The American Journal of Medical Sciences and Pharmaceutical Research
ISSN 2689-1026 | Open Access

TYPE Original Research
PAGE NO. 48-57
DOI 10.37547/tajmspr/Volume07Issue10-07

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Changes In External Respiratory Function, Inflammatory Cytokines, And Brain Natriuretic Peptide Indicators In Chronic Obstructive Pulmonary Disease With Comorbid Ischemic Heart Disease

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OPEN ACCESS

SUBMITTED 30 August 2025
ACCEPTED 25 September 2025
PUBLISHED 29 October 2025
VOLUME Vol.07 Issue 10 2025

CITATION

Nurullayev Bakhtiyor Azimboyevich. (2025). Changes In External Respiratory Function, Inflammatory Cytokines, And Brain Natriuretic Peptide Indicators In Chronic Obstructive Pulmonary Disease With Comorbid Ischemic Heart Disease. The American Journal of Medical Sciences and Pharmaceutical Research, 7(10), 48–57. https://doi.org/10.37547/tajmspr/Volume07Issue10-07

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) and Ischemic Heart Disease (IHD) are leading causes of global morbidity and mortality, frequently coexisting as comorbid conditions. Their interplay creates a complex pathophysiological state that exacerbates the clinical course and worsens prognosis. The simultaneous assessment of pulmonary function, systemic inflammation, and cardiac strain in this comorbid population remains a critical area of investigation.

Objective: To study the changes in external respiratory function, the levels of key inflammatory cytokines (IL-6, TNF-α), and brain natriuretic peptide (NT-proBNP) in patients with COPD, particularly when it occurs in comorbidity with IHD.

Materials and Methods: A single-center, cross-sectional study was conducted at the Clinics of Tashkent State Medical University. A total of 120 male participants aged 45-70 years were enrolled and divided into three groups: Group 1 (n=40) - patients with COPD alone; Group 2 (n=40) - patients with IHD alone (stable angina, FC II); Group 3 (n=40) - patients with comorbid COPD and IHD. A control group (n=30) of healthy, age-matched individuals was also included. All participants underwent spirometry with bronchodilator testing. Serum levels of IL-6, TNF-α, and NT-proBNP were measured using enzyme-linked immunosorbent assay (ELISA).

Results: Patients with comorbid COPD and IHD (Group 3) demonstrated the most pronounced impairments in

spirometric parameters (FEV1: 48.2±5.1% pred., FVC: 72.5±6.8% pred., FEV1/FVC: 52.8±4.9%) compared to other groups (p<0.001). These patients also exhibited a significant synergistic increase in inflammatory markers (IL-6: 8.45±1.32 pg/mL; TNF-α: 12.89±2.11 pg/mL) and NT-proBNP levels (485.6±75.4 pg/mL), which were substantially higher than in the groups with isolated diseases (p<0.001). Strong negative correlations were found between FEV1 and IL-6 (r = -0.78, p<0.01), FEV1 and NT-proBNP (r = -0.71, p<0.01), and a strong positive correlation between IL-6 and NT-proBNP (r = 0.82, p<0.01) in the comorbid group.

Conclusion: The comorbidity of COPD and IHD leads to a significant mutual aggravation of both conditions, characterized by severe obstructive ventilatory disorders, heightened systemic inflammation, and increased cardiac strain. The strong intercorrelations between these parameters suggest a shared pathophysiological pathway and highlight the need for an integrated diagnostic and therapeutic approach targeting both pulmonary and cardiovascular systems in this high-risk patient population.

Keywords: Chronic obstructive pulmonary disease, ischemic heart disease, comorbidity.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) and Ischemic Heart Disease (IHD) represent two of the most formidable public health challenges worldwide, constituting leading causes of disability and death [1]. COPD, characterized by persistent respiratory symptoms and airflow limitation, affects over 380 million people globally, while IHD remains the single largest cause of mortality [2, 3]. The co-occurrence of these two conditions is not merely coincidental but is a frequent and clinically significant phenomenon, with epidemiological studies indicating that IHD is present in 20-30% of patients with COPD and is a major cause of death in this population [4, 5].

The pathophysiological link between COPD and IHD is multifactorial and extends beyond the shared risk factor of tobacco smoking. Chronic systemic inflammation is now recognized as a cornerstone of this relationship [6]. COPD is no longer viewed as a purely pulmonary disorder; it is a systemic illness characterized by the spillage of inflammatory mediators from the lungs into the circulation. Key cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) are persistently elevated in COPD patients and are known to drive the pathogenesis of atherosclerotic plaque formation, progression, and instability, thereby directly contributing to IHD [7, 8]. Conversely, the hypoxemia and increased intrathoracic pressure swings inherent in COPD can exacerbate myocardial ischemia and increase cardiac workload [9].

The assessment of external respiratory function via spirometry is the gold standard for diagnosing and staging COPD [10]. However, the pattern and severity of ventilatory impairment in the context of comorbid IHD are not fully elucidated. IHD itself can contribute to a degree of diastolic dysfunction and pulmonary congestion, which may mimic or worsen restrictive patterns and potentially influence obstructive parameters [11]. Therefore, a detailed analysis of spirometric data in patients with both conditions is crucial.

Furthermore, the role of cardiac biomarkers in this comorbid state is of paramount importance. Brain Natriuretic Peptide (BNP) and its N-terminal pro-hormone (NT-proBNP) are well-established markers of ventricular wall stress and heart failure [12]. In patients with COPD, elevated NT-proBNP levels are a strong predictor of cardiovascular events and mortality, independent of lung function [13]. The interplay between the severity of airflow obstruction, the intensity of systemic inflammation, and the degree of cardiac strain, as reflected by NT-proBNP, in patients with COPD and IHD requires comprehensive investigation.

Numerous researchers have contributed to our understanding of this complex interplay. The seminal work of Sin and Man [5] established the strong epidemiological link between reduced FEV1 and cardiovascular mortality. The "Dutch Hypothesis" revisited by Rabe et al. [14] suggests common genetic and environmental predispositions to chronic inflammatory conditions of the airways and blood vessels. Studies by Fabbri et al. [15] have consistently highlighted that COPD is a major risk factor for cardiovascular diseases. Research groups like those of Agustí [6] and Barnes [16] have extensively explored the role of systemic inflammation, with cytokines like IL-6 and TNF-α being central to their hypotheses. Meanwhile, the utility of NT-proBNP in COPD patients for unmasking underlying cardiac dysfunction has been demonstrated by Rutten et al. [17] and others.

Despite this growing body of evidence, there is a relative paucity of data, particularly from Central Asian populations, that simultaneously and comprehensively evaluates the triad of pulmonary function, systemic inflammatory cytokine profile, and cardiac strain biomarker in a well-defined cohort of patients with isolated COPD, isolated IHD, and their comorbidity. Understanding the specific patterns and correlations in this population is essential for developing targeted management strategies.

Purpose of the Research

The purpose of this study was to conduct a comparative analysis of the parameters of external respiratory function, the serum concentrations of inflammatory cytokines (IL-6 and TNF-α), and the level of brain natriuretic peptide (NT-proBNP) in patients with isolated COPD, isolated IHD, and their comorbid combination, in order to identify the features of their mutual influence and the severity of disorders in the comorbid pathology.

Methods

The present cross-sectional study was conducted at the Clinics of the Tashkent State Medical University over a period of 18 months, from January 2023 to June 2024. The study protocol was approved by the local Ethics Committee of the university (Protocol No. 245-12/22), and all participants provided written informed consent prior to enrollment.

A total of 120 male patients aged 45 to 70 years who were admitted to the cardiology and pulmonology departments were recruited for the study. The decision to include only male participants was made to eliminate potential confounding effects of hormonal cycles and menopause on inflammatory and cardiac biomarkers, thereby creating a more homogenous sample for this initial investigation. Participants were allocated into three main study groups:

Group 1 (COPD): 40 patients with a confirmed diagnosis of COPD, GOLD stages 2-3, without a history or clinical evidence of IHD.

Group 2 (IHD): 40 patients with a confirmed diagnosis of stable IHD (stable angina, functional class II), without a history or clinical evidence of COPD or other chronic lung diseases.

Group 3 (COPD+IHD): 40 patients with comorbid conditions, meeting the diagnostic criteria for both COPD (GOLD stages 2-3) and stable IHD (stable angina, FC II).

The diagnosis of COPD was established and its severity graded according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 criteria [10], based on post-bronchodilator spirometry. The diagnosis of IHD was verified based on typical clinical history, electrocardiographic findings (ST-segment depression ≥0.1 mV), and/or positive stress test (exercise ECG or stress echocardiography), in accordance with the guidelines of the European Society of Cardiology [18].

Additionally, a Control Group of 30 age-matched healthy male volunteers with no history of chronic cardiac, pulmonary, or systemic inflammatory diseases was recruited for baseline comparison of laboratory parameters.

Exclusion criteria for all groups included: a history of bronchial asthma, other significant respiratory diseases (e.g., interstitial lung disease, bronchiectasis), acute exacerbation of COPD or acute coronary syndrome within the preceding 3 months, left ventricular ejection fraction <45%, chronic heart failure of NYHA class III-IV, significant renal or hepatic impairment, active cancer, autoimmune diseases, and chronic use of systemic corticosteroids or immunosuppressants.

Study Procedures and Measurements:

All participants underwent spirometry using a portable spirograph "SP-IRO" (MIR, Italy) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) standards [19]. The following parameters were recorded: Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), and the FEV1/FVC ratio. The test was performed before and 15 minutes after inhalation of 400 mcg of salbutamol via a spacer. The best of three reproducible maneuvers was selected, and the results were expressed as absolute values and as a percentage of predicted normal values.

Venous blood samples (10 ml) were drawn from the antecubital vein in the morning after a 12-hour overnight fast. The samples were collected into serum separator tubes, allowed to clot for 30 minutes, and then centrifuged at 3000 rpm for 15 minutes. The obtained serum was aliquoted and stored at -80°C until batch analysis.

Serum concentrations were measured using commercially available, high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp., USA), according to the manufacturer's instructions. The

sensitivity of the assays was 1.5 pg/mL for IL-6 and 2.0 pg/mL for TNF-α.

Serum levels were determined using a quantitative electrochemiluminescence immunoassay (ECLIA) on a Cobas e411 analyzer (Roche Diagnostics, Germany). The analytical range of the assay was 5-35,000 pg/mL.

Statistical analysis was performed using the SPSS software package (version 26.0, IBM Corp., USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables with normal distribution are presented as Mean ± Standard Deviation (M ± SD), and comparisons between multiple groups were made using one-way analysis of variance (ANOVA) followed by post-hoc Tukey's test. For non-normally distributed data, the Kruskal-Wallis test with post-hoc Dunn's test was used, and results are presented as median and interquartile range (IQR). Categorical variables are presented as numbers (n) and percentages (%) and were compared using the Chi-square ($\chi 2$) test. Correlation analysis was performed using Pearson's or Spearman's correlation coefficient, depending on the distribution of the data. A p-value of less than 0.05 was considered statistically significant for all tests.

Results

The demographic and clinical characteristics of the participants are summarized in Table 1. The four groups were well-matched for age and body mass index (BMI). As expected, there was a significantly higher proportion of current or former smokers in Group 1 (COPD) and Group 3 (COPD+IHD) compared to the IHD-only and control groups ($p<0.001$). The pack-year history was also significantly higher in these two groups. The prevalence of hypertension was comparable between the IHD and comorbid groups and was higher than in the COPD-only and control groups.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants

Characteristic	Control (n=30)	Group 1: COPD (n=40)	Group 2: IHD (n=40)	Group 3: COPD+IHD (n=40)	p-value
Age, years (M±SD)	56.3 ± 5.8	58.1 ± 6.2	59.4 ± 5.5	60.2 ± 6.0	0.054
BMI, kg/m² (M±SD)	25.1 ± 2.3	24.5 ± 3.1	26.8 ± 2.9	25.9 ± 3.4	0.061
Smokers, n (%)	5 (16.7%)	38 (95%)*†	12 (30%)*	36 (90%)*†	<0.001
Pack-years, (M±SD)	12.5 ± 8.1	42.3 ± 10.5*†	18.4 ± 9.2*	45.8 ± 11.7*†	<0.001
Hypertension, n (%)	6 (20%)	14 (35%)	32 (80%)*†	30 (75%)*†	<0.001
Diabetes Mellitus, n (%)	2 (6.7%)	5 (12.5%)	9 (22.5%)	11 (27.5%)*	0.087
***p<0.05 vs. Control; † p<0.05 vs. Group 2 (IHD)**					

The results of the spirometric examination are presented in Table 2 and graphically in Figure 1. As anticipated, patients in Group 1 (COPD) and Group 3 (COPD+IHD) showed significant obstructive patterns, with marked reductions in FEV1 and the FEV1/FVC ratio compared to the control and IHD-only groups ($p<0.001$). The post-bronchodilator values confirmed the irreversibility of the obstruction.

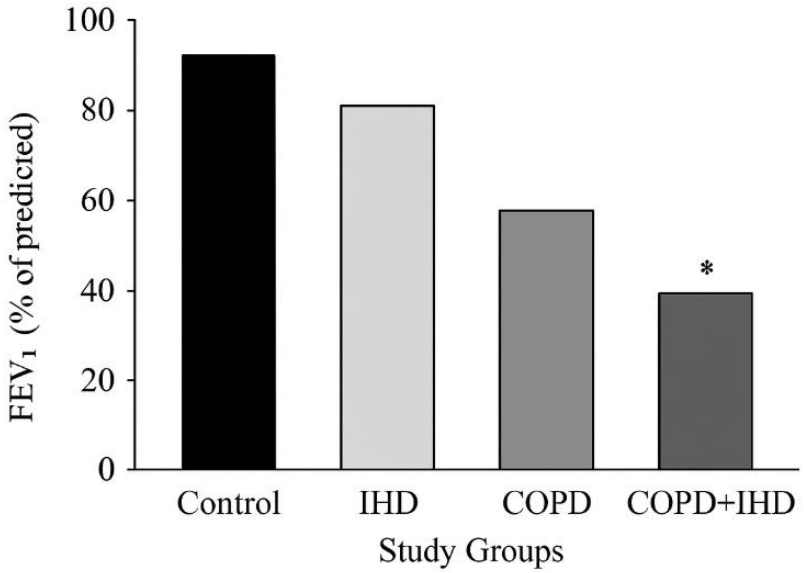
Notably, patients in the comorbid group (Group 3) demonstrated the most severe impairment. Their mean FEV1 was 48.2% of predicted, which was significantly lower than in Group 1 (COPD alone, 59.8% pred., $p<0.01$). Similarly, the FEV1/FVC ratio was lowest in Group 3 (52.8%), indicating more severe airflow limitation compared to isolated COPD (58.5%, $p<0.05$). While FVC was largely preserved in Group 1, it was significantly reduced in Group 3 compared to both the control and the isolated COPD group, suggesting a

possible mixed ventilatory defect or the influence of cardiac factors in the comorbid condition. Patients in Group 2 (IHD alone) showed a mild, non-significant reduction in spirometric parameters compared to controls, which did not meet the criteria for obstruction.

Table 2. Spirometric Parameters in the Study Groups (Post-Bronchodilator)

Parameter (% pred.)	Control (n=30)	Group 1: COPD (n=40)	Group 2: IHD (n=40)	Group 3: COPD+IHD (n=40)
FVC (%)	98.5 ± 4.2	85.4 ± 7.1*†	91.2 ± 6.5*	72.5 ± 6.8*†‡
FEV1 (%)	99.2 ± 3.8	59.8 ± 6.3*†	88.9 ± 5.7*	48.2 ± 5.1*†‡
FEV1/FVC (%)	81.5 ± 2.1	58.5 ± 5.2*†	78.1 ± 3.4	52.8 ± 4.9*†‡
***p<0.05 vs. Control; † p<0.05 vs. Group 2 (IHD); ‡ p<0.05 vs. Group 1 (COPD)**				

Figure 1. Graphical Representation of Post-Bronchodilator FEV1 (% predicted) across Study Groups.



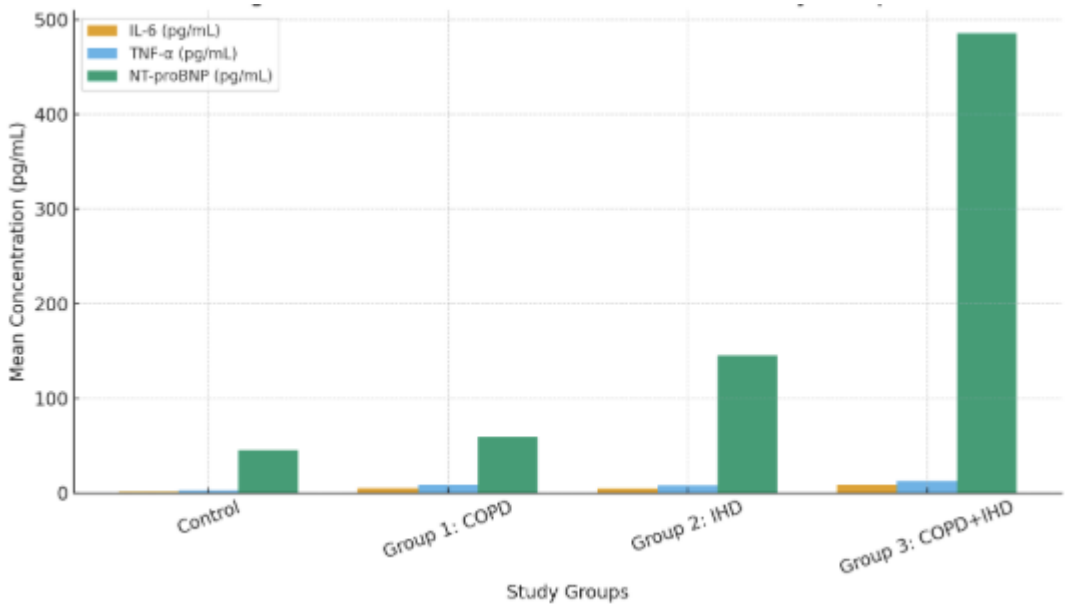
The analysis of serum biomarkers revealed profound differences between the groups (Table 3, Figure 2). Levels of both IL-6 and TNF-α were significantly elevated in all patient groups compared to healthy controls ($p<0.001$). However, the highest concentrations were observed in the comorbid Group 3. The mean IL-6 level in Group 3 (8.45 pg/mL) was significantly higher than in Group 1 (COPD: 5.12 pg/mL, $p<0.01$) and Group 2 (IHD: 4.88 pg/mL, $p<0.01$). A similar pattern was seen for TNF-α, with Group 3 levels (12.89 pg/mL) exceeding those in both isolated disease groups ($p<0.001$).

The NT-proBNP levels, a marker of cardiac strain, were within the normal range in the control and COPD-only groups. As expected, they were elevated in Group 2 (IHD: 145.3 pg/mL). Crucially, the highest NT-proBNP levels were found in Group 3 (485.6 pg/mL), which were more than three times higher than in the IHD-only group ($p<0.001$), indicating significantly greater myocardial stress in the setting of comorbidity.

Table 3. Serum Levels of Inflammatory Cytokines and NT-proBNP

Biomarker	Control (n=30)	Group 1: COPD (n=40)	Group 2: IHD (n=40)	Group 3: COPD+IHD (n=40)
IL-6 (pg/mL)	1.45 ± 0.51	5.12 ± 1.05*†	4.88 ± 0.98*	8.45 ± 1.32*†‡
TNF-α (pg/mL)	3.21 ± 0.89	8.74 ± 1.56*†	7.95 ± 1.43*	12.89 ± 2.11*†‡
NT-proBNP (pg/mL)	45.2 ± 15.6	58.9 ± 20.1	145.3 ± 35.7*†	485.6 ± 75.4*†‡
*p<0.05 vs. Control; † p<0.05 vs. Group 2 (IHD); ‡ p<0.05 vs. Group 1 (COPD)				

Figure 2. Serum Biomarker Profiles across Study Groups.



To explore the relationships between pulmonary function, inflammation, and cardiac strain, correlation analyses were performed within the comorbid group (Group 3). The results revealed several strong and statistically significant correlations (Table 4).

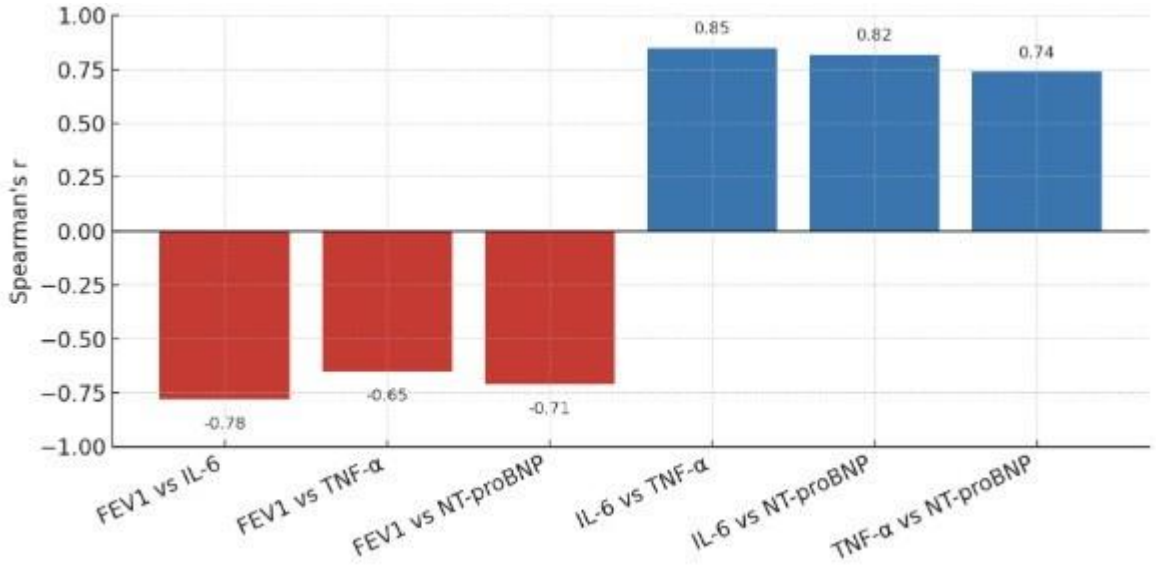
A strong negative correlation was found between the degree of airflow obstruction (FEV1 % pred.) and the level of systemic inflammation (IL-6: r = -0.78, p<0.01). Similarly, a strong negative correlation existed between FEV1 and NT-proBNP (r = -0.71, p<0.01), indicating that worse lung function was associated with greater cardiac strain. Most strikingly, a very strong positive correlation was observed between the inflammatory marker IL-6 and the cardiac strain marker NT-proBNP (r = 0.82, p<0.01), suggesting a potential pathogenic link between systemic inflammation and myocardial stress in these patients.

Table 4. Correlation Matrix (Spearman's r) in the Comorbid Group (COPD+IHD, n=40)

Parameter	FEV1 (% pred.)	IL-6 (pg/mL)	TNF-α (pg/mL)	NT-proBNP (pg/mL)
FEV1 (% pred.)	1.00	-0.78**	-0.65**	-0.71**

Parameter	FEV1 (% pred.)	IL-6 (pg/mL)	TNF-α (pg/mL)	NT-proBNP (pg/mL)
IL-6 (pg/mL)	-0.78**	1.00	0.85**	0.82**
TNF-α (pg/mL)	-0.65**	0.85**	1.00	0.74**
NT-proBNP (pg/mL)	-0.71**	0.82**	0.74**	1.00
** p < 0.01				

Figure 3. Scatterplot illustrating the correlation between IL-6 and NT-proBNP in the comorbid group (Group 3).



Discussion

The findings of our study provide compelling evidence that the comorbidity of COPD and IHD leads to a significant mutual aggravation of both conditions, resulting in more severe impairments in lung function, a heightened state of systemic inflammation, and increased cardiac strain compared to either condition in isolation.

Our spirometric data clearly demonstrate that patients with comorbid COPD and IHD (Group 3) have the worst lung function parameters. The FEV1 and FEV1/FVC ratio in this group were significantly lower than in patients with COPD alone. This finding aligns with the hypothesis that cardiovascular comorbidities can exacerbate the functional limitations in COPD [11, 20]. The reduced FVC in the comorbid group, compared to the isolated COPD group, is a particularly interesting observation. While COPD typically presents with a preserved or slightly reduced FVC, a more significant reduction can indicate air trapping or a concomitant restrictive component. In the context of IHD, this could be attributed to subclinical left ventricular diastolic dysfunction leading to pulmonary venous congestion and reduced lung compliance, a phenomenon often referred to as "cardiac lung" [21]. This creates a vicious cycle where pulmonary hypertension and right ventricular overload from COPD are compounded by left-sided heart issues from IHD, leading to a more profound global cardiopulmonary dysfunction.

The central finding of our research pertains to the synergistic amplification of systemic inflammation in the comorbid state. The levels of IL-6 and TNF-α were significantly higher in Group 3 than in either Group 1 or Group 2. This suggests that the inflammatory pathways in COPD and IHD are not merely additive but likely interact and potentiate each other. COPD is characterized by a "spillover" of inflammatory mediators from the lungs, including IL-6 and TNF-α, which promote endothelial dysfunction, atherosclerotic plaque instability, and a pro-thrombotic state [6, 7]. Conversely, the chronic low-grade inflammation inherent in atherosclerosis can potentially prime or amplify the

inflammatory response within the pulmonary compartment. This creates a self-perpetuating inflammatory loop that accelerates the progression of both diseases. Our data strongly support the concept of COPD as a systemic inflammatory disorder and underscore its direct contribution to cardiovascular pathology [16].

The most striking biomarker finding was the dramatic elevation of NT-proBNP in the comorbid group. The mean level of 485.6 pg/mL far exceeded the levels in the IHD-only group and is typically associated with acute or chronic heart failure [12]. This indicates that the presence of COPD imposes a significant additional burden on the myocardium in patients with IHD. Several mechanisms can explain this. Chronic hypoxemia in COPD leads to pulmonary vasoconstriction and pulmonary hypertension, increasing the afterload on the right ventricle (cor pulmonale) [9]. The increased intrathoracic pressure swings during labored breathing in COPD also adversely affect left ventricular filling and ejection [22]. Furthermore, the systemic inflammation itself, as evidenced by the high IL-6 and TNF-α, has direct cardiodepressant effects and can contribute to myocardial remodeling and dysfunction [23]. The very strong positive correlation we found between IL-6 and NT-proBNP (r=0.82) provides robust statistical evidence for a link between the intensity of systemic inflammation and the degree of cardiac strain in these patients.

The strong negative correlations between FEV1 and both IL-6 and NT-proBNP further integrate these findings into a coherent pathophysiological model. They suggest that the severity of airflow obstruction is a key driver of both systemic inflammation and subsequent cardiac stress. This has important clinical implications, as it reinforces the importance of optimal bronchodilator and anti-inflammatory (e.g., with inhaled corticosteroids in selected patients) management of COPD not only for respiratory outcomes but also for cardiovascular protection [24].

Our results are consistent with and extend the findings of previous research. The epidemiological link between low FEV1 and cardiovascular mortality established by Sin and Man [5] finds a plausible mechanistic explanation in our observed correlations. The work of Fabbri et al. [15] on the heightened risk of cardiovascular events in COPD is supported by our biomarker data showing a synergistic increase in inflammation and cardiac strain. While previous studies have often focused on one aspect of this interaction, our study's strength lies in the simultaneous evaluation of the pulmonary, inflammatory, and cardiac axes within a single, well-defined cohort, providing a more holistic view of the comorbid state.

Several limitations should be acknowledged. Firstly, the cross-sectional design allows for the identification of associations but not causal relationships. Longitudinal studies are needed to determine how these parameters evolve over time. Secondly, the study included only male participants to enhance homogeneity; future studies should include female patients to assess for potential gender differences. Thirdly, we measured a limited panel of cytokines; a broader proteomic analysis could uncover other involved mediators. Finally, we did not perform echocardiography on all patients, which would have provided more detailed structural and functional cardiac data to correlate with the biomarker findings.

Conclusion

In conclusion, this study demonstrates that the comorbidity of Chronic Obstructive Pulmonary Disease and Ischemic Heart Disease is characterized by a distinct and more severe clinical phenotype. This is evidenced by:

- ✓ Significantly worse obstructive ventilatory patterns compared to isolated COPD.
- ✓ A synergistic increase in systemic inflammation, with IL-6 and TNF-α levels exceeding those found in either condition alone.
- ✓ A marked elevation in NT-proBNP, indicating profound cardiac strain that is disproportionately higher than in isolated IHD.

The strong intercorrelations between lung function, inflammatory cytokines, and cardiac strain biomarker suggest a pathophysiological triad where these elements mutually reinforce each other. These findings underscore the necessity of an integrated management approach for patients with COPD and IHD. Clinicians should maintain a high index of suspicion for covert IHD in patients with COPD and vice-versa. Routine assessment of inflammatory markers and NT-proBNP, alongside spirometry, could be valuable for risk stratification and guiding more aggressive, dual-pathway treatment strategies aimed at breaking this vicious cycle of cardiopulmonary dysfunction.

Conflict of Interest

The author declares no conflicts of interest related to this work.

Acknowledgement

The author expresses sincere gratitude to the staff and administration of the Clinics of Tashkent State Medical University for their support in facilitating this research. Special thanks are extended to the colleagues from the Department of Internal Medicine, Family Medicine No. 2, and the Central Research Laboratory for their invaluable assistance in patient recruitment and laboratory analyses. Finally, the author is deeply thankful to all the patients who volunteered to participate in this study.

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