

CLINICAL AND PARACLINICAL PARTICULARITIES IN PATIENTS WITH COPD AND PULMONARY HYPERTENSION

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition frequently associated with pulmonary hypertension (PH), a severe vascular complication contributing to worsened prognosis and increased mortality. The present study aimed to evaluate the clinical and paraclinical particularities in patients with COPD and associated PH, highlighting relevant risk factors, biological markers, and disease severity. **Methods:** This retrospective observational study included 150 patients diagnosed with COPD, admitted to the Internal Medicine Department of "Anton Cincu" Hospital, Tecuci, Romania, between November 2023 and October 2024. Patients were divided into two groups: Group A (COPD with PH, n=30) and Group B (COPD without PH, n=120). Clinical examination, pulmonary function tests, echocardiography, 6-minute walk test (6MWT), and laboratory evaluations were performed. **Results:** Patients with COPD and PH exhibited a higher mean age (67±12 years), greater smoking prevalence (76.6%), and a higher incidence of comorbidities, such as congestive heart failure (63.3%) and arterial hypertension (36.6%), compared to those without PH. A significantly higher proportion of patients in Group A presented with severe airflow limitation (FEV1 <60%), advanced COPD stages, and reduced exercise tolerance (mean 6MWT distance 417.8±98.5 meters). Elevated inflammatory markers, including C-reactive protein, leukocytosis, and thrombocytosis, were more prevalent in COPD patients with PH. **Conclusion:** Pulmonary hypertension in COPD patients is associated with a more severe clinical profile, reduced functional capacity, and elevated systemic inflammation. Identifying specific clinical and biological parameters may aid in risk stratification, prognosis estimation, and therapeutic decision-making in COPD patients at risk of developing PH.

Key words: chronic obstructive pulmonary disease, pulmonary hypertension, risk factors, systemic inflammation, endothelial dysfunction, cardiovascular complications, sleep apnea, vascular remodeling, multidisciplinary management

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic pulmonary condition that affects both the bronchi (chronic bronchitis) and the lungs (emphysema), and manifests through a progressive and irreversible narrowing of the airways, leading to a gradual decrease in respiratory capacity. The diagnosis should be considered in any patient presenting

cough, sputum production, or dyspnea, and/or with a history of exposure to risk factors for the disease. COPD is a major cause of morbidity and mortality, ranking as the fourth leading cause of death worldwide, with increasing prevalence in mortality rates. [1-4]

Pulmonary hypertension (PH) is a vascular disorder of the pulmonary arteries, characterized by varying degrees of vascular

proliferation and remodeling, leading to a progressive increase in pulmonary vascular resistance, and ultimately evolving toward right ventricular failure and death. PH is associated with systemic diseases, worsening both their prognosis and progression. Common causes include hypoxia, oxidative stress, increased blood flow in pulmonary circulation, autonomic nervous system malfunctioning, inflammatory lesions, and hypercoagulability. PH is defined as a mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg at rest. PH is commonly observed in advanced stages of pulmonary parenchymal and interstitial diseases. Studies have shown that 1-5% of patients with advanced COPD and chronic respiratory failure have pulmonary hypertension. [5-7]

The onset and progression of PH associated with COPD involve several mechanisms: inflammatory exacerbations, hypoxia, in situ thrombosis, hyperviscosity, and vascular remodeling, all contributing to a poor prognosis, major pulmonary and cardiac complications, as well as therapeutic failure. The essential role of the endothelium in the pulmonary microcirculation and the complex array of the local mediators have fundamentally changed the understanding not only of each condition individually but especially of the understanding of their association. [8-14]

MATERIALS AND METHODS

The study included 150 patients, both men and women, aged between 44 and 80 years old, from both urban and rural areas, diagnosed based on clinical criteria, functional

respiratory tests, and echocardiographic criteria with COPD, selected from a total sample of 1825 patients who presented to the Internal Medicine Department of “Anton Cincu” Hospital in Tecuci between November 1st 2023 and October 31st 2024, for various medical conditions.

For each study participant, demographic data were recorded, and clinical examination, chest radiography, electrocardiogram, echocardiogram, six-minute walk test (6MWT), biological status, pulmonary function tests were performed.

Based on the presence or absence of PH, the study group was divided into two subgroups: Group A – COPD patients with PH, and Group B – COPD patients without PH.

RESULTS

Following data analysis, the following characteristics were noted: out of the 150 COPD patients, 30 were in group A (COPD with PH), and 120 were in Group B (COPD without PH). The average age was 61.75 ± 3.4 years in both groups.

Age group distribution:

- Patients under 55 years: 13 (9% of the total study lot), including 10 men and 3 women;
- Patients aged 56-65: 39 (26%), including 26 men and 13 women;
- Patients aged 66-75: 65 (43%), including 39 men and 26 women;
- Patients over 75 years: 33 (22%), including 20 men and 13 women.

The predominant age group was 66-75 years old, with a predominance of males across all age groups.

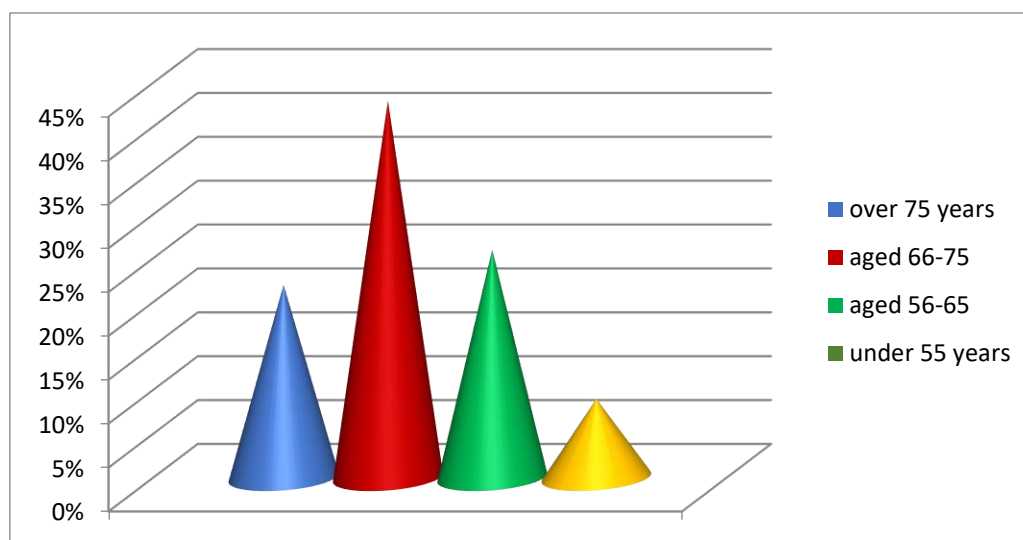


Figure 1. Age group distribution

Risk Factor Distribution in the Two Study Groups

Any form of exposure to cigarette smoke

(active smoker, ex-smoker, passive smoker) predisposes to a higher incidence of COPD in the studied population.

Table 1. Risk Factor Distribution in the Two Study Groups

Risk Factor	COPD with PH (Group A)	COPD without PH (Group B)
Smoker	19 patients (63.3%)	49 patients (40.8%)
Non-smoker	4 patients (13.3%)	14 patients (11.6%)
Ex-smoker	5 patients (16.6%)	22 patients (18.3%)
Passive smoker	4 patients (13.3%)	34 patients (28.3%)
Occupational exposure	14 patients (46.6%)	47 patients (39.16%)

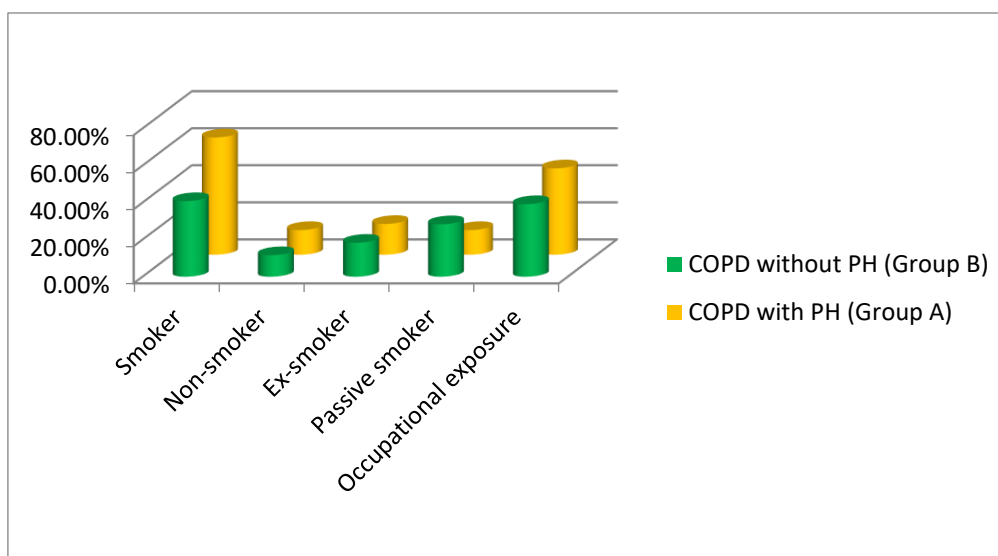


Figure 2. Risk Factor Distribution in the Two Study Groups

Table 2. Clinical Characteristics of Studied COPD Patients

Variable	COPD with PH (Group A)	COPD without PH (Group B)
Mean age	67 ± 12 years	60 ± 15 years
Female/Male ratio	12 / 18	49 / 71
Smokers	23 patients (76.6%)	70 patients (58.3%)
Arterial hypertension	11 patients (36.6%)	34 patients (28.3%)
Congestive heart failure (CHF)	19 patients (63.3%)	12 patients (10%)
FEV1 < 60%	18 patients (60%)	39 patients (32.5%)
SaO ₂ <90%	19 patients (63.3%)	38 patients (31.6%)
Sleep apnea syndrome	16 patients (53.3%)	17 patients (14.1%)

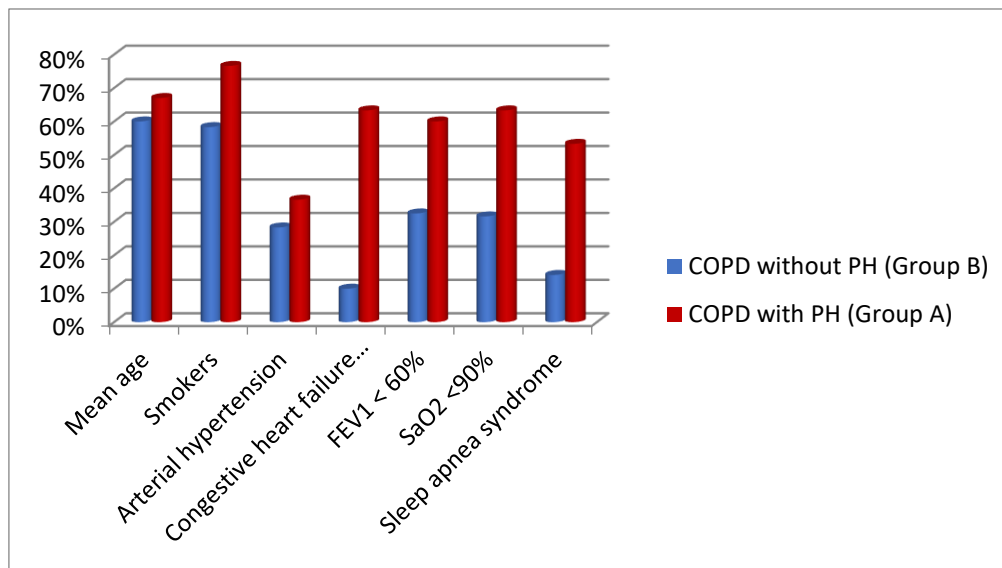


Figure 3. Clinical Characteristics of Studied COPD Patients

Table 3. Classification According to COPD Severity (Based on FEV1 Values)

COPD Stage	COPD with PH (Group A)	COPD without PH (Group B)
Stage 0: At risk	-	-
Stage I: Mild	77.5 ± 5.2	79.1 ± 4.4
Stage II: Moderate	59.8 ± 10.3	62.2 ± 9.8
Stage III: Severe	48.9 ± 7.9	49.8 ± 8.8
Stage IV: Very severe	28.6 ± 8.1	29.1 ± 7.4

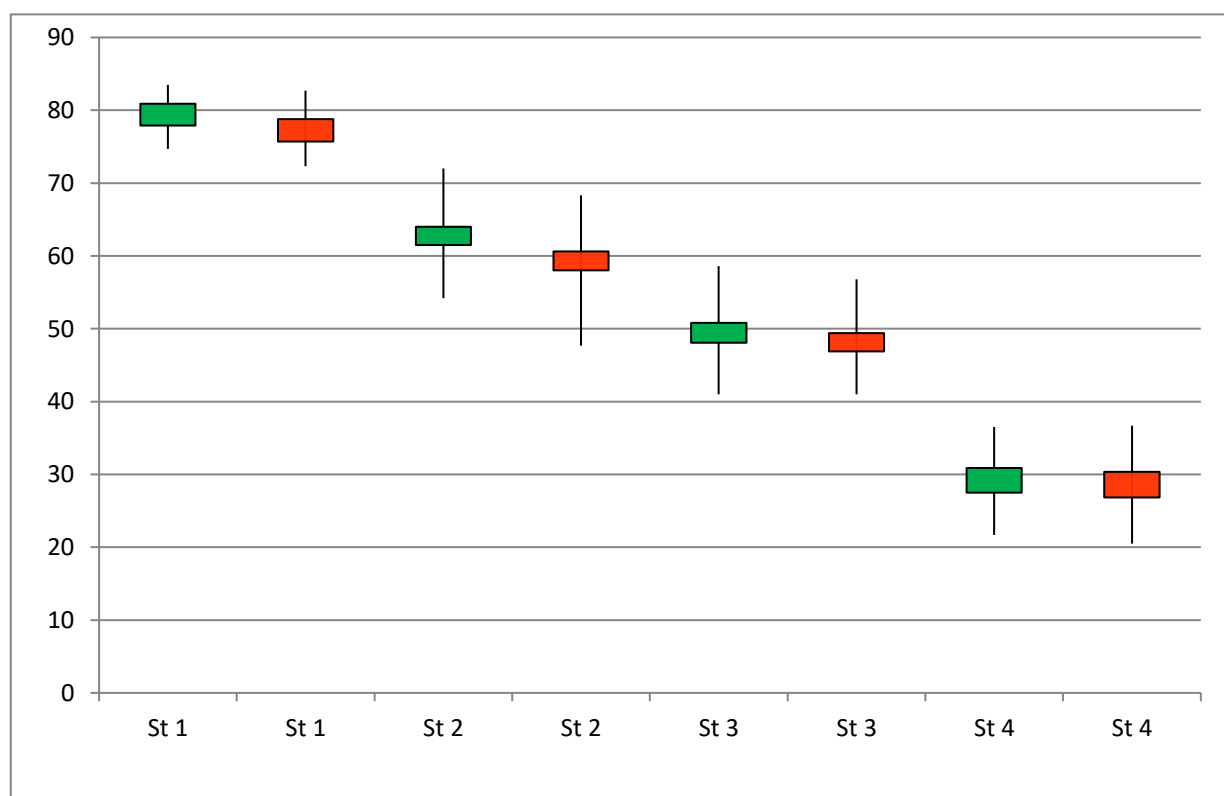


Figure 4. Classification According to COPD Severity (Based on FEV1 Values)

Table 4. FEV1 Severity Staging by Patient Count

Stage	COPD without PH (Group A)	COPD without PH (Group B)
Stage 0: At risk	-	-
Stage I: Mild	7 patients (23.3%)	65 patients (54.1%)
Stage II: Moderate	5 patients (16.6%)	19 patients (15.8%)
Stage III: Severe	12 patients (40%)	29 patients (24.1%)
Stage IV: Very severe	6 patients (16.6%)	7 patients (5.8%)

A significantly higher percentage of patients in Group A were in the more severe stages of COPD compared to the patients in Group B.

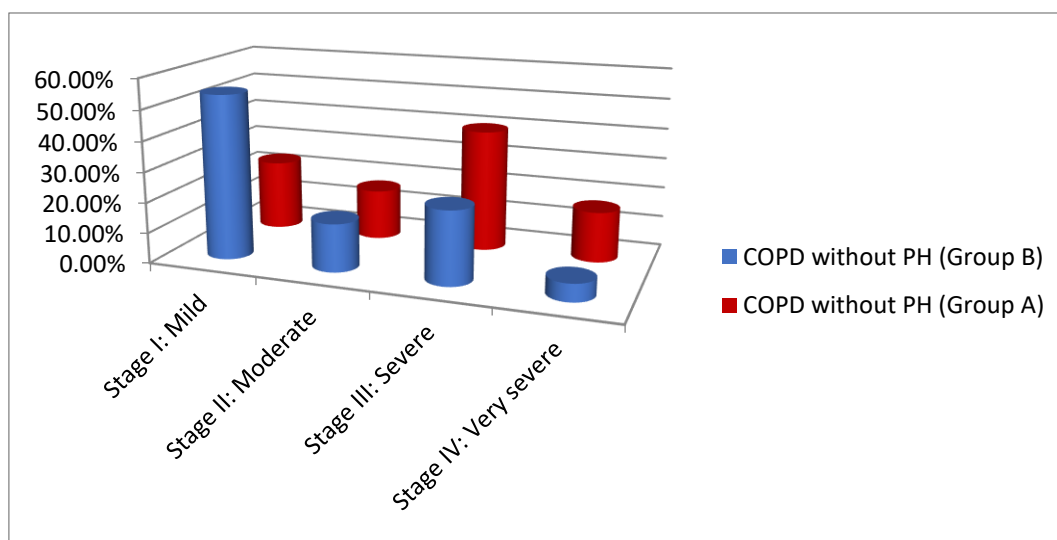


Figure 5. FEV1 Severity Staging by Patient Count

Table 5. Functional Classification of Patients with COPD and PH (NYHA Classes)

NYHA Class	Number of Patients
Class I	12 patients (40%)
Class II	7 patients (23.3%)
Class III	6 patients (20%)
Class IV	5 patients (16.6%)

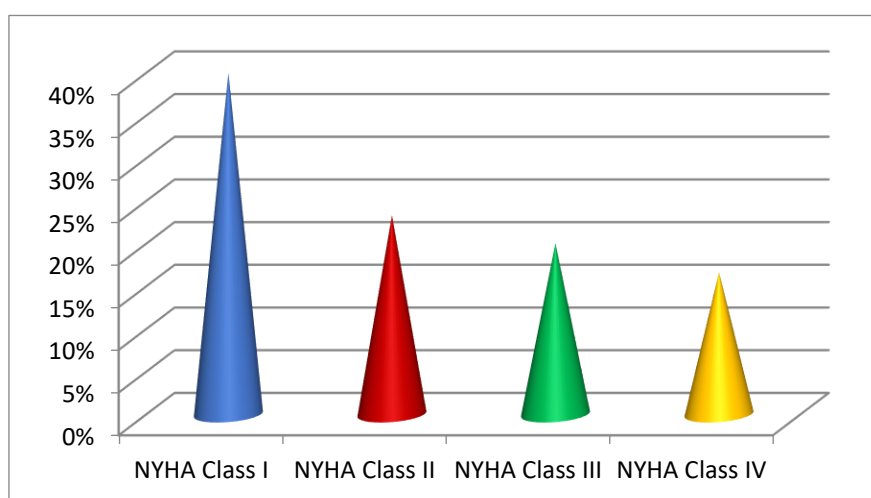


Figure 6. Functional Classification of Patients with COPD and PH (NYHA Classes)

Six-Minute Walk Test (6MWT)

Effort tolerance, as assessed by walking distance, was influenced not only by cardiac performance, but also by the level of physical conditioning of each subject.

All patients in Group B (COPD without

PH) completed the 6MWT without interruption. In contrast, 3 patients in the COPD with PH group were unable to complete the test. The mean walking distance was significantly lower in Group A compared to Group B.

Table 6. Six-Minute Walk Test (6MWT)

Group	Average Distance Walked
COPD without PH (Group B)	489.2 ± 94.3 meters
COPD with PH (Group A)	417.8 ± 98.5 meters

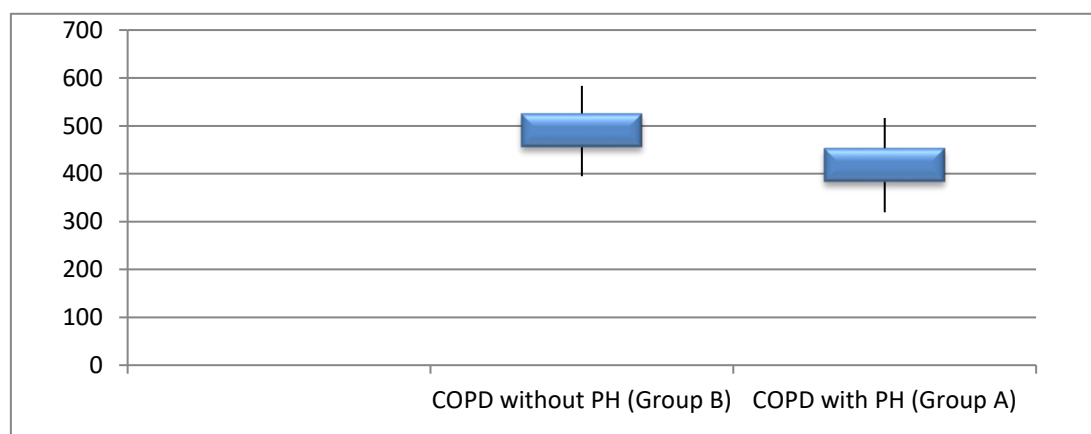


Figure 7. Six-Minute Walk Test (6MWT)

Biological Status Assessment in the Two Groups

Routine blood work and inflammatory markers were obtained as follows:

Table 7. Biological Status Assessment in the Two Groups

Parameter	COPD with PH (Group A)	COPD without PH (Group B)
Polycythemia	9 patients (30%)	26 patients (22%)
Leukocytosis	13 patients (43%)	45 patients (38%)

Thrombocytosis	14 patients (47%)	50 patients (42%)
Elevated ESR	15 patients (50%)	55 patients (46%)
Hyperfibrinogenemia	16 patients (53%)	53 patients (44%)
C-reactive protein	17 patients (57%)	48 patients (40%)
Hyperglycemia	4 patients (14%)	14 patients (12%)
Hyperuricemia	7 patients (24%)	19 patients (16%)
Dyslipidemia	17 patients (57%)	62 patients (52%)
Electrolyte imbalance	4 patients (13%)	10 patients (8%)
Hepatic cytolysis syndrome	8 patients (27%)	17 patients (14%)
Nitrogen retention syndrome	2 patients (8%)	7 patients (6%)

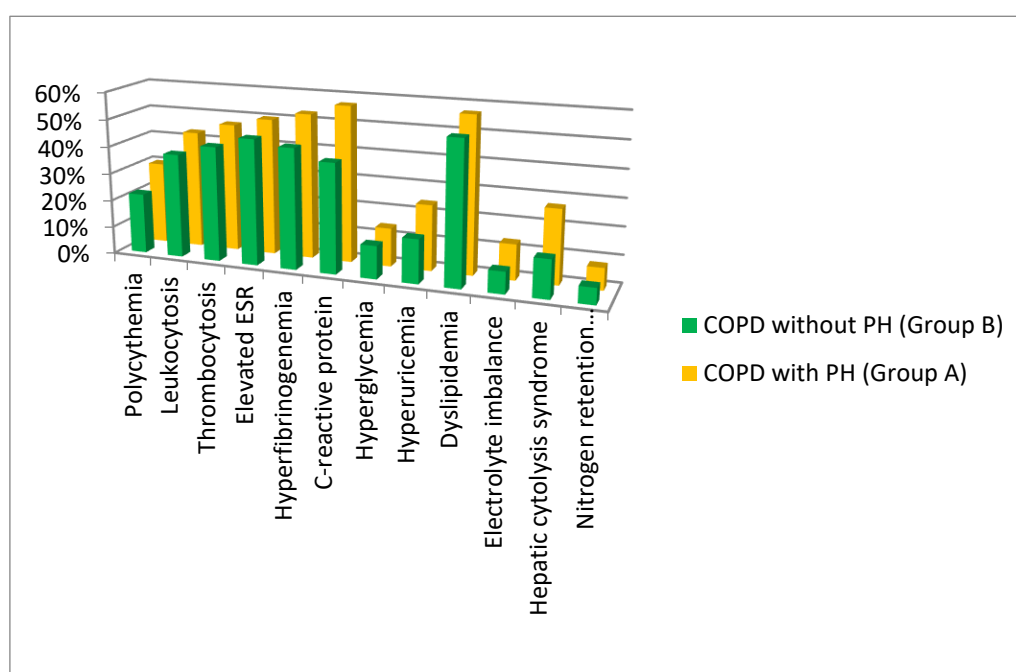


Figure 8. Biological Status Assessment in the Two Groups

Notably, elevated levels of C-reactive protein (a marker of systemic inflammation), along with other inflammatory parameters such as leukocytosis, thrombocytosis, elevated

ESR, and hyperfibrinogenemia, were significantly higher in COPD patients with pulmonary hypertension than in those without PH.

DISCUSSIONS

Pulmonary hypertension (PH) represents a complex and severe complication frequently encountered in patients diagnosed with chronic obstructive pulmonary disease (COPD). The coexistence of these pathologies generates a significant negative impact on both the functional respiratory capacity of the patient and their overall prognosis. In the present study, several relevant aspects regarding the clinical and paraclinical profile of patients with COPD and PH were outlined, bringing valuable contributions to existing literature. [15-22]

Pulmonary hypertension is a common associated with persistent inflammation, chronic hypoxia, and a prothrombotic state. In order to identify risk factors affecting the progression of COPD, a total of 150 patients were evaluated, of whom 120 had COPD without PH and 30 had COPD with PH. [13,14,23-27]

The analysis of obtained data revealed several defining characteristics: in both groups, the majority of those affected were male, smokers, from urban areas, predominantly within the 44-80-year age group. From the perspective of disease severity, a significantly larger proportion of patients with COPD and PH were found in higher severity classes compared to those without PH. Furthermore, the average distance walked during the six-minute walk test was longer in patients with COPD without PH compared to those with both COPD and PH. [28-30]

The inflammatory cascade is considered central to the pathogenesis and progression of COPD. Inflammatory mediators promote hyperviscosity and amplify pulmonary vascular injury, representing a key link between hypoxia, vascular injury, and endothelial dysfunction. [10-12,31-36]

One of the key findings of this study is the significantly higher average age of patients with both COPD and PH (61.75 ± 3.4 years), suggesting the progressive character of the disease and its accentuation with advancing age. Furthermore, male gender predominance and smoking status were confirmed as essential risk factors contributing to the onset and progression of COPD and PH, consistent with data from existing literature. [37,38]

The study highlights the more severe clinical profile of patients with associated PH, demonstrated by the higher prevalence of comorbidities such as congestive heart failure (63.3%) and arterial hypertension (36.6%), which aggravate the symptomatology and evolution of the disease. From a functional point of view, a significant reduction in FEV1 values was observed in patients with COPD and PH, with 60% of these patients falling into the severe or very severe stages of COPD. In contrast, only 32.5% of patients without PH presented such advanced stages of airway obstruction. [39-42]

The six-minute walk test (6MWT) provided valuable information about exercise tolerance, confirming the significant reduction in physical performance in patients with COPD and PH (mean distance: 417.8 ± 98.5 m) compared to those without PH (mean distance: 489.2 ± 94.3 m). This result underlines the dual contribution of both ventilatory and vascular limitations to exercise intolerance in these patients. [43-47]

Biologically, the presence of a systemic inflammatory syndrome was confirmed in the PH group, expressed by the increased levels of C-reactive protein (57%), leukocytosis (43%), thrombocytosis (47%), and elevated erythrocyte sedimentation rate (50%). These results support the hypothesis that systemic inflammation plays a fundamental role in the pathophysiological mechanisms involved in the onset and

progression of pulmonary vascular remodeling and hypoxia-induced injury. [48-52]

Additionally, the presence of polycythemia in 30% of patients with COPD and PH suggests a compensatory response to chronic hypoxia, contributing to the increase in blood viscosity and implicitly to the aggravation of pulmonary vascular resistance. [53-55]

An important element to emphasize is that the coexistence of COPD and PH determines a significantly worse prognosis due to the synergistic action of several pathogenic mechanisms: chronic hypoxia, systemic inflammation, vascular endothelial dysfunction, and the presence of comorbidities such as heart failure or sleep apnea syndrome. [56-59]

The findings of the present study reinforce the need for complex and individualized management of these patients. Monitoring biological markers of inflammation, assessing functional respiratory capacity, and performing echocardiographic evaluations should become routine practices in the clinical approach of patients with COPD, especially in those at risk of developing PH. [50-63]

Identifying modifiable risk factors, such as smoking cessation, early control of comorbidities, and optimizing oxygen therapy, are essential therapeutic strategies that can improve prognosis and quality of life. [4]

The present study provides relevant clinical and paraclinical data that complement existing knowledge about the impact of PH in COPD patients. The recognition of specific clinical patterns and systemic inflammation parameters allows for a more accurate stratification of risk and a better individualization of therapeutic approaches in this category of patients. [62,64-66]

The analysis of the clinical, functional, and biological particularities in patients

diagnosed with chronic obstructive pulmonary disease (COPD) associated with pulmonary hypertension (PH), emphasize the significant impact of this vascular complication on disease evolution and patient prognosis. [10,19,22,24,67]

The coexistence of PH in COPD patients was associated with a more severe clinical profile characterized by advanced age, higher prevalence of cardiovascular comorbidities, and a history of smoking, confirming the well-established role of these factors in the pathogenesis and progression of respiratory and vascular impairment. From a functional perspective, the study revealed that the presence of PH contributes to a pronounced reduction of pulmonary ventilatory capacity, with significantly lower FEV1 values and a higher distribution of patients in the severe and very severe stages of COPD. [27,68-70]

The study highlighted a marked reduction in physical performance and exercise tolerance in COPD patients with PH, as demonstrated by the significant decrease in the distance covered during the six-minute walk test. This aspect underlines the multifactorial limitation of effort capacity due to the synergistic contribution of both obstructive ventilatory dysfunction and pulmonary vascular impairment.

A particularly important element revealed by the present research was the identification of systemic inflammation as a central pathogenic mechanism in COPD patients with PH. The elevated levels of inflammatory markers, such as C-reactive protein, leukocytosis, thrombocytosis, and erythrocyte sedimentation rate, reinforce the hypothesis that chronic inflammation plays a key role in the development and progression of pulmonary vascular remodeling, aggravating disease severity.

Additionally, the presence of

polycythemia in a considerable percentage of patients reflects the compensatory response of the organism to chronic hypoxia, while also suggesting its potential negative role in increasing blood viscosity and pulmonary vascular resistance.

These findings highlight the importance of early identification of PH in COPD patients, given its negative impact on prognosis and quality of life. Routine clinical practice should include the assessment of specific biological markers, regular evaluation of ventilatory function, echocardiographic monitoring, and exercise capacity testing, especially in COPD patients with risk factors for developing PH.

The management of COPD patients with PH requires a multidisciplinary and individualized therapeutic approach, targeting not only the control of respiratory symptoms but also the reduction of systemic inflammation, optimization of oxygen therapy, and aggressive management of cardiovascular comorbidities.

CONCLUSIONS

The presence of pulmonary hypertension in patients with COPD is significantly correlated with smoking status, severity of pulmonary impairment, the coexistence of heart failure, and elevated levels of inflammatory biomarkers. These findings are associated with a moderately to severely aggravated clinical course and an unfavorable prognosis.

The evaluation of these clinical and biological parameters can serve not only as important prognostic tools in the monitoring of PH evolution in COPD but may also hold therapeutic relevance, representing potential targets for future interventions.

The results of the present study contribute substantially to the current knowledge regarding the clinical and paraclinical profile of COPD patients with PH and emphasize the need for early detection, continuous monitoring, and personalized intervention strategies to improve the prognosis and life expectancy of these patients. Future studies with larger sample sizes and prospective designs are recommended to validate and expand these findings.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of “Anton Cincu” Hospital in Tecuci.

Informed Consent Statement

Written informed consent for participation in the study and for publication of this paper was obtained from the patients.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding authors.

Conflicts of Interest

The authors declare no conflict of interest.

Author's contribution

The authors GS, IDF, CND, CD, CS and NM had an equal scientific contribution to this research as SST, the first author.

REFERENCES

1. Societatea Europeană de Cardiologie, Societatea Europeană Respiratorie. Ghidul ESC/ERS 2022 pentru diagnosticul și tratamentul hipertensiunii pulmonare. Eur Heart J. 2022;43(38):3618-3731.
2. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. Overview: Chronic obstructive pulmonary disease (COPD) [Updated 2022 Dec 28]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK315789/>
3. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(3):228-237.
4. Khan KS, Jawaid S, Memon UA, et al. Management of Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in Hospitalized Patients From Admission to Discharge: A Comprehensive Review of Therapeutic Interventions. Cureus. 2023;15(8):e43694.
5. Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. Circ Res. 2014;115(1):115-130.
6. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J. 2019;53(1):1801887.
7. Das BB. Mechanism and Treatment of Right Ventricular Failure Due to Pulmonary Hypertension in Children. Children. 2025; 12(4):476.
8. Wrobel JP, Thompson BR, Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. J Heart Lung Transplant. 2012;31(6):557-564.
9. Shujaat A, Bajwa AA, Cury JD. Pulmonary Hypertension Secondary to COPD. Pulm Med. 2012;2012:203952.
10. Karnati S, Seimetz M, Kleefeldt F, et al. Chronic Obstructive Pulmonary Disease and the Cardiovascular System: Vascular Repair and Regeneration as a Therapeutic Target. Front Cardiovasc Med. 2021;8:649512.
11. Tatarciuc D, Vasincu D, Stoleriu G, Iancu RI, Costuleanu M. Biochemical Effects of Intraliposomal Angiotensins on Isolated Vascular Smooth Muscle Cells. REV.CHIM.(Bucharest) 2018;69(5):1187-1190.
12. Tatarciuc D, Gentimir C, Zaharia CA, Costin A, Chelaru L, Cazan I, Stoleriu G, Costuleanu M. Biochemical Interactions Between Angiotensin II and Apelin in Isolated Vascular Smooth Muscle Cells. REV.CHIM.(Bucharest) 2017;68(10):2431-2435.
13. Nakamura K, Akagi S, Ejiri K, Taya S, Saito Y, Kuroda K, Takaya Y, Toh N, Nakayama R, Katanosaka Y, et al. Pathophysiology of Group 3 Pulmonary Hypertension Associated with Lung Diseases and/or Hypoxia. International Journal of Molecular Sciences. 2025; 26(2):835.
14. Farishta M, Sankari A. Pulmonary Hypertension Due to Lung Disease or Hypoxia. [Updated 2023 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK587358/>
15. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for The Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Raport 2024. Available from: <https://goldcopd.org/>
16. Tanaseanu C, Tudor S, Tamsulea I, Marta D, Manea G. Vascular endothelial growth factor, lipoprotein-associated phospholipase A2, sP-selectin and antiphospholipid antibodies,

- biological markers with prognostic value in pulmonary hypertension associated with chronic obstructive pulmonary disease and systemic lupus erithematosus. *Eur J Med Res*. 2007.
17. Blanco I, Tura-Ceide O, Peinado VI, Barberà JA. Updated Perspectives on Pulmonary Hypertension in COPD. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1315-1324.
 18. Krompa A, Marino P. Diagnosis and management of pulmonary hypertension related to chronic respiratory disease. *Breathe (Sheff)*. 2022;18(4):220205.
 19. Shlobin OA, Adir Y, Barbera JA, et al. Pulmonary hypertension associated with lung diseases. *Eur Respir J*. 2024;64(4):2401200.
 20. Cassady SJ, Reed RM. Pulmonary Hypertension in COPD: A Case Study and Review of the Literature. *Medicina (Kaunas)*. 2019;55(8):432.
 21. Jyothula S, Safdar Z. Update on pulmonary hypertension complicating chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2009;4:351-363.
 22. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J*. 2008;32(5):1371-1385.
 23. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53(1):1801914.
 24. Elwing J, Panos RJ. Pulmonary hypertension associated with COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(1):55-70.
 25. Montani D, Günther S, Dorfmueller P, et al. Pulmonary arterial hypertension. *Orphanet J Rare Dis*. 2013;8:97.
 26. Steger M, Canuet M, Enache I, Goetsch T, Labani A, Meyer L, Martin G, Kessler R, Montani D, Riou M. Survie et réponse aux traitements vasodilatateurs pulmonaires spécifiques de l'HTAP des patients atteints de BPCO et d'hypertension pulmonaire sévère: cohorte rétrospective strasbourgeoise. *Rev Mal Respir Actual*. 2024;16(1):47.
 27. Papaportfyriou A, Bartziokas K, Gompelmann D, Idzko M, Fouka E, Zaneli S, Bakakos P, Loukides S, Papaioannou AI. Cardiovascular Diseases in COPD: From Diagnosis and Prevalence to Therapy. *Life*. 2023; 13(6):1299.
 28. Valentine JA. The Transformative Role of Authentic Partnership in the Tuskegee Public Health Ethics Program. *J Health Sci Humanit*. 2018;8(1):21-29.
 29. Hitchman SC, Fong GT, Zanna MP, Thrasher JF, Chung-Hall J, Siahpush M. Socioeconomic status and smokers' number of smoking friends: findings from the International Tobacco Control (ITC) Four Country Survey. *Drug Alcohol Depend*. 2014;143:158-166.
 30. Miyara M, Tubach F, Pourcher V, et al. Lower Rate of Daily Smokers With Symptomatic COVID-19: A Monocentric Self-Report of Smoking Habit Study. *Front Med (Lausanne)*. 2022;8:668995.
 31. Chaouat A, Bugnet A, Kadaoui N, Schott R, Enache I, Ducoloné A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;172:189-194.
 32. King PT. Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer. *Clin Transl Med*. 2015;4(1):68.
 33. Marriott E, Singanayagam A, El-Awaisi J. Inflammation as the nexus: exploring the link between acute myocardial infarction and chronic obstructive pulmonary disease. *Front Cardiovasc Med*. 2024;11:1362564.

34. Rodrigues SO, Cunha CMCD, Soares GMV, Silva PL, Silva AR, Gonçalves-de-Albuquerque CF. Mechanisms, Pathophysiology and Currently Proposed Treatments of Chronic Obstructive Pulmonary Disease. *Pharmaceuticals (Basel)*. 2021;14(10):979.
35. Szucs B, Szucs C, Petrekanits M, Varga JT. Molecular Characteristics and Treatment of Endothelial Dysfunction in Patients with COPD: A Review Article. *International Journal of Molecular Sciences*. 2019; 20(18):4329.
36. Rovina N, Koutsoukou A, Koulouris NG. Inflammation and immune response in COPD: where do we stand?. *Mediators Inflamm*. 2013;2013:413735.
37. Fekete M, Horvath A, Santa B, et al. Analysis of COPD: Distinguishing Characteristics and Management of Smoking vs Never Smoking Patients. *Int J Chron Obstruct Pulmon Dis*. 2024;19:2671-2688.
38. Ancel J, Chen E, Pavot A, Regard L, Le Rouzic O, Guecamburu M, et al. Principaux messages de la deuxième Biennale BPCO 2023 de la SPLF. Le patient au cœur du parcours de soins. *Rev Mal Respir*. 2024.
39. Hussain N, Charalampopoulos A, Ramjug S, et al. Pulmonary hypertension in patients with heart failure and preserved ejection fraction: differential diagnosis and management. *Pulm Circ*. 2016;6(1):3-14.
40. Berthelot E, Bauer F, Eicher JC, et al. Pulmonary hypertension in chronic heart failure: definitions, advances, and unanswered issues. *ESC Heart Fail*. 2018;5(5):755-763.
41. Desai N, Olewinska E, Famulska A, Remuzat C, Francois C, Folkerts K. Heart failure with mildly reduced and preserved ejection fraction: A review of disease burden and remaining unmet medical needs within a new treatment landscape. *Heart Fail Rev*. 2024;29(3):631-662.
42. Brittain EL, Thenappan T, Huston JH, et al. Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Call to Action: A Science Advisory From the American Heart Association. *Circulation*. 2022;146(7):e73-e88.
43. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Intern Med J*. 2009;39(8):495-501.
44. Vlase CM, Gutu C, Bogdan Goroftei RE, Boghean A, Iordachi TFD, Arbune AA, Arbune M. Echocardiographic Left Ventricular Function in the Third Year After COVID-19 Hospitalization: A Follow-Up Pilot Study in South-East of Romania. *Medicina (Kaunas)*. 2025;61(2):333. doi:10.3390/medicina61020333
45. Holland AE, Rasekaba T, Fiore JF Jr, Burge AT, Lee AL. The 6-minute walk distance cannot be accurately assessed at home in people with COPD. *Disabil Rehabil*. 2015;37(12):1102-1106.
46. Rejbi IB, Trabelsi Y, Chouchene A, et al. Changes in six-minute walking distance during pulmonary rehabilitation in patients with COPD and in healthy subjects. *Int J Chron Obstruct Pulmon Dis*. 2010;5:209-215.
47. Oki Y, Kaneko M, Fujimoto Y, Sakai H, Misu S, Mitani Y, Yamaguchi T, Yasuda H, Ishikawa A. Usefulness of the 6-minute walk test as a screening test for pulmonary arterial enlargement in COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11(1):2869-2875.
48. Pugliese SC, Poth JM, Fini MA, Olschewski A, El Kasmi KC, Stenmark KR. The role of inflammation in hypoxic pulmonary hypertension: from cellular mechanisms to clinical phenotypes. *Am J Physiol Lung Cell Mol Physiol*. 2015;308(3):L229-L252.

49. Balan R, Bălăşescu E, Ion DA. Inflammation and arterial hypertension-pathophysiological links and clinical aspects. *Curr Health Sci J*. 2020;46(4):383.
50. Tobal R, Potjewijd J, van Empel VPM, et al. Vascular Remodeling in Pulmonary Arterial Hypertension: The Potential Involvement of Innate and Adaptive Immunity. *Front Med (Lausanne)*. 2021;8:806899.
51. Bousseau S, Sobrano Fais R, Gu S, Frump A, Lahm T. Pathophysiology and new advances in pulmonary hypertension. *BMJ Med*. 2023;2(1):e000137.
52. Adu-Amankwaah J, You Q, Liu X, et al. Pulmonary Hypertension: Molecular Mechanisms and Clinical Studies. *MedComm (2020)*. 2025;6(3):e70134.
53. Thapa KB, Paudel A, Dhital S, Shrestha A, Ojha L, Shrestha A. Polycythemia among Patients with Chronic Obstructive Pulmonary Disease Admitted to the Department of Medicine in a Tertiary Care Center: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc*. 2023;61(260):343-346.
54. Zhang J, DeMeo DL, Silverman EK, et al. Secondary polycythemia in chronic obstructive pulmonary disease: prevalence and risk factors. *BMC Pulm Med*. 2021;21(1):235.
55. Guo L, Chughtai AR, Jiang H, et al. Relationship between polycythemia and in-hospital mortality in chronic obstructive pulmonary disease patients with low-risk pulmonary embolism. *J Thorac Dis*. 2016;8(11):3119-3131.
56. Chan SMH, Selemidis S, Bozinovski S, Vlahos R. Pathobiological mechanisms underlying metabolic syndrome (MetS) in chronic obstructive pulmonary disease (COPD): clinical significance and therapeutic strategies. *Pharmacol Ther*. 2019;198:160-188.
57. Mariniello DF, D'Agnano V, Cennamo D, et al. Comorbidities in COPD: Current and Future Treatment Challenges. *J Clin Med*. 2024;13(3):743.
58. Owens RL, Malhotra A. Sleep-disordered breathing and COPD: the overlap syndrome. *Respir Care*. 2010;55(10):1333-1346.
59. Fanaridis M, Bouloukaki I, Stathakis G, Steiropoulos P, Tzanakis N, Moniaki V, Mavroudi E, Tsiligianni I, Schiza S. Prevalence and Characteristics of Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease: Overlap Syndrome. *Life*. 2024; 14(5):547.
60. Cardoso J, Ferreira AJ, Guimarães M, Oliveira AS, Simão P, Sucena M. Treatable Traits in COPD - A Proposed Approach. *Int J Chron Obstruct Pulmon Dis*. 2021;16:3167-3182.
61. Bailey KL. The importance of the assessment of pulmonary function in COPD. *Med Clin North Am*. 2012;96(4):745-752.
62. Pantazopoulos I, Magounaki K, Kotsiou O, et al. Incorporating Biomarkers in COPD Management: The Research Keeps Going. *J Pers Med*. 2022;12(3):379.
63. Khedr L, Khedr NF, Werida RH. Functional capacity and inflammatory biomarkers as predictors for right atrial volume index in COPD patients. *Int J Cardiovasc Imaging*. 2023;39(8):1493-1504.
64. Sonar M, Jayadeva BT, Shashibhushan BL. Comparative Study of Systemic Inflammatory Markers in Clinical Phenotypes of Chronic Obstructive Pulmonary Disease. *Tanaffos*. 2023;22(2):215-220.
65. Tkacova R. Systemic inflammation in chronic obstructive pulmonary disease: may adipose tissue play a role? Review of the literature and future perspectives. *Mediators Inflamm*. 2010;2010:585989.

66. Kovacs G, Avian A, Bachmaier G, et al. Severe Pulmonary Hypertension in COPD: Impact on Survival and Diagnostic Approach. *Chest*. 2022;162(1):202-212.
67. Gologanu D, Stanescu C, Ursica T, Balea MI, Ionita D, Bogdan MA. Prevalence and Characteristics of Pulmonary Hypertension Associated with COPD - A Pilot Study in Patients Referred to a Pulmonary Rehabilitation Program Clinic. *Maedica (Bucur)*. 2013;8(3):243-248.
68. Ragnoli B, Chiazza F, Tarsi G, Malerba M. Biological pathways and mechanisms linking COPD and cardiovascular disease. *Ther Adv Chronic Dis*. 2025;16:20406223251314286.
69. Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? [published correction appears in *Eur Respir Rev*. 2018 Nov 21;27(150):185057. doi: 10.1183/16000617.5057-2018.]. *Eur Respir Rev*. 2018;27(149):180057.
70. Zangiabadi A, De Pasquale CG, Sajkov D. Pulmonary hypertension and right heart dysfunction in chronic lung disease. *Biomed Res Int*. 2014;2014:739674.