Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.2.20

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (2): 408–414

ORIGINAL PAPER

D-dimer as a potential biomarker in chronic obstructive pulmonary disease

Anish V. Patel [1], Mayurika S. Tyagi [2], Adreena Mittal [1], Sumit Chandra [1], Hina Kausar [1], Sivanesan Dhandayuthapani [3]

[1] Department of Pathology, Santosh Medical College & Hospital, Santosh Deemed to be University, Ghaziabad, Delhi, Uttar Pradesh, India
[2] Department of Immunohematology and Blood Transfusion, Santosh Medical College & Hospital, Santosh Deemed to be University, Ghaziabad, Delhi, Uttar Pradesh, India
[3] Central Research Facility, Santosh Deemed to be University, Ghaziabad, Delhi, Uttar Pradesh, India

ABSTRACT

Introduction and aim. Despite signs of drop in tuberculosis in the middle of the twentieth century, up to 75% of men were smokers at that time, which contributed to the epidemic of chronic obstructive pulmonary disease (COPD) in the latter half of the century. The present study was conducted with the main focus of establishing a relation between D-dimer and lung function in patients with COPD.

Material and methods. A hospital-based observational cross-sectional study involved 108 subjects, divided into 54 cases (COPD patients) and 54 healthy controls (41-80 years old). The dry volume spirometer was used to assess the lung health of the study population. D-dimer assay was performed on peripheral blood drawn from study subjects using the second generation latex-enhanced immunoturbidimetric assay on the Diagon Fully Automatic COAG XL Coagulation Analyzer.

Results. Spirometry tests revealed COPD patients showing reduced lung function (42.59% with normal, 51.85% with mild, and 5.56% with moderate degree of forced expiratory volume in 1 second and forced expiratory volume in 1 second/ forced vital capacity). Patients with COPD under different age groups and both the genders showed an elevated level ($p<0.05$) of D-dimer in correlation with the spirometry measurements.

Conclusion. The D-dimer is promising plasma biomarker which demonstrated a strong correlation with the spirometry measurements and different morphological categories in patients with COPD. The D-dimer could serve as a reliable biomarker for validating and confirming the various morphological classifications among individuals with COPD.

Keywords. chronic obstructive pulmonary disease, D-dimer, inflammatory markers, smoking, spirometry

Introduction

In India, chronic obstructive pulmonary disease (COPD) is considered the second most common cause of death with disability adjusted life years. In addition, 7% of Indian adults over 30 years of age have had COPD.[1] Over the years, the smoking epidemic has been rapidly declining in western nations, but things are different in other parts of the world. COPD was one of the leading causes of illness and death worldwide in the 2020s, with a predicted increase in morbidity.[1]

COPD is a progressive lung disease characterized by persistent airflow limitation. The pathophysiology

Corresponding author: Mayurika S. Tyagi, e-mail: somyamayuri@hotmail.com

Received: 28.10.2024 / Revised: 6.02.2025 / Accepted: 8.02.2025 / Published: 30.06.2025

Patel AV, Tyagi MS, Mittal A, Chandra S, Kausar H, Dhandayuthapani S. D-dimer as a potential biomarker in chronic obstructive pulmonary disease. *Eur J Clin Exp Med.* 2025;23(2):408–414. doi: 10.15584/ejcem.2025.2.20.

of COPD involves chronic inflammation of the airways and lung tissue, primarily due to long-term exposure to harmful particles like cigarette smoke (Fig. 1). This leads to structural changes in the lungs, including airway remodeling, mucus hypersecretion, and destruction of alveolar walls (emphysema), which alter gas exchange. Inflammation in COPD is primarily driven by immune cells such as neutrophils, macrophages, and T lymphocytes, which release pro-inflammatory cytokines and proteases. These mediators contribute to airway narrowing, fibrosis, and alveolar destruction. The imbalance between proteases and antiproteases (e.g., α1-antitrypsin deficiency) accelerates lung tissue damage. Additionally, oxidative stress plays a crucial role in exacerbating inflammation and tissue injury. As the disease progresses, patients experience increased dyspnea, reduced lung function, and frequent exacerbations, significantly affecting quality of life.[2,3]

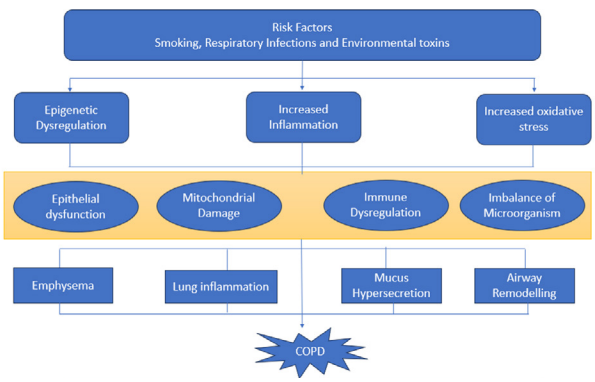

Fig. 1. Pathophysiology of COPD

Most of morbidity associated with COPD worldwide usually begins with persistent respiratory symptoms, such as progressive dyspnea, sputum production, coughing, wheezing, and tightness in the chest.[4] With some daily fluctuation, symptoms manifest differently from asthma. In addition, periods of clinical stability are sometimes interspersed with abrupt worsening, also known as acute exacerbations. However, some patients also reported non-respiratory symptoms such as anxiety, depression, anorexia, exhaustion, and weight loss.[5,6]

A D-dimer is a protein fragment that the body makes when a blood clot dissolves in the body. The D-dimer is normally undetectable or detectable only at a very low level unless the body forms and breaks down significant blood clots. The presence of D-dimers in the blood is a reliable clue that clotting has begun. The study evaluated that patients with COPD are prone to clinical exacerbations that may be associated with a powerful prothrombotic stimulus. Prothrombotic markers are also significantly altered in the state of COPD and exacerbation, which could predispose to venous thromboembolism in these patients, thus modifying the severity of the disease.[7]

COPD is a curable and preventable. However, it also has some important extrapulmonary side effects that may influence a patient's condition with nonreversible airflow limitation as the hallmark of its pulmonary component.[8] The restriction of airflow is typically progressive and linked to an aberrant inflammatory reaction of the lungs to harmful particles or gases.

Aim

The purpose of this study is to assess the clinical value of specific biomarkers in chronic diseases by evaluating their ability to diagnose and predict disease outcomes. As precision medicine gains momentum, it is crucial to identify biomarkers that accurately reflect disease progression and treatment response. Additionally, exploring the biological pathways linked to these biomarkers can offer valuable insight into disease development and possible therapeutic targets. The current study specifically examines the biomarker with significant translational potential, focusing on their ability to predict disease progression and response to treatment. The novelty of this study stems from its robust methodological approach, the diverse functionality of patients, and the focus on practical application, which makes it relevant to both researchers and clinicians. The results have the potential to influence future guidelines, contributing to more personalized and effective treatment of COPD.

Material and methods

A hospital observational cross-sectional study conducted in the Central Clinical Laboratory of Pathology in a tertiary care hospital at NCR-Delhi. Men and women in all age groups attending the outpatient and inpatient department of the Department of Medicine from January 2023 to January 2024 in a tertiary care hospital with a confirmed diagnosis of COPD were involved in the present study with proper informed written consent along with healthy persons with the same age and sex. The study was carried out after receiving approval from the Institutional Ethics Committee (IEC) Lr. No.: SU/2022/3108[37]

Sample size calculated by using the formula:

$$n = [Np(1 - p)]/[(d2/Z12 - \alpha/2*(N - 1) + p*(1 - p)]$$

Where,

- N: Population size (for finite population correction factor) 60
- *p:* Hypothesized % frequency of outcome factor in the population 16.67%+/-3.2
- *d:* Confidence limits as % of (absolute +/-%) 3.2%

With 95% confidence interval. The study group consists of a total of 108 subjects, including 54 cases and 54 controls.

Inclusion and exclusion of cases: known cases of COPD and those who have given their informed consent were included in the study. Whereas patients with

comorbid conditions such as sepsis, pulmonary embolism, venous thromboembolism, patients on anticoagulant therapy, known cases of malignancy, and patients who refuse to sign the written informed consent form were excluded from the current study.

The relevant patient history, including the time of diagnosis of COPD, past history, and treatment, was obtained from the patients' outpatient and inpatient department files according to the standard proforma. The dry volume spirometer was used to assess the lung health of the study population by a set of well-trained residents and technicians. The dry volume spirometer, which was used in other large population-based studies, such as the European Community Respiratory Health Survey (ECRHS).[9] The calibration / quality check of the spirometers was carried out daily basis following the American Thoracic Society standardization of spirometry.[10] Furthermore, the D-dimer assay was performed on peripheral blood drawn from study subjects under aseptic precautions in a 3.2% sodium citrate vacutainer tube with a blood to anticoagulant ratio of 9: 1. Following the manufacturer's instructions, the D dimer assay was done using the second generation latex-enhanced immunoturbidimetric assay, which is Dia-D dimer kit (Catalog No. 32120) from Diagon, on the Diagon Fully Automatic COAG XL Coagulation Analyzer. It is a fully automatic, quantitative assay, using agglutination and photometric analysis to measure the D-dimer levels. In the presence of D-dimer antigens, antibody-coated latex beads will cause agglutination. In the presence of D-dimer antigens, agglutination occurs because of antibody-coated latex beads which are directly proportional to the degree of light absorption, as measured by the integrated absorbance reader of the COAG XL analyzer (Budapest, Hungary).

Statistical analysis

Data were collected and entered in MS Excel 2021. Different statistical analyzes were performed using SPSS trial software (IBM, Armonk, NY, USA).

Results

The study consists of a total of 108 subjects, including 54 cases and 54 controls (Table 1).

Table 1. Distribution by age of study subjects

Age distribution	Control		COPD patients	
	Frequency	Percentage	Frequency	Percentage
41–50	23	42.59	26	48.15
51–60	16	29.63	13	24.07
61–70	9	16.67	8	14.81
71–80	6	11.11	8	12.96

The control and study subjects ranged from 41 to 80 years of age with maximum subjects in the 41 to 50 years age group (42.59% controls and 49.15% cases) followed by the 51 to 60-year age group. (Table 1). The male to female ratio in the control group was 1:1 (27 males and 27 females) and for the COPD patient group was 1.07:1 (28 males and 26 females).

There was no significant difference in the number of male and female participants between the two study groups.

The distribution of control and COPD patients according to their occupations showed that among study subjects, 37.04% of the control group and 31.48% of the COPD group were farmers. Additionally, 35.19% of the control and COPD groups were manual workers, while 27.78% of the control group and 33.33% of the COPD group were skilled professionals (Table 2).

Table 2. Occupational distribution of the study subjects

Occupation	Control		COPD patients	
	Frequency	Percentage	Frequency	Percentage
Farmer	20	37.04	17	31.48
Manual	19	35.19	19	35.19
Skilled/Professional	15	27.78	18	33.33

The degrees of forced expiratory volume in 1 second (FEV1) of the study groups are presented in Table 3. It is clearly recorded that 94.44% of control subjects with normal and only 5.56% with mild degree of FEV1 and FEV1/forced vital capacity (FEV1/FVC) were recorded. However, in patients with COPD only 42.59% with normal, 51.85% with mild, and 5.56% with moderate degree of FEV1 and FEV1/FVC were recorded. No patient found with sever degree of FEV1 and FEV1/FVC was found (Table 3). The results observed in COPD patients were significant ($p<0.05$) on comparison with the normal subjects.

Table 3. Degree of 'FEV1' and "FEV1/FVC ratio" of the study subjects

Category	Category	Control		COPD patients	
		Frequency	Percentage	Frequency	Percentage
GOLD I (>80%)	FEV1/FVC (>0.7)	51	94.44	23	42.59
GOLD II (50 to 80%)	FEV1/FVC (<0.7)	3	5.56	28	51.85
GOLD III (30 to 50%)	FEV1/FVC (<0.6)	0	0	3	5.56
GOLD IV (<30%)	FEV1/FVC (<0.5)	0	0	0	0

The results recorded from the control and COPD patients with respect to forced expiratory flow (FEF) 25% to 75% as tabulated in Table 4 the FEV1 and FEV1/FVC observed in the control and COPD patients in the current study. The results showed that the statistical significance was $p<0.05$.

Table 5 showed the various morphological types observed among patients with COPD. Approximately 61.11% of the patients were classified as chronic bronchitis, whereas 33.33% were classified as emphysema

and only 5.56% were with small airway disease. The results were highly significant (p<0.005) among the various categories of morphological types observed in patients with COPD.

Table 4. FEF over the middle half of the FVC. FEF 25% to 75% of the study subjects

Category	Control		COPD patients	
	Frequency	Percentage	Frequency	Percentage
GOLD I (>79%)	51	94.44	23	42.59
GOLD II (60 to 79%)	3	5.56	28	51.85
GOLD III (40 to 59%)	0	0	3	5.56
GOLD IV (<40%)	0	0	0	0

Table 5. Morphological types of COPD cases among study subjects

Cases	Frequency	Percentage
Chronic bronchitis	33	61.11
Emphysema	18	33.33
Small airway disease	3	5.56

The D-dimer levels determined in the COPD patients have been classified according to morphological variations and tabulated in Table 6. The results showed that the majority of COPD under the chronic bronchitis, emphysema, and Small Airway disease are found to have elevated levels of D-dimer, which is significant (p<0.05) between the other morphologically varied categories. On comparison using ANOVA, the values are significant (p<0.05)

Table 6. Level of D-dimer amongst the various morphological cases of COPD

D-dimer level	Chronic bronchitis	Emphysema	Small airway disease	Total
<0.5 µg/mL	3	6	1	10
0.5–3.9 µg/mL	18	12	2	32
>4 µg/mL	12	0	0	12
Total	33	18	3	54

The D-dimer levels determined in the COPD patients have been compared with the different age groups of the patients and are tabulated in Table 7. The results showed that COPD under different age groups showed an elevated level of D-dimer, which is significant (p<0.05) on compared to the age group against the control subjects. On comparison, the values are significant (p<0.05)

Table 7. Comparison of age group with D-dimer

Age in years	Control	COPD	p
41–50	0.24±0.12	1.36±1.24	<0.0001
51–60	0.27±0.12	2.52±1.31	<0.0001
61–70	0.23±0.14	3.86±0.93	<0.0001
71–80	0.24±0.13	5.17±0.92	<0.0001

The levels of D-dimer determined in study subjects have been compared with the gender of the control patients and tabulated in Table 8. The results showed that COPD under both the genders showed an elevated level of D-dimer, which is significant (p<0.05) on compared to the age group against the control subjects. In comparison, the values are significant (p<0.05).

Table 8. D-dimer of male vs. female between control and COPD patients

D-dimer value (µg/mL)			
Gender	Control	COPD patients	p
Male	0.24±0.13	2.64±1.96	<0.0001
Female	0.25±0.12	2.36±1.60	<0.0001

Table 9 shows the positive correlation with elevated D-dimer against the spirometry measurements. In correlation coefficient analysis, it was determined that the levels of elevated D-dimer showed a positive correlation with the spirometry measurements. Values are statistically significant (p<0.05).

Table 9. Correlation coefficient of D-dimer of COPD cases against spirometry values

D-dimer level		FEV1	Degrees of FEV1/FVC	FEF 25% to 75%	Correlation coefficient	p
<0.5 µg/mL	0.232	23	23	23	0.792	0.032
0.5–3.9 µg/mL	2.05	28	28	28		
>4 µg/mL	5.75	3	3	3		

Discussion

In the current study, the highest prevalence of COPD among the group was determined to be in the age group 40–50 (48.15%) and followed by 50-60 (24.07%), respectively, with the least number observed in the age group 70–80 (12.96%). Although earlier studies have reported that COPD is most commonly affects males than the female, in our current study we have observed that the prevalence of COPD in both men and female are almost equal, which might be one of key findings of the current research.[11] Similar to the other studies, in the current study also the GOLD criteria grade II followed by grade III, 28% and 23% were observed respectively.[12-14]

COPD is a heterogeneous disease with varying pathophysiological mechanisms in different GOLD stages, which may influence biomarkers differently. The D dimer, as a marker of fibrinolysis and inflammation, is likely to vary in clinical utility across stages, particularly as the disease progresses from mild (GOLD-1) to more severe stages (GOLD-4). Limiting the study to only GOLD-1 patients would compromise the ability to assess D-dimer as a reliable biomarker across the full spectrum of severity of COPD. By excluding higher stages, key insights related to systemic inflammation, comorbidities, and disease complications, which are more pronounced in moderate to severe COPD, could be missed or lead to a false negative result. Therefore,

including patients in the full GOLD spectrum ensures a more comprehensive and accurate evaluation of the potential as a biomarker in COPD.[15,16]

In the present study, we confirmed that the D-dimer level was higher in COPD compared to healthy individuals. This was in contrast to studies by Maclay et al. and Arregui et al., where there was no significant difference in D-dimer compared to normal level.[17,18] Comparison of D-dimer values with respect to the Spirometer findings of our current study is also compared to the earlier studies where a significant correlation has been established.[19,20]

COPD is a common, debilitating and life-threatening respiratory disease and healthcare costs for many years worldwide, including India. 'GOLD' is best explained as 'a common, preventable, and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.' Exacerbations and comorbidities contribute to the overall severity in individual patients.[21]

The D-dimer has been increasingly studied as a potential biomarker to predict mortality and survival in various diseases, including COPD. In the context of COPD, D-dimer levels reflect fibrinolysis and systemic inflammation, both of which are involved in disease progression and exacerbations. Elevated D-dimer levels in patients with COPD can indicate an increased thrombotic risk, endothelial dysfunction, and inflammatory state, all of which are associated with worse outcomes.[22]

A recent study has suggested that elevated levels of D-dimer correlate with higher mortality in patients with COPD, likely due to the increased risk of cardiovascular events, deep vein thrombosis, and pulmonary embolism, which are common comorbidities in COPD.[23] Additionally, D-dimer has been shown to correlate with exacerbations and disease severity, further supporting its role as a prognostic tool.[24] However, while elevated D-dimer is associated with poor outcomes, it is not specific to COPD and can be influenced by other factors such as infection, cancer, and systemic inflammation, making its use as a solitary biomarker challenging. The referenced study supports the utility of D-dimer as an indicator of mortality risk in patients with COPD, particularly in the context of exacerbations or comorbidities.[25] However, its predictive value is enhanced when combined with other clinical markers or diagnostic tools, such as lung function tests or biomarkers of systemic inflammation, to improve accuracy and clinical applicability.[25]

COPD occurs in most of the morbidity all over the world and usually manifests with chronic respiratory symptoms including progressive dyspnea, sputum production, coughing, wheezing and tightness of the chest.[4] The symptoms show different to asthma with a little variation day by day.[26] Furthermore, durations of clinical stability are most often punctuated with sudden episodes of deterioration, called acute exacerbations. On the other hand, several patients would also experience nonrespiratory symptoms,including fatigue, anorexia, weight loss, mood down, and anxiety.[5-6] Moreover, periods of clinical stability in COPD are often disrupted by abrupt episodes of worsening, referred to as acute exacerbations. In addition, numerous patients also encounter nonrespiratory symptoms, including lethargy, loss of appetite, reduced body weight, depression, and anxiety.[5-6]

COPD is termed the second leading cause of mortality with disability adjusted life years in India. Furthermore, the prevalence rate of COPD among the Indian population above the age of 30 years is also reported to be 7%.[27] In western countries, the smoking epidemic was on a rapid decline, where the situation on the other side of the world is different. COPD was determined to be one of the leading causes of morbidity globally and was expected to be the third leading cause of death worldwide during the 2020s.[1] In many Western nations, the smoking crisis has decreased rapidly, while the condition in other parts of the world remains quite different. Chronic obstructive lung disease (COPD) has been identified as a growing contributor to global morbidity and is projected to become the third major cause of death globally during the 2020s.[1]

COPD symptoms appear before the age of 40, and are usually preceded by a minimum period of a decade of smoking habits or any other harmful airway exposure as well. Symptoms of COPD usually do not appear before the age of 40 years and are often preceded by a minimum of 10 years of smoking or other harmful exposures to the airways. Chronic dyspnea is determined to be one of the main symptoms of COPD.[16] During the initial days, it was only possible to recognize by means of exercise, as and when the disease progressed, and dyspnea might also be present with minimal exertion, even at rest. Increased sputum or phlegm with or without cough could be one of the first symptoms of COPD, which is persistent in approximately 30% of patients.[28] Along with dyspnea, another symptom that accompany COPD is the wheezing or tightness in the chest.[29] However, the intensity of symptoms might vary differently, but the patient will never completely resolve them, at best. On the other side of the scale, the patient may experience different episodes of worsening symptoms called as "Acute Exacerbations of COPD (AECOPD)".[30] The severity of symptoms can fluctuate, but the patient will likely never experience complete resolution, even under the best circumstances. On the contrary, the patient may encounter periodic episodes of symptom aggravation, referred to as "Acute Exacerbations of COPD (AECOPD)".[30]

In addition to poor lung function, patients with COPD may also have other medical concerns, such as muscle loss, fatigue and the development of cachexia, which are identified as some of the common findings in advanced COPD. To add a few more, anxiety and depression are some of the other closely related conditions to COPD, especially during the progressive stage of the disease. Furthermore, cardiovascular diseases, diabetes mellitus, and lung cancer are some of the few examples of common comorbidities associated with COPD. Overall, the total disease burden in patients with COPD is formidable. It is not only determined by lung function but also requires additional diagnosis, one of which may be the determination of the levels of D-dimers.

Conclusion

Measurements of FEV1, FEV1/FVC ratio and FEF 25% to 75%, showed a significant difference with a p-value of less than 0.05 when comparing control subjects with patients with COPD. The morphological variations observed in patients with COPD include Chronic Bronchitis, Emphysema, and small bowel disease. In particular, the D-dimer, the promising plasma biomarker identified in this study, demonstrated a strong correlation with these different morphological categories in patients with COPD. This suggests that the D-dimer could serve as a reliable biomarker for validating and confirming the various morphological classifications among individuals with COPD.

The correlation between biomarkers and disease severity is well established in the study, however causality remains unproven, which might be due to a smaller sample size could be considered as a limitation of the present investigation. Therefore, prospective cohort studies or mechanistic investigations would strengthen these findings and could address the limitation identified in our study. Furthermore, conducting larger, multicenter studies will also be necessary to validate the findings across diverse populations to establish predictive values to track the changes based on biomarkers.

Declarations

Funding

This research did not receive funding.

Author contributions

Conceptualization, A.P. and M.T.; Methodology, A.P., A.M. and M.T.; Software, A.P. and M.T.; Data Validation, A.P., A.M, M.T. and S.D.; Formal Analysis, A.P., M.T., S.C. and H.K.; Investigation, A.P, M.T., S.C. and H.K; Writing – Original Draft, A.P.; Writing – Review & Editing, A.P. and M.T.; Visualization, A.P., A.M. and M.T.; Supervision, A.M. and M.T.; Project Administration, A.M. and M.T.

Conflicts of interest

The authors declare no competing interests.

Data availability

All data generated or analyzed during the study are included in this published article.

Ethical approval

The approval of the ethics committee was obtained before the initiation of the study (meeting date; 23/12/2022, decision number: SU/2022/3108[37]).

References

1. Ferkol T, Schraufnagel D. The global burden of respiratory disease. *Ann Am Thorac Soc*. 2014;11(3):404-406. doi: 10.1513/AnnalsATS.201311-405PS
2. Hansel TT, Barnes PJ. *An Atlas of Chronic Obstructive Pulmonary Disease* (1st ed.). CRC Press. 2003. doi: 10.3109/9780203490723
3. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*. 2016;21(1):14-23. doi: 10.1111/resp.12660
4. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J.* 2011;37(2):264-272. doi: 10.1183/09031936.00051110
5. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis*. 1993;147:1151-1156. doi: 10.1164/ajrccm/147.5.1151
6. Daga MK, Mahapatra SJ, Prakash SK, Gupta N. The Study Of Prothrombotic Markers In Patients With Chronic Obstructive Pulmonary Disease And Its Correlation With Acute Exacerbation." *D41. COPD: BIOMARKERS IN STABLE DISEASE AND EXACERBATIONS. American Thoracic Society.* 2014;A5899-A5899.
7. Hanania NA, Mullerova H, Locantore N, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med*. 2011;183:604-611. doi: 10.1164/rccm.201003-0472OC
8. Sin DD. Asthma-COPD Overlap Syndrome: What We Know and What We Don't. *Tuberc Respir Dis (Seoul).* 2017;80:11-20. doi: 10.4046/trd.2017.80.1.11
9. Norbäck D, Zock JP, Plana E, et al. Lung function decline in relation to mould and dampness in the home: the longitudinal European Community Respiratory Health Survey ECRHS II. *Thorax*. 2011;66(5):396-401. doi: 10.1136/thx.2010.146613
10. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. *Am J Respir Crit Care Med*. 2019;200(8):e70-88. doi: 10.1164/rccm.201908-1590ST

11. Silveyra P, Fuentes N, Rodriguez Bauza DE. Sex and gender differences in lung disease. InLung Inflammation in Health and Disease, Volume II 2021 May 22. Cham: Springer International Publishing. 2021:227-258.
12. Eich A, Urban V, Jutel M, et al. A Randomized, Placebo-Controlled Phase 2 Trial of CNTO 6785 in Chronic Obstructive Pulmonary Disease. *COPD.* 2017,14(5):476-483. doi: 10.1080/15412555.2017.1335697
13. Akpinar EE, Hoşgün D, Doğanay B, Ataç GK, Gülhan M. Should the cut-off value of D-dimer be elevated to exclude pulmonary embolism in acute exacerbation of COPD?. *J Thorac Dis*. 2013;5(4):430-434. doi: 10.3978/j.issn.2072-1439.2013.07.34
14. Manon-Jensen T, Langholm LL, Rønnow SR, et al. End-product of fibrinogen is elevated in emphysematous chronic obstructive pulmonary disease and is predictive of mortality in the ECLIPSE cohort. *Respir Med*. 2019;160:105814. doi: 10.1016/j.rmed.2019.105814
15. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176(6):532-555. doi: 10.1164/rccm.200703-456SO
16. Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J*. 2008;31(1):204-212. doi: 10.1183/09031936.00114307
17. Maclay JD, McAllister DA, Johnston S, et al. Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax.* 2011;66(9):769-774. doi: 10.1136/thx.2010.157529
18. Arregui MA, Ezquerra KL, López FC, Lacasa RC. Hypercoagulability state and endotelial injury in stable chronic obstructive pulmonary disease patients. *An Sist Sanit Navar.* 2010;33(1):43-50.
19. Kattainen S, Pitkänen H, Reijula J, Hästbacka J. Complete blood count, coagulation biomarkers, and lung function 6 months after critical COVID-19. *Acta Anaesthesiol Scand.* 2024;68(7):940-948. doi: 10.1111/aas.14437
20. Baidya A, Sangle S, Marbaniang I, et al. Clinical and immunological markers of pulmonary impairment among people with HIV in India. InOpen Forum Infectious Diseases 2022 Jul 1 (Vol. 9, No. 7, p. ofac233). Oxford University Press.
21. GOLD (Global Initiative for Chronic Obstructive Pulmonary Disease). 2015. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. http://goldcopd.org/. Accessed November 8, 2024.
22. Fruchter O, Yigla M, Kramer MR. D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. *Am J Med Sci*. 2015;349(1):29-35. doi: 10.1097/MAJ.0000000000000332
23. Sadeghi S, Emami Ardestani M, Raofi E, Jalaie Esfandabadi A. Diagnostic Value of D-dimer in Detecting Pulmonary Embolism in Patients with Acute COPD Exacerbation. *Tanaffos*. 2020;19(4):371-379.
24. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care*. 2020;8:49. doi: 10.1186/s40560-020-00466-z
25. Saymaz ZT, Çelik D, Yıldız M, Ertan Ö. The effects of D-dimer high rates on prognosis and mortality in chronic obstructive respiratory disease. *Anatolian Current Medical Journal*. 2022;4(1):44-50. doi: 10.38053/acmj.1023590
26. NICE (National Institute for Health and Care Excellence). 2010. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. Guideline CG101. https://www.nice.org.uk/guidance/cg101. Accessed November 8, 2024.
27. Verma A, Gudi N, Yadav UN, et al. Prevalence of COPD among population above 30 years in India: A systematic review and meta-analysis. *Journal of Global Health*. 2021;11:04038. doi: 10.7189/jogh.11.04038
28. Baqdunes MW, Leap J, Young M, Kaura A, Cheema T. Acute exacerbation of chronic obstructive pulmonary disease. *Critical Care Nursing Quarterly*. 2021;44(1):74-90. doi: 10.1097/CNQ.0000000000000341
29. Amin N. An overview of COPD, causes, clinical manifestations, complications and its management. *J Nurs Sci Pract Res Adv.* 2023;5(1):33-40.
30. Claxton S, Porter P, Brisbane J, et al. Identifying acute exacerbations of chronic obstructive pulmonary disease using patient-reported symptoms and cough feature analysis. *NPJ Digital Medicine*. 2021;4(1):107. doi: 10.1038/s41746-021-00472-x