Comparison of normal D-dimer in different category in patient with pulmonary embolism

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Abstract
Aim: Quantitative D-dimer is used to exclude pulmonary embolism in patients with low clinical probability. In this study, we aimed to compare quantitative d-dimer, age-adjusted D-dimer, and age-adjusted D-dimer suggested by the American College of Emergency Physicians (ACEP).

Materials and Methods: Emergency service patients above the age of 18, whose D-dimer values were tested due to the suspicion of pulmonary thromboembolism were evaluated retrospectively. Quantitative d-dimer level, age-adjusted D-dimer, and age-adjusted D-dimer suggested by the ACEP levels were compared with patient data. SPSS (Statistical Package for Social Sciences) Windows 20.0 software was used for statistical analysis of all data obtained.

Results: Three different categories of D-dimer values were compared. According to ACEP, the D-dimer value skipped the least number of PE diagnosis compared to the other values and it was found to be the most significant in determining PE. sPESI was not significant in predicting mortality in PE patients.

Discussion: D-Dimer values vary according to the devices and kits used. Today, D-dimer values are used in many clinics to exclude PE. These include the quantitative d-dimer, age-adjusted d-dimer, and the age-adjusted d-dimer suggested by ACEP. It is identified that the cut-off value of d-dimer, calculated according to age, reduced the need for imaging tests significantly compared to quantitative d-dimer. A systemic meta-analysis found that the d-dimer test results calculated for age reduced the need for imaging by 5% compared to normal d-dimer test results when combined with Wells score.

Conclusion: Recommended by ACEP age-adjusted D-Dimer may be preferred for the evaluation of pulmonary embolism patients.

Keywords
Pulmonary embolism; D-Dimer; Age-Adjusted
Introduction
The clinical presentation can vary and the diagnosis of pulmonary embolism (PE) can be difficult to rule out on the basis of the clinical presentation alone, and it is estimated that 25% of patients who present with symptoms and signs of PE actually have the condition [1]. Many attempts have therefore been made to identify patients with suspected PE in whom the disease can be ruled out based on the combination of clinical decision rules and D-dimer testing without additional imaging. Frequently used clinical decision rules in the diagnostic management of PE include the extensively validated Wells and revised Geneva rules [2,3].

In cases with negative D-dimer test results, together with low or no clinical probability, the venous thromboembolism (VTE) risk is quite low, and advanced, specific imaging methods are not necessary. In prospective study that have supported this suggestion, the risk of VTE at a 3-month interval has been reported to be between 0-0.5% [4]. In cases having high or intermediate probability, the D-dimer test becomes less sensitive, and imaging tests for VTE are recommended [5]. In patients with good hemodynamics, planning should be done according to the preliminary assessment score. D-dimer test has no place because of the false positive results; if the possibility of PE is high in clinical evaluation or the risk is high according to the scoring, direct pulmonary CT angiography is recommended [6]. If a patient is at non-high risk of PE according to one of these rules, a D-dimer below 500 μg/L can safely rule out the diagnosis in about 20% to 30% of patients without additional imaging. An important next step to improve the diagnostic management of PE was the derivation of an age-adjusted D-dimer positivity threshold, which is defined as a patient's age times 10 μg/L in those older than 50 years [7]. In February 2018, the American College of Emergency Physicians (ACEP) recommended the use of age-adjusted D-dimer values in appropriate patients over 50 years old [4]. By applying this threshold, the proportion of patients in whom imaging can be safely withheld is increased by another 5% to 6%. Among patients in a large general hospital who died from pulmonary embolism, the diagnosis (confirmed at necropsy) was unsuspected in 70% of patients [8]. Ninety three percent of these deaths occurred within 2.5 hours of the onset of symptoms, emphasising the importance of clinical suspicion and timely initiation of diagnostic testing and subsequent treatment.

Material and Methods

Study design
Emergency services patients older than 18 years of age whose D-Dimer values were tested with the suspicion of pulmonary thromboembolism were retrospectively screened.

Study Settings and Population
This study was planned in the emergency department of a training and research hospital with a capacity of 1100 beds and approximately 260 thousand emergency applications. The diagnosis of patients with pulmonary embolism by emergency physicians and chest disease specialist was confirmed with CT pulmonary angiography via the detection of filling defect by specialist radiologist. Patients with known renal or blood disease, cardiovascular disease, patients diagnosed with pulmonary embolism prior to admission to the emergency room with an ongoing treatment, pregnant women, those who underwent cardiopulmonary resuscitation, patients with incomplete data and patients under 18 years of age were excluded from the study. Patient data were obtained from hospital automation system and patient record archive.

Study Protocol
Ethics committee approval was obtained before patient data were collected. Patients with pulmonary embolism in the ICD diagnostic code, admitted to the emergency department were retrospectively screened via electronic data base and 91 patients were identified. Thirty-nine patients who met the inclusion criteria were included in the study. The patients’ gender, age, presentation at the admission, duration of symptoms, vital signs, wells, revised genova and sPESI scores, 3-month mortality, quantitative d-dimer, age-adjusted d-dimer and age-adjusted d-dimer suggested by ACEP were recorded. Gender, presentation at the admission, admission time (<24 hours, >24 hours), MAP positivity (>90/60 mmHg), echocardiography (ECHO) findings (positive for normal or pulmonary embolism), the presence of mortality, patient’s age being over or under 65 and saturation (90% and above) were compared according to quantitative d-dimer positivity, age-adjusted d-dimer positivity and age-adjusted d-dimer positivity suggested by ACEP, which will be referred as three different categories of D-dimer evaluation.

Measurements
The D-Dimer was measured quantitatively with the ACL TOP 500 CTS-IL-Coagulation Analyzer and <243 μg/l was considered as a negative value. The d-dimer value for patients over 50 was calculated according to ACEP formula ((age × 5) – 20), and according to age-adjusted d-dimer formula (age× 10).

Statistical analysis
SPSS (Statistical Package for Social Sciences) Windows 20.0 software was used for statistical analysis of all data obtained. All data are summarized in the tables during the evaluation. Frequency tests for frequency, mean and standard deviation values of the obtained data, the Mann-Whitney U test to compare the mean values of the obtained data, the Pearson Chi-Square (and exact test when necessary) to compare the nonparametric data were used. Only results with confidence interval above 95% and p<0.05 were accepted as significant.

Results
Characteristics of study subjects
Of the 39 patients with PE, 46% were women and 53% were men. The mean age was 57.48 ± 11.52 (24-93) years.

Main results
Three different categories of D-dimer values were compared. According to ACEP, the D-dimer value skipped the least number of PE diagnoses compared to the other values and it was found to be the most significant in determining PE (Table 1).

In our study, vital signs and PE scores of the patients were calculated according to three different categories of D-dimer evaluation, and the relationship among them was evaluated. While the specific score was found to be significant according to quantitative D-dimer (p<0.05), the PERC score was found to
Three different categories of D-dimer evaluation

Table 1.

| Parameter                  | Quantitative d-dimer | Age-adjusted d-dimer | Age-adjusted d-dimer suggested by ACEP |
|----------------------------|----------------------|----------------------|----------------------------------------|
|                            | Positive (n=26)      | Negative (n=13)      | Positive (n=24)                        | Negative (n=15) | Positive (n=33) | Negative (n=6) | p*       |
| Age                        | 57,58 ± 5,41         | 57,69 ± 18,96        | 57,33 ± 5,63                          | 57,73 ± 17,55  | .918            | 59,54 ± 10,11 | .007     |
| MAP                        | 90,84 ± 14,72        | 92,82 ± 21,69        | 91,47 ± 14,66                         | 91,55 ± 20,97  | .988            | 91,33 ± 17,39 | .886     |
| Systolic                   | 119,84 ± 10,38       | 126,30 ± 29,17       | 120,66 ± 19,09                        | 124,13 ± 28,62 | .652            | 121,81 ± 22,76| .009     |
| Diastolic                  | 76,34 ± 13,89        | 76,07 ± 18,88        | 76,87 ± 14,04                         | 75,26 ± 18,01  | .757            | 76,09 ± 16,10 | .878     |
| Saturation                 | 91,53 ± 6,15         | 91,23 ± 9,13         | 91,58 ± 6,40                          | 91,20 ± 8,46   | .873            | 91,00 ± 6,88  | .380     |
| Pulse                      | 91,48 ± 17,98        | 95,84 ± 24,94        | 90,91 ± 18,58                         | 96,13 ± 23,22  | .448            | 90,87 ± 17,58 | .145     |
| Wells                      | 3,19 ± 1,64          | 3,84 ± 3,50          | 3,29 ± 1,56                           | 3,60 ± 1,72    | .701            | 3,18 ± 2,04  | .166     |
| Revize Genova              | 3,96 ± 2,64          | 3,46 ± 1,71          | 3,01 ± 2,71                           | 3,60 ± 1,72    | .690            | 3,00 ± 2,50  | .487     |
| Spesi                      | 0,88 ± 0,86          | 1,84 ± 1,51          | 0,91 ± 0,88                           | 1,66 ± 1,49    | .056            | 1,09 ± 1,04  | .165     |
| Perc                       | 1,72 ± 0,97          | 2,61 ± 1,44          | 0,30 ± 1,73                           | 2,46 ± 1,40    | .072            | 1,84 ± 1,05  | .031     |
| Gender                     |                      |                      |                                        |                |                |                |          |
| Female                     | 11 (61,1)            | 7 (58,9)             | 9 (50,0)                              | 9 (50,0)       | .170            | 15 (85,3)   | .316     |
| Male                       | 15 (71,4)            | 6 (28,6)             | 15 (71,4)                             | 6 (28,6)       | 18 (85,7)       | 3 (14,3)    | .100     |
| Dyspnea                    | 16 (64,0)            | 9 (36,0)             | 15 (60,0)                             | 10 (40,0)      | .792            | 21 (84,0)   | 4 (16,0)  | .008     |
| Duration                   | 9 (56,2)             | 7 (43,8)             | 8 (50,0)                              | 8 (50,0)       | .217            | 11 (68,8)   | 5 (31,2)  | .053     |
| >24 saat                   | 17 (73,9)            | 6 (26,1)             | 16 (69,6)                             | 7 (30,4)       | 22 (95,7)       | 1 (43)      | .052     |
| MAP positive               | 24 (88,6)            | 11 (31,4)            | 22 (82,9)                             | 13 (37,1)      | .631            | 30 (85,7)   | 5 (14,3)  | .145     |
| EKHO finding               | 20 (87,0)            | 3 (13,0)             | 18 (73,8)                             | 5 (21,7)       | 0,010           | 21 (91,3)   | 2 (8,7)   | .205     |
| Normal                     | 6 (37,5)             | 10 (62,5)            | 6 (37,5)                              | 10 (62,5)      | 12 (75,0)       | 4 (25,0)    |          |
| mortality                  | 1 (25,0)             | 3 (75,0)             | 0 (0,0)                               | 4 (100,0)      | 0,017           | 4 (100,0)   | 0,001    | 1,000    |
| <65                        | 24 (75,0)            | 8 (25,0)             | 22 (68,8)                             | 10 (31,2)      | .085            | 26 (81,2)   | 6 (18,8)  | .568     |
| >65                        | 2 (28,6)             | 5 (71,4)             | 2 (28,6)                              | 5 (71,4)       | 7 (100,0)       | 0,000       |          |
| Sat. ≥90                   | 18 (64,3)            | 10 (35,7)            | 16 (57,1)                             | 12 (42,9)      | .477            | 23 (82,1)   | 5 (17,9)  | .655     |
| Sat. <90                   | 8 (72,7)             | 3 (27,3)             | 8 (72,7)                              | 3 (27,3)       | 10 (90,9)       | 1 (9,1)     |          |

Table 2. Statistical significance and distribution of data according to three categories of D-dimer values

Comparison of normal D-dimer level in patients with pulmonary embolism

Discussion

Various radiological and laboratory tests are used to diagnose PE, which vary in accuracy, have different costs, and some are associated with different levels of risk because they are invasive and others are not invasive [9]. D-Dimer is one of the non-invasive tests and D-Dimer values vary according to the devices and kits used [10].

Today, D-dimer values are used in many clinics to exclude PE. These include the quantitative d-dimer, age-adjusted d-dimer, and the age-adjusted d-dimer suggested by ACEP. There are many studies investigating the sensitivity and negative predictive values of these tests to exclude PE. Carrier et al. reported that there was a very low probability (0.41%) of occurrence of PE in the 3 month-follow-up of low- and medium-risk patients with negative d-dimer results [11].

Legnani et al.’s study showed 100% sensitivity and negative predictive value in PE exclusion using the same d-dimer test [12]. In a meta-analysis study conducted by Parks et al., only age-adjusted d-dimer calculation revealed that PE exclusion sensitivity was increased from 64.9% to 74.7% compared to the quantitative d-dimer value. The same study compared age-adjusted d-dimer with age-adjusted d-dimer suggested by ACEP and it was shown that the formula showed a tendency towards more sensitivity and negative predictive value while the test properties showed the potential to miss lower PEs [13]. It is identified that the cut-off value of d-dimer calculated to ACEP cannot be captured (p = 0.205). D-dimer calculation by age does not predict mortality, when D-dimer values are compared with mortality (p = 0.017) (Table 2).
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according to age, reduced the need for imaging tests significantly compared to quantitative d-dimer. A systemic meta-analysis found that the quantitative d-dimer test results calculated for age, reduced the need for imaging by 5% compared to normal d-dimer test results when combined with Wells score [14]. In our study, when three different categories of D-dimer evaluation were compared in PE determination, it was seen that D-dimer positivity suggested by ACEP was the most significant calculation in determining PE. Wells and Revised Geneva Scores are among the most frequently used scoring systems for PE detection and exclusion. In the literature, these scoring systems were frequently compared among themselves in the detection of PE. In a meta-analysis, it was found that Wells score was better than Revised Geneva score in PE exclusion [15]. In another study, Wells score was found to be more successful in detecting PE than Revised Geneva Score in elderly patients; the use of d-dimer test together was shown to increase success rates in two scores [16]. Cheng et al. reported that using Wells score with D-dimer test was more successful than Revised Geneva score with D-dimer test to determine the success of PE detection [17]. In a study by Harringa et al., it was found that there was no difference between the prevalence of PE when comparing low- and medium-risk patients identified using Wells and Revised Geneva Scores; and that the negative d-dimer test alone had a 100% sensitivity and negative predictive value (even for high-risk patients), regardless of the risk classification for PE exclusion alone [18].

In Di Marca et al.’s study in high-risk in-patients, Wells was found to be more successful than the Revised Geneva Score in the detection of PE [19]. However, a study by Girarda et al. showed that Wells and Revised Geneva Scores were not successful in determining PE in critically ill or high-risk patients for PE [20]. In our study, there was no significant difference between Wells score and Revised Geneva score calculated among patients, and none of them were found to be significant in PE detection and predicting mortality. There was also no difference among three different categories of D-dimer evaluation.

PERC criteria are still used today by some clinics to exclude PE. In the study performed by Singh et al., PERC rule was stated to be used safely in clinically low probability population environments because of high sensitivity and low negative probability ratio [21]. In addition, some studies reported that the PERC criteria had a very low sensitivity for PE alone, and was not suitable for use because it requires scoring systems and additional laboratory tests [22,23]. In our study, the use of PERC criterion with quantitative d-dimer positivity and d-dimer positivity according to ACEP increased the success in PE detection, whereas there was no significant difference in use with d-dimer value according to age. sPESI score has been and is being investigated in many studies in the literature for PE and its effectiveness in determining mortality or serious vital effects. In the study conducted by Tamizifar et al. it was stated that sPESI score accurately predicted the mortality rate for low-risk patients, but could not predict prognosis significantly in high-risk patients [24]. Kliç et al.’s study indicated that sPESI was significant in determining mortality for PE in the short and long term, and that no additional laboratory and imaging tests were required at low sPESI values [25]. In our study, the sPESI score was found to be high in only quantitative d-dimer negative cases. In addition, it was not significant in determining mortality in PE patients.

Conclusion

Unnecessary imaging in PE leads to a waste of time, economic losses, and unnecessary exposure of patients to the harmful effects of radiation. While attempting to cope with these losses, many early diagnosis tests or scoring systems are being investigated in order to detect or exclude PE. In our study, the evaluation of age-adjusted d-dimer suggested by ACEP is considered to be an appropriate method in the evaluation of PE.

Limitations

The greatest limitation to our study is the low number of PE patients undergoing D-dimer examination, data losses and not being able to track patients due to referrals to other hospitals.

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