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ORIGINAL ARTICLE

Association of Serum D-dimer Level with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

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Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) is a major global health problem and is often associated with systemic inflammation. D-dimer level, an end product of degradation of cross-linked fibrin by plasmin, have been shown in some studies to be increased in patients with COPD exacerbation. But still, there is a debate regarding the diagnostic efficiency of D-dimers tests in COPD exacerbation patients. Therefore, this study is aimed to find the association of D-dimer with acute exacerbation of COPD.*

Methods*: This was a cross-sectional study conducted at the National Institute of Diseases of the Chest and Hospital (NIDCH) from March 2020 to February 2021. A total of 90 patients with a confirmed diagnosis of COPD were included after screening in according to the inclusion and exclusion criteria. Following informed written consent, physical examination, relevant investigations were done for all patients. In all cases, ethical issues and health issues were maintained properly and collected data were analysed by SPSS 16.*

Results: *Among 90 COPD patients, mean age of the study population was 56.24±11.24 (SD) years with a majority in age group 51-60 years (50%). Male-female distribution was 97%-male vs 3%-female. Overall frequency of higher D-dimer level was 57.8%. Higher serum D-dimer level was observed in AECOPD patients ($p<0.05$). Increased serum D-Dimer level was also significantly associated with increased $PaCO_2$ and decreased P_{aO2}. In multivariate analysis, PaCO2 (>45 mmHg) and serum D-Dimer (>0.5 pg /ml) were found to be independent predictors for severe exacerbation of chronic obstructive pulmonary disease.*

Conclusion:*There is association between serum D-dimer level with acute exacerbation of COPD patients.*

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Introduction:

Chronic obstructive pulmonary disease (COPD) is a global health concern that contributes significantly to mortality and morbidity.[1]In Bangladesh, pooled COPD prevalence among Bangladeshi adult was 12.5%. It is anticipated that COPD will be the third leading cause of global death by 2030, and almost all (90%) of the deaths caused by COPD occurred in low and middle-income countries.[2]Acute exacerbations in COPD are episodes of worsening of respiratory

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symptoms that cause physiological changes and associated with an increase in the airway and systemic inflammation that needs further treatment.The frequency and severity of exacerbation are the most important factors determining the overall prognosis in COPD. Hence, accurate individual risk assessment during an exacerbation is essential for clinical management and rational allocation of medical resources. Consequently, reliable predictors for in-hospital mortality, which are easily obtained upon admission, namely biomarkers, are urgently needed.[3] The biomarker D-dimer is often linked with COPD. The mechanisms behind this could be COPD being a chronic inflammatory state leading to hypercoagulability, and it causes other systematic inflammations and the increased chances of venous thrombo-embolism, causing a pulmonary embolism. D-dimer has been seen to increase in COPD patients than controls and rises more in acute exacerbations.The association of D-dimer with acute COPD may help indicatethe severity and prognosis, but it is still controversial. With the high prevalence of COPD, an easily available biomarker such as D-dimer could help triage these patients leading to proper patient and hospital management. Therefore, this study aimed to determine whether D-dimer levels obtained upon admission in patients with AECOPD correlates with both in-hospital mortality and long-term prognosis.

Materials and Methods:

This wasa cross-sectional study and was conducted at the National Institute of Diseases of the Chest and Hospital (NIDCH) from March 2020 to February 2021. A total of 90 patients with a confirmed diagnosis of COPD included after screening in according to the inclusion and exclusion criteria. Following informed written consent, physical examination, relevant investigations were done for all patients.

General objectives:

To determine the association of serum D-dimer level with acute exacerbation of COPD patients

Specific objectives:

- To measure serum D-dimer in AECOPD patients
- To establish the relationship between AECOPD with serum D-dimer level
- To determine the association of serum D-dimer level with arterial blood gas and SpO2 in AE COPD

Selection Criteria:

Inclusion criteria:

- All patients admitted to the in-patient department of NIDCH, diagnosed as a case of AE-COPD based on: at least 2 of the three following symptoms:
- Age>40 years
- Sex- both male and female
- Patient willing to participate in this study

Exclusion criteria:

- Patients who are laboratory confirmation (RT-PCR) of COVID-19 infection
- Other Known acute respiratory infections
- Patient any coagulation disorder, previous history of venous thromboembolism,haematological disorder
- Receiving current anticoagulation treatment
- Patient with any malignancy.

Results:

Mean age of the study population was 56.24±11.24 (SD) years with majority in age group 51-60 years (50%) with male predominance (97%).[Table-I]. Among total population 70% were smoker and 30% were non-smoker. [Figure-1].Serum D-Dimer level was significantly associated with PaO2 and PaCO2 ($p<0.05$).[Table-IV]. Increased serum D-Dimer level was also significantly associated with increased PaCO2 and decreased PaO2 [Table-VI]. Serum D-dimer level with PaO2 in AE COPD patients were significantly associated ($r= -0.745$, $p(<0.001)$[Figure-2]. Serum D-Dimer level had a positive correlation with PaCO2 level ($r=0.835$ and <0.001)[Figure-3].Serum D-dimer level with pH in AE COPD patients were significantly associated ($r= -0.510$, $p<0.001$) that means pH level decreases with increased serum D-dimer level.[Figure-4].Serum D-dimer level with Spo2 in AE COPD patients were significantly associated ($r=-0.651$, $p<0.001$) that means Spo2 level decreases with increased serum D-dimer level.[Figure-5].In multivariate analysis, PaCO2 (>45 mmHg) and serum D-Dimer (>0.5 pg / ml) were found to be independent predictors for severe exacerbation of chronic obstructive pulmonary disease. [Table-IX].

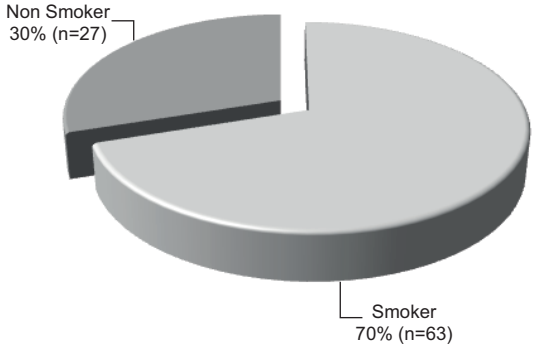

Fig.-1: *Distribution of patients according to presence of smoking (n=90)*

Table-I

Demographic characteristics of the study patients (n=90)

Demographic characteristics	Frequency(n)	Percentage
Age (years)		
41-50	24	26.7
51-60	45	50.0
61-70	13	14.4
>70	8	8.9
Mean±SD	56.24	±11.24
Gender		
Male	87	96.7
Female	3	3.3
BMI (kg/m^2)		
Underweight	2	2.2
Normal	49	54.4
Overweight	37	41.1
Obese	2	2.2
Mean±SD	24.1	±1.66

Table-II

Co morbidities among the patients of acute exacerbation of COPD (n=90).

Co morbidities	Frequency(n)	Percentage
Diabetes mellitus		
Present	15	16.7
Absent	75	83.3
Hypertension		
Present	23	25.6
Absent	67	74.4

Among the respondents 16.7% had diabetes mellitus and 25.6% had hypertension.

Table-III

Distribution of patients of AECOPD patients according to hospital ward (n=90).

Hospital Unit	Gender		Total
	Male	Female	
Indoor ward	56(62.2)	2(2.2)	58(64.4)
Respiratory Care Unit	31(34.4)	1(1.1)	32(35.6)
Total	87(96.6)	3(3.3)	90(100)

Table-IV

Laboratory investigations among acute exacerbation of Chronic obstructive pulmonary disease patients (n=90)

Investigation profile	Mean±SD
White blood cell count ($\times 10^9$/L)	11.84±4.35
Lymphocyte ($\times 10^9$/L)	4.04±2.23
Neutrophil count ($\times 10^9$/L)	6.64±2.54
$PaCO_2$ (mm Hg)	51.8±10.1
PaO_2 (mm Hg)	53.4±9.97
pH	7.17±0.28
Spo_2 (%)	90.7±2.6
C-reactive protein (mg/L)	14.5±5.95
Serum D-Dimer level (pg /ml)	1.09±0.66

Table-V

Investigations profile among AECOPDpatients (n=90)

Investigation profile		Frequency (n)	Percentage (%)
Serum D-Dimer level (pg/ml)	<0.5	38	42.2
	>0.5	52	57.8
PaO_2 (mmHg)	>60	34	37.8
	<60	56	62.2
$PaCO_2$ (mmHg)	>50	55	61.1
	<50	35	38.9

Table-VI

Types of exacerbationamong AECOPD patients (n=90)

COPD Stages	Frequency (n)	Percentage (%)
Type 1- Mild exacerbation	8	8.9
Type 2 - Moderate exacerbation	31	34.4
Type 3 - Severe exacerbation	51	56.6

Table-VII

Association of serum D-dimer level with PaO_2 in AE COPD patients (n=90)

Serum D-Dimer level (pg/ml)	PaO_2 (mmHg)		P value
	>60	<60	
<0.5	34	4	0.001
>0.5	0	52	

*P value was determined by Chi-square Test (χ^2)

Table-VIII

Association of serum D-dimer level with paCO2 in AE COPD patients (n=90)

Serum D-Dimer level (pg/ml)	$PaCO_2$ (mm Hg)		P value
	>50	<50	
<0.5	4	34	0.001
>0.5	51	1	

*P value was determined by Chi-square Test (χ^2)

Table-IX

Association of Types of exacerbation of COPD with serum D-Dimer, PaO_2,$PaCO_2$, pH, Spo_2 level among AECOPD patients (n=90)

Variable	Types of exacerbation of COPD			P value
	Mild exacerbation	Moderate exacerbation	Severe exacerbation	
Serum D-Dimer level (pg/ml)	0.4±0.3	1.1±0.2*$	1.8±0.7*$*µ	*<0.001$
PaO_2 (mmHg)	62.5±7.2	46.5±4.8*β	45.2±4.7	*<0.001$
$PaCO_2$ þ(mmHg)	42.4±7.4	58.8±5.1*γ	57.2±3.3	*<0.001$
pH	7.50±0.28	7.26±0.23*&	7.06±0.25	*<0.001$
Spo_2 (%)	93.4±3.4	92.5±2.3	89.2±1.4*^	*<0.001$

*P value was determined by One way ANOVA test. Post-Hoc analysis by Bonferroni method done. *â and *ã Significantly low in comparison to mild group vs moderate group, *$ Significantly low in comparison to mild group vs moderate group,*$*µin comparison to moderate group vs severe group,*&Significantly low in comparison to mild group vs moderate group and *^Significantly low in comparison to moderate group vs severe group.

Table-X

Multivariable regression analysis for severe exacerbation of COPD

	Adjusted OR	95% CI		P value
		Lower	Upper	
Smoker	0.321	0.017	6.134	0.450ns
Diabetes mellitus	0.010	0.002	1.897	0.998ns
Hypertension	2.398	0.049	17.068	0.659ns
$PaCO_2$ (>45 mmHg)	51.941	1.011	68.733	0.049s
PaO_2 (<60 mmHg)	0.468	0.004	60.952	0.760ns
pH (<7.35 or >7.45)	4.240	0.364	49.335	0.249ns
Spo_2 (<96 %)	2.419	0.005	37.245	0.781ns
Serum D-Dimer level (>0.5 pg /ml)	25.523	1.469	43.456	0.026s

s= significant, ns= not significant
p-value reached from multivariate analysis by binary logistic regression analysis
OR=Odd's Ratio

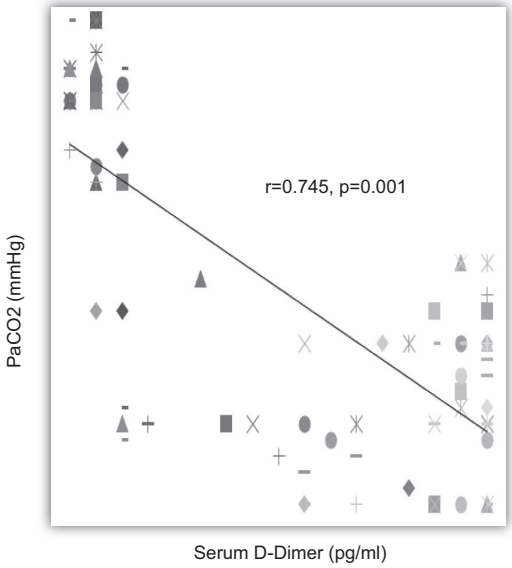

Fig.-2: *Correlation between serum D-dimer level with PaO_2 in AE COPD*

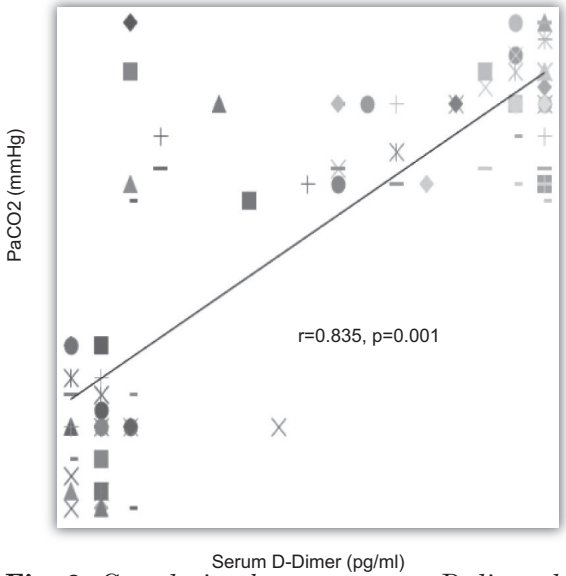

Fig.-3: *Correlation between serum D-dimer level with PaCO2 in AE COPD patients (n=90)*

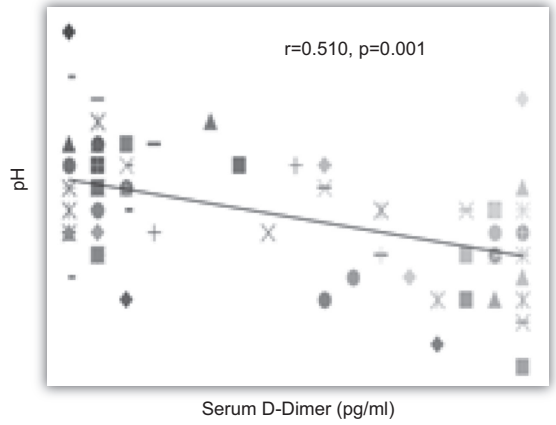

Fig.-4: *Correlation between serum D-dimer level with p^H in AE COPD patients (n=90)*

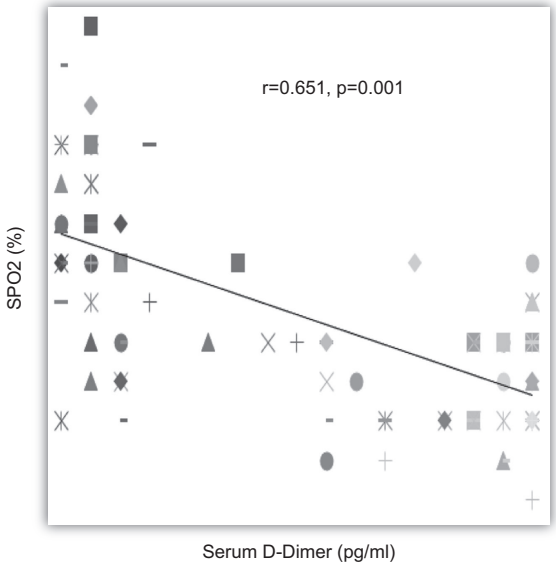

Fig.-5: *Correlation between serum D-dimer level with Spo_2 in AE COPD patients (n=90)*

Discussion:

Majority of respondents belonged to the age group 50-60years (50%) and followed in decreasing order by 41-50 years (26.7%), 61-70years (14.4%) and >70years (8.9%). Mean age was 56.24±11.24 years. In Rashid et al.[4] study, most of the patients of acute exacerbation of COPD (AECOPD) (56%) in the age group 55-65 years which corresponds with the recent study.

According to the study, among the respondent majority BMI were within normal limit followed in decreased order by 41.1% were overweight, 2.2% were underweight and 2.2% were obese. The mean body mass index was 24.1±1.66(SD) kg/m^2. Moreover, among the respondents 16.7% had diabetes mellitus and 25.6% had hypertension.In Hersh et al.[5] study, family history of COPD may contribute to nearly 20% of the risk of COPD in the population. Subjects with a parental history of COPD had more severe disease, with lower lung function, exercise capacity, and quality of life. In Ajit et al.[6] study, they found DM was present in 23.05% in patients with acute exacerbation of COPD which corresponds with the current study. They also found acute exacerbations were seen more in diabetics than non-diabetics with a significant difference.In Assal and Kamal study, the mean BMI was 23.54±6.42 (SD) kg/$m^2$and they also found with the severity of the obstruction (GOLD staging) BMI of the patient decreases, and it was statistically significant.

In this study, the most common features acute exacerbation of COPD was cough (96.7%) followed in decreasing order by dyspnea (91.1%), sputum (87.8%), fatigue (73.3%), fever (16.7%) and accessory muscle use (11.1%). Majority had crepitation (87.8%) followed in decreasing order by wheezing (42.2%) and cyanosis (33.3%) as clinical signs. In Mohan et al.[8] study they found that, common symptoms of acute exacerbation of COPD were cough, sputum production, fatigue, fever and accessory muscle and among them cough and sputum production were most common clinical feature which similar to our result also. Furthermore, the most common signs we found in COPD patients were crepitation (90.7%) followed by wheezing (40.7%) and cyanosis (34.9%) which corresponds with this study findings.

In this study, among the patients of acute exacerbation of chronic obstructive pulmonary disease majority 56.6% were in type 3 – severe exacerbation followed in decreasing order by 34.4% were in type 2 – moderateexacerbation, 8.9% were in type 1-mild exacerbationby types of exacerbation of COPD.Wong et al.[9] study, more than 85% of admissions had the severity of COPD equal to or greater type 3 which corresponds with the study results.

According to this study, among the respondents, the white blood cell count was 11.84±4.35 (SD) $\times 10^9$/ L, lymphocyte count was 4.04±2.23 (SD) $\times 10^9$/L, neutrophil count was 6.64±2.54 (SD) $\times 10^9$/L, $PaCO_2$was 51.8±10.1 (SD) mm Hg, PaO_2 was 53.4±9.97 (SD) mm Hg, pH level 7.17±0.28 (SD), Spo_2 (%) 90.7±2.6 (SD), C-reactive protein was 14.5±5.95(SD) mg/L, serum D-Dimer level was 1.09±0.66 (SD)pg /ml.Moreover, 57.8% had serum D-Dimer level >0.5pg /ml, 62.2% had PaO_2 <60 mmHg, 61.1% had $PaCO_2$>50 mmHg. In Taylan et al.[10] study, they found inflammatory markers, such as WBC, CRP, neutrophil, lymphocyte and ESR were found to be significantly elevated in exacerbated COPD compared to stable COPD and control participants. Cukic[11] study, in patients with COPD there is the decrease of PaO2 and increase of $PaCO_2$ level, and there was a statistically significant decrease of PaO2 ($p<0.01$) and an increase of PaCO2 ($p<0.01$) during in patients with acute exacerbation of COPD which corresponds with recurrent study. According to Akpinar et al.[12] study, the mean D-dimer level of the patients was 1.56±2.18 pg/mL in ÿþpatients with COPD exacerbation.

In this study,serum D-Dimer levelwas significantly associated with PaO_2 and $PaCO_2$ ($p<0.05$). Serum D-dimer level with PaO_2 in AE COPD patients were significantly associated ($r= -0.745$, $p<0.001$) that means PaO_2level decreases with increased serum D-dimer level and Serum D-Dimer level increased when $PaCO_2$was increased. Serum D-Dimer level had a positive correlation with $PaCO_2$ level (r=0.835 and <0.001). That means serum D-Dimerlevel increases along with $PaCO_2$level. Serum D-dimer level with p^H in AE COPD patients were significantly associated ($r= -0.510$, $p<0.001$) that means $p_H$level decreases with increasedserum D-dimer level.Serum D-dimer level with SpO_2in AE COPD patients were significantly associated ($r=-0.651$, $p<0.001$) that means SpO_2level decreases with increasedserum D-dimer level.Moreover, thetypes of exacerbation COPD were significantly associated with serum D-Dimer level, PaO_2, $PaCO_2$, pH and Spo_2. The serum D-Dimer level and $PaCO_2$increased with increasing the stage of COPD. The PaO_2 decreased with increasing the stage of COPD. The pH and SpO_2 decreased with increasing the stage of COPD.In Mohan et al.[8] study, they also found that the level of PaO_2 and $PaCO_2$ significantly associated with the stage of COPD by Gold criteria. PaO_2 decreased and $PaCO_2$ increased with increasing the severity of the disease. According to Ishikawa et al.[13] study, elevated serum D-dimer is associated with the risk of developing acute exacerbation.In Hu et al.[14] study, they found serum D-dimer was a risk predictor both for in- hospital and 1-year mortality of AECOPD patients Moreoverserum D-dimer level increased with the severity of the disease which corresponds with the study.

Conclusion:

There is association between serum D-dimer level with acute exacerbation of COPD patients.Further studies with larger sample size are recommended. Further study can be done to establish predictive value of serum d-dimer level in AECOPD.This study may be carried on other hospital.

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