of computed tomography pulmonary angiogram (CTPA) or single photon emission computed tomography ventilation/perfusion scintigraphy (V/Q) were recorded. The characteristics of the patients with PE were statistically compared with the patients without PE. The specificity and sensitivity for higher cut-off levels (age × 10–15) were presented.
Results
PE was detected in 39.2% ($n = 246$) of 628 patients aged 65 years and older included in the study. The multivariate analysis revealed that higher D-dimer level (OR = 1,00011; $p < 0.001$) and BUN level (OR = 1.025; $p = 0.013$) were independent risk factors for PE diagnosis in elderly patients. Diagnostic statistics for D-dimer cut-off levels selected from ROC analysis and calculated values as 10–15 times of age showed that if the D-dimer cut-off value used is chosen higher, lower sensitivity rates are obtained. Our results also indicated that the patients with malignancy, renal failure, central PE on CTPA and PE with high probability on SPECT VQ were presented with higher D-dimer values.
Conclusion
Our results do not support the use of higher D-dimer cut-off levels such as 15 times the age in geriatric population. The impact of the location of PE and comorbidities on the outcomes of these patients must be clarified for determining cut-offs with higher specificity.

1. Introduction

Venous thromboembolism ranks 3rd among emergency admissions due to acute cardiovascular events, and its frequency increases with age [1]. The patients admitted to the emergency department with suspected pulmonary embolism (PE) show non-specific clinical signs and symptoms. The most common symptoms can be listed as dyspnea, chest pain, presyncope, syncope and hemoptysis [2]. The investigations for PE in every patient admit with dyspnea and chest pain undoubtedly cause many unnecessary tests and is not a cost-effective algorithm [1]. The clinical parameters for predicting the risk of PE must be identified to select the patients who must undergo further investigation for PE.

D-dimer increases in the presence of acute thrombosis due to coagulation and activation of the fibrinolytic system. However, D-dimer is not specific for PE, it also increases in cancer, hospitalized patients, inflammatory diseases, and pregnancy [3,4]. Although D-dimer is a non-specific test, its negative predictive value is high. It is recommended to use D-dimer to exclude PE for scenarios with low and moderate clinical probability [5]. The previous studies showed that a normal D-dimer value together with the low clinical probability can exclude 30% of the patients with the suspicion of PE without further examination and the risk of developing VTE in their 3-month follow-up was <1% [6,7]. D-dimer increases with age, as comorbidities increase with age, the

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dimer also increases due to reasons other than thrombosis [8,9]. Therefore, it is recommended to use age-adjusted D-dimer (age × 10) cut-off value over 50 years of age [1,10,11].

In the Adjust-PE study evaluating patients over 75 years of age, the age-adjusted cut-off yielded a rise in specificity of dimer in mild/moderate clinical probability group from 6.5% to 30% compared to the conventional dimer level [10].

This study was conducted to evaluate the relationship of age-adjusted D-dimer value with other comorbidities and its success in excluding PE in patients with suspected PE who were admitted to the emergency department. It was aimed to evaluate the diagnostic sensitivity-specificity by increasing the age-corrected d-dimer cut-off values.

2. Methods

The study was conducted in the emergency service of an education and research hospital. The study comprised the patients aged 65 and over with suspected PE who admitted to the emergency room between January 1st and December 31st 2018. Patients who had a D-dimer>500 ng/mL and underwent computed tomography pulmonary angiogram (CTPA) or ventilation/perfusion scintigraphy (V/Q) were included in the study. The demographic characteristics (age, gender), comorbidities and clinical laboratory test results including white blood cell, lymphocyte and platelet counts, C-reactive protein (CRP), troponin-I, D-dimer, creatinine and blood urea nitrogen (BUN) were reviewed retrospectively from the hospital database. Lower extremity compression ultrasonography results were also recorded if available.

The patients who were younger than 65 years old, already receiving anticoagulant treatment for any other reason (such as atrial fibrillation, stroke, etc.), or had recurrent PE, were excluded.

D-dimer was measured with coagulation method at The Sysmex Coagulation System-2500 (CS-2500, Siemens, UK).

All patients were imaged either with scintigraphy scanning system (Siemens E Cam signature SPECT, USA) or a multi-detector CT scanner (Ingenuity CT Core 128; Philips Medical Systems, Cleveland, Ohio, USA) with 128 detector rows. According to the results of CTPA or V/Q, the patients were divided into two groups as with and without PE. Patients who were reported as medium-high risk PE in V/Q evaluations were accepted as PE. In CT angiography examination the PE in subsegmental, segmental and main pulmonary arteries were reported as PE.

Ethical approval for this study was obtained from the local ethics committee in 2018. Informed consent was not obtained from the patients due to retrospective design. The study was conducted in accordance with the principles of the World Medical Association (WMA) Declaration of Helsinki.

2.1. Statistical method

Statistical analysis of was performed with SPSS for Windows, 16.0 program. Shapiro-Wilk test was used for normality analysis of continuous data and the data with p value of >0.05 was accepted as normally distributed. Normally distributed parameters are expressed as mean ± standard deviation, non-normally distributed parameters are expressed as median with interquartile range. Mann Whitney-*U* test was used to compare the medians whereas independent samples-*t*-test was used to evaluate the differences in means between two independent groups. For the comparison of the medians of multiple independent groups, The Kruskal Wallis test was used. To compare the frequency distribution of ordinal data between groups, Pearson's Chi-Square test was performed. Diagnostic statistics (sensitivity, specificity, negative predictive value, positive predictive value, negative likelihood ratio, positive likelihood ratio) were calculated through a conventional two-by-two (2 × 2) table. Correlation analysis of non-normally distributed data was performed with Spearman correlation test. To assess independent relation with PE, a multiple logistic regression analysis was conducted. A receiver operating characteristics (ROC) analysis was used to determine the optimal value of D- dimer for the diagnosis of PE. The AUC (area under the curve) was used to quantify the variables' ability to predict diagnosis of PE. A value of $p < 0.05$ was used for statistical significance.

3. Results

The data of 628 patients 54.1% of whom were female ($n = 340$) were reviewed retrospectively. In terms of age groups, the patients aged between 65 and 74 comprised 50.5% of the total ($n = 317$), those 75–84 years 40% ($n = 251$), those over 85 years was as 9.6% ($n = 60$). Although D-dimer level was above the 500 ng/mL cut-off value in all patients, 39.2% of this geriatric population ($n = 246$) were diagnosed with PE. Deep vein thrombosis was detected in 34 (11.3%) of 300 patients who underwent Doppler USG. PE was diagnosed in 32.8% of 460 patients ($n = 151$) for whom CTPA was performed. As to location of PE, most of the patients had peripheral embolism. Segmental or subsegmental arteries were involved in 145 patients. Main vessels were occluded in only 6 patients. V/Q resulted in low probability for PE in 39.3% of 168 patients ($n = 66$) and normal in 4.2% ($n = 7$). 36.3% of the patients showed intermediate probability ($n = 61$) and 20.2% had high probability for PE ($n = 34$). 246 patients with embolism detected on CT angiography and evaluated as medium-high probability with V/Q were recorded as PE.

The demographical and clinical characteristics of the patients were compared between the groups according to the presence or absence of PE. The gender distribution was homogeneous between the two groups. However, PE group was slightly older than non-PE group which was statistically significant. Patients with diagnosis of PE had higher prevalence of heart failure and renal failure. However other diseases including diabetes mellitus, asthma, chronic obstructive pulmonary disease, atrial fibrillation, coronary artery disease, hypertension, hyperlipidemia, active cancer or dementia were seen to be distributed homogeneously between the two groups (Table 1).

Table 1
Demographic features and laboratory.

Parameters	PTE		*p*-value
	No	Yes	
	$n = 382$ (60.8%)	$n = 246$ (39.2%)	
Female gender- *n* (%)	214 (56.0)	126 (51.2)	0.239*
Male gender- *n* (%)	168 (44.0)	120 (48.8)	
Age (year)- med (IQR)	74 (69–79)	75 (70–80)	0.021**
Asthma- *n* (%)	30 (7.9)	12 (4.9)	0.145*
COPD- *n* (%)	165 (43.2)	116 (47.2)	0.330*
AF- *n* (%)	22 (5.8)	19 (7.7)	0.331*
CHF - *n* (%)	58 (15.2)	56 (22.8)	0.016*
CAD - *n* (%)	87 (22.8)	47 (19.1)	0.273*
DM - *n* (%)	105 (27.5)	66 (26.8)	0.857*
HT - *n* (%)	219 (57.3)	159 (64.6)	0.068*
HLP- *n* (%)	47 (12.3)	22 (8.9)	0.189*
Ca - *n* (%)	29 (7.6)	19 (7.7)	0.952*
CVD - *n* (%)	8 (2.1)	4 (1.6)	0.676*
Dementia - *n* (%)	2 (0.5)	5 (2.0)	0.079*
CKF or AKF - *n* (%)	13 (3.4)	18 (7.3)	0.027*
D-dimer- med (IQR) (ng/mL)	1515 (1050–2810)	2260 (1460–4680)	<0.001**
Cre- med (IQR)(mg/dL)	0.89 (0.78–1.09)	1.01 (0.83–1.32)	<0.001**
BUN- med (IQR) (mg/dL)	19 (15–24)	21 (16–29)	<0.001**
CRP- med (IQR) (mg/L)	13 (5–45)	23 (9–60)	0.001**
WBC- med (IQR) ($\times 10^3/\mu L$)	8180 (6660–10,760)	8600 (6930–11,000)	0.238**
Lymph- med (IQR) ($\times 10^3/\mu L$)	1690 (1220–2370)	1550 (1200−2120)	0.050**
PLT- med (IQR) ($\times 10^3/\mu L$)	240 (194–301)	227 (194–282)	0.216**

* Chi-square test.
** Mann Whitney-U test.

Table 2
Multiple logistic regression analysis (PTE diagnosis).

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Gender(1)	−0.103	0.201	0.265	1	0.607	0.902	0.609	1.337
	Age	0.019	0.014	1.777	1	0.183	1.019	0.991	1.047
	Asthma(1)	−0.315	0.391	0.652	1	0.419	0.729	0.339	1.569
	CHF(1)	0.413	0.239	2.982	1	0.084	1.512	0.946	2.417
	HT(1)	0.248	0.198	1.579	1	0.209	1.282	0.870	1.888
	Dementia(1)	1.033	0.941	1.205	1	0.272	2.810	0.444	17.781
	CKForAKF(1)	−0.037	0.464	0.006	1	0.937	0.964	0.388	2.393
	Dimer(ng/mL)	0.000	0.000	15.786	1	0.000	1.000	1.000	1.000
	BUN(mg/dL)	0.025	0.010	6.169	1	0.013	1.025	1.005	1.045
	CRP(mg/L)	0.001	0.002	0.552	1	0.458	1.001	0.998	1.004
	WBC ($\times 10^3/\mu L$)	0.000	0.000	0.182	1	0.670	1.000	1.000	1.000
	Lymph ($\times 10^3/\mu L$)	−0.002	0.002	0.984	1	0.321	0.998	0.995	1.002
	PLT ($\times 10^3/\mu L$)	0.000	0.001	0.007	1	0.932	1.000	0.998	1.002
	Constant	−2.121	1.228	2.981	1	0.084	0.120		

[a] Variable(s) entered on step 1: Gender, Age, Asthma, CHF, HT, Dementia, CKForAKF, Dimer, BUN, CRP, WBC, Lymph, PLT.

As expected, the median of D-dimer was found to be significantly higher in the PE group (1515 ng/mL vs 2260 ng/mL). Besides, the patients with PE had higher levels of creatinine, BUN and CRP (Table 1).

The multivariate analysis for the diagnosis of PE revealed that higher D-dimer level (OR = 1.00011; $p < 0.001$) and BUN level (OR = 1.025; $p = 0.013$) were independent risk factors. (Table 2). In the ROC analysis performed with the D-dimer level, the area under the ROC curve was calculated as 0.652 ($p < 0.001$) (Fig. 1). Diagnostic statistics for cut-off levels selected as a result of this analysis and calculated values as 10–15 times of patient age are given in Table 3. In addition, when the patients were analyzed separately by age groups, the areas under the ROC curve for D-dimer level were calculated as 0.642/0.663/0.642, respectively ($p < 0.001/p < 0.001/p = 0.059$; respectively). For BUN, the area under the curve in the ROC analysis was calculated as 0.585 ($p < 0.001$).

D-dimer levels were not found to be statistically different between the age groups (Table 4). However, the analysis of PE cases showed that patients with malignancy (2280 vs 1715 ng/mL; $p = 0.014$) or renal failure (2780 vs 1720 ng/mL; $p = 0.016$) had higher dimer level; oppositely patients with diabetes mellitus had lower D-dimer levels (1870 vs 1600 ng/mL; $p = 0.027$). No statistical relationship was found between other comorbid diseases and D-dimer. Correlation analysis of D-dimer level with age, creatinine, BUN and CRP was performed. In this analysis, D-dimer was not significantly correlated with any parameter (rho <0.2 for all).

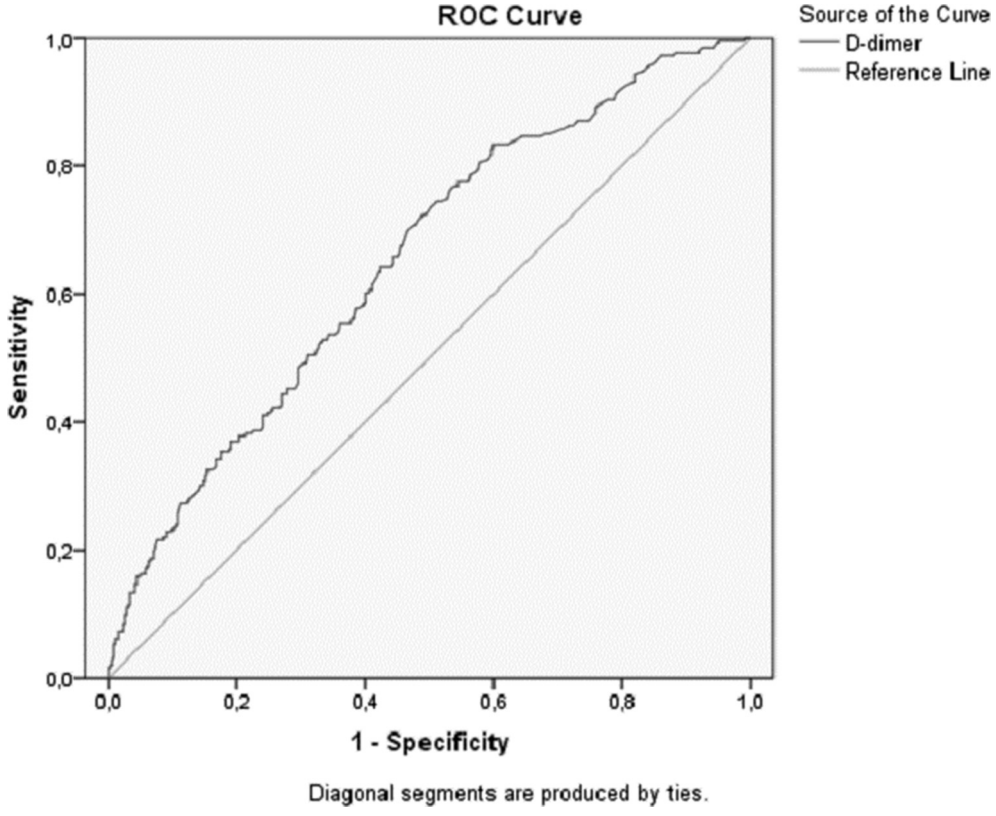

Fig. 1. ROC curve (D-dimer).

Table 3
D-Dimer cut-off levels adjusted with age.

D-Dimer cut-off (ng/mL)	Sensitivity- % (95% CI)	Specificity- % (95% CI)	NPV- % (%95 CI)	PPV- % (%95 CI)	+LR (95% CI)	−LR (95% CI)
695	99.59 (97.76–99.99)	4.97 (3.02–7.66)	95.00 (71.91–99.30)	40.30 (39.71–40.88)	1.05 (1.02–1.07)	0.08 (0.01–0.61)
905	95.93 (92.65–98.03)	14.92 (11.50–18.90)	85.07 (74.80–91.63)	42.07 (40.87–43.27)	1.13 (1.07–1.18)	0.27 (0.14–0.52)
1005	90.24 (85.83–93.65)	22.25 (18.18–26.76)	77.98 (69.86–84.40)	42.77 (41.13–44.44)	1.16 (1.08–1.24)	0.44 (0.29–0.67)
1275	83.33 (78.08–87.77)	40.05 (35.10–45.16)	78.87 (73.34–83.51)	47.24 (44.77–49.71)	1.39 (1.26–1.54)	0.42 (0.31–0.56)
AgeX10	99.19 (97.09–99.90)	5.24 (3.23–7.97)	90.91 (70.22–97.70)	40.26 (39.64–40.89)	1.05 (1.02–1.07)	0.16 (0.04–0.66)
AgeX11	97.15 (94.23–98.85)	9.95 (7.14–13.40)	84.44 (71.13–92.29)	40.99 (40.04–41.96)	1.08 (1.04–1.12)	0.29 (0.13–0.63)
AgeX12	95.53 (92.14–97.75)	14.14 (10.80–18.04)	83.08 (72.37–90.20)	41.74 (40.56–42.93)	1.11 (1.06–1.17)	0.32 (0.17–0.59)
AgeX13	92.68 (88.68–95.61)	19.11 (15.29–23.42)	80.22 (71.30–86.88)	42.46 (41.00–43.93)	1.15 (1.08–1.22)	0.38 (0.23–0.63)
AgeX14	88.21 (83.51–91.96)	24.35 (20.12–28.97)	76.23 (68.58–82.49)	42.89 (41.11–44.68)	1.17 (1.08–1.25)	0.48 (0.33–0.71)
AgeX15	85.37 (80.32–89.54)	30.10 (25.54–34-98)	76.16 (69.49–81.75)	44.03 (41.97–46.10)	1.22 (1.12–1.33)	0.49 (0.35–0.68)

LR: Likelihood ratio, NPV: Negative predictive value, PPV: Positive predictive value.

Table 4
D-dimer values in age groups.

		Age groups						*p*-value*
		65–74 age		75–84 age		>84 age		
		Median (IQR)	Min-max	Median (IQR)	Min-max	Median (IQR)	Min-max	
D-dimer (ng/mL)	PTE (−)	1480 (1050–2870)	500–22,440	1580 (1070–2730)	530–24,000	1435 (1050–3580)	550–7810	0.828
	PTE (+)	2110 (1500–4230)	520–23,320	2345 (1455–5170)	790–35,200	2390 (1460–4060)	920–25,010	0.572
	Total	1670 (1130–3270)	500–23,320	1980 (1160–3960)	530–35,200	1915 (1265–3755)	550–25,010	0.300

* Kruskal Wallis test.

4. Discussion

Several studies comparing conventional (>500 ng/mL) and age-adjusted (such as age × 10) cut-offs for D-dimer available in the literature. In the study of Broen et al. it was stated that the NPV for age-adjusted cut-off was 97–100% while it was found to be 89.7% for the standard cut-off [12]. On the other hand, Lapner et al. found no benefit of using age-adjusted cut-off in diagnosis of PE despite its non-inferiority to conventional cut-off [13]. In another cohort, it was also claimed that age-adjusted cut-off may cause a small but significant increase in missing the diagnosis of PE [14]. In this study, we aimed to compare different cut-offs and to show the factors causing high-dimer levels in geriatric population.

It is well-known that D-dimer may also increase due to several comorbidities [8]. The high frequency of comorbidities in geriatric population raises the question of whether "age × 10" is sufficient for age-adjusted cut-off. It is recommended to use D-dimer for the patients who are considered to have low pre-test probability at admission to the emergency department due its high NPV. This approach reduces unnecessary imaging tests, radiation exposure and contrast material uptake. In our study, we investigated if higher coefficients for age-adjusted cut off (age × 11, age × , age × 13, age × 14, age × 15) could serve as a better diagnostic tool for PE in geriatric patients. We also analyzed higher constant cut-offs using ROC curve analysis. Our results showed that higher coefficient and constant cut offs yielded a better specificity increases at a great expense of sensitivity. For diseases with high morbidity and mortality, a diagnostic test should have high sensitivity. The analysis of our data underlined the superiority of age × 10 cut-off in geriatric population in terms of sensitivity. In a meta-analysis, when conventional cut-off was compared with age-adjusted cut off, no significant difference was found in sensitivity, but the specificity was found to be 67% in <50 years of age and 15% in>80 years of age in the conventional group [15].

In a similar retrospective study, which evaluated age × 8, age × 9, and age × 10 cut-offs for 3117 patients, it was stated that due to the higher sensitivity conventional cut-off and the inverse ratio between the sensitivity and the coefficient, age-adjusted cut-off is unacceptable [16]. Our results showed that sensitivity of age × 10 decreased from 99.2% to 85.7% for age × 15 cut-off. To avoid false negative results, it is not recommended to prefer higher coefficients for geriatric population. Despite the significant difference in D-Dimer for the patients with PE, the medians of D-Dimer in age groups of 65–75 years old, 75–85 years old and > 85 years old were found to be statistically same. Supporting our previous finding, this result proves that there is not a further increase in the dimer with age in elderly patients.

The analysis of the relationship between the comorbidities and PE revealed that chronic heart disease and kidney disease were more prevalent in PE patients. As expected, creatine and BUN were also significantly higher in PE group. When the correlation between D-dimer and comorbidities was examined, it was seen that the D-dimer increased significantly in malignancy and renal failure and decreased in diabetes mellitus (DM). These results suggest whether different cut-off values can be used in the presence of comorbidities. The effect of comorbidities on 30-day mortality in PE has been demonstrated with pulmonary severity index [1]. However, the effect of comorbidities on diagnostic processes is an important issue that needs to be highlighted. Nevertheless, in this study, the effect of comorbidities on the diagnosis of PE could not be demonstrated in multivariate analysis. This result may be a consequence of the relationship between comorbidities and the D-dimer. Evaluation of pre-test probability by Wells and Geneva scores include only malignancy [1].

The use of contrast material for CTPA in the geriatric patients with multiple comorbidities poses an unnecessary risk for the patients with false positive results of D-dimer. As recommended in current guidelines with strong evidence, PE can be excluded by combining D-dimer result with the assessment of pretest clinical probability [1,6,17]. As a limitation of our study, data on assessment of pretest probability could not be reached due to retrospective design. Prospective studies are needed in which pretest probability is evaluated to demonstrate the role of D-dimer in further investigations for PE in geriatric patients. The comparison with conventional cut-off could not be made, either because D- dimer was higher than age × 10 cut-off in 97.8% of the patients and above 500 ng/mL for all. Another limitation of our study is that the drugs used by the patients were not recorded although some drugs are known to affect the dimer level [18].

5. Conclusion

In conclusion, the use of age-adjusted D-dimer reduces the need for further examinations, but despite the increase in D-dimer with age, there is no evidence to suggest the use of higher dimer cut-off values. Studies evaluating the effect of comorbidities on diagnostic processes and the clinical significance of peripheral embolism in the geriatric group are needed.

Declaration of competing interest

The authors report no conflict of interest.

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Author contributions

MUŞ, SŞD, ZSÖ, AŞ designed and conceived this study and wrote the manuscript. AŞ performed the statistical analysis. MUŞ and SŞD provided professional suggestions and wrote the manuscript. All authors read and approved the final manuscript.

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