Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1023590

Anatolian Curr Med J 2022; 4(1); 44-50

The effects of D-dimer high rates on prognosis and mortality in chronic obstructive respiratory disease

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Cite this article as: Tilbe Saymaz Z, Çelik D, Yıldız M, Ertan Ö. The effects of D-dimer high rates on prognosis and mortality in chronic obstructive respiratory disease. Anatolian Curr Med J 2022; 4(1); 44-50.

ABSTRACT

Aim: We aim to answer the question of "Can D-dimer be an indicator of prognosis and mortality in COPD exacerbations?" by doing retrospective research on the prognosis and mortality of patients who had high D-dimer levels in COPD exacerbations with no thromboembolism detected.

Material and Method: Our research is retrospective and cross-sectional. A total of 115 patients who had applied to our hospital between January 2018 and January 2019 with COPD acute exacerbations and who had higher D-dimer levels detected than the 0.44 mg/L upper limit of our hospital's laboratory are included in this research. All patients have been previously diagnosed with COPD by a pulmonologist and have been undergoing treatment. Patients under the age of 18, patients whose information was not accessible through their files, pregnant patients, patients who have not been diagnosed with COPD by a pulmonologist, patients who had been diagnosed with lung malignancy through pathology, patients where pulmonary embolism was detected through pulmonary CT angiography, patients with renal function test disorder and patients with known renal failure are not included in this study.

Results: A total of 115 patients were included in the study. Patients who developed mortality had statistically significant lower levels of OSAS, higher rates of pneumonia, anemia, and liver failure, higher numbers of applications to emergency services in 1 year, higher numbers of hospitalizations due to COPD acute exacerbations in 1 year, higher numbers of intensive care unit admissions due to COPD acute exacerbations in 1 year and lower survival time. In addition, patients who developed mortality had statistically significant lower rates of group B and C and higher rates of group D according to the classification of Global Initiative of Chronic Obstructive Lung Disease (GOLD). Although the D-dimer levels were higher in patients who developed mortality, there were no statistically significant differences between groups. No significant cut-off value for D-dimer was calculated.

Conclusion: As a result, although our study has found higher D-dimer levels in patients who develop mortality, these results were not statistically significant.

Keywords: COPD, D-dimer, mortality, prognosis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airway obstruction and it causes chronic airway inflammation (1,2). COPD is one of the most common reasons for mortality, hospitalization, and repeated visits to hospitals worldwide (1,3). It is the 3rd most common cause of death in the world and 4th in Turkey (4). Due to its high mortality, morbidity rates, and high costs, a global initiative named Global Initiative for Chronic Obstructive Lung Disease (GOLD) and a burden group called Burden of Obstructive Lung Disease (BOLD) have been established against COPD (4,5). The studies conducted by these groups show that the COPD prevalence and burden keeps increasing and it might turn into larger scales in the future (4,5). COPD characteristically progresses with acute exacerbations and these exacerbations increase mortality and morbidity (1-3). Acute exacerbations are related to the mortality rates of patients in hospitals and their prognosis in the long term (6). This creates a need for laboratory biomarkers that can be correlated with acute exacerbations and that should be easily accessible (6-9). COPD acute exacerbations can occur due to pneumonia, additional diseases, seasonal or thromboembolism-related incidents (1-3,10). In the course of COPD, it is common for thromboembolism incidents to occur which are related to hypoxemia and

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Received: 14.11.2021 **Accepted:** 08.12.2021

carbon dioxide retention caused by hypercoagulation (11). It is known that D-dimer is a biomarker for in vivo thrombin and plasmin activation which are used in the prediction and prognosis of thromboembolism incidents (11). However, only a few studies have researched the prognostic importance of D-dimer on acute exacerbated COPD patients who have high rates of D-dimer with excluded pulmonary thromboembolism. In our study we planned to research the effects D-dimer has on prognosis and 1-year survival on patients who have high D-dimer rates detected during COPD acute exacerbations and who have excluded pulmonary thromboembolism.

MATERIAL AND METHOD

Patients who have applied to our hospital between January 2018 and January 2019 with COPD acute exacerbations and who had higher D-dimer levels detected than the 0.44 mg/L upper limit of our hospital's laboratory have been scanned and 115 patients who have met the requirements of our study have been included in the study. All patients have been previously diagnosed with COPD by a pulmonologist and have been undergoing treatment. Patients under the age of 18, patients whose information was not accessible through their files, pregnant patients, patients who have not been diagnosed with COPD by a pulmonologist, patients who had been diagnosed with lung malignancy through pathology, patients where pulmonary embolism was detected through pulmonary CT angiography, patients with renal function test disorder and patients with known renal failure are not included in this study.

D-dimer levels were limited to an upper limit of 0.44 mg/L according to our hospital's cut-off value. Complete blood count, routine biochemistry, C Reactive protein, arterial blood gas, thorax X-Ray screening have been performed on all patients as part of the standard protocol and have been evaluated in terms of pulmonary thromboembolism (PTE) according to Modified Wells criteria (12). All patients who had a Pulmonary CT (Computed Tomography) angiography and embolism were excluded. In patients with contrast agent allergies, the embolism was excluded by V/Q (ventilation/perfusion scintigraphy).

Demographic data of patients such as their age, gender, use of cigarettes, or comorbid diseases were recorded. Whether the patients received additional corticosteroid, antibiotic, nasal oxygen, or non-invasive mechanical ventilation treatments during their hospitalizations were analyzed and the intensity of the acute exacerbations was determined. Patients were classified as mild acute exacerbations, those who did not receive these treatments, moderate acute exacerbations, those who had steroids and antibiotics and severe acute exacerbations, those who received steroids, antibiotics, nasal O2, and non-invasive mechanical ventilation treatments. The prognosis of the patients was evaluated according to the number of their applications to the emergency service in 1 year, their hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year, and their admission to intensive care units with COPD acute exacerbations in 1 year. The patients were classified according to GOLD criteria and grouped as A-B-C-D (13).

The data will be evaluated in the IBM SPSS Statistics 25.0 package program. Unit number (n), percentage (%), average±standard deviation (), Median (Q1-Q3) values will be provided as part of descriptive statistics. In the evaluation of categorical variables, the Pearson Chi-Square test will be used. For the continuous variables' evaluation Shapiro Wilk, normality test, and Q-Q graphics will be used. When comparing the continuous variables of two groups, the Unpaired T-Test will be used for variables with normal distribution and the Mann-Whitney U test will be used for variables with non-normal distribution. While comparing the continuous variables of three or more groups, the homogeneity of variances with normal distribution will be analyzed with the Levene Test. If the variances are homogenous single direction variance analysis will be used and if the variances are not homogenous the Welch Test will be used. For non-normal distributed variables Kruskal-Wallis analysis will be applied. As a multi comparison test, for the normally distributed variables, if the variances are homogenous Tukey HSD and if the variances are not homogenous Games-Howell will be used, and for the non normally distributed variables Dunn-Bonferroni test will be used. To determine the relationship between two numeric values, normally distributed variables will use Pearson, and non-normally distributed variables will use Spearman correlation analysis. To identify risk factors, the logistic regression model will be analyzed. For univariate analyses, any variables with $p<0.1$ value will be included in the logistic regression model. The appropriateness of the logistic regression model will be analyzed with the Hosmer-Lemeshow test. The diagnostic performance of the test will be evaluated by drawing ROC (receiving operating characteristics) curves. The threshold value will be determined with the Youden index and the sensitive, specific, positive predictive and negative predictive values will be calculated based on the predetermined threshold value. ($p<0.05$ value will be considered statistically significant.)

Necessary permissions for our study were granted by the decision (Date: 26.10.2021 Decree no. 2012-KAEK-15/4207) of the Clinical Studies Ethics Comittee of Health Sciences University Ankara Keçiören Educational and Research Hospital.

RESULTS

The demographic data, general features, and comorbidity situations of the patients included in this study are shown in **Table 1**. The average age for the patients was 68.57±10.16 and 79 of the patients (68.7%) were male. During their hospitalization 96.5 % (n=111) received systemic steroids, 87.0% (100 patients) received antibiotics, 96.5% (111 patients) received nasal oxygen and 24.3% (28 patients) received non-invasive mechanical ventilation treatment.

Table 1. Demographic data, general features and comorbidity situations

Patient Features (n=115)	Rates n (%)
Gender	
Female	36 (31.3%)
Male	79 (68.7%)
Age (Year)	68.57±10.16
Smoking	
Non-smoker	24 (20.9%)
Active Smoker	19 (16.5%)
Quit	72 (62.6%)
Diabetes Mellitus	42 (36.5%)
Hypertension	53 (46.1%)
Obstructive Sleep Apnea Syndrome (OSAS)	15 (13.0%)
Coronary artery Disease	29 (25.2%)
Congestive Heart Failure	19 (16.5%)
Cardiac Arrhythmia	5 (4.3%)
Dementia	1 (0.9%)
Previous Cerebrovascular Accident	2 (1.7%)
Epilepsy	1 (0.9%)
Malignancy	1 (0.9%)
Moderate-Severe Kidney Failure	3 (2.6%)
Pneumonia	80 (69.6%)
Systemic Steroid Use During Hospitalization	111 (96.5%)
Antibiotic Use During Hospitalization	100 (87.0%)
Oxygen Support Need During Hospitalization	111 (96.5%)
Non-Invasive mechanical ventilation support use During Hospitalization	28 (24.3%)
COPD exacerbation intensity	
Mild Acute Exacerbation	-
Moderate Acute Exacerbation	4 (3.5%)
Severe Acute Exacerbation	111 (96.5%)
Number of applications to the emergency service in 1 year	3 (1-112)
Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	2 (1-18)
Number of admission to intensive care units with COPD acute exacerbations in 1 year.	0 (0-6)
Decompensated Respiratory Failure in Application Artery Blood Gas Analysis	98 (85.2%)
GOLD Classification	
B	21 (18.3%)
C	49 (42.6%)
D	45 (39.1%)
Creatinin	0.82 (0.51-19)
D-dimer	1.4 (0.1-13.2)
Survival Time (Month)	28.97 (1.53-39)

Continuous variables are expressed as either the mean±Standard deviation (SD) or median (minimum-maximum value) and categorical variables are expressed as either frequency (percentage).

Acute exacerbation intensity was determined after analyzing whether the patients have received intravenous methylprednisolone, antibiotic, nasal oxygen, or non-invasive mechanical ventilation treatments during their hospitalization. No patients with mild acute exacerbations were hospitalized. The number of patients with moderate acute exacerbations was 4 (3.5%) and the number of patients with severe acute exacerbations was 111 (96.5%).

Among the patients that were included in this study, Pulmonary CT angiography examination to 110 (95.7%) of patients and Pulmonary ventilation/ perfusion (V/Q) examination to 15 (13.0%) patients were made. Pulmonary thromboembolism (PTE) was excluded in all patients. All patients that have received V/Q examination were reported with a low possibility of PTE.

Patients were evaluated according to GOLD criteria and classified as A-B-C-D groups. Among the patients that have applied to the hospital, group A patients were non-existent. 21 (18.3%) Group B, 49 (42.6%) Group C and 45 (39.1%) Group D patients were present. The average survival time for the patients included in this study was 28.97 (1.53-39) months.

In **Table 2**, the mortality rates of 115 patients with COPD acute exacerbations, who were included in this study, were compared in terms of related factors. According to the table, in patients that have developed mortality, the frequency of OSAS (p=0.008) was lower, frequency of pneumonia (p=0.033) was higher, the number of applications to the emergency service in 1 year, the number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year and the number of admission to intensive care units with COPD acute exacerbations in 1 year were higher and the survival time was lower (respectively p=0.003, p=0.003, p<0.001 ve p<0.001) on statistically significant levels. In addition, with patients that have developed mortality and were classified according to GOLD classification, the rate of Group B and C patients were lower and the rate of Group D patients was higher and these rates were statistically significant (p<0.001).

Although D-dimer levels were higher in patients that have developed mortality, no statistically significant differences were found between the groups (p=0.128) (**Figure**).

To determine the factors that predict survival in COPD patients with acute exacerbations, univariate cox regression analysis was applied. As we had a monitoring period we have used cox regression instead of logistic regression. It was seen that the variants with p<0.05 value were able to predict or foresee survival (**Table 3**).

Table 2. The comparison of mortality rates in terms of related factors

Patient features (n:115)	Mortality (+) (n : 43)		Mortality (-) (n : 72)		p
	n	%	n	%	
Gender					0.544
Female	12	(27.9%)	24	(33.3%)	
Male	31	(72.1%)	48	(66.7%)	
Age (year)	70.77±10.90		67.26±9.53		0.073
Smoking					0.794
Non-smoker	10	(23.3%)	14	(19.4%)	
Active smoker	6	(14.0%)	13	(18.1%)	
Quit	27	(62.8%)	45	(62.5%)	
Diabetes mellitus	16	(37.2%)	26	(36.1%)	0.906
Hypertension	19	(44.2%)	34	(47.2%)	0.752
Obstructive sleep apnea syndrome	1	(2.3%)	14	(19.4%)	0.008
Coronaryartery disease	11	(25.6%)	18	(25.0%)	0.945
Congestive heart failure	8	(18.6%)	11	(15.3%)	0.642
Cardiac arrhythmia	1	(2.3%)	4	(5.6%9	0.649
Dementia	1	(2.3%)	-		0.374
Pneumonia	35	(81.4%)	45	(62.5%)	0.033
Systemic steroid use during hospitalization	43	(100%)	68	(94.4%)	0.295
Antibiotic use during hospitalization	39	(90.7%)	61	(84.7%)	0.357
Oxygen support need during hospitalization	42	(97.7%)	69	(95.8%)	0.999
Non-invasive mechanical ventilation support use during hospitalization	15	(34.9%)	13	(18.1%)	0.042
Moderate-severe kidney failure	-		3	(4.2%)	0.292
COPD exacerbation intensity					0.999
Moderate acute exacerbation	1	(2.3%)	3	(4.2%)	
Severe acute exacerbation	42	(97.7%)	69	(95.8%)	
Number of applications to the emergency service in 1 year	5 (1-112)		3 (1-22)		0.003
Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	2 (1-18)		2 (1.11)		0.003
Number of admission to intensive care units with COPD acute exacerbations in 1 year.	0 (0-6)		0 (0.3)		<0.001
Application artery blood gas analysis					0.727
Decompensated	7	(16.3%)	10	(13.9%)	
Compensated	36	(83.7%)	62	(86.1%)	
Gold classification					<0.001
B	2	(4.7%)	19	(26.4%)	
C	14	(32.6%)	35	(48.6%)	
D	27	(62.8%)	18	(25.0%)	
Creatinin (mg/dL)	0.8 (0.53-19)		0.84 (0.51-1.67)		0.422
D.Dimer (mg/L)	1640 (600-11900)		1305 (100-13200)		0.128
Survival Time (Month)	15.8 (1.53-36.87)		30.77 (23.27-39)		<0.001

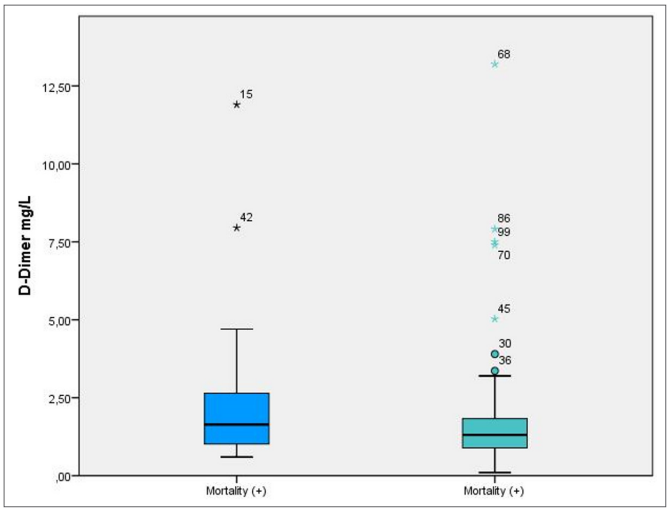

Figure. Box plotsgraphicforD-dimer in terms of mortality development.

Pneumonia existence, increase in the number of hospitalization in the pulmonary diseases unit with COPD acute exacerbations and the number of admission to intensive care units with COPD acute exacerbations, non-existence of OSAS, and survival rates of D compared to B according to GOLD classification is lower and all these predict mortality.

The p-value of <0.25, which was marked with bold, in the univariate cox regression analysis has been included in the multivariate cox regression analysis as well. D-dimer, which is the main subject of the study, was not included in the multivariate analysis as no p>0.25 value has been detected in the univariate analysis. In the multivariate analysis, the backward LR method has been used. In the table below, the first step results of all the variants included in the analysis are given first and then the 5th step results, which are the most significant model, are given (**Table 4**). An increase in the number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations and the number of admission to intensive care units with COPD acute exacerbations are considered as the predictive or foreseeing incidents in the decrease of survival. Pneumonia remains outside of the limit of significance.

Table 3. The univariate coxregression analysis that was applied to identify the variables that predict survival in COPD patients

Univariate cox regression	Wald	p	HR	95.0% CI for HR
Age	3.526	0.060	1.030	(0.999-1.063)
Gender (ref: female)	1.008	0.315	1.408	(0.722-2.745)
Smoking (ref: non-smoker)				
Active smoker	0.107	0.744	0.844	(0.306-2.327)
Quit	0.035	0.852	0.933	(0.451-1.930)
D-dimer level	0.596	0.440	1.051	(0.927-1.191)
Creatinin level	2.687	0.101	1.101	(0.981-1.235)
Diabetes mellitus	0.002	0.962	1.015	(0.547-1.884)
Hipertansion	0.078	0.780	0.918	(0.503-1.676)
Obstructive sleep apnea syndrome (OSAS)	4.447	0.035	0.118	(0.016-0.860)
Coronaryartery disease	0.004	0.952	1.021	(0.515-2.026)
Congestive heart failure	0.331	0.565	1.254	(0.581-2.707)
Cardiac arrhythmia	0.351	0.554	0.549	(0.076-3.993)
Dementia	0.852	0.356	2.551	(0.349-18.624)
Pneumonia	4.630	0.031	2.328	(1.078-5.024)
Systemic steroid use during hospitalization	0.919	0.338	1.732	(0.040-3.091)
Antibiotic use during hospitalization	1.366	0.242	1.851	(0.659-5.195)
Oxygen support need during hospitalization	0.208	0.648	1.588	(0.218-11.576)
Non-invasiv emechanical ventilation support use during hospitalization	2.894	0.089	1.724	(0.920-3.230)
COPD exacerbation intensity (ref: moderate acute exacerbations)	0.208	0.648	1.588	(0.218-11.576)
Moderate-severe kidney failure	0.559	0.455	0.048	(0.000-139.927)
Number of applications to the emergency service in 1 yearwith COPD acute exacerbations	3.656	0.056	1.012	(1.000-1.024)
Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	5.084	0.024	1.093	(1.012-1.180)
Number of admission to intensive care units with COPD acute exacerbations in 1 year.	13.424	<0.001	1.446	(1.187-1.761)
Application artery blood gas analysis (ref: decompensated)	0.005	0.944	0.972	(0.432-2.187)
GOLD Classification				
C	3.047	0.081	3.746	(0.850-16.500)
D	10.361	0.001	10.832	(2.539-46.212)

Wald: test statistics, HR: hazardradio, CI: ConfidentalInterval

Table 4. The multivariate cox regression test which was applied in order to identify the variables that predict survival in COPD patients.

Multivariate cox regression		Wald	p	HR	95.0% CI for HR	
Step 1	Age	16.157	<0.001	1.080	1.040	1.121
	Creatinin level	3.462	0.063	1.123	0.994	1.269
	Pneumonia	3.474	0.062	2.575	0.952	6.963
	Antibiotic use during hospitalization	0.487	0.485	.639	0.181	2.251
	Non-Invasive mechanical ventilation support Use During Hospitalization	1.202	0.273	1.460	0.742	2.875
	Number of applications to the emergency service in 1 year	0.820	0.365	1.011	0.987	1.037
	Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	2.738	0.098	1.150	0.975	1.356
	Number of admission to intensive care units with COPD acute exacerbations in 1 year.	14.673	0.000	1.632	1.270	2.096
Step 5	Age	14.521	<0.001	1.071	1.034	1.109
	Pneumonia	2.853	0.091	1.990	0.895	4.420
	Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	11.386	0.001	1.204	1.081	1.342
	Number of admission to intensive care units with COPD acute exacerbations in 1 year.	16.485	<0.001	1.662	1.301	2.125

Wald: test statistics, HR: hazardradio

When the study population was divided into two according to the median (median 1400 mg/L) of D-dimer value, the Kaplan-Meier curve was used to determine the survival rate between the groups, and the log-rank tests were applied to find out whether there are any differences between the groups in terms of survival. According to the D-dimer median value,there are no statistically significant differences between the groups in terms of survival (p>0.05). Whether D-dimer can make a distinction between those who develop mortality and those who don't and whether a cut-off value can be given to determine mortality for D-dimer has been evaluated. According to the results, the area that remains below the curve for mortality in the D-dimer level is 0.585 and this value has no statistical significance (p=0.128). Therefore a D-dimer cut-off value could not be calculated.

In addition, after dividing the groups into two according to the D-dimer median, there have been no statistically significant differences between the two groups in terms of the comparison made between demographic features, additional diseases, and all variables that are present in **Table 1** and **2**.

DISCUSSION

The studies in the literature show that D-dimer levels can be related to many diseases and it can be used in the prognosis (14-20). The thrombotic incidents that occur in COPD are explained by carbon dioxide retention and hypercoagulation (11,21,22). It is known that thromboembolism is one of the most common causes of COPD acute exacerbations (1-3). D-dimer is used as a biomarker for thromboembolism incidents (11).

In a study conducted by Christian H. Nickel et al. (14), the 90-day survival of patients with high D-dimer levels that have been applied to emergency services has been examined. It has been observed that these patients were diagnosed with venous thromboembolism, cancer, anemia, or infection and 8.1% of the patients were confirmed dead within the first 90 days. In another study, 30 days and 365 days survival of the patients were examined and it has been observed that 9 patients with high D-dimer levels died within 30 days and 60% of the patients with high D-dimer levels died within 365 days (15). In our study, while the patients who developed mortality had higher D-dimer levels, there were no statistically significant differences between the groups.

In a study conducted by Guoping Hu et al. (11), D-dimer is detected to be a risk factor in terms of hospital mortality and 1-year mortality. Oren Fruchter et al. (6) have also discovered in a study that high D-dimer levels were significant when showing mortality. The study we have conducted shows that there is a relation between mortality and pneumonia, an increase in hospitalization and admission to intensive care units in 1 year due to COPD acute exacerbations, non-existence of OSAS, and being in Group D in GOLD classification. The increase in age, increase in hospitalization in 1 year with COPD acute exacerbations, and admission to intensive care units in 1 year due to COPD acute exacerbations are situations that predict a decrease in survival. While pneumonia has a significant difference between groups that develop mortality and groups that do not, it has been determined in the multivariate analysis that it carried no significance. A study conducted by Oren Fruchter et al shows that the GOLD phase and mortality are related, which conforms with our study. Alongside this, high D-dimer levels were found to be relatedto mortality (6).

Guoping Hu et al.(11) have determined the D-dimer cut-off value as 985 ng/dL, and Oren Fruchter et al. (6) have determined it as 1.52 mg/dL. In another study that was conducted on COPD patients with venous thromboembolism, D-dimer cut-off value was determined as 0.95 pg/mL (22). Our study has evaluated whether D-dimer can make a distinction between groups that develop mortality and groups that don't and whether a cut-off value can be given to identify mortality. D-dimer levels were not statistically significant while identifying mortality. In the groups that have been divided according to the D-dimer value median (median 1400), no statistically significant differences could be detected between the groups in terms of survival.

It is known that biomarkers can be affected by multiple factors (1,2,6). In our study, we have tried to exclude these factors as much as possible and tried to solely focus on finding COPD acute exacerbation effects for D-dimer. The reasons why D-dimer was found to be related to mortality and why the cut-off value could be calculated could be affiliated with the high levels of D-dimer other factors had or the inefficacy of the methods which were applied to exclude thromboembolism. In other studies, the inclusion of patients with thromboembolism could be considered as a situation that could increase D-dimer levels with no relation to COPD acute exacerbations.

Limitations

The fact that our study is single-centered and the analysis was retrospective creates limitations. The respectively low number of cases might have affected the analysis. In our study, all patients who had high levels of D-dimer and pulmonary thromboembolism were excluded by pulmonary CT angiography. None of the patients had clinical evidence of peripheral venous thromboembolism. However, this was not verified with a Doppler ultrasonography and this might have created a limitation as well. Our study has only included patients with COPD acute exacerbations and some of the patients were identified with pneumonia. This could have increased mortality in the patients and might have affected the increase in D-dimer levels. We believe it is necessary to conduct prospective studies with more patients where pneumonia is also excluded.

CONCLUSION

While D-dimer levels were higher in patients who developed mortality in the follow-up period after COPD acute exacerbations, there could be no statistical significance found when determining mortality. While other studies in the literature prove otherwise, it should

be noted that biomarkers can be affected by many clinical incidents and therefore it does not seem likely to have a prognosis in COPD acute exacerbations with only one biomarker.

ETHICAL DECLARATION

Ethics Committee Approval: Necessary permissions for our study were granted by the decision (Date: 26.10.2021, No. 2012-KAEK-15/4207) of the Clinical Studies Ethics Comittee of Health Sciences University Ankara Keçiören Educational and Research Hospital.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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