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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

Can Previous D-Dimer Levels Predict Future Elevations in Emergency Department Patients?

Acil Servis Hastalarında Önceki D-Dimer Seviyeleri Gelecekteki Yükselmeleri Tahmin Edebilir mi?

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ABSTRACT

Aim: Excluding or confirming pulmonary embolism in the emergency department requires an effective and rapid strategy. The D-dimer cut-off value adjusted for age and clinical probability has been determined in prospective studies, allowing safe exclusion in more patients. However, no recommendations exist for predicting new test results based on the previous D-dimer values. This study aimed to investigate the risk of high d-dimer test results in patients undergoing D-dimer testing in the emergency department, based on patient characteristics and previous test results.

Material and Methods: This retrospective study used data from patients who underwent D-dimer testing between January 1, 2009, and December 31, 2019, in a tertiary hospital ED. Patients with an interval between two D-dimer results of 30 days to 1095 days were included in the study. The D-dimer value to be estimated was expressed as the index D-dimer value, and the D-dimer value used to estimate this value was expressed as the previous D-dimer value. The upper limit value of D-dimer was determined according to the patient's age at the test date. Binary logistic regression analysis was used in the analysis of factors associated with high D-dimer values. All analyses were performed at a 95% confidence interval. p-values below 0.05 were considered significant.

Results: The median age of the 358 patients included in the study was 61 years, and 60.6% were female. If the previous D-dimer value was above the normal value, the odds of an elevated index value increased 4.170-fold. In addition, If the previous D-dimer value exceeded 1,000 µg/L FEU, the odds increased 4.704-fold.

Conclusion: In patients with previously elevated D-dimer values within the past three years, the new D-dimer value is likely to be high. In such cases, performing advanced diagnostic tests instead of waiting for the test results may save time.

Keywords: D-dimer, emergency department, emergency medicine, pulmonary embolism, venous thromboembolism

ÖZ

Amaç: Acil serviste pulmoner emboliyi dışlamak veya doğrulamak etkili ve hızlı bir strateji gerektirir. Daha önceki prospektif çalışmalarda; yaş ve klinik olasılık için ayarlanmış D-dimer kesme değerleri belirlenmiştir ve daha fazla hastayı güvenli bir şekilde dışlamamızı sağlamıştır. Ancak, önceki test sonuçlarına dayanarak yeni test sonucu hakkında bir tahminde bulunma önerisi yoktur. Bu çalışma, acil serviste D-dimer test istemi yapılacak hastalarda, önceki test sonuçlarına ve hasta özelliklerine dayanarak, D-dimer test sonuçlarının yüksek çıkma riskini araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Bu çalışma, üçüncü basamak bir hastanenin acil servisinde 01.01.2009-31.12.2019 tarihleri arasında, D-dimer değerleri bakılan hastaların verileriyle retrospektif olarak yapılmıştır. İki D-dimer sonucu arasındaki süre 30 gün ile 1095 gün arasında olan hastalar çalışmaya dahil edildi. Hesaplanması gereken D-dimer değeri indeks D-dimer değeri olarak ifade edildi ve bu değeri tahmin etmek için kullanılan D-dimer değeri önceki D-dimer değeri olarak ifade edildi. D-dimerin üst sınır değeri hastanın test tarihindeki yaşına göre belirlendi. Yüksek D-dimer değerleriyle ilişkili faktörlerin analizinde ikili lojistik regresyon analizi kullanıldı. Tüm analizler %95 güven aralığında yapıldı. 0,05'in altındaki p değerleri anlamlı kabul edildi.

Bulgular: Çalışmaya dahil edilen 358 hastanın median yaşı 61 yıl olup, %60,6'sı kadındı. Önceki D-dimer değeri normal değerden yüksek ise, indeks D-dimer değerinin de yüksek olma olasılığı 4,170 kat daha fazla bulundu. Ayrıca, önceki D-dimer değeri 1.000 µg/L FEU'den yüksek ise, indeks D-dimer değerinin de yüksek olma olasılığı 4,704 kat daha fazla tespit edildi.

Sonuç: Son üç yıldır D-dimer değerleri sınır değerin üstünde olan hastalarda yeni D-dimer değerinin yüksek olma olasılığı yüksektir. Bu gibi durumlarda test sonuçlarını beklemek yerine ileri tanı testleri yapmak zamandan tasarruf sağlayabilir.

Anahtar Kelimeler: D-dimer, acil servis, acil tıp, pulmoner emboli, venöz tromboembolizm

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Introduction

D-dimer is a soluble fibrin product resulting from the breakdown of vascular thrombi via the fibrinolytic mechanism. This molecule is a biomarker of hemostatic abnormalities as well as an indicator of intravascular thrombosis. Therefore, it is used as a marker of coagulation and fibrinolysis activation in many clinical conditions (1). D-dimer values increase for many reasons (venous/arterial thrombosis, disseminated intravascular coagulation, inflammation, age, surgery, trauma/burn, aortic dissection, cancer, infection/sepsis, pregnancy, liver diseases, thrombolytic therapy, renal diseases, cardiovascular diseases) (2). However, elevated values are not diagnostic of any disease.

Excluding or confirming pulmonary embolism in emergency department (ED) patients presenting with shortness of breath and/or chest pain requires an effective and rapid strategy. The pulmonary embolism diagnostic algorithm is based on clinical risk scores, D-dimer measurement, and computed tomography pulmonary angiography (CTPA) imaging. The efficacy and reliability of this sequential diagnostic algorithm have been confirmed in large prospective studies (3,4). Additionally, D-dimer has been studied extensively to exclude the diagnosis of venous thromboembolism (VTE) and is routinely used for this indication (5). While D-dimer allows accurate exclusion of thromboembolic diseases, its positive predictive value is limited and is heavily influenced by age and comorbidities (6).

Many diseases and clinical features have been reported to affect D-dimer values. The most important of these are age, renal failure, presence of malignancy, and previous thromboembolic events (7-9). The D-dimer cut-off value adjusted for age and clinical probability has been determined in prospective studies, allowing us to safely exclude more patients (10-12). However, there is no recommendation to predict the new test result based on the previous test results. In our clinical experience, in patients whose previous D-dimer value was high for any reason, the new D-dimer value is also found to be elevated. In patients in the low-risk group, D-dimer is requested to exclude the diagnosis of pulmonary embolism, and most physicians do not estimate that the test result will be high, yet they still wait for new test outcomes. Waiting for test results due to diagnostic algorithms not only negatively impacts ED crowding but also causes a delay in the diagnosis of venous thromboembolism.

This study aimed to investigate the risk of high D-dimer test results in patients undergoing D-dimer testing in the ED, based on patient characteristics and previous test results.

Material and Methods

This retrospective study was conducted with data from patients whose D-dimer values were obtained between 01.01.2009 and 31.12.2019 in the ED of a tertiary hospital. Since it has been reported that D-dimer values increase in COVID-19 infection (13), the research was conducted with patients who applied prior to the COVID-19 pandemic. All D-dimer test results during the study period were obtained from the hospital electronic information system (HIS). Ethichal approval was obtained from the University of Health Sciences Tepecik Training and Research Hospital Ethics Committee (Decision No: 2023/06-37, dated July 13, 2023).

Patients with two or more D-dimer results recorded in HIS within the specified 11-year period were included in the study. Patients were excluded from the study if the interval between two D-dimer results was shorter than 30 days or longer than 1095 days. If a patient had more than two D-dimer results, only the last consecutive measurements were considered. The interval between d-dimer measurements is at the discretion of the researchers. We chose an interval that was neither excessively frequent nor infrequent. Demographic data of the patients and the presence of active malignancy were determined from HIS and recorded.

D-dimer levels were measured using latex particle-enhanced turbidimetric immunoassay method by Sysmex CS-2500™ automated blood coagulation analyzer. The D-dimer value to be estimated was expressed as the “index D-dimer value”, and the D-dimer value used to estimate this value was expressed as the “previous D-dimer value”. Cut-off values for D-dimer was defined according to the patient's age at the test date. In the literature, the upper limit value for D-dimer is accepted as 500 µg/L FEU for those under 50 years of age and as age×10 µg/L FEU for those over 50 years of age (10).

Statistical Analysis

Data were obtained from HIS in excel format. SPSS (v20; IBM, Armonk, NY) was used in the analysis of the obtained data. The distribution of the data was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. It was determined that the data did not follow a normal distribution. Therefore, qualitative data were expressed as frequency, quantitative data as median and interquartile range. Binary logistic regression analysis was used in the analysis of factors associated with high D-dimer values. All analyses were performed at a 95% confidence interval. p-values below 0.05 were considered significant.

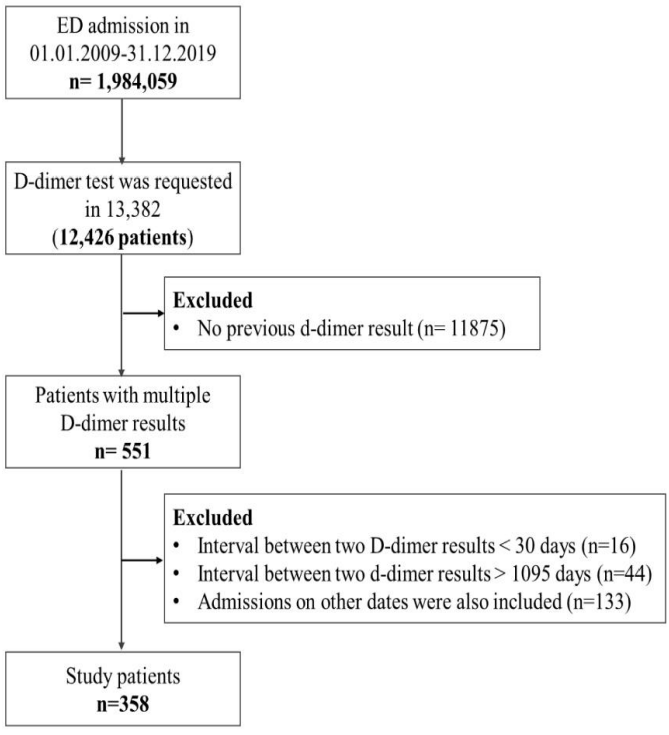

Figure 1. Patient Flow Diagram

Results

Of the 1,984,059 admissions to the ED in an 11-year period, D-dimer test was requested in 13,382 (0.67%) (12,426 patients). Of the 12,426 patients, 12,068 were excluded on the exclusion criteria (Figure 1). All analyses in this study were performed using data from the remaining 358 patients. The median age of the patients included in the study was 61 years, and 60.6% (217) were female. The median value of the index D-dimer test was 300 µg/L FEU. The patients' ages and D-dimer test results are shown in Table 1.

In 94 (26.3%) of the patients, the index D-dimer value was above the limit value determined according to age. Index D-dimer value was >1,000 µg/L FEU in 66 patients (18.4%). 90 (25.1%) of the patients, had the previous D-dimer value was above the limit value. The previous D-dimer value was >1,000 µg/L FEU in 56 patients (15.6%). The previous D-dimer value was obtained in 47.8% of patients within 1 year, 33% within 2 years, and 19.3% within 3 years.

When the index test was requested, 20 (5.6%) patients had malignancy. Factors associated with higher-than-normal levels of the index D-dimer test results are shown in Table 2.

Variables	Median value	(IQR; minimum-maximum)
Index D-dimer value (µg/L FEU)	330	(533; 30-16,504)
Patient age at the date of the index D-dimer test	61	(31;19-109)
Previous D-dimer value (µg/L FEU)	300	(499; 0-6,880)
Patient age at the date of the previous D-dimer test	60	(31;17-107)

Table 1. The ages and D-dimer test values of the patients
IQR: Interquartile Range.

Variables	p	OR	CI (%95)
Sex	0.802	0.940	0.580-1.524
Age	0.233	1.008	0.995-1.021
Malignancy	0.696	1.218	0.454-3.266
Previous D-dimer value > the limit value	<0.001	4.170	2.492-6.980
Previous D-dimer value >1,000 µg/L FEU	<0.001	4.704	2.593-8.533

Table 2. Binary logistic regression analyses for factors associated with high index D-dimer values
OR: Odds ratio, CI: confidence interval

Discussion

In this retrospective study, we found that D-dimer test was requested in 0.67% of ED visits. In 26.3% of the patients included in our study, the index D-dimer value was above the limit value determined by age, and in 25.1%, the previous D-dimer value was also above the limit value determined by age. In 18.4% of patients, the index D-dimer value was >1,000 µg/L FEU, and in 15.6%, the previous D-dimer value was also >1,000 µg/L FEU. If the previous D-dimer value was higher than the normal value, the odds of an elevated index value increased 4.170-fold. In addition, If the previous D-dimer value exceeded 1,000 µg/L FEU, the odds increased 4.704-fold.

However, in ED patients undergoing D-dimer testing, the patient's sex, age, and presence of a malignancy diagnosis were not significant predictors of high D-dimer test results.

Infections have been reported as the most common cause of elevated D-dimer levels in patients admitted to a large urban ED (14). A recent study reported that elevated D-dimer levels in ED patients were frequently (78.3%) caused by non-thrombotic factors, such as infections, inflammation, or chronic diseases (15). Additionally, elevated D-dimer levels are known to be associated with mortality and prognosis in patients without clinical evidence of thrombosis (16, 17). Given these findings, it is clear that this test, which has low specificity, should be used selectively in patients. In many patients, elevated D-dimer levels can create diagnostic uncertainty for emergency physicians. In our study conducted at a tertiary education and research hospital over an 11-year period prior to the Covid-19 pandemic, we found that D-dimer testing was requested in only 0.67% of ED patients. We believe that ED physicians may be hesitant to order this test. Further studies are needed to determine the clinical significance of elevated D-dimer levels and their impact on patient management, particularly in non-thrombotic conditions.

The ED physician aims to diagnose PE without missing any cases, reduce unnecessary CTPA, and do so as quickly as possible. To achieve this, emergency medicine clinics use the current European Society of Cardiology (ESC) guidelines (5) for patient management. D-dimer levels obtained to exclude thromboembolic diseases may be elevated due to various other conditions, often necessitating advanced diagnostic tests (5). During this period, waiting for the D-dimer test result may take a long time due to overcrowding in the ED and various technical issues. Therefore, to save time, we sought to determine whether the index D-dimer test value could be predicted based on the previous D-dimer test result

in ED patients. As a result, the probability of the index D-dimer value exceeding the age-determined limit is 4.170 times higher if the previous D-dimer value was above the limit and 4.704 times higher if the previous D-dimer value exceeded 1,000 µg/L FEU. In these cases, we believe that employing alternative diagnostic strategies, rather than waiting for the D-dimer result, may save time.

In our study, the probability of the D-dimer test result exceeding the age-adjusted threshold was not associated with the patient's gender, age, or malignancy status. The median age of the population was 61 ± 31 years, and 60.6% were female. There are conflicting data regarding the frequency of VTE between genders. While some studies suggest that gender is not an independent risk factor, others indicate that female gender may be protective against VTE (18). Additionally, many studies have reported a higher frequency of VTE recurrence in men than in women, leading to recommendations for gender-specific cut-off values (19, 20). In this study, while the relationship between gender and VTE was not investigated, no association was found between gender and elevated D-dimer levels. Since we used age-adjusted D-dimer thresholds, the lack of association between age and elevated D-dimer levels is consistent with the literature (10-12). Patients with malignancy often present to the ED with signs and symptoms suggestive of acute PE, and D-dimer levels are frequently elevated (10). It is also well-established that patients with malignancy have a four to seven times higher risk of VTE compared to those without malignancy (7,21). These patients typically have high clinical risk scores, which explains why D-dimer testing is rarely requested for malignancy patients in the ED. In our study population, only 20 (5.6%) patients had a diagnosis of malignancy. We believe that our findings are not statistically significant due to the small number of cases. Current guidelines provide clear recommendations for the diagnostic approach in non-malignant patients with suspected PE (15). However, recommendations for the diagnostic approach in patients with malignancy and suspected PE remain limited. Changes in D-dimer levels across different populations, factors influencing its elevation, and its prognostic significance should continue to be investigated.

Important limitations include the single-center, retrospective design and small sample size. Although the study covered a large time period of 11 years, the number of patients included in the study was relatively small. This was due to the fact that patients had not had previous D-dimer results within three years. This may be because different patients visited, and a new D-dimer test was not requested since the patients' previous D-dimer results were high. For some reason, D-dimer testing is rarely requested in emergency departments. This suggests that D-dimer has many aspects that need to be investigated. Other limitations are the small number of elderly patients and those with malignancy.

Conclusion

Thanks to widespread electronic record systems, patients' previous laboratory results have become more accessible. In patients whose D-dimer values have been above the limit value in the last three years, the new D-dimer value is likely to be high. In such cases, performing advanced diagnostic tests instead of waiting for the test results may save time.

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All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Ethical Approval: Ethichal approval was obtained from the University of Health Sciences Tepecik Training and Research Hospital Ethics Committee (Decision No: 2023/06-37, dated July 13, 2023).

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