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D-dimer level as a prognostic factor in patients with acute exacerbation of chronic obstructive pulmonary disease at admission to hospital

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Abstract: Introduction: D-dimer is a marker of thrombin and plasmin activation that has been used in the diagnostic workup of venous thromboembolism in patients with chronic obstructive pulmonary disease (COPD) admitted for acute respiratory distress. The prognostic role of elevated D-dimer levels for hospital course and in-hospital mortality in patients with AECOPD in whom deep venous thrombosis/ pulmonary embolism is excluded has rarely been evaluated.

Aim: This study was designed to investigate the effect of D-dimer obtained upon admission on in-hospital mortality, the need for intensive care unit ICU admission, and the need for mechanical ventilation after acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Materials and Methods: 125 participants were investigated at admission for an acute exacerbation of COPD, The age of them was between 40 and ≥70. This was an observational analytical prospective study conducted at Pulmonology Department in Tishreen University Hospital, Lattakia, Syria, during the period between June 2020 and June 2021. Clinical and laboratory data were evaluated in 108 patients (77 males,31 females) admitted for AECOPD in whom D-dimer levels were obtained upon admission and in whom (17 patients) Deep vein thrombosis/Pulmonary embolism DVT/ PE was excluded.

Results: 28 (25.9%) patients needed ICU admission, 22 (20.3%) patients needed mechanical ventilation, and 19 (17.6%) patients died in the in-hospital period.

D-dimer ≥ 0.5 mg/l was a risk factor for ICU admission (Relative Risk: RR 5, 95%CI: Confidence interval 1.97-12.6), for mechanical ventilation (RR 5.77, 95%CI 2.1 – 15.7), and in-hospital mortality (Relative Risk: RR 6.76, 95%CI 2.32 – 19.6). The mean age of patients with elevated D-dimer was significantly higher than patients with normal D-dimer (69.2 ± 10 VS 64 ± 12 years, P=0.037). D-dimer levels were higher in patients with renal dysfunction and congestive heart failure. A significant correlation was found between D-dimer level with hemoglobin, creatinine, and C – reactive protein (CRP).

Conclusion: Elevated D-dimer is a reliable prognostic marker for short-term outcomes in patients admitted for AECOPD.

Keywords: AECOPD, COPD, chronic obstructive pulmonary diseases, D-dimer, mortality.

مستوى D-dimer كمشعر إنذاري في المرضى الذين يعانون من الهجمة الحادة للداء الرئوي الانسدادي المزمن عند الدخول إلى المستشفى

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المستخلص: الخلفية: إن D-dimer هو واسمٌ لتنشيط الثرومبين والبلازمين يُستخدم في العمل التشخيصي للانصمام الخثاري الوريدي في مرضى COPD المقبولين في المستشفى بسبب ازمه تنفسية حادة. نادراً ما تمّ تقييم الدور الإنذاري لمستويات D-dimer المرتفعة للنتائج في المستشفى في مرضى سورة COPD (AECOPD) بعد استبعاد الخثار الوريدي العميق/الصمة الرئوية.

الهدف: تمّ تصميم هذه الدراسة للتحقيق في تأثير D-dimer عند القبول على الوفيات داخل المستشفى، الحاجة إلى دخول وحدة العناية المشدّدة، والحاجة إلى التهوية الآلية بعد AECOPD.

المواد والطرق: تم قياس ال D_dimer عند القبول لدى 125 مريضاً لديه هجمة حادة للداء الرئوي الانسدادي المزمن (تراوحت اعمارهم بين ال 40 و≤70)، حيث تم استبعاد 17 مريضاً مع انصمام خثاري وريدي.كانت هذه دراسة تحليلية استقبالية قائمة على الملاحظة أجريت في شعبة الأمراض الصدرية بمستشفى تشرين الجامعي، اللاذقية، خلال الفترة ما بين حزيران 2020- حزيران 2021. تم تقييم البيانات السريرية والمخبرية لدى 108 مرضى (77 ذكر و31 أنثى) تم قبولهم بتشخيص AECOPD وقياس مستوى D-dimer عند القبول مع استبعاد الخثار الوريدي العميق/الصمة الرئوية.

النتائج: بالمجمل، احتاج 28 مريض (25.9%) إلى دخول وحدة العناية المشدّدة، واحتاج 22 مريض (20.3%) إلى التهوية الآلية، وتوفي 19 مريض (17.6%) في فترة الاستشفاء. كانت قيمة D-dimer ≤ 0.5 مغ/ لتر عامل خطر لدخول وحدة العناية المشدّدة (خطر نسبي = 5)، للتهوية الميكانيكية (خطر نسبي = 5.77)، وللوفاة في المستشفى (خطر نسبي= 6.76).

كان متوسط عمر المرضى مع ارتفاع D-dimer أعلى بفرق هام إحصائياً من المرضى مع D-dimer طبيعي (P = 0.037). كانت مستويات D-dimer أعلى في المرضى مع سوء وظيفة كلية وقصور قلب احتقاني. وجد ارتباط هام إحصائياً بين مستوى D-dimer والخضاب، الكرياتينين، وCRP.

الخلاصة: يعتبر D-dimer المرتفع علامة تنبؤية موثوقة للنتائج قصيرة المدى في المرضى المقبولين بتشخيص سورة COPD حادّة.

الكلمات المفتاحية: الهجمة الحادة للداء الرئوي الانسدادي المزمن.

1- Introduction.

Acute exacerbations of COPD (AECOPD) are the main drivers for the poor outcomes of COPD, which is consequently ranked as a leading cause of death and disability globally [(1)].

It is estimated that every year 22%–40% of all patients with COPD experience at least one moderate or severe exacerbation, while 9%–16% experience more than one [(2)]. COPD, even in the stable phase, is considered to be an independent risk factor for pulmonary embolism (PE). Systemic inflammation is the main atherothrombotic abnormality in COPD, but hypoxia- related platelet activation, procoagulant status, and oxidative stress may also play a role [(3)] [(4)]. An increase of C- reactive protein, fibrinogen, interleukin (IL)‐6, IL‐8, and tumor necrosis factor (TNF- α), hypoxemia, oxidative stress, and endothelial dysfunction may alter the coagulation profile by increasing plasminogen activator inhibitor‐1 and decreasing prostacyclin release [(5)].

Emerging evidence suggests that chronic inflammation may be a cause as well as a consequence of venous thromboembolism (VTE). Underlying mechanisms associated with chronic inflammation associated with coagulopathy have been postulated but not yet defined clearly. Pulmonary thrombosis may not always result from embolization of a peripheral clot to the pulmonary arteries.

Immunothrombosis normally facilitates the entrapment and disposal of pathogens and cellular debris. However, once getting beyond control, it contributes to the formation of thrombus in situ. There is evidence that the patients with inflammatory diseases of the lungs are at great risk of thrombosis directly in the pulmonary vasculature. In these cases, there is an activation of endothelial cells, platelets, and leukocytes with subsequent formation of microparticles that can trigger the coagulation system through the induction of tissue factors [(6)].

D-dimer molecules are generated through the degradation of cross-linked fibrin during fibrinolysis. The presence of D-dimer molecules is suggestive of intravascular coagulation because it can only be generated after thrombin formation and subsequent degradation of cross-linked fibrin [(7)]. Because of this, D-dimer measurements serve as a global marker of activation of the coagulation and fibrinolytic systems, and function as an indirect marker of thrombotic and subsequent thrombolytic activity [(8)].

Studies have shown that elevated plasma D-dimer was associated with adverse outcomes, and D-dimer has been recommended as a prognostic factor for these conditions such as stroke [(9)] and infective endocarditis [(10)].

D-dimer has been used in the diagnostic workup of venous thromboembolism in patients with COPD admitted for acute respiratory distress. The prognostic role of elevated D-dimer levels for hospital course and in-hospital mortality in patients with AECOPD in whom deep venous thrombosis/pulmonary embolism is excluded has rarely been evaluated. Therefore, we performed a prospective observational analytical study to investigate the role of plasma D-dimer in the prediction of in-hospital mortality in AECOPD patients.

2- Patients and methods.

2-1 Study design:

Observational analytical prospective study of patients previously diagnosed with chronic obstructive pulmonary disease (COPD) and who are currently admitted for acute exacerbation of COPD (AECOPD) to Pulmonology Department at Tishreen University Hospital, Lattakia, Syria, during the period between June 2020 and June 2021.

2-2 participants

Patients were included if the following criteria were met: diagnosis of COPD according to the criteria set by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (11) (all patients had postbronchodilator FEV1/FVC < 70% and symptoms indicating COPD, that is, history of chronic progressive symptoms such as dyspnea, cough and wheeze and a history of smoking).

AECOPD was defined by the presence of at least two of the following major symptoms or at least one major and one minor symptom. Major symptoms: Increased sputum volume; increased sputum

purulence; breathlessness. Minor symptoms: cough; wheeze; nasal discharge; sore throat; pyrexia severe enough to warrant hospital admission without concomitant evidence of pneumonia.

Patients treated with long-term oxygen treatment or hospitalized for a reason other than AECOPD were excluded. Subjects with the acute coronary syndrome (electrocardiogram changes with elevated troponin I) were excluded. Patients with pulmonary edema, pneumothorax, and pneumonia (based on chest x-ray) were excluded. Patients who were initially admitted to the intensive care unit were excluded. Also, pregnant patients and who had liver failure were excluded.

Ethical approval:

Ethical approval to conduct the study was obtained before the commencement of the study. Informed consent was sought from each patient before being enrolled in the study.

2-3 Variables:

D-dimer Testing:

D-dimer levels were obtained in all patients upon admission by Finecare™ D-Dimer Rapid Quantitative Test. Levels < 0.5 mg/l were considered normal, and levels ≥ 0.5 mg/l were considered elevated.

Epidemiological and Baseline Laboratory Data:

Data were collected prospectively. The age, gender, smoking status, frequency of exacerbations of the patients were documented. Non-smoking status was defined as never smoking within the past 12 months. Frequent exacerbations were defined as patients who had at least one hospitalization for AECOPD in the past year.

For all included patients, the following data were assessed: Medical history and comorbid conditions (diabetes mellitus, ischemic heart disease, renal dysfunction, and congestive heart failure) were recorded. The following laboratory tests were performed within 24 hours of admission: CBC, CRP, creatinine, Arterial blood gases: PH, PaO2, and PaCO2. All patients underwent a chest X-ray and electrocardiogram.

Diagnosis/Exclusion of Deep vein thrombosis /Pulmonary embolism DVT/PE:

The clinical likelihood of DVT/PE was assessed according to the modified Wales criteria [12]:

- Patients with likely pulmonary embolism (Wells score ≥ 4):

Patients underwent Doppler's ultrasound technique with or without computerized tomography pulmonary angiography (CTPA). If results were positive, the diagnosis of DVT/PE was confirmed and these

patients were excluded from the subsequent statistical analysis in the study. If results were negative, the diagnosis of DVT/PE was excluded and these patients were included in the statistical analysis.

- Patients with unlikely pulmonary embolism (Wells score > 4): If D-dimer level was normal, the diagnosis of DVT/PE was excluded and these patients were included in the study. If D-dimer level was elevated, patients underwent Doppler's ultrasound with or without CTPA and treated as in the case of a likely pulmonary embolism.

Outcome and Follow-up:

The endpoint of the study was hospital discharge or death in hospital. The length of hospital stay was determined for each patient, and the clinical outcomes documented were in-hospital mortality, the need for ICU, and the need for mechanical ventilation were also documented.

2-4 Statistical Analysis:

Descriptive data are presented as mean (±SD). Comparisons between groups were made by using the t student test (for continuous variables) or X^2 test (for categorical variables), where appropriate. A Cox proportional multivariate hazards model using all potential predictors of mortality was performed. The results are presented as relative risk (RR) with 95% confidence interval (CI). A two-sided P value of < 0.05 was considered statistically significant. All of the statistical analyses were performed using SPSS (IBM Corporation, Armonk, New York, USA) (20^{th} version).

3- Result.

D-dimer levels were obtained in 125 patients upon admission. VTE/PE was confirmed in 17 patients (13.6%) and excluded in 108 patients who constituted the study cohort. The mean (±SD) age of the study population was 65.9 ± 12 years (range 40-≥ 70), baseline characteristics of 108 patients with AECOPD whom VTE/PE were excluded are presented in Table 1.

Table (1) Demographic and clinical characteristics of patients

Characteristics	No. of patients	Percent%
Age		
40 – 49	7	6.5%
50 – 59	15	13.9%
60 – 69	39	36.1%
≥ 70	47	43.5%
Gender		
Males	77	71.3%
Females	31	28.7%
Smoking		
Smoker	88	81.5%

Characteristics	No. of patients	Percent%
Non-smoker	20	18.5%
Frequent exacerbation		
Yes	22	20.4%
No	86	79.6%
Comorbidities		
Ischemic heart disease	33	30.5%
Diabetes mellitus	27	25%
Congestive heart failure	18	16.7%
Renal dysfunction	13	12%
Thromboembolism	N.of patients	Percent%
With DVT/PE	17	13.6%
Without DVT/PE	108	86.3%

Baseline laboratory tests are presented in Table 2.

We collected the blood samples from each patient at the time of admission to the department of respiratory disease for D-dimer and standard laboratory measurements (creatinine,WBC, arterial blood gases, hemoglobin, and C-reactive protein (CRP).

Table (2) Laboratory tests of patients

Laboratory test	Mean ± SD	Range of the research's resultse
WBC (X 10^3/mL)	10.5 ± 4.5	5.5 – 14.8
Hemoglobin (g/dl)	13.1 ± 2.2	10 – 16
CRP (mg/dl)	50.5 ± 25	10 – 132
D-dimer (mg/l)	1.9 ± 1.1	0.5 – 3
Creatinine (mg/dl)	1.3 ± 0.6	0.7 – 2.8
PH	7.34 ± 0.12	7.1 – 7.42
PaO2 (mmHg)	75 ± 20	40 – 95
PaCo2 (mmHg)	45.6 ± 19	30 – 79

The mean length of hospital stay for all patients was 7.8 ± 2 days, with a range between 3-17 days. In-hospital death occurred in 19 patients (17.6%), 28 patients (25.9%) required admission to ICU, and 22 patients (20.3%) required mechanical ventilation.

Result	N.of patients	Percent%
In_hospital death	19	%17.6
Admission to ICU	28	% 25.9
Mechanical ventilation	22	%20.3

Associations between Plasma D-dimer levels and clinically relevant outcomes:

30 patients (27.8%) had elevated D-dimer level (≥ 0.5 mg/l), and 78 patients (72.2%) had normal D-dimer level(table 1). The mean D-dimer level for patients with confirmed DVT/PE was significantly greater than patients without DVT/PE (2.6 ± 1 VS 1.9 ± 1.1 mg/l, respectively) (P= 0.015).

Characteristic	Patients with DVT/PE (17 patients)	Patients without DVT/PE (108 patients)	T_test	P_value
D_dimer (mg/l)	1 ±2.6	1.9 ±1.1	2.46	0.015

Plasma D-dimer level ≥ 0.5 mg/L was associated with in-hospital mortality as shown in table 3.

Table (3) The association between Plasma D-dimer levels and In-hospital mortality

Characteristics	In-hospital death	survivors	RR: Relative Risk (95% CI)	P-value
D-dimer < 0.5 (mg/L)	7(8.9%)	71 (91.1%)	1	0.0004
D-dimer ≥ 0.5 (mg/L)	12 (40%)	18 (60%)	6.76(2.32 – 19.6)	

Plasma D-dimer level ≥ 0.5 mg/L was associated with ICU admission as shown in table 4.

Table (4) The association between Plasma D-dimer levels and ICU admission

Characteristics	ICU admission	No ICU admission	RR (95% CI)	P-value
D-dimer < 0.5 (mg/L)	13 (16.7%)	65 (83.3%)	1	0.0007
D-dimer ≥ 0.5 (mg/L)	15 (50%)	15 (50%)	5 (1.97 – 12.6)	

Plasma D-dimer level ≥ 0.5 mg/L was associated with the need for mechanical ventilation as shown in table 5.

Table (5) The association between Plasma D-dimer levels and the need for mechanical ventilation

Characteristics	Mechanical ventilation	No Mechanical ventilation	RR (95% CI)	P-value
D-dimer < 0.5 (mg/L)	9(11.5%)	69 (88.5%)	1	0.0006
D-dimer ≥ 0.5 (mg/L)	13 (43.3%)	17(56.7%)	5.77 (2.1 – 15.7)	

No significant difference was found in respect to the length of stay between patients with elevated D-dimer levels and patients with normal D-dimer level (8.3 ± 2.2 VS 7.6 ± 2 days, respectively) (P=0.116).

	Elevated D_dimer ≥ 0.5 (mg/L) 30 patiens	Normal D-dimer < 0.5 (mg/L) 78 patients	T_test	P_value
Length of stay in hospital(day)	8.3±2.2	±2 7.6	1.58	0.116

Associations between Plasma D-dimer levels and baseline characteristics:

30 patients (27.8%) had elevated D-dimer level (≥ 0.5 mg/l), and 78 patients (72.2%) had normal D-dimer level. Table 6 shows Baseline characteristics stratified by the D-dimer concentration. Non-statistically significant associations of D-dimer levels with gender, gender, smoking, frequent exacerbation, ischemic heart disease, diabetes mellitus, WBC, pH, PaCO2, and PaO2 were found (P>0.05). We found statistically significant associations with age, renal dysfunction, hemoglobin, and the concentration of creatinine (P<0.05) table (6).

Table (6) Baseline characteristics stratified by the D-dimer concentration

Patients characteristics	D-dimer ≥ 0.5 (mg/L)	D-dimer < 0.5 (mg/L)	test	P-value
Age	69.2 ± 10	64 ± 12	2.1	0.037
Gender (F/M)	10/20	21/57	0.435	0.509
Smoking (yes/NO)	25/5	63/15	0.049	0.759
Frequent exacerbation (yes/NO)	7/23	15/63	0.225	0.635
Ischemic heart disease (yes/NO)	10/20	23/55	0.151	0.69
Diabetes mellitus (yes/NO)	9/21	18/60	0.554	0.456
Congestive heart failure (yes/NO)	9/21	8/70	6.36	0.01
Renal dysfunction(yes/NO)	8/22	5/73	8.39	0.003
WBC (X 10^3/mL)	10.7 ±4.9	9 ± 5	1.59	0.114
Hemoglobin (g/dl)	12.5 ± 2	13.5 ± 2	2.3	0.023
CRP (mg/dl)	59 ± 23	46 ± 22	2.7	0.007
Creatinine (mg/dl)	1.5 ± 0.5	1.2 ± 0.55	2.6	0.01
pH	7.33 ± 0.2	7.36 ± 0.11	0.014	0.98
PaO2 (mmHg)	72 ± 20	76 ± 19	0.96	0.336
PaCO2 (mmHg)	46.8 ± 18	40 ± 20	1.62	0.107

During index hospitalization, 19 patients (17.6%) died. The differences in main parameters between survivors and non-survivors are listed in Table (7). There were no significant differences between survivors and non-survivors with respect to age, smoking status, exacerbation frequency, and diabetes mellitus (DM).

There were more patients who suffered from ischemic heart disease (IHD), renal dysfunction (RD), and congestive heart failure (CHF) in the non-survivor group. Additionally, the non-survivors were significantly more hypercapnic, hypoxemic, and had lower PH table (7).

Table (7) Comparison of clinical and laboratory data between patients stratified according to survival during index hospitalization

Characteristics	Alive (89 patients)	Death (19 patients)	RR (95% CI)	P-value
Age (years)				
< 60	19 (21.3%)	3 (15.8%)	1	0.586
≥ 60	70 (78.7%)	16 (84.2%)	1.44 (0.34 – 5.4)	
Gender				
male	64 (72%)	13 (68.4%)	1	0.76
female	25 (28%)	6 (31.6%)	1.18 (0.4 – 3.45)	
Smoking				
No	16 (18%)	4 (21.1%)	1	0.75
Yes	73 (82%)	15 (78.9%)	0.82 (0.24 – 2.8)	
Frequent exacerbation				
No	74 (83.1%)	12 (63.2%)	1	0.056
Yes	15 (16.9%)	7 (36.8%)	2.87 (0.97 – 8.5)	
IHD Ischemic heart disease				
No	66 (74.1%)	9 (47.4%)	1	0.025
Yes	23 (25.9%)	10 (52.6%)	3.1 (1.1 – 8.8)	
DM Diabetes mellitus				
No	67 (75.3%)	14 (73.7%)	1	0.88
Yes	22 (24.7%)	5 (26.3%)	1.08 (0.35 – 3.36)	
CHF Congestive heart failure				
No	79 (88.7%)	11 (57.9%)	1	0.002
Yes	10 (11.3%)	8 (42.1%)	5.7 (1.86 – 17.6)	
RD Renal dysfunction				
No	82 (92.1%)	13 (68.4%)	1	0.007
Yes	7 (7.9%)	6 (31.6%)	5.4 (1.5 – 18.6)	
PH				
> 7.35	75 (84.3%)	10 (52.6%)	1	
7.2 – 7.35	13 (14.6%)	7 (36.9%)	4.03 (1.3 – 12.5)	0.015
< 7.2	1 (1.1%)	2 (10.2%)	15 (1.2- 180)	0.033
PaO2 (mmHg)				
≥ 60	80 (89.9%)	12 (63.1%)	1	0.005
< 60	9 (10.1%)	7 (36.9%)	5.1 (1.6 – 16.5)	
PaCO2 (mmHg)				
< 50	70 (78.7%)	9 (47.4%)	1	0.007
≥ 50	19 (21.3%)	10 (52.6%)	4.09 (1.45 – 11.5)	

4- Discussion.

The diagnostic workup of patients with suspected VTE/PE has been simplified by the use of D-dimer testing. It has been showing that D-dimer testing is a reliable marker for VTE/PE in patients with AECOPD with a high negative predictive value [(13)].

In our study, the prevalence of DVT/PE in patients with AECOPD was 13.6%, which is similar to that reported by Agkun et al [(14)] who diagnosed VTE in 13.3% of 120 patients with COPD. Fruchter et al [(15)], in a retrospective study of 61 AECOPD patients, reported a prevalence of DVT/PE of 16.4%.

We excluded patients with confirmed venous thromboembolism (DVT/PE), however, we found that the mean D-dimer level in patients with AECOPD and a confirmed DVT/PE was significantly higher compared to patients without DVT/PE (2.6 ± 1 mg/L vs. 1.9 ± 1.1 mg/L, P=0.015).

For AECOPD patients without DVT/PE,the mean D-dimer level was 1.9 mg/L (which is approximately 4 times greater than the upper limit of normal in our laboratory), and 27.8% of patients had a high D-dimer level (≥ 0.5 mg/L).). D-dimer concentration is known to be increased not only by VTE/PE but also by solid tumors, leukemia, chronic liver diseases, severe infections, after trauma, recent operations, disseminated intravascular coagulation, pregnancy, preeclampsia, exercise, vasculitis, sickle cell anemia crisis, myocardial infarction and unstable angina pectoris [(7)]. D-dimer is also elevated in smokers and stable COPD patients, possibly reflecting increased coagulation activation [(16)].

The significance of elevated D-dimer levels in patients presenting with AECOPD in whom thrombosis (of peripheral veins or pulmonary arteries) has been excluded, is unknown.

The most important finding in our study was the significant association between D-dimer level and the prognostic parameters in AECOPD. A higher D-dimer level was associated with increased in-hospital mortality (RR 6.76, 95%CI 2.32 – 19.7), increased admission to intensive care unit (RR 5, 95%CI 1.97-12.6), and an increased need for mechanical ventilation (RR 5.77, 95%CI 2.1 – 15.7). No statistically significant difference in the mean length of hospital stays according to D-dimer levels.

Previous studies have shown that elevated plasma D-dimer was associated with adverse outcomes in several conditions. Zhou et al [(9)] reported that a high D-dimer level upon admission was an independent risk factor for poor functional outcome and mortality in patients with spontaneous intracranial hemorrhage. Turak et al [(10)] showed that D-dimer level upon admission was a simple and valuable biomarker that allows to identifying high-risk infective endocarditis patients for in-hospital mortality. D-dimer ≥ 4.2 mg/L was independently associated with IE- related in-hospital death.

Hu et al [(17)] in their prospective study of 343 AECOPD patients, showed a significant association between D-dimer levels and in-hospital mortality. Elevated D-dimer at admission (≥ 985 mcg/L) increased the risk of in-hospital mortality (RR 6.51, P<0.05). In that study, AECOPD patients with VTE were not excluded.

Fruchter et al [15], in their retrospective study of 61 AECOPD patients (patients with VTE were excluded) showed that the level of D-dimer at admission could be used as a predictive biomarker of in-hospital mortality in AECOPD patients. D-dimer level > 1.52 mg/L predicted in-hospital mortality with a sensitivity and specificity of 100% and 63.6%, respectively.

Jinling Ma et al [18] in a retrospective study of 2,206 elderly AECOPD patients (80 years of age and older) who were followed up for 30 days after admission, found that D-dimer levels in patients who died within 30 days were higher compared to survivors ($p<0.001$). Patients who required mechanical ventilation had higher D-dimer levels than patients who did not require mechanical ventilation ($P<0.001$). A D-dimer value ≥ 1.66 mg/L on admission predicted death within 30 days with a sensitivity of 87.6% and specificity of 89.1%, and a D-dimer value ≥ 1.33 mg/L predicted the need for mechanical ventilation with a sensitivity of 89.4% and specificity of 82.9 %.

Raimondi et al [19] reported that plasma D-dimer levels increased in various infectious diseases. Querol-Ribelles et al [20] showed that plasma D-dimer levels increase with the severity of the community-acquired pneumonia. The observation of Piras et al [21] that demonstrated chronic systemic inflammatory syndrome in the vast majority of patients presenting to the emergency department with AECOPD is consistent with this]hypothesis. Because bacterial and viral respiratory tract infection is thought to play a major role in the pathogenesis of AECOPD, elevated D-dimer level may represent an increased inflammatory burden during exacerbation and consequently be associated with poor prognosis.

We explored the association between D-dimer levels with laboratory tests and clinical characteristics for AECOPD patients. The mean age of patients with a high D-dimer was significantly higher than patients with normal D-dimer ($P=0.037$). D-dimer level is known to increase with age. D-dimer levels were not associated with gender, smoking, frequency of exacerbations, ischemic heart disease, or diabetes mellitus, the results of our study are in agreement with Hu et al [17]. D-dimer levels were higher in patients with renal dysfunction and congestive heart failure. There were also some studies that showed D-dimer levels in patients with renal dysfunction were elevated [17] [22]. Hu et al [17] and Jafri et al [23] showed that D-dimer levels in patients with heart failure were higher than in patients without heart failure. D-dimer levels were associated with CRP, hemoglobin, and creatinine and were not associated with PH, PaCO2, PaO2. Our results are consistent with Hu et al [17]. Ya Jun Song et al [24], have reported that the plasma D-dimer levels significantly negatively related to PaO2 and positively related to PaCO2 in the patients with AECOPD combined with respiratory failure

We also explored other factors that affected in-hospital mortality in AECOPD patients. Age, gender, smoking, frequency of exacerbations, or diabetes mellitus did not correlate with in-hospital mortality. Whereas, ischemic heart disease (RR 3.1, 95%CI 1.1 – 8.8), congestive heart failure (RR 5.7, 95%CI 1.86 – 17.6), and renal dysfunction (RR 5.4, 95%CI 1.5- 18.6) increased the risk of death in hospital. Low PH on admission increased the risk of in-hospital mortality, and the risk was increased with

the severity of the low PH. A decrease in PaO2 below 60 mmHg increased the risk of in-hospital mortality by 5.1 (P=0.005). A PaCO2 elevation of more than 50 mmHg increased the risk of in-hospital mortality by 4.09 (P=0.007).

Several factors have been previously reported to be risk factors for death, including the frequency of AECOPD. Soler-Cataluna et al [25] have reported that frequent exacerbations were a risk factor for mortality. However, in the present study, we found that frequent exacerbations were not a risk factor for in-hospital mortality. The differing outcomes between studies may be related to the dissimilar definitions of frequent exacerbations. In our study, we could not collect the exact data on the exacerbations in the past year. But, we could collect the previous year's information of hospitalization due to AECOPD; therefore, frequent exacerbations were defined as patients who had at least one hospitalization for AECOPD in the past year.

We found that AECOPD patients with renal dysfunction and congestive heart failure had higher in-hospital mortality, which is consistent with previous studies [15] [17]. Ischemic heart disease was also a risk factor for in-hospital mortality. There is increasing awareness that ischemic heart disease IHD and cardiac comorbidity are major contributors to mortality in patients with COPD [15]. Chronic inflammation in patients with COPD promotes endothelial dysfunction and interacts with the fibrinogenesis, thrombogenesis and fibrinolysis sequence in the atherosclerosis lesion. Furthermore, increased inflammatory response during AECOPD may increase the ongoing inflammatory process associated with atherosclerosis and result in escalation of atherosclerosis and coronary artery luminal narrowing possibly through processes that involve fibrinolysis releasing D-dimer into the circulation thereby increasing the likelihood of atheroma plaque rupture and subsequent ischemia and myocardial events [26]. Thus, elevated D-dimer during AECOPD may be a useful marker for increased risk of developing cardiovascular events and death.

Limitations:

Our study has several limitations. We could not collect the exacerbation times in the past years. The frequent exacerbations were defined as patients with at least one hospitalization for AECOPD in the previous year.

One of the strengths of our study is the prospective method and exclusion of patients with confirmed DVT/PE which may reduce bias. An additional potential limitation is afact that VTE/PE was excluded by imaging modalities only in patients who presented with D-dimer levels above 0.5 mg/L (the upper limit of the normal range in our laboratory). It is hypothetically possible that VTE/PE was present and not detected in some patients with COPD with low D-dimer levels. Since, according to previous data, D-dimer has a very high negative predictive value for the exclusion of VTE/PE in patients with COPD, we assume that an insignificant proportion of patients with low D-dimer levels had undiagnosed clinically

important VTE/PE. Furthermore, the fact that patients with low D-dimer had lower in-hospital mortality strengthens this assumption.

5- Conclusion.

Conclusively, D-dimer was a risk predictor for in-hospital mortality, need for ICU admission, and need for mechanical ventilation of AECOPD patients. Additionally, the plasma D-dimer is a widely and rapidly examined cheaper biomarker, which means that D-dimer could be used as a predictive biomarker that allows to identify high-risk AECOPD patients

6- Recommendations.

Based on our results, it can be recommended to rely on D-dimer level upon admission as a prognostic indicator for short-term outcomes in AECOPD. We recommend further studies in the future on the role of D-dimer upon admission as a prognostic indicator of long-term outcomes in AECOPD. Further prospective studies are needed to establish its exact role as a possible novel prognostic marker in patients with COPD.

Authors' contributions:

LA, MH, MIK: designed the study. LA collected the data, analysis and interpretation of the result, and draft the manuscript. MH, MIK revised the manuscript. All authors read and approved the final manuscript.

Conflicts interests:

The authors have no conflict of interest associated with this article.

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