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Original Article

Retrospective Analysis of Follow-up and Results of Patients with High D-Dimer Value and Discharged without Emergency Pathology

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ABSTRACT

Background This study aimed to retrospectively examine the morbidity and mortality rates after discharge of patients who applied to the emergency department with high D-dimer values but had no pathology upon evaluation.

Material and Methods Patients over the age of 18 who applied to Bursa Uludağ University Faculty of Medicine Emergency Department with preliminary diagnosis of pulmonary embolism in a two-year period between January 2018 and December 2019 were included in the study. The patient group consisted of cases with high D-dimer levels while the control group inluded patients with negative D-dimer and no pathology on discharge.

Results A total of 594 cases; 297 D-dimer positive (+) and 297 D-dimer negative (-), were included in the study. A significant difference existed between the percentage of patients developing illness post-discharge in the D-dimer (+) 18.86% (n=56) and D-dimer (-) 1.68% (n=5) groups, respectively. The most common illness identified in the dimer (+) group after discharge up was pneumonia (n=11), followed by Coronary Artery Disease (n=5). Death rate was 1.68% (n=5) in the D-dimer (-) group and 11.78% (n=35) in the D-dimer (+) group; a statistically significant difference (p=0.001).

Conclusions In conclusion, both morbidity and mortality rates were found to be significantly higher in the D-dimer positive group.

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Introduction

D-dimer is a fibrin degradation product.[1] Blood D-dimer level increases in various conditions related to coagulation.[2] D-dimer; a fast, simple and cheap test, is performed to rule out deep vein thrombosis (DVT) and pulmonary embolism (PE).[3] Normal plasma D-dimer level is usually less than 500 micrograms per liter (µg/L).[4] In many studies, the formula; Agex10=ng/mL, is proposed for the threshold value in patients over 50 years of age.[5] Blood D-dimer levels may be high in old patients, patients with cancer or systemic infection, pregnancy, recent surgery or trauma.[4] D-dimer may also increase in infectious diseases such as endocarditis and mycoplasma pneumonia.[6,7] D-dimer has high sensitivity and low specificity in the diagnosis of acute aortic dissection (AAD).[8]

D-dimer is not only a diagnostic tool, but also a useful biomarker in predicting prognosis.[9] D-dimer levels are found to be high in patients with community-acquired pneumonia and may help in determining the risk of mortality.[10] Rodelo et al.[11] Reported higher mortality rates in septic patients with elevated D-dimer levels. High D-dimer values, especially in lung malignancies, is associated with poor prognosis.[12] Our objective was to retrospectively examine the morbidity and mortality rates after discharge of patients who applied to the emergency department with high D-dimer values but had no pathology upon evaluation.

Material and Methods

This study, a specialization thesis, was carried out retrospectively with the approval of Uludag University Faculty of Medicine Clinical Research Ethics Committee dated 16 June 2021 number 2021-8/25. Patients over the age of 18 who applied to Bursa Uludag University Faculty of Medicine Emergency Department with preliminary diagnosis of pulmonary embolism in a two-year period between January 2018 and December 2019 were included in the study. Data was obtained through Mia-Med Hospital Information and Management System and E-pulse electronic system. The patient group consisted of cases with high D-dimer levels while the control group included patients with negative D-dimer without any pathology upon discharge.

The upper limit for plasma D-dimer concentration was accepted as 500 ng/mL in young patients, whereas the corrected formula (Agex10=ng/mL) was used in patients over 50 years of age. D-dimer above these values were accepted as positive (+) while D-dimer below these values were considered negative (−). Patients were followed up through Mia-Med and E-pulse electronic system until January 2022. In cases where sufficient data could not be found, patients or their relatives were reached to using the contact information registered in our system.

Statistical Analysis

In calculating the sample size of the study, Power was 0.80 for each variable, Effect size was 0.2, and Type-1 error (a) was 0.05. Descriptive statistics for continuous variables were; Mean/median, standard deviation, minimum and maximum whereas categorical variables were expressed as number (n) and percentage (%). Continuous measurements' distribution was examined by Kolmogorov-Smirnov (n>50) and Skewness-Kurtosis tests. In the case of normal (parametric) distribution of continuous variables, comparisons according to categorical factors were made using the independent T-test (Single-test).

Results

A total of 594 cases; 297 D-dimer (+) and 297 D-dimer (−), were included in the study. Table 1 showed the distribution of cases according to age, D-dimer, period after discharge and gender. As seen in Table 1, the mean age of D-Dimer (+) patients was significantly higher ($p<0.05$). The period (days) between discharge and control dates had no significant difference according to the D-Dimer groups ($p>0.05$). Distribution of patients according to D-dimer groups and the outcomes were shown in Table 2 and Figure 1. As seen in Table 2, morbility and mortality rate was significantly higher in the D-dimer (+) group ($p<0.001$). Diseases detected in both groups are shown in Table 3. As seen in Table 3, the most common disease identified in the dimer (+) group was pneumonia (n: 11), followed by coronary artery disease (n: 5), cholecystitis (n: 4), and pyelonephritis (n: 4), respectively.

Table 1. Comparison between the distribution of patients' age, D-dimer, period after discharge and gender according to D-dimer groups.

	D-dimer negative	D-dimer positive	P value
Age (years)	43.26±15.21	50.03±18.99	0.001*
Gender (male/female) n (%)	184 (61.95)/113 (38.05)	143 (48.15)/154 (51.85)	0.001**
D-dimer (ng/mL)	325.12±116.44	1691.95±1656.63	0.001*
Period (days)	1201.98±78.99	1250.48±692.85	0.231*

*Student's t test, ¶ Fisher's exact test, † Pearson Chi-Square test, ϕ Mann-Whitney U test.
ER: estrogen receptor, PR: progesterone receptor, DCIS: ductal carcinoma in situ, LVI: lymphovascular invasion, LN: lymph node metastasis.

Table 2. Distribution of patients according to D-dimer groups and the outcomes.

	D-dimer negative	D-dimer positive	P value*
Healthy n (%)	287 (96.63)	206 (69.36)	0.001
Ill n (%)	5 (1.68)	56 (18.86)	0.001
Exitus n (%)	5 (1.68)	35 (11.78)	0.001
Total n	297	297	0.231

*significance levels according to two-ratio Z-test results.

Discussion

D-dimer is a fast and cheap test included in PE diagnostic algorithms.[3,13] However, blood D-dimer values can increase in many diseases other than PE.[4,6,7] D-dimer is also a useful biomarker in predicting prognosis.[8] In our study, we followed up patients with high D-dimer levels that were discharged after evaluation in the ED without any pathology. Blood D-dimer level is generally higher in the elderly.[4] For this reason, the corrected formula (Agex10=ng/mL) is recommended for the threshold value in patients over 50 years old.[5] In our study, the mean age of D-Dimer (+) patients was found to be significantly higher.

High D-dimer levels in pneumonia is directly proportional to severity.[12] In our study, the most common disease in the dimer (+) group during follow-up was found to be pneumonia (n:11). Studies have revealed high D-dimer levels in patients with coronary arter disease.[14] Another study has shown that high D-dimer levels are associated with coronary

Table 3. Distribution of illnesses according to D-dimer groups.

	Illness	n (%)
D-dimer negative	Factor 5 Leiden mutation	1 (20)
	Hepatitis B infection	1 (20)
	Myocardial infarction	1 (20)
	Stomach carcinoma	1 (20)
	Papillary thyroid carcinoma	1 (20)
	Total	5 (100)
D-dimer positive	Pneumonia	11 (19.6)
	Coronary artery disease	5 (8.9)
	Cholecystitis	4 (7.1)
	Pyelonephritis	4 (7.1)
	COVID-19	3 (5.4)
	Malignancy	3 (5.4)
	Pulmonary embolism	3 (5.4)
	Peripheral artery disease	3 (5.4)
	Sepsis	2 (3.6)
	Others	18 (32.1)
	Total	56 (100)

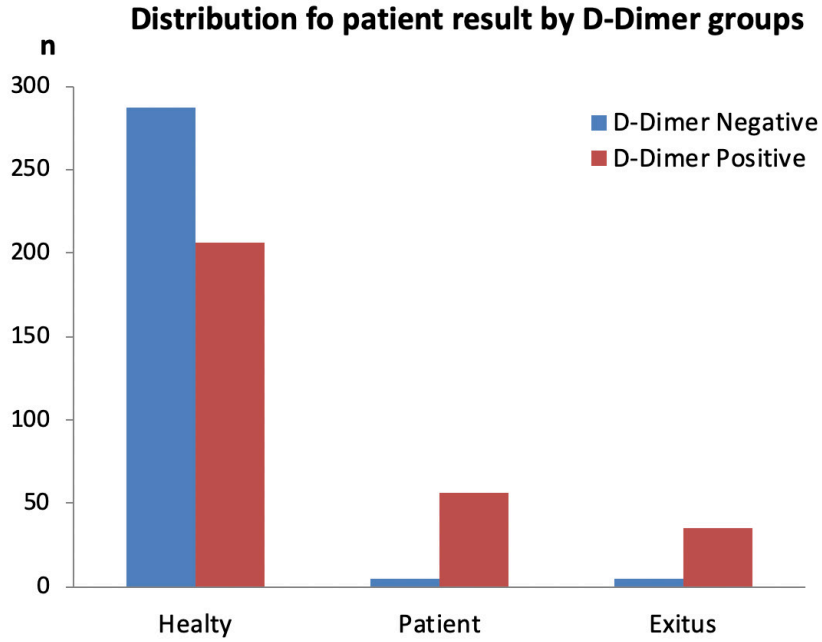

Figure 1. Distribution of patient outcomes according to D-dimer groups.

arter disease occurring under the age of 45.[15] In our study, we also encountered coronary arter disease in the D-dimer (+) group. A study has shown that D-dimer predicts the presence of bacteremia in septic patients and is correlated with the severity of sepsis.[16] In another study, high D-dimer levels were associated with severe organ dysfunction and high mortality.[17] Sepsis was another disease identified in the dimer (+) group during our follow-up. Peripheral artery disease is also related to high D-dimer levels.[18] In our study, peripheral arterial disease was detected in some cases among the dimer (+) group.

D-dimer is a test with high sensitivity but low specificity in the diagnosis of PE.[3] We identified only 3 (5.4%) PE patients in the dimer (+) group during our follow up period. In cases of malignancy, intravascular stasis, released cytokines and coagulation factors, and vascular injuries caused by chemotherapy lead to increased D-dimer values.[19] High blood D-dimer concentration during pre-treatment period in small cell lung cancer may be a reliable factor to predict prognosis.[11] Another disease group encountered in the dimer (+) group during our follow-up was malignancy.

Elevated D-dimer is frequently detected in patients with COVID-19 and is significantly associated with high mortality risk.[20] In our study, we came across some COVID-19 cases in the dimer (+) group.

D-dimer is not only a diagnostic tool, but also a useful biomarker in predicting prognosis.[9] High D-dimer is frequently encountered in critically ill patients and is inversely proportional to survival.[21] D-dimer levels may be helpful in determining the risk of mortality in patients with community-acquired pneumonia.[10] Elevated D-dimer in COVID pneumonia are associated with severity and increased risk of mortality.[22] D-dimer has been found to correlate with the severity of sepsis.[16] D-dimer correlate with the prognosis in cancer patients.[23] High D-dimer, especially in lung malignancies, is associated with poor prognosis.[12]

Conclusions

As a result, both morbidity and mortality rates were found to be significantly higher in the D-dimer (+) group during follow-up. A closer follow-up of D-dimer positive cases will be beneficial in cases discharged without acute pathologies during ED evaluation and adding D-dimer to the screening program is likely to positively affect prognosis.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Local ethics committee approved the study protocol.

Authors' Contribution

Study Conception: KFB; Study Design: CHI, DVA; Supervision: KFB; Literature Review: KFB, KB; Critical Review: AE; Data Collection and/or Processing: KB, KFB; Statistical Analysis and/or Data Interpretation: KFB, OIM; Manuscript preparing: KFB, OIM.

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